Section 6: Research on Naturopathic Therapeutics and Practices

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HIGHLIGHTS

- There is strong consensus on the core naturopathic treatments with a typical naturopathic visit generally involving the prescription, recommendation or use of an average of four different naturopathic therapeutic modalities or practices.
- Naturopathic care is known for its diverse and flexible therapeutic approach to healthcare. It includes the prescription of internal and topical substances; counselling with respect to diet, lifestyle, and mind-body medicine; naturopathic physical medicine and other therapies.
- The use of a complex intervention approach to care allows naturopaths/NDs to utilize the synergistic properties of various treatments and to individualize the treatment of each patient.
- The naturopathic workforce can play an essential role in addressing non-communicable diseases and other diseases that are strongly influenced by lifestyle factors.
- Dietary and nutritional factors are foundational to naturopathic care and herbal medicine is one of the most common therapies used globally by naturopaths/NDs.
- The naturopathic multi-modal, complex intervention approach warrants further investigation.

Naturopathic practice is known for its complexity and flexibility with a range of treatments, therapies, and practices. There is strong consensus on seven core naturopathic modalities used in practice including applied nutrition and diet modifications, clinical nutrition and the use of natural health products, herbal medicines, lifestyle counselling, hydrotherapy, homeopathic remedies, and various physical modalities such as yoga, naturopathic manipulation, and muscle release techniques.

This Section highlights the original naturopathic research on naturopathic therapeutic modalities and practices with a focus on how they are employed – singularly and in combination – in clinical interventions. The clinical research presented in this section is based on work undertaken by naturopathic researchers across five WHO Regions. However, it is important to note that this is not the summation of research investigating naturopathic treatments accessed and used by the naturopathic workforce. The diversity of knowledge and information used, shared, and produced by naturopaths/NDs is described in more detail in Chapters 13 and 16.

Overall this section presents the results of 304 original clinical research articles covering over 140 conditions and including randomized controlled trials (n=165), case reports (n=52), uncontrolled trials (n=37), secondary analyses (n=20), cohort studies (n=6), comparative controlled trials (n=6), pilot studies (n=3), non-randomized controlled studies (n=3), observational studies (n=2), and one each of non-randomized control trial and an exploratory analysis. It features clinical studies that commonly employ pragmatic elements such as multi-modal interventions, flexibility in administration, and real-world settings and demonstrates a positive response to at least one primary or secondary outcome measure in 77.6% of clinical studies.

The chapter on **Complex Naturopathic Interventions (Chapter 29)** highlights the evidence associated with the holistic, patient-centered, multi-modal treatment approach central to naturopathic care. This chapter provides an overview of 25 clinical research papers investigating complex interventions, with 85.7% reporting a positive outcome in at least one primary or secondary outcome measure. This clinical research is supplemented by over 70 observational studies and 19 reviews or meta-analysis conducted by naturopathic researchers on this topic, as outlined in Chapter 40. The complex interventions studied include:

- Ingestive medicine-based interventions
- Non-ingestive medicine-based interventions

The chapter on **Applied Nutrition (Chapter 30)** highlights the essential and foundational role of dietary counselling and prescription in naturopathic care. Naturopathic applied nutritional interventions include diet therapy (therapeutic diets, fasting and individualized

diet modification), therapeutic application of specific foods and behavioral or lifestyle counselling related to eating behaviors. This chapter provides an overview of 31 clinical research papers, with 88% reporting a positive outcome in at least one primary or secondary outcome. This body of naturopathic research is supplemented by over 20 observational studies and more than 30 reviews or meta-analysis conducted by naturopathic researchers on this topic, as outlined in Chapter 40. The applied interventions studied include:

- Food as medicine
- Diet programs
- Food intolerance testing and support
- Dietary education

The chapter on **Clinical Nutrition (Chapter 31)** outlines one of the top therapeutic modalities used by naturopaths/NDs. Clinical nutrition includes vitamins and minerals, nutrients that have physiological effects such as amino acids and other amino-based compounds, food-based constituents, and other compounds that are important to foundational human biochemistry and physiology. This section provides an overview of 59 clinical research papers with 62.5% reporting a positive outcome in at least one primary or secondary outcome. This body of naturopathic research on clinical nutrition is also supported by over 50 observational studies and more than 90 reviews or meta-analysis conducted by naturopathic researchers on this topic, as outlined in Chapter 40. The clinical nutrition interventions studied include:

- Essential fatty acids
- Multivitamin and/or mineral formulas
- Single vitamins, minerals, and non-essential nutrients
- Medicinal foods and nutraceutical interventions

The chapter on **Herbal Medicine (Chapter 32)** outlines the importance of herbal medicine in naturopathic practice with more than half of naturopathic visits including some form of herbal prescription. Naturopaths/NDs are trained to use a wide range of herbs from mild herbs to extremely powerful herbs that arguably are the basis of modern pharmacological medicine. The range of herbs and the form and dosage, vary based on access to specific herbal medicines in a region as well as the education and scope of practice in a jurisdiction. This section provides an overview of 48 clinical research papers with 71.7% reporting a positive outcome in at least one primary or secondary outcome. This body of naturopathic research on herbal medicine is also supported by over 30 observational studies and more than 120 reviews or meta-analysis conducted by naturopathic researchers on this topic, as outlined in Chapter 40. The herbal medicine interventions studied include:

- Single-herb interventions
- Complex herbal formulations
- Essential oils
- Topical applications

The chapter on **Lifestyle Modifications (Chapter 33)** outlines that early naturopath were among the first health professionals to formally acknowledge lifestyle modifications as an important element of care. The importance of lifestyle counselling in naturopathic practice is considered one of the core therapeutic elements. This section provides an overview of three clinical research papers with 100% reporting a positive outcome in at least one primary or secondary outcome. The lifestyle interventions studied include:

- Lifestyle interventions
- Lifestyle-based risk factor identification

The chapter on **Mind-Body Medicine (MBM) Counselling (Chapter 34)** is prescribed and practiced by naturopaths/NDs with patients of all ages presenting with functional disorders (e.g., gastrointestinal, endocrine, neurological or cardiovascular conditions), structural disorders (e.g., musculoskeletal conditions, chronic pain), psychological conditions (anxiety, depression, ADHD), and as part of preventive and palliative care. This section provides an overview of nine clinical research papers with 88.9% reporting a positive outcome in at least one primary or secondary outcome. The MBM interventions studied include:

- Mindfulness-based stress reduction and meditation
- Other MBM Interventions

The chapter on **Naturopathic Physical Medicine (Chapter 35)** describes how addressing or correcting structural integrity is considered an essential step of the Naturopathic Therapeutic Order. Naturopaths/NDs recognize a correlation between an individual's alignment and structure, the functioning of internal organs and a person's psychological state. Naturopathic physical medicine includes various forms of bodywork ranging from muscle release and massage techniques, naturopathic manipulation, and techniques including yoga and acupuncture which are covered off in other chapters. This section provides an overview of nine clinical research papers with 66.7% reporting a positive outcome in at least one primary or secondary outcome. This body of naturopathic research on naturopathic physical medicine is also supported by over 20 observational studies and seven reviews or meta-analysis conducted by naturopathic researchers on this topic, as outlined in Chapter 40. The physical medicine interventions studied include:

- Massage
- Other manual therapies including osteopathy, breathing techniques, and craniosacral therapy.

The chapter on **Hydrotherapy (Chapter 36)** outlines that hydrotherapy – the application of water for therapeutic purposes – has been used for thousands of years and has been part of naturopathic care since its inception. This section provides an overview of 17 clinical

research papers with 84.2% reporting a positive outcome in at least one primary or secondary outcome. The hydrotherapy interventions studied include:

- Hydrotherapy baths
- Topical compresses
- Complex hydrotherapy

The chapter on **Acupuncture (Chapter 37)** outlines that acupuncture is included in the curriculum in some naturopathic educational programs and is part of the scope of naturopathic care in countries such as Canada, the USA, South Africa, India, Germany, Switzerland, and Brazil. Various acupuncture techniques are practiced by naturopaths/NDs including needling, electroacupuncture, auricular acupuncture, acupressure, cupping and moxibustion. This section provides an overview of 32 clinical research papers with 84.8% reporting a positive outcome in at least one primary or secondary outcome. This body of naturopathic research on acupuncture is also supported by 10 observational studies and 15 reviews or meta-analysis conducted by naturopathic researchers on this topic, as outlined in Chapter 40. The acupuncture interventions studied include:

- Combination acupuncture interventions
- Standalone acupuncture
- Standalone cupping therapy
- Other forms of standalone acupuncture-related treatments including electroacupuncture, self-administered needle pads, acupressure, *gua sha therapy* and auricular acupuncture.

The chapter on **Yoga (Chapter 38)** outlines the significant role of yoga in naturopathic care, especially in India. In India, yoga and naturopathy are integrated in naturopathic educational programs and practice. Naturopaths/NDs use a variety of yogic practices, such as *asanas*, *pranayama*, and meditation to achieve demonstrable improvements in patient health and wellbeing. This section provides an overview of 58 clinical research papers with 86.3% reporting a positive outcome in at least one primary or secondary outcome. This body of naturopathic research on yoga is supplemented by over 20 observational studies and more than 50 reviews or meta-analysis conducted by naturopathic researchers on this topic, as outlined in Chapter 40. The interventions studied include:

- Combination yoga practices
- Yoga breathing
- Yoga meditation

The chapter on **Optimizing Pharmaceutical-Based Interventions (Chapter 39)** outlines the importance of naturopaths/NDs being well-informed on drug-herb and nutrient interactions, and the comparison of pharmaceutical and naturopathic-based interventions. It also highlights that in some jurisdictions, primarily with North America, naturopathic doctors have prescribing rights as part of their defined scope of practice. This section provides an overview of 8 clinical research papers. The pharmaceutical-based interventions studied include:

- Pharmaceuticals and adjunctive treatments for disease or symptom management
- Pharmaceuticals and adjunctive treatments for pharmaceutical side-effect management
- Pharmaceuticals compared to non-pharmaceutical treatments

The chapter on **Other Research Publications Regarding Naturopathic Therapies and Practices (Chapter 40)** highlights the immense volume of research additional to clinical studies produced by the naturopathic research community. A substantial proportion of observational studies including research using survey, interview or focus group methods (n=195; 16.2%), and reviews and meta-analyses (n=297; 24.6%) have been published by naturopathic researchers. These articles present an important contribution to the understanding of clinical treatment options for the management of health and illness. This reinforces the knowledge translation behaviours of naturopaths/NDs (outlined in Chapter 13) through which research from many areas of health and medicine may be used by naturopaths/NDs to inform clinical decisions.

29 Complex Naturopathic Interventions

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HIGHLIGHTS

- Naturopathic care is known for its diverse and flexible therapeutic approach to healthcare which incorporates a range of therapeutic interventions that can be customized to each patient's needs.
- The use of a complex intervention approach to care allows naturopaths/NDs to utilize the synergistic properties of various treatments and to treat patients holistically.
- Complex interventions may be based on ingestive or non-ingestive treatments, or a combination of both.
- Clinical research examining complex interventions delivered by a naturopath/ND involve an average of five types of treatment, which aligns with naturopathic practice behaviours.
- Complex interventions often include dietary counselling, lifestyle modification, herbal medicine, and clinical nutrition.
- In line with the role of primary care, naturopathic researchers have investigated complex interventions in individuals with endocrine conditions, cardiovascular conditions, mental health conditions, musculoskeletal conditions, gastrointestinal conditions, and a range of other conditions.

The holistic, patient-centered, multi-modal treatment approach that is central to naturopathic philosophy comprises the clinical application of different forms of naturopathic therapeutic modalities and practices [1] such as applied nutrition (dietary advice and food as medicine), clinical nutrition (use of vitamins, minerals and other natural health products), herbal medicine, hydrotherapy, lifestyle counselling, acupuncture, bodywork and homeopathy. In some countries naturopathic care may also include intravenous therapies, the prescribing of prescription medicines (i.e., bioidentical hormones or high-dose nutrients), regenerative injective therapies, and minor surgery [2].

Naturopaths/naturopathic doctors aim to alleviate suffering, prevent and/or treat illness, prevent the progression of disease conditions, and to educate and empower patients to facilitate optimal health. These objectives are realized through a combination of behavioural-based counselling and treatments individualized to each patient and their presenting symptoms and condition in a collaborative and patient-centered process. An international study of naturopathic practice confirmed that on average naturopaths and naturopathic doctors use four or more naturopathic treatments or practices during each patient visit [3].

The tendency for naturopathic practice to employ complex interventions follows the naturopathic principle of *treating the whole person.* An example of a complex intervention is the combination of two or more types of treatments, such as herbal medicine and dietary advice, or exercise and nutritional supplementation, along with lifestyle counselling or recommendations with the goal of addressing the lifestyle, external and environmental factors that are impacting a patient's health with the aim of supporting healing and overall wellness. This multi-modal, complex intervention, and whole-practice approach deserves and indeed needs to be researched to better understand its importance in naturopathic practice [4]. Research demonstrates considerable evidence of benefit of complex naturopathic interventions in several conditions and disease states [5] some of which have considerable importance globally, including for example: cardiovascular disease and type II diabetes mellitus [6].

Overview of Studies

This chapter is dedicated to highlighting the original clinical research (n=25) naturopathic clinicians undertook in the field of complex naturopathic interventions. This research includes a total of 1,424 participants and was conducted in the United States of America (USA) (n=9), India (n=7), Canada (n=5), Australia (n=3), and Germany (n=1). The study designs include case reports (n=10), randomized controlled trials (n=6), retrospective cohort studies (n=4), uncontrolled studies (n=4) and

a non-randomized trial (n=1). The interventions used include dietary counselling (n=22), lifestyle counselling (n=19), herbal medicine (n=15), nutritional medicine (n=14), yoga (n=8), massage/self-massage (n=8), hydrotherapy (n=8), mud therapy (n=7), exercise (n=6), and acupuncture (n=5).

The number of therapeutics prescribed ranged from two to twelve with an average of five interventions prescribed across all studies. Naturopaths/naturopathic doctors from the South-East Asian and European WHO Regions employed an average of eight types of treatment in their interventions whereas naturopaths/naturopathic doctors from other Regions used an average of four treatment types. Average duration of treatment across the studies was approximately 13 weeks. The shortest intervention was five days of treatment and the longest was 18 months.

The conditions treated in the studies using complex interventions varied significantly and included endocrine conditions (type II diabetes, thyroid dysfunctions, polycystic ovary syndrome, metabolic syndrome, pancreatitis) (n=8), cardiovascular conditions (cardiovascular disease, hypertension) (n=4), mental health conditions (anxiety, depression) (n=3), musculoskeletal conditions (low back pain, tendonitis) (n=3), gastrointestinal conditions (n=2), and a range of other conditions (eating disorders, obesity, ovarian cancer, HIV, Hepatitis C, interstitial cystitis) (n=6). Of all the naturopathic clinical studies examining populations receiving complex interventions, 85.7% reported a positive outcome in at least one primary or secondary outcome measure. Details of the studies are available in *Table 29.1: Original research on complex naturopathic interventions conducted by naturopathic researchers*. This body of naturopathic research employing complex interventions is also supported by more than 70 observational studies and 19 reviews or meta-analysis conducted by naturopathic researchers on this topic, as outlined in Chapter 40.

Implications

The research to date indicates that naturopaths/naturopathic doctors provide complex intervention care for a range of symptoms and conditions, choosing a variety of treatments in combination to produce the best outcomes for individual patients. There is no one standard treatment applied for a particular set of symptoms or conditions, which is consistent with the person-centered focus of naturopathic practice in accordance with key naturopathic philosophies and principles. Almost all studies involved dietary counselling, more than half involved lifestyle counselling, and around half of all studies prescribed nutritional and/or herbal medicines. These treatments form the basis of naturopathic complex interventions. However, naturopaths/naturopathic doctors frequently employed a variety of other treatments, acupuncture, relaxation/stress reduction techniques, yoga, exercise recommendations, and/or hydrotherapy/mud therapy, depending on the presenting case. Some naturopathic interventions were directed at supporting mental and emotional aspects of health, while others supported elimination and detoxification pathways. Most often though, a variety of different types of naturopathic treatments were combined to treat the entirety of the patient; psychological, functional and structural. This multi-modal approach to patient treatment is the hallmark of naturopathic clinical practice.

Within conventional primary care, most efforts to address chronic disease have historically focused on development of standardized forms of care involving individual therapies or practices, yet it is increasingly recognized that this approach has disadvantages for patients with multimorbidity or complex conditions [7-9]. Moreover, failure to embrace such complexity in primary care practice can also result in additional costs, adverse events, lower satisfaction with care and resource implications in managing patients with complex care needs [10]. Despite this acknowledgement, most primary care is still not appropriately tailored to those with complex health needs in a person-centered multi-modal or multi-disciplinary way, and difficulties in making health care more person-centered persist [11].

The historical basis of naturopathic care has been based on treating each individual and hence the naturopathic workforce has a history of delivering person-centered care in practice, and routinely incorporates factors associated with managing multi-morbidity and complex conditions [12]. While further research is needed to confirm the findings of uncontrolled studies and case reports presented in this review there is sufficient evidence that the complex intervention approach taken by naturopathic practitioners in every day clinical practice provides improvements in patient health and wellbeing. As a whole system of care, there are many conditions that would benefit from additional research to comprehensively evaluate this system of care using a research approach that reflects the complexity of naturopathic practice.

Studies investigating specific interventions:

Ingestive Medicine-based Interventions

Sixteen studies involving a total of 1,186 participants focused on complex naturopathic interventions with a focus on ingestive components, most frequently herbal medicines (n=14) [13-26] and nutritional supplements (n=12) [17-28] prescribed in combination with each other

and/or with dietary counselling (n=13) [13, 15-20, 22-25, 27, 28], lifestyle and exercise counselling (n=12) [13, 15, 16, 18-20, 22-25, 27, 28], pharmaceuticals (n=2) [21, 24], acupuncture (n=1) [28] and homeopathics (n=1) [21]. Studies were predominantly case reports (n=5) [13, 15-17, 22] and controlled trials (n=5) [20, 23, 25, 27, 28], with four retrospective cohort studies [18, 19, 24, 26] and two uncontrolled trials [14, 21].

A randomized controlled trial (n=246) conducted in Canada assessed the application of individualized naturopathic care, primarily involving diet, nutritional supplements, exercise, and deep breathing for the prevention of cardiovascular disease risk [27]. The interventions provided over the course of a year were semi-standardized with respect to supplementation, whereas lifestyle-based recommendations were individually crafted based on the participant. Results from this study found that compared to usual care controls there were significant reductions in metabolic syndrome (p=0.002) and projected 10-year associated cardiovascular event risk (p<0.001) after one year of treatment.

A randomized controlled trial (n=85) conducted in Canada investigating rotator cuff tendinitis found that 12 weeks of acupuncture, individualized dietary counselling, and a standardized encapsulated supplement containing bromelain, trypsin and rutin resulted in significant improvements in pain and disability (Shoulder Pain and Disability Index [SPADI] total: -29.66, p<0.0001); pain: -13.00, p<0.0001; disability: -15.64, p=0.0002), pain score (Visual Analog Scale: -1.67, p<0.0001), quality of life measures for physical (SF-36 physical component: +5.71, p=0.0004; functioning: +13.52, p=0.0025; physical role: +17.34, p=0.0015) and mental (SF-36 mental component: +5.73, p<0.0107; emotional role: +16.09, p=0.002; mental health: +14.66, p=0.0015) domains, as well as improved shoulder extension, flexion and abduction (all p<0.0001), but not adduction [28].

A pilot 3-armed randomized controlled trial conducted in the USA with patients with temporomandibular disorder (n=160) [25] compared Traditional Chinese Medicine, specialty dental care and naturopathic care (NM) (consisting of herbal medicine, nutritional supplements, lifestyle, and stress reduction counselling). Naturopathic care group demonstrated greater reductions in worst facial pain during the treatment intervention period (6-8 months: TCM -2.2; NM -2.3; Specialty -1.2 NM/Speciality, p=0.025) and at end of treatment, naturopathic care provided significantly greater decrease in the impact of symptoms on social life (9-11 months: TCM -2.5; NM -3.2; Specialty -1.7 NM/Specialty, p=0.019).

A randomized controlled trial (n=75) conducted in Canada evaluated the use of naturopathic treatment, consisting of individualized diet and lifestyle counselling, exercise advice, a standard extract of the herb *Withania somnifera* and a multivitamin/mineral formula, compared to controls given psychotherapy, diet and lifestyle education, exercise advice and matched placebo for individuals with severe anxiety [23]. Results showed significantly greater declines in anxiety scores in the naturopathic care group (Beck Anxiety Inventory -6.16, p<0.0036). This study also reported significantly greater improvements in domains of fatigue, measured by The Fatigue Questionnaire compared to controls (subjective: -18.01, p<0.0001; physical: -13.19, p=0.0033; motivation: -20.32, p<0.0001; concentration: -17.51, p<0.0001). Furthermore, participants receiving naturopathic care had reduced weight (-1.47 kg, p=0.00146) and body mass index (-0.56 kg/m2, p=0.0128) compared to controls.

An open label intervention trial (n=60) conducted in the USA of patients with depression and anxiety found that individualized naturopathic care consisting of nutritional, pharmaceutical, homeopathic and/or herbal medicine led to significant reduction in anxiety (-5.2, p<0.0001 based on the Generalized Anxiety Disorder 7-item Scale) and depression (-7.8, p<0.0001 based on the Patient Health Questionnaire) with 50% of participants achieving more than 50% improvement in both scores [21]. A second open label study (n=30) conducted in the USA determined that naturopathic care involving an herbal-mineral combination significantly reduced systolic and diastolic blood pressure (both p<0.0001), and significantly improved serum potassium (p<0.019) without altering liver and kidney enzyme markers or calcium and magnesium readings [14] .

Several observational studies found that naturopathic care – all of which included nutritional and herbal supplementation as well as dietary education and counselling, plus various combinations of stress reduction techniques, exercise, and other lifestyle advice relevant to the particular condition – improved markers of type II diabetes mellitus [18, 20], hypertension [19], and hepatitis C virus [24].

An uncontrolled study (n=14) conducted in the USA with adults with hepatitis C investigated the effect of a naturopathic intervention encompassing a standardized extract of silymarin (from *Silybum marianum*), a multivitamin and mineral formula, n-acetyl cysteine, dietary and lifestyle advice, and pharmaceutical medications (colchicine and ursodeoxycholic acid) [24]. Some participants also received deglycyrrhizinated licorice and a complex herbal formula containing 12 Ayurvedic herbs. All participants received treatment for a minimum of one month by which time 50% of participants had a greater than 25% reduction in the liver enzyme alanine aminotransferase (average reduction -35U/L, p=0.026). None of the participants reported any symptoms of advanced liver disease by the end of their treatment and most reported an increased sense of well-being.

A case report conducted in India with a patient with metabolic syndrome demonstrated improvements

in anthropometric measures (weight, -9.5kg; BMI, -3.2 kg/m2), blood pressure (systolic, -38mmHg; diastolic, -10mmHg), blood glucose levels (fasting, -130mg/dL; postprandial, -192mg/dL) and lipid levels (triglycerides,-6mg/dL; total cholesterol, -41mg/dL; HDL, -3mg/dL; LDL -36 mg/dL; VLDL -2mg/dL) as well as a reduction in insulin use following three weeks of herbal and nutritional treatment, yoga, hydrotherapy, massage therapy, and mud therapy [29]. Further case studies described patient reported improvements using combined naturopathic treatments involving herbal and/or nutritional supplementation along with dietary counselling and various lifestyle interventions in conditions as varied as depression and anxiety [17], gastrointestinal disorders [22], pancreatitis [15], ulcerative colitis, chronic ischemic heart disease [13], and interstitial cystitis [16], as well as greater acceptance, coping and self-efficacy scores in pain conditions [13].

Non-ingestive Medicine-based Interventions

Nine studies with a total of 238 participants involved complex interventions focused primarily on non-ingestive treatments, which were typically delivered as programs integrating naturopathic approaches with dietary interventions (n=9) [29-36], yoga (n=7) [29-32, 34, 35, 37], hydrotherapy (n=7) [29-32, 34, 35, 37], mud therapy (n=5) [29-31, 34, 37], acupuncture (n=3) [30, 32, 36], massage (n=3) [29, 30, 35] and lifestyle interventions (n=3) [31, 33, 36]. The studies were predominantly case reports (n=5) [29, 30, 32, 35, 37] with two uncontrolled trials [31, 33] and two randomized controlled trials [34, 36].

A randomized controlled trial (n=75) conducted in Canada investigated a semi-standardized intervention for chronic low back pain and found that compared to standard physiotherapy, naturopathic treatment comprising acupuncture, dietary counselling, deep breathing, and relaxation techniques over 12 weeks significantly improved lower back pain (Oswestry Low Back Pain Disability Questionnaire: -5.0 vs -0.0, $p<0.0001$), disability (Roland Morris Disability Questionnaire: -6.0; $p<0.0001$), range of motion (forward lumbar flexion: +5.0, $p<0.0001$) and quality-of-life (SF-36 physical component: +8.47, $p<0.0001$; mental component: +5.56, $p<0.0045$) [36].

A single blind clinical trial (n=50) conducted in India with patients with polycystic ovary syndrome found that compared to waitlisted controls, naturopathic care encompassing hydrotherapy, mud therapy, manipulative therapy, fasting, dietary counselling, and yoga significantly increased ovarian quality (+6.0 vs -3.5, $p<0.001$) however there was no significant difference in consecutive menstrual cycle days [34]. An open label four-arm study (n=96) conducted in India demonstrated that hydrotherapy, mud therapy, dietary counselling, raw juices, sunbathing, counselling, deep relaxation techniques, and yoga treatment for HIV patients improved CD4 counts after 30 days of treatment ($p=0.00038$) [31].

An observational study conducted in the USA found that nutrition counselling and education together with lifestyle advice improved markers of type II diabetes [33]. A number of case studies reported clinical improvements in markers of non-alcoholic fatty liver disease [30], metabolic syndrome [37], hypothyroidism [32, 37], hyperprolactinemia [32], and obesity [35] when patients were prescribed various combinations of acupuncture, manipulative therapy, hydrotherapy, chromotherapy, mud therapy, reflexology, yoga, dietary therapy, and fasting treatments. Additionally cessation or reduction of medication was noted following naturopathic treatment in case reports of metabolic syndrome [37] and hypothyroidism [32, 37], and in one randomized controlled trial examining chronic low back pain [36].

Table 29.1 Clinical research investigating complex naturopathic interventions conducted by naturopathic researchers

Author (year) [Country, World Region]	Design	Study Population	Intervention(s)	Concomitant therapies	Control or comparison group	No. Participants (Intervention/ Control)	Outcome measure	Outcome
Aucoin. (2017) [Canada, AMRO] [17]	Case report	Major depressive disorder and social anxiety disorder	Breakfast smoothies, increased vegetable intake, herbal formula *(Hypericum perfortum*, *Passiflora incarnata*, *Valeriana officinalis)* and fish oil supplement (4 weeks)	Nil	Nil	1	Subjective mood and anxiety symptoms	**Improved mood at each return visit, increased tolerance to anxiety provoking situations, increased energy, and no headaches**
Bradley and Oberg. (2006) [USA, AMRO] [18]	Retrospective cohort study	Type II Diabetes Mellitus	Adjunctive or primary naturopathic care over at least 6 months. 81% received adjunctive naturopathic care, 100% received dietary counseling, 69% were instructed in stress reduction techniques, 94% were prescribed exercise, 100% received nutritional supplements, botanical supplements included *Gymnema* sp., *Trigonella* sp., *Momordica* sp., or Cinnamon.	81% received adjunctive medication including one or more of oral anti-diabetic, insulin, lipid-lowering, anti-hypertensive, or aspirin	Nil	16	HbA1c	**Improved control** Good control: 31% Making improvement: 60%
							LDL Cholesterol	**Improved LDL-cholesterol control** Good control: 13% Making improvement: 63%
							HDL Cholesterol	**Improved HDL-cholesterol control** Good control: 80% Making improvement: 63%
							Triglycerides (TG)	**Improved triglyceride control** Good control: 43% Making improvement: 57%
							Blood Pressure (BP)	**Improved BP control** Good control: 44% Making improvement: 60%
Bradley, et al. (2011) [USA, AMRO] [19]	Retrospective cohort study	Hypertension	Adjunctive or primary naturopathic care over at least 6 months. 76.5% received adjunctive naturopathic care, 97.6% received dietary advice, 68.2% exercise advice, 56.5% preventive advice regarding alcohol, 47.1% preventive advice regarding tobacco, 100% recommended dietary supplementation including omega-3 oil from fish, magnesium, coenzyme Q10, vitamin B6, resveratrol potassium, botanical	Nil	Nil	85	Proportion with systolic blood pressure (BP) <140mmHg (%)	**Increased proportion with <140mmHg systolic BP** +34.1 (p=0.038)
							Proportion with diastolic blood pressure <90mmHg (%)	**Increased proportion with <90mmHg diastolic BP** +26 (p=0.026)
							Neither systolic nor diastolic <140/90mmHg	**Reduced proportion with neither systolic nor diastolic BP <140/90mmHg** -35.3 (p=0.033)

Author (year) [Country, World Region]	Design	Study Population	Intervention(s)	Concomitant therapies	Control or comparison group	No. Participants (Intervention/ Control)	Outcome measure	Outcome
			supplements including *Rauwolfia, Arjuna, Convolvulus, Tribulus, Crataegus, Allium sativa, Taraxacum, Leonurus, Passiflora.*				Either systolic or diastolic blood pressure <140/90mmHg	**Increased proportion with either systolic or diastolic BP <140/90mmHg** +5.9 (p=0.033)
							Both systolic and diastolic blood pressure <140/90mmHg	**Increased proportion with both systolic and diastolic blood pressure <140/90mmHg** +29.3 (p=0.033)
Bradley, et al. (2012) [USA, AMRO] [20]	Non-randomized controlled trial	Type II Diabetes (Inadequately controlled)	12 months: Up to eight naturopathic visits for up to one year, or usual care. - 95% received dietary advice - 100% exercise advice - 59% stress management advice - 74% received dietary supplementation including omega-3 fatty acids, chromium, multivitamin with B-complex, vitamin C and E fiber, coenzyme Q10, probiotics, bioflavonoid/polyphenol - Botanical supplements; 18% received *Cinnamomum cassia, 13% Gymnema sylvestre*	95% diabetes glucose self-monitoring and reinforcement of medication adherence (sulfonylurea, metformin, or insulin). Oral medication (prescription refills) increased in the intervention group	Usual care	369 (40/329)	Summary of Diabetes Self-Care Activities [BL to Mth 6, Mth 12]	**Increased self-care activities** Mth 6: Glucose checking, improved (p = 0.001); Diet quality, improved (p = 0.001); Physical activity, improved (p = 0.02) Mth 12: Glucose testing, improved (p=0.003); Physical activity, NS; Diet quality, NS
							Personal Health Depression Scale [BL to Mth 6, Mth 12]	**Increased mood** Mth 6: Mood, improved (p = 0.001); % non-depressed, NS Mth 12: NS
							Self-Efficacy Scale [BL to Mth 6, Mth 12]	**Increased self-efficacy** Mth 6: Self- efficacy, improved (p = 0.0001) Mth 12: Self-efficacy, improved (p=0.002)
							Readiness Index [BL to Mth 6, Mth 12]	**Increased** Mth 6 Lifestyle change: improved (p=0.003) Commitment to change: NS Mth 12 Lifestyle change: improved (p=0.004) Commitment to change: NS

Author (year) [Country, World Region]	Design	Study Population	Intervention(s)	Concomitant therapies	Control or comparison group	No. Participants (Intervention/ Control)	Outcome measure	Outcome
							Perceived Stress Scale [BL to Mth 6, Mth 12]	NS
							Problem Areas in Diabetes [BL to Mth 6, Mth 12]	NS
							Subjective rating of satisfaction with and self-perceived effectiveness of ANC [BL to Mth 6, Mth 12]	NS
							Hemoglobin AIC (%) [BL to Mth 6, Mth 12]	NS
							Total cholesterol: HDL ratio [BL to Mth 6, Mth 12]	NS
							Blood pressure [BL to Mth 6, Mth 12]	NS
							Number of new prescriptions for insulin, sulfonylureas, and metformin per year [BL to Mth 12]	**Increased number of new prescriptions**
							Number of prescription refills for insulin, sulfonylureas, and metformin per year [BL to Mth 12]	**Increased prescription refills** ANC: +1.2; UC: -0.2

Author (year) [Country, World Region]	Design	Study Population	Intervention(s)	Concomitant therapies	Control or comparison group	No. Participants (Intervention/ Control)	Outcome measure	Outcome
							Number of primary care visits, per year [BL to Mth 12]	**Increased number of primary care visits** ANC: +1.5; UC: +0.0
							Number of nutritionist visits, per year [BL to Mth 12]	**No change**
							Number of specialist doctor visits, per year [BL to Mth 12]	**No change**
Breed and Bereznay (2017) [USA, AMRO] [21]	Uncontrolled trial	Generalized anxiety disorder	Individualized naturopathic care commonly consisting of nutraceuticals, pharmaceuticals, homeopathics, and/or Herbal Medicines At least 2 community health center visits over 26 months, mean number of visits 3.3	Nil	Nil	60	Generalized Anxiety Disorder 7-item scale (GAD-7)	**Reduced anxiety** -5.2 ($p<0.0001$) >50% improvement: 50%
							Patient Health Questionnaire 9-item depression assessment tool	**Reduced depression** -7.8 ($p < 0.0001$) >50% improvement: 58.6%
Carter, et al. (2019) [Australia, WPRO] [22]	Case report	Functional gastrointestinal disorder	Case 1 (3 visits): Botanical supplements: Flordis Iberogast liquid herbal formula containing, *Foeniculum vulgare* seed, *Gentiana lutea* root, chamomile, or dandelion root teas; Nutritional supplements: Bioceuticals MultiGest Enzymes, Metagenics CalmX; Lifestyle advice: mindfulness/meditation practices, mindful eating, exercise, self-massage. Dietary advice: plant based whole foods, fiber, low FODMAP, bone broths. Case 2 (4 visits): Liquid herbal formula containing *Matricaria chamomilla* 1:2, *Cynara scolymus* 1:2, *Taraxacum officinale* radix	Nil	Nil	2	Gastrointestinal Symptom Rating Scale (self-reported) [BL to Visit 2, 3, 4]	**Reduced gastrointestinal symptoms** Case 1: Visit 2, -5 Visit 3, -2 Total, -2 Case 2: Visit 2, -6 Visit 3, -6 Visit 4, -11 Total, -11

Author (year) [Country, World Region]	Design	Study Population	Intervention(s)	Concomitant therapies	Control or comparison group	No. Participants (Intervention/ Control)	Outcome measure	Outcome
			1:2, *Althea officinalis* 1:5, *Lavandula angustifolia* 1:2; *Eschscholzia californica* 1:2; *Scutellaria lateriflora* 1:2; Lifestyle advice: sleep hygiene, mindful eating; Dietary advice: apple cider vinegar, protein, legumes, vegetables, fruit, fibrous food. 5 weeks treatment.					
Cooley, et al. (2009) [Canada, AMRO] [23]	Randomized controlled trial	Anxiety	12 weeks: Naturopathic care-lifestyle and diet counseling, exercise, *Withania somnifera*, multivitamin/mineral formula.	Anxiety medication (but not benzodiazepine drug class)	Psychotherapy care: patient directed counseling, cognitive behavioral therapy, educated on healthy diet, reducing caffeine/tobacco stimulants, deep-breathing techniques, exercise advice, matched placebo supplement	75 (36/39)	Beck Anxiety Inventory (BAI)	**Reduced anxiety** NC, -13.31; PC, -7.15 Between group, -6.16 (p=0.0036)
							The Fatigue Questionnaire	**Reduced fatigue** Subjective: NC -20.39; PC -2.38 Between group -18.01 (p<0.0001) Physical: NC -14.29; PC -1.10 Between group -13.19 (p=0.0033) Motivation: NC -18.95; PC +1.37 Between group -20.32 (p<0.0001) Concentration: NC -1.98; PC +0.37 Between group -17.51 (p<0.0001)
							Measure Yourself Medical Outcomes	**Reduced self-identified symptoms** Symptom 1: NC -2.24; PC -0.46 Between group -1.77 (p<0.0001) Symptom 2: NC -1.94; PC -0.86 Between group -1.08 (p=0.0115)
							Weight (kg)	**Reduced weight** -1.47 (p=0.00146)
							Body mass index (kg/m^2)	**Reduced body mass index** -0.56 (p=0.00128)

Author (year) [Country, World Region]	Design	Study Population	Intervention(s)	Concomitant therapies	Control or comparison group	No. Participants (Intervention/ Control)	Outcome measure	Outcome
Fathima-Jebin, et al. (2018) [India, SEARO] [30]	Case report	Ovarian malignancy and non-alcoholic fatty liver disease with ascites	Integrated naturopathy & yoga therapy (INYT) (yoga, acupuncture, massage, hydrotherapy, chromotherapy, mud therapy, reflexology) Diet therapy	Nil	Nil	1	Weight (kg) [BL to Dy 30]	**Reduced weight** - 4
							Body mass index (kg/m^2) [BL to Dy 30]	**Reduced body mass index** -1.5
							Abdominal girth (cm) [BL to Dy 30]	**Reduced abdominal girth** -5
							Blood pressure (BP) (mmHg) [BL to Dy 30]	**Reduced BP** Systolic: -10 Diastolic: -2
							CT imaging of liver density [BL to Dy 30]	**Reduced tumor size** BL: 12.4cm x 12cm x 9.3cm Dy 30: 12.8cm x 9cm x 8.6cm
							CT fluid estimate [BL to Dy 30]	**No change**
							Fasting plasma glucose (mg/DL) [BL to Dy 30]	**Reduced fasting plasma glucose** -7
							Postprandial glucose (mg/dL) [BL to Dy 30]	**Reduced postprandial glucose** -2
							Bilirubin, total (mg/dL) [BL to Dy 30]	**Reduced total bilirubin** -0.03
							Bilirubin, direct (mg/DL) [BL to Dy 30]	**Reduced direct bilirubin** -0.11
							Alkaline phosphatase (ALP) (U/L) [BL to Dy 30]	**Reduced ALP** -11

Author (year) [Country, World Region]	Design	Study Population	Intervention(s)	Concomitant therapies	Control or comparison group	No. Participants (Intervention/ Control)	Outcome measure	Outcome
							Aspartate transaminase (AST) (U/L) [BL to Dy 30]	**Reduced AST** -4.1
							Alanine transaminase (ALT) (U/L) [BL to Dy 30]	**Reduced ALT** -8.3
							Gamma-glutamyl transaminase (GGT) (U/L) [BL to Dy 30]	**Reduced GGT** -6
							Urea (mg/dL) [BL to Dy 30]	**Reduced urea** -31.3
							Creatinine (mg/dL) [BL to Dy 30]	**Reduced creatinine** -0.26
							Uric acid (mg/dL) [BL to Dy 30]	**Reduced uric acid** -4.9
Gowda, et al. (2017) [India, SEARO] [37]	Case report	Metabolic syndrome and hypothyroidism	Over 12 weeks (total: 45 days) Integrated Yoga Naturopathy (IYN): a combination of naturopathic therapies focused on detoxification (therapeutic fasting, calorie restricted diet, hydrotherapy, mud therapy, and manipulative therapies) and yoga therapies (*asanas*, *pranayama*, meditation, relaxation techniques, *kriyas*, educational lectures, and yoga-based counseling sessions).	Hypoglycemic medication (Glimepiride and Metformin BD), Voglibose BD, Levothyroxine OD, Telmisartan OD, Aceclofenac BD	Nil	1	Total cholesterol (mg/dl) [BL to Wk 6]	**Reduced total cholesterol** -47
							High-density lipoprotein (HDL) – cholesterol (mg/dl) [BL to Wk 6]	**Increased HDL cholesterol** +6
							Low-density lipoprotein (LDL) – cholesterol (mg/dl) [BL to Wk 6]	**Reduced LDL cholesterol** -43
							Triglycerides (mg/dl) [BL to Wk 6]	**Reduced triglycerides** -63

Author (year) [Country, World Region]	Design	Study Population	Intervention(s)	Concomitant therapies	Control or comparison group	No. Participants (Intervention/ Control)	Outcome measure	Outcome
							Thyroid stimulating hormone (TSH) (mIU/ml) [BL to Wk 6]	**Reduced TSH** -3.85
							Fasting blood glucose [BL to Wk 6]	**Reduced fasting blood glucose** -35
							Post-prandial blood glucose [BL to Wk 6]	**Reduced post-prandial glucose** -167
							HbA1c (%) [BL to Wk 6]	**Reduced HbA1c** -0.7
							Visual Analog Scale [BL to Wk 6]	**Reduced pain** Knee pain: -5; Neck pain: -4
							Body weight (kg) [BL to Wk 6]	**Reduced body weight** -20.3
							Body mass index (kg/m^2) [BL to Wk 6]	**Reduced body mass index** -7.3
							Blood pressure (BP) (mmHg) [BL to Wk 6]	**Reduced BP** -22/16
							Medication use [BL to Wk 6]	**Reduced medication use** All able to be discontinued: anti-hypertensive (Telmisartan 20 mg), oral hypoglycemics (glimepiride, metformin, and Voglibose 0.03 mg), thyroid (levothyroxine sodium 100 mg), and analgesic (Aceclofenac)
Joseph, et al. (2015) [India, SEARO] [31]	Uncontrolled trial	HIV1 and HIV2	Four study arms based on duration of stay: Group 1: 1-7 days; Group 2 8-15 days; Group 3 16-30 days; Group 4 >30 days) Naturopathy treatment: hydrotherapy, dietary advice,	Antiretroviral medications	Nil	96 (G1: 21/ G2: 28/ G3: 23/ G4: 24)	CD4 count [BL to Discharge]	**Reduced for >30 days treatment** G1: NS G2: NS G3: NS G4: p=0.00038

Author (year) [Country, World Region]	Design	Study Population	Intervention(s)	Concomitant therapies	Control or comparison group	No. Participants (Intervention/ Control)	Outcome measure	Outcome
			raw juices, mud therapy, counseling, sun bath. Yoga treatment: loosening exercises, *asanas*, *pranayama*, and deep relaxation techniques.					
Milliman, et al. (2000) [USA, AMRO] [24]	Retrospective cohort study	Hepatitis C	All patients (minimum one month treatment): (a) Silymarin 80% standardized extract (150 mg); (b) d-alpha tocopherol (400IU), vitamin C (500 mg), beta carotene (15 mg), selenium amino acid chelate (50 mcg) (c) N-acetyl-L-cysteine (1000mg); (d) cod liver oil 1-2 tsp daily (e) dietary and lifestyle advice including breakfast muesli. (f) colchicine (1.2 mg); (g) ursodeoxycholic acid (300 mg) Some patients: (h) herbal mixture of *Phyllanthus nigrum or amarus*, *Picrorrhiza kurroa*, *Zingiber officinale*, *Boerhaavia diffusa*, *Andrographis paniculata*, *Cichorium intybus*, *Emblica officinalis*, *Embelia ribes*, *Terminalia chebula*, *Terminalia arjuna*, *Piper longum*, *and Eclipta alba* (i) deglycyrrhizinated licorice 500 mg	All patients: colchicine (1.2 mg daily, five days per week); ursodeoxycholic acid (300 mg bid pc)	Nil	14	Alanine aminotransferase (ALT) (U/L; % reduction)	**Reduced ALT** -35 U/L (p=0.026) Reduction of greater than 25% in 7 of 14 patients
							Self-reported symptoms of advancing liver disease (liver pain, enlarged liver, jaundice, ascites, generalized edema, or liver-related bowel dysfunction)	**No change**
							Self-reported symptoms of wellbeing	**Most patients reported an increased sense of well-being on the treatment program.**
Mooventhan and Shetty (2015) [India, SEARO] [29]	Case report	Metabolic syndrome (40 year old male)	3 weeks: Integrative naturopathic care 60 – 90 min/day of hydrotherapy, mud therapy, massage therapy and diet therapy including fenugreek powder and yoga 120-min/day.	Mixed insulin and candesartan.	Nil	1	Weight (kg) [BL to Wk 3]	**Reduced weight** -9.5
							Body mass index (kg/m^2) [BL to Week 3]	**Reduced body mass index** -3.2

Author (year) [Country, World Region]	Design	Study Population	Intervention(s)	Concomitant therapies	Control or comparison group	No. Participants (Intervention/ Control)	Outcome measure	Outcome
							Waist Circumference (cm) [BL to Wk 3]	**Reduced waist circumference** -9
							Insulin Intake (units) [BL to Wk 3]	**Reduced insulin intake** -40-0-40
							Fasting blood glucose (mg/dL) [BL to Wk 3]	**Reduced fasting blood glucose** -130
							Postprandial blood glucose (mg/dL) [BL to Wk 3]	**Reduced postprandial glucose** -192
							Systolic blood pressure (BP) (mmHg) [BL to Wk 3]	**Reduced systolic BP** -38
							Diastolic blood pressure (mmHg) [BL to Wk 3]	**Reduced diastolic BP** -10
							Serum total triglycerides (mg/dL) [BL to Wk 3]	**Reduced triglycerides** -6
							Serum total cholesterol (mg/dL) [BL to Wk 3]	**Reduced total cholesterol** -41
							High-density lipoprotein (HDL) – cholesterol (mg/dL) [BL to Wk 3]	**Reduced HDL cholesterol** -3
							Low-density lipoprotein (LDL) – cholesterol (mg/dL) [BL to Wk 3]	**Reduced LDL cholesterol** -36

Author (year) [Country, World Region]	Design	Study Population	Intervention(s)	Concomitant therapies	Control or comparison group	No. Participants (Intervention/ Control)	Outcome measure	Outcome
							Very-low-density lipoprotein (VLDL) – cholesterol (mg/dL) [BL to Wk 3]	**Reduced VLDL cholesterol** -2
Nair (2016) [India, SEARO] [32]	Case report	Hypothyroidism hyperprolactinemia, hot flushes (Female, 37 years)	Naturopathy and yoga-based lifestyle modification program including dietary recommendations (50-60% of diet as raw fruit + elimination of leafy greens), therapeutic fasting (2 days/week coconut water only), water-based therapies (immersion, mud and cold baths, water throat and abdominal packs), and 1-hour daily yoga interventions (alternate nostril breathing, fast abdominal breathing, sun salutations), and 21 daily acupuncture sessions.	Thyronorm (levothyroxine sodium) 125 mcg	Nil	1	Weight (kg) [BL to Mth 18]	**Reduced weight** -12
							Thyroid stimulating hormone (U/ml) [BL to Mth 18]	**Reduced TSH** -4.6
							Prolactin (ng/ml) [BL to Mth 18]	**Reduced prolactin** -15.1
							Anti-mullerian hormone (AMH) (ng/ml) [BL to Mth 18]	**Increased AMH** +2.3
							Thyroxine use [BL to Mth 18]	**Reduced thyroxine use** Discontinued (from 125 mcg per day)
Oberg, et al. (2011) [USA, AMRO] [33]	Uncontrolled trial	Type II diabetes mellitus (Adults)	Individual and group nutrition and lifestyle education program including basic nutrition, reading food labels, selecting healthier food, what happens in the body with T2DM, problem-solving dietary habits, organic and wild foods, and understanding and address eating behaviors such as emotional eating. 10 hours intervention over 12 weeks.	None reported	Nil	12	Hemoglobin A1c (%) [BL to Wk 12]	**Reduced HbA1c** -0.4% (p=0.02)
							Serum lipid profile [BL to Wk 12]	NS
							Blood pressure [BL to Wk 12]	NS
							Body Mass Index [BL to Wk 12]	NS
							Summary of Diabetes Self-Care Activities [BL to Wk 12]	**Increased self-care activities** Healthy eating pattern (days in last week): +1.8 (p=0.05) Healthy eating pattern (days per week in last month): +1.2 (p=0.02)

Author (year) [Country, World Region]	Design	Study Population	Intervention(s)	Concomitant therapies	Control or comparison group	No. Participants (Intervention/ Control)	Outcome measure	Outcome
								>5 fruits/vegetables per day (days in last week): +1.3 (p=0.01) Physical activity (days in last week): +3.4 (p=0.02) Blood glucose checking (% of time): +38% (p=0.05) Checked blood sugar as recommended (days in last week): +3.0 (p=0.04)
							Problem Areas in Diabetes [BL to Wk 12]	**Reduced concern about diabetes** Feeling scared about living with diabetes: -1.8 (p=0.006) Feeling overwhelmed by diabetes: -1.9 (p=0.03) Feeling discouraged about diabetes treatment plan: NS Composite score: -18.9% (p=0.05)
							Three-day diary [BL to Week 12]	**Increased healthy eating behaviors** Adherence to healthy eating increased (p=0.05)
							Perceptions about Nutritional Counseling [BL to Wk 12]	**Increased confidence with health eating** Average daily carbohydrate intake: NS Attention to type of dietary fat consumed: From 'Seldom' to 'Often' (p=0.04) Know how to follow dietary guidelines: From 'Definitely no' to 'Yes' (p=0.02) Feel in control of my diabetes: From 'Definitely no' to 'Yes' (p=0.01)

Author (year) [Country, World Region]	Design	Study Population	Intervention(s)	Concomitant therapies	Control or comparison group	No. Participants (Intervention/ Control)	Outcome measure	Outcome
							Seven Eating Styles Questionnaire [BL to Wk 12]	**Reduced problem eating behaviors** Emotional eating -0.7 (p=0.02) Food fretting NS Selecting fast food/fresh food -0.8 (p=0.05) Attention to sensory/spiritual dimensions of food -1.2 (p<0.01) Task snacking NS Attention to dining atmosphere -0.6 (p=0.01) Attention to positive social settings NS Integrated eating score -3.7 (p=0.03)
Paul, et al. (2012) [Germany, EURO] [13]	Case reports	1. Chronic pain 2. Active ulcerative colitis 3. Chronic ischemic heart disease patients at an academic teaching hospital integrative clinic	Therapies include stress management training such as meditation, moderate exercise such as yoga, dietary counseling and weekly cooking lessons, naturopathic methods including cataplasms, cupping, phytotherapy, massages, acupressure, and hydrotherapy. 60 hour program over 10 weeks.	Cognitive behavior techniques focusing on self-care strategies	Nil	3	Qualitative interview regarding acceptance of program, lifestyle modifications and symptom severity	Self-reported increased acceptance of health condition, improved coping, and self-efficacy in the management of condition especially in stressful situations
							Satisfaction with therapy at interview	Satisfaction with the therapy was high
Ratnakumari, et al. (2018) [India, SEARO] [34]	Randomized controlled trial	Polycystic ovarian syndrome	12 weeks: (a) Cold abdominal mud pack (b) Cold water enema (c) Cold hip bath; (d) Hot foot immersion bath; (e) Partial massage to abdomen; (f) Partial massage to back; (g) Dietary changes: Fasting using fruit and vegetable juices and fluids;	Nil	Waitlist	50 (25/25)	Ovarian volume [BL to Wk 12]	**Increased ovarian volume (left)** Right: NS; Left Intervention +3.68; Control -0.79 Between group p=0.032
							Ovarian size (cm) [BL to Wk 12]	Right: NS Left: NS

Author (year) [Country, World Region]	Design	Study Population	Intervention(s)	Concomitant therapies	Control or comparison group	No. Participants (Intervention/ Control)	Outcome measure	Outcome
			(h) Dietary changes: Raw vegetables, fruits, sprouts, vegetable soup for breakfast, and short vegetarian lunch meal; (i) Dietary changes: Boiled vegetables, steamed food; (j) yogic practice: *Asanas* [supine: *uttanapadasana, pawanmuktasana, naukasana, setu bandhasana;* prone: *bhujangasana, dhanurasana;* sitting: *vakrasana, baddha konasana;* standing: *katichakrasana, ardhakatichakrasana, dwikonasana, padahastasana], Pranayama [bhramari pranayama, surya bhedana pranayama, nadi shodhana pranayama], Kriya [kapalhati], Mudra [yoni mudra],* Relaxation *[savasana]*				Follicles antrum [BL to Wk 12]	**Increased follicle antrum (right)** Right: Intervention +5; Control -4 Between group p<0.001 Left: NS
							Largest follicle size (cm) [BL to Wk 12]	**Reduced follicle length** Right, Length: Intervention -0.1; Control +0.15 Between group p=0.016 Right, Width: NS Left, Length: NS Left, Width: NS
							Total ovarian assessment (instrument not specified) [BL to Wk 12]	**Increased total ovarian quality** Intervention +6.0; Control -3.5 Between group p<0.001
							Body weight (kg) [BL to Wk 12]	**Increased body weight** Intervention +6; Control +0.0 Between group p<0.001
							Body mass index (BMI) (kg/m^2) [BL to Wk 12]	**Increased body mass index** Intervention +2.36; Control 0.0 Between group p<0.001
							Chest circumference (cm) [BL to Wk 12]	**Increased chest circumference** Intervention +4.25; Control +0.75 Between group p<0.001
							Waist circumference (cm) [BL to Wk 12]	**Increased waist circumference** Intervention +5; Control -1.25 Between group p<0.001
							Hip circumference (cm) [BL to Wk 12]	**Increased hip circumference** Intervention +6.75; Control -0.25 Between group p<0.001

Author (year) [Country, World Region]	Design	Study Population	Intervention(s)	Concomitant therapies	Control or comparison group	No. Participants (Intervention/ Control)	Outcome measure	Outcome
							Mid-arm circumference (cm) [BL to Wk 12]	**Increased mid-arm circumference** Intervention +3; Control +0.0 Between group p<0.001
							Waist-hip ratio [BL to Wk 12]	NS
							Cycle length [days] [BL to Wk 12]	Last menstrual period and first cycle NS First and second cycle NS Second and third cycle NS
Ritenbaugh, et al. (2008) [USA, AMRO] [25]	Randomized clinical trial	Temporomandibular disorder (TMD)	Traditional Chinese Medicine (TCM) including acupuncture, herbal therapy, massage, relaxation tapes, 2 visits per week for 6 wks, then 1 per week for 5 – 6 months. OR Naturopathic medicine (NM) including herbal medicine, nutritional supplements, nutritional and lifestyle advice, stress-reduction advice, 9.5 hours over 6 – 8 moths.	Nil	Speciality dental care for TMD treatment including education, bite splints, self-care counselling, and pain management strategies, 2 hr class sessions plus optional referrals for massage, psychological and counseling support.	160 (50/50/ 60)	Worst Facial Pain [BL to Mth 6/8, 9/11]	**Reduced worst facial pain** Mth 6/8: TCM -2.2; NM -2.3; Specialty -1.2 Between group (Specialty vs TCM) p=0.010 Between group (Specialty vs NM) p=0.025 Mth 9/11: TCM -2.5; NM -3.2; Specialty -1.7 Between group (Specialty vs TCM) p=0.037 Between group (Specialty vs NM) p=0.019
							Average Facial Pain [BL to Mth 6/8, 9/11]	**Reduced average facial pain** Mth 6/8: TCM -1.9; NM NS; Specialty -0.9 Between group (Specialty vs TCM) p=0.004 Between group (Specialty vs NM) NS Mth 9/11: TCM -2.3; NM NS; Specialty -1.5 Between group (Specialty vs TCM) p=0.017 Between group (Specialty vs NM) p=NS

Author (year) [Country, World Region]	Design	Study Population	Intervention(s)	Concomitant therapies	Control or comparison group	No. Participants (Intervention/ Control)	Outcome measure	Outcome
							Impact on Social Life [BL to Mth 6/8, 9/11]	Mth 6/8: TCM, NS; NM -1.2; Specialty -0.5 Between group (Specialty vs TCM) NS Between group (Specialty vs NM) p=0.012 Mth 9/11: NS
Ross, et al (2008) [USA, AMRO] [26]	Retrospective cohort study	Eating disorders	6 months: Naturopathic integrative therapies for insomnia and constipation: insomnia treated with instructions on sleep hygiene and herbal product (containing valerian root extract, *Rhodiola rosea* root extract, *Hops strobiles* extract, *Passiflora incarnata* aerial extract, and German chamomile flower extract) and/or 5-hydroxytryptophan. Constipation treated with plant-based digestive enzymes at mealtimes and a daily probiotic supplement containing *Lactobacillus rhamnosus*	Nil		38	Medications used for sleep [After Dy 3]	NS
							Sleep medications [After Dy 3]	NS
							Constipation medications [After Dy 3]	NS
Ryan, et al. (2019) [USA, AMRO] [14]	Uncontrolled trial	Pre-hypertension or Stage 1 hypertension	1 herbal-mineral caplet per day over a period of 6 months containing *Rosa centifolia*, *Boerhaavia diffusa*, *Dendrogyra cylindrus* (coral powder) (350 mg), magnesium aspartate (200 mg), *Convolvulus pluricaulis* (100mg), *Terminalia arjuna* (100mg), *Tribulus terrestris* (100mg), low-reserpine *Rauwolfia serpentina* (50 mg), and *Rosa vinca* (25 mg).	Anti-hypertensive medication	Nil	30	Serum sodium (nmol.\/L) [BL to Mth 6]	NS
							Serum potassium (nmol/L) [BL to Mth 6]	**Increased serum potassium** Mth 3: +0.12 (p=0.04) Mth 6: +0.18 (p=0.019)
							Serum calcium (mg/dL) [BL to Mth 6]	NS
							Serum magnesium (mg/dL) [BL to Mth 6]	NS
							Aspartate transferase (U/L) [BL to Mth 6]	NS

Author (year) [Country, World Region]	Design	Study Population	Intervention(s)	Concomitant therapies	Control or comparison group	No. Participants (Intervention/ Control)	Outcome measure	Outcome
							Alanine transferase (U/L) [BL to Mth 6]	NS
							e-Glomerular filtration rate (mL/min/BSA) [BL to Mth 6]	NS
							b-type natriuretic peptide (pg/mL) [BL to Mth 6]	NS
							Patient Health Questionnaire-9 [BL to Mth 6]	NS
							Blood pressure (BP) (mmHg) [BL to Mth 6]	**Reduced BP** Systolic: not shown (p<0.0001) Diastolic: not shown (p<0.0001)
Seely, et al. (2013) [Canada, AMRO] [27]	Randomized controlled trial	Cardiovascular disease	Individualized naturopathic care (NC) and enhanced usual care including diet and lifestyle counseling, nutritional medicine & supplementation, 7 visits over 1 year.	Anti-hypertensive, lipid lowering, anti-diabetic medications. Natural health product use. Acupuncture, chiropractic, massage, and physiotherapy treatments	Enhanced usual care plus biometric measurement (UC)	246 (124/122)	10-year CVD event risk (Framingham) [BL Wk 25 and 52]	**Reduced CVD risk** NC 7.74%; UC 10.81% Between group -3.07% (p=0.001)
							Prevalent metabolic syndrome [BL to Wk 25 and 52]	**Reduced metabolic syndrome prevalence** NC 31.58%; UC 48.48% Between group -16.9% p=0.002)
							Body weight (kg) [BL Wk 25 and 52]	NS
							Waist (cm) [BL Wk 25 and 52]	NS
							Lipid profile [BL Wk 25 and 52]	NS
							Fasting glucose (mg/dL) [BL Wk 25 and 52]	NS
							Blood pressure (mmHg) [BL Wk 25 and 52]	NS

Author (year) [Country, World Region]	Design	Study Population	Intervention(s)	Concomitant therapies	Control or comparison group	No. Participants (Intervention/ Control)	Outcome measure	Outcome
Shetty and Mooventhan (2015) [India, SEARO] [35]	Case report	Obesity	Initial 15-day admission: yoga sessions (60 mins day), naturopathic treatment (90-120 minutes per day) involving hydrotherapy, diet and fasting, mud therapy and massage therapy. Following 2 years of self-care patient was admitted for 10 days every 2 years (2010, 2012, 2014).	Nil	Nil	1	Body weight (kg) [BL to Dy 15, Yr 2, Yr 6]	**Reduced body weight** Dy 15: -6.1 Yr 2: Weight maintained Yr 6: -22.7 (101 kg to 94.9 kg)
							Body mass index [BL to Dy 15, Yr 2, Yr 6]	**Reduced body mass index** Dy 15: -2.35 Yr 2: Changed from Class-II Obesity to Class-I Obesity Yr 6: Changed to Overweight or Pre-obese (-8.61)
Sinclair (2015) [Australia, WPRO] [15]	Case report	Acute pancreatitis	Dietary changes: avoid coffee, stimulants, purified sugar and fatty meals; increase nutrient- and phytochemical-dense foods; Vegetable soup (butter, onions, garlic, carrot, celery, cauliflower, broccoli, zucchini) cooked for 2-3 hrs in a base of *Curcuma longa* (3 tablespoons, dried), *Zingiber officinale* (1 tablespoon, fresh), *Allium sativum* (3 bulbs, fresh), *Coriandum sativum* (1 bunch, leaf and roots; 2 tablespoons, dried), *Cuminum cyminum* (1 table -spoon, dried) *Illicium verum* (3 x fruit), *Foeniculum vulgare* (1 table spoon, crushed seed), *Ellettaria cardamomum* (5 x pods), *Piper nigrum* (1/2 tea- spoon) Herbal medicines: *Ulmus rubra* (2 tablespoons); *Plantago ovata* (2 tablespoons); *Zingiber officinale* and *Matricaria chamomilla floz* infusion. Exercise: Gentle hike in local nature reserve (6km; 3 hours)	Nil	Nil	1	Pain	**Reduced pain** Resolved within 1 hour
							Nausea	**Reduced nausea** Resolved within 1 hour
							Bowel motions	**Normalized bowel motions** Normalized on day 2 of treatment

Author (year) [Country, World Region]	Design	Study Population	Intervention(s)	Concomitant therapies	Control or comparison group	No. Participants (Intervention/ Control)	Outcome measure	Outcome
Szczurko, et al. (2007) [Canada, AMRO] [36]	Randomized controlled trial	Chronic low back pain	12-weeks treatment with twice weekly naturopathic care (NM) including dietary counseling, deep breathing relaxation techniques and acupuncture.	NSAIDs	Standardized physiotherapy involving education and instruction on physiotherapy exercises using an approved education booklet.	75 (39/36)	Oswestry Low Back Pain Disability Questionnaire [BL to Wk 12]	**Reduced back pain** NM: -5.0; Education: -0.0 Between group: p<0.0001
							Short Form 36 [BL to Wk 12]	**Increased quality of life** Physical component: NM +9.25; Education +0.78 Between group +8.47 (p<0.0001) Mental component: NM +4.26; Education -2.74 Between group +5.56 (p<0.0045) Physical functioning: NM +7.12; Education +1.56 Between group +5.56 (p<0.0033) Physical role: NM +8.67; Education -2.81 Between group +11.48 (p<0.001) Bodily pain: NM +11.12; Education +0.29 Between group +10.83 (p<0.0001) General health: NM +6.05; Education -1.13 Between group +7.18 (p=0.0002) Vitality: NS Social functioning; NM +8.95; Education -1.62 Between group +10.57 (p<0.0001) Emotional role: NM +4.88; Education -3.17 Between group +8.05 (p=0.0090) Mental health: NM +4.62; Education -2.82 Between group +7.44 (p=0.0003)

Author (year) [Country, World Region]	Design	Study Population	Intervention(s)	Concomitant therapies	Control or comparison group	No. Participants (Intervention/ Control)	Outcome measure	Outcome
							Self-reported Pain Scale [BL to Wk 12]	**Reduced pain** NM -1.0; Education -0.0 Between group p<0.0001
							Roland Morris Disability Questionnaire [BL to Wk 12]	**Reduced disability** NM -4.0; Education +2.0 Between group p<0.0001
							Forward Lumbar Flexion Range of Motion (cm) [BL to Wk 12]	**Increased range of motion** NM +4.5; Education -0.5 Between group p<0.0001
							Weight (kg) [BL to Wk 12]	**Reduced weight** NM -1.51; Education -0.05 Between group p<0.0052
							Body Mass Index (kg/m^2) [BL to Wk 12]	**Reduced body mass index** NM -0.58; Education -0.06 Between group p<0.0106
Szczurko, et al. (2009) [Canada, AMRO] [28]	Randomized controlled trial	Rotator cuff tendonitis	12-weeks of 30 minutes of treatment with naturopathic care including dietary counseling, acupuncture, Phlogenzym containing 90mg bromelain, 48mg trypsin and 100mg rutin (2 tablets TID). OR Standardized physical exercises including passive, active assisted and active range of motion exercises and matched placebo.	Nil	Standardized physical exercise	85 (43/42)	Shoulder Pain and Disability Index [BL to Wk 12]	**Reduced shoulder pain and disability** Total: NM -42.34; PE -23.59 Between group -29.66 (p<0.0001) Pain: NM -18.70; PE -5.7 Between group -13.00 (p<0.0001) Disability: NM -21.64; PE -6.00 Between group -15.64 (p=0.0002)
							Pain Visual Analog Scale [BL to Wk 12]	**Reduced pain** NM -2.34; PE -0.67 Between group -1.67 (p<0.0001)
							Short Form 36 [BL to Wk 12]	**Increased quality of life** Physical component: NM +7.75; PE +2.04 Between group +5.71 (p=0.0004) Mental component: NM +5.85; PE +0.13 Between group +5.73

Author (year) [Country, World Region]	Design	Study Population	Intervention(s)	Concomitant therapies	Control or comparison group	No. Participants (Intervention/ Control)	Outcome measure	Outcome
								(p=0.0107) Physical functioning: NM +14.88; PE +1.36 Between group +13.52 (p=0.0025) Physical role: NM +21.09; PE +3.75 Between group +17.34 (p=0.0015) Bodily pain: NM +24.16; PE +7.64 Between group +16.52 (p=0.0004) General health: NM +10.07; PE -1.54 Between group -11.62 (p=0.0029) Vitality: NM +14.33; PE +4.17 Between group +10.16 (p=0.0047) Social function: NM +14.02; PE +3.65 Between group +10.38 (p=0.0378) Emotional role: NM +13.82; PE -2.27 Between group +16.09 (p=0.002) Mental health: NM +12.44; PE -2.22 Between group +14.66 (p=0.0015)
							Measure Yourself Medical Outcomes Profile [BL to Wk 12]	**Reduced symptoms** MYMOP Symptom 1: NM -2.20; PE -1.29 Between group -0.91 (p=0.0225) MYMOP Symptom 2: NM -3.13; PE -0.66 Between group -1.86 (p=0.0001)

Author (year) [Country, World Region]	Design	Study Population	Intervention(s)	Concomitant therapies	Control or comparison group	No. Participants (Intervention/ Control)	Outcome measure	Outcome
							Maximal range of motion (goniometer readings) [BL to Wk 12]	**Increased range of motion** Flexion: NM +37.24; PE -3.69 Between group: +40.94 ($p<0.0001$) Extension: NM +6.1; PE -3.58 Between group: +9.68 ($p<0.0001$) Abduction: NM +47.46; PE +0.89 Between group: +46.57 ($p<0.0001$) Adduction: NS
Taylor, et al. (2018) (Australia, WPRO) [16]	Case report	Interstitial cystitis	Naturopathic care including liquid herbal formula containing *Hypericum perforatum*, *Eleutherococcus senticosus*, *Scutellaria lateriflora*, *Schisandra chinensis*, *Crocus sativus*, (7.5ml BD), herbal tablet containing *Boswellia serrata*, *Curcuma longa*, *Apium graveolens*, *Zingiber officinale*, (2 tablespoons BD); lifestyle counseling including sleep hygiene, stress reduction techniques; dietary advice including increased water consumption and reduction of aggravating foods. Treatment over 2 weeks.	Nil	Nil	1	Client self-reported symptom reduction	**Increased energy and vitality, marked reduction in frequency and urgency of urinary symptoms, improved sleep onset and quality, reduction in edema in feet and ankles.**

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30 Applied Nutrition

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HIGHLIGHTS

- Assessing food choices and dietary patterns – known as applied nutrition – is one of the core therapies used in naturopathic care.
- Poor nutrition has been identified as a modifiable risk factor associated with several non-communicable diseases.
- Naturopaths/NDs provide individualized dietary recommendations and education around food and dietary patterns to patients as part of their patient-centered care.
- Clinical research by the naturopathic community has examined the application of food as medicine, specific dietary interventions, dietary modification based on food intolerance assessments, and dietary education interventions.
- In line with the role of primary care, naturopathic researchers have investigated the effects of applied nutrition interventions on individuals with irritable bowel syndrome, cancer, overweight/obesity, type II diabetes mellitus and prediabetes, metabolic syndrome, generalised anxiety disorder, acne, and asthma as well as in healthy adults.

Applied nutrition involves the modification of dietary patterns and food choices with the goal of optimizing nutritional status in the treatment and/or prevention of disease. For centuries, humans have recognized the connection between food and health [1]. Contemporary research recognizes poor nutrition as a modifiable risk factor in the development and progression of illnesses that contribute heavily to the global burden of disease (e.g., cancer [2], cardiovascular disease [3], diabetes [4] and depression [5]) and establishes nutrition interventions as effective therapeutic options for many of these conditions [6, 7].

Nutritional intervention has historically been one of the key focus areas of naturopathic practice globally, with both applied nutrition and clinical nutrition (the prescribing of specific nutrients – see Chapter 31) being seen as foundational to naturopathic practice, with cross-sectional data suggesting that both are an essential component of the treatment offered to patients seeking naturopathic care globally [8]. Naturopathic applied nutritional interventions include diet therapy (therapeutic diets, fasting and individualized diet modification), therapeutic application of specific foods and behavioural and lifestyle counselling related to eating behaviours [9].

Naturopathic practice incorporates the scientific and empirical knowledge of food and nutrition, it recognizes the value of whole foods beyond their individual constituents, as well as the traditional knowledge of food as a form of medicine – in some cases interfacing with herbal medicines through the use of plant-based foods to improve health – and the importance of considering the constitution and uniqueness of every patient, the thoughts and emotions that they have around food and their environment when applying nutrition therapeutically. Dietary modification is a common component of a multi-faceted comprehensive naturopathic treatment plan and hence is also discussed in *Chapter 29: Complex Naturopathic Interventions.*

Overview of studies

This chapter is dedicated to highlighting the original clinical research (n=25; published in 31 papers) naturopathic clinicians undertook in the field of applied nutrition. This research includes a total of 2,568 participants and was conducted in the United States of America (USA) (n=18), India (n=6), Canada (n=3), New Zealand (n=2), Germany (n=1), and Australia (n=1). The study designs include randomized controlled trials (RCT) (n=14) and subsequent secondary analyses or long-term follow up data related to the RCTs (n=6), uncontrolled trials (n=6), case reports (n=4), and a retrospective cohort study (n=1). Trials were primarily conducted in out-patient community settings and non-medical residential facility.

The study populations treated with applied nutrition include healthy adults (n=4), individuals with irritable bowel syndrome (IBS) (n=3), breast cancer (n=3), overweight/obesity (n=3), type II diabetes mellitus (n=3) or

prediabetes (n=1), prostate cancer (n=2), generalized anxiety disorder (n=2), metabolic syndrome (n=2), acne (n=1), asthma (n=1). Of all the naturopathic clinical studies employing applied nutrition interventions, 88% reported a positive outcome in at least one primary or secondary outcome measure. Details of the studies are available in *Table 30.1: Clinical research investigating applied nutrition interventions conducted by naturopathic researchers.* This body of naturopathic research on applied nutrition is also supported by 20 observational studies and more than 30 reviews or meta-analysis conducted by naturopathic researchers on this topic, as outlined in Chapter 40.

Implications

Naturopathic applied nutrition interventions have been tested using rigorous study designs. The case reports detailed significant clinical improvement in response to diet modification. Changes in patient-reported diet quality and objective biomarker levels suggest that these interventions can successfully modify participant behaviour, with clinically meaningful improvements in symptom severity. Although studies of specific naturopathic interventions are limited, this data complements and is consistent with observational studies and health services research which show demonstrable sustained improvement in diets for patients receiving naturopathic dietary advice [10, 11].

While the use of clinical nutrition (e.g., dietary supplements) by naturopaths/naturopathic doctors may lead to assumptions that the prescription of products is the main nutritional intervention of the profession, research has shown that applied nutrition via dietary modification is used significantly more by the global naturopathic profession [8]. Where comparative examination with dietitians has occurred, naturopaths/naturopathic doctors are found to follow evidence-based approaches to applied nutrition at least as consistently as dietitians, with the key differences relating to the increased scope of treatment options available to the naturopathic workforce beyond applied nutrition, as well as an emphasis on combining traditional approaches to understanding food and health to complement evidence-based care [12].

Poor dietary habits are one of the major contributors to non-communicable disease and global burden of disease [13]. Naturopathic applied nutrition is frequently used in clinical practice around the globe and evidence suggests that it plays a role in achieving meaningful clinical outcomes. The high level of public trust and preference for naturopathic advice on nutrition by the community [14] suggest that naturopaths/NDs may be able to effectively translate evidence-based dietary guidelines in clinical practice, and integration of the naturopathic workforce in initiatives aimed at improving health through nutrition may be warranted.

Studies investigating specific interventions:

Food as Medicine

Six of the studies involving 277 participants focused on the therapeutic effectiveness of specific foods [15-20]. These studies included interventions to address metabolic syndrome [15], type II diabetes mellitus [18, 19] and obesity [20]. Two of the studies included healthy volunteers with a focus on measuring the impact of chocolate on blood pressure [16]; and the impact of coconut on blood cholesterol readings [17]. Other foods assessed included vegetable and fruit powders [15], lemon and lemon juice [20], bittergourds [19] and bell peppers [18].

A randomized controlled cross-over trial conducted in the USA with 45 overweight adults involved the administration of dark chocolate, cocoa products and placebo [16]. Ingestion of solid dark chocolate and liquid cocoa resulted in an improvement in endothelial function as measured by flow-mediated dilatation. Dark chocolate improved dilatation by 4.3% vs placebo -1.8% ($p<0.001$). Compared to placebo, ingestion of sugar-free and sugared cocoa resulted in improved blood pressure (dark chocolate: systolic -3.2mmHg vs +2.7mmHg, $p<0.001$; diastolic -1.4mmHg vs +2.7mmHg, $p=0.01$).

A pilot randomized controlled trial conducted in India measured the impact of three different bittergourds on patients (n=30) diagnosed with type II diabetes mellitus [19]. Group 1 (n=10) were prescribed 250 ml bittergourd juice (30% concentrate), group 2 (n=10) 250 ml Knol-khol (80% concentrate – also known as kohl rabi) and group 3 (n=10) were prescribed 250 ml ashgourd juice (88% concentrate) [18]. The participants' fasting plasma glucose was measured every 30 minutes from baseline for two hours. A reduction in plasma glucose was found in the Knol-khol group at 30-, 90-, and 120-minutes with effect seen over time ($p=0.029$).

Diet Programs

Eleven studies (published in 13 articles) (n=1,895) focused on specific dietary interventions including low fermentable oligosaccharides, disaccharides, monosaccharides and polyols (FODMAP) diet [21], organic [22], modified Mediterranean [23, 24], vegetarian or vegan [25, 26], fasting [27], low-fat [28, 29], healthy diet patterns [30-32], low glycemic index [33] and individualized naturopathic dietary recommendations [34]. Most often, the programs advised participants to increase intake of vegetables and fruits, foods high in omega-3 fatty acids, fiber and whole grains and to decrease total or saturated fat. The populations included in these studies were individuals with irritable bowel syndrome (n=1) [21], prostate cancer (n=1; 2 published papers) [23, 24], cardiovascular

risk factors (e.g., high cholesterol, hypertension, overweight) (n=1) [25], obesity (n=1) [26], acne vulgaris (n=1) [27], anxiety (n=1) [33], and type II diabetes (n=1) [34]. Studies also sampled breast cancer survivors (n=3) [28, 29, 32], and healthy adult populations (n=3) [22, 30, 31].

A single-blind randomized controlled trial conducted in Germany involving 59 participants with IBS, compared the low FODMAP diet to a yoga intervention [21]. The diet intervention was delivered through a combination of group and individual counselling sessions. Improvements were noted for both the FODMAP (-96.18, p<0.001) and yoga (-66.16, p<0.001) groups across all IBS-SSS domains. Improvements were maintained at the 24-week follow-up. Between group analysis found no significant differences between groups except for a decrease in abdominal distension from baseline to the end of the 12-week intervention (IBS symptom severity score [IBS-SSS]: +14.13, p=0.04) for participants following the low FODMAP diet but not those in the yoga group. This difference was not maintained at Week 24. FODMAP diet participants also reported less food avoidance in Week 12 compared to the yoga group (-17.1; p=0.005). Yoga participants experienced reduced anxiety at Week 12 (Hospital Anxiety and Depression Scale: -1.35, p=0.035) and increased body awareness at Week 24 (Body Awareness Questionnaire: +7.6, p=0.02) compared to the FODMAP group.

In a pilot randomized controlled trial conducted in the USA (n=30) breast cancer survivors were allocated to receive either a 'fatigue reduction diet' or a general health curriculum, delivered individually through a combination of in-person and brief (15-minute) telephone sessions [32]. Using the theoretical framework of social cognitive theory, participants were advised to increase levels of dietary antioxidants through increased intake of fruits, vegetables, wholegrains, and omega-3 fatty acids. Compared with individuals in the control group, those receiving the intervention reported a significant reduction in fatigue (-2.4 vs -0.77; p<0.01) and an improvement in sleep (Pittsburgh Sleep Quality Index +2.5 vs +0.9; p=0.03) at the end of the intervention. Significant improvement in biomarkers, such as blood levels of vitamins and omega-3 fatty acids, among the intervention participants suggested compliance with the intervention.

An uncontrolled study conducted in India involving 47 patients with obesity examined the impact of a low fat, high fiber, vegetarian diet along with daily yoga practice [26]. The study lasted for 6 days and resulted in a reduction of BMI (-0.57kg/m^2; p<0.01), a reduction in waist circumference (-1.69cm; ;p<0.01), reduction in hip circumference (-1.69cm; p<0.01), reduced HDL (-2.88mg/dL; <p<0.01) a reduction in leptin (-23.75ng/mL; p<0.01), an increase in hand grip strength (Right: +2.09, p<0.001; Left: +2.00, p<0.01) and postural stability (20sec: +11.03, p<0.001; 40sec: +24.41, p<0.001; 60sec: +33.91, p<0.001).

Food Intolerance Testing and Support

Five studies [35-39] evaluated the effects of avoiding specific foods that were identified through food sensitivity testing or elimination/challenge procedures. The immunological tests used to determine food sensitivity were leucocyte antigen tests (n=1) [35], immunoglobulin G-reactivity test (n=2) [36, 39], enzyme-linked immunosorbent assay (ELISA) (n=1) [37]. One study used an elimination diet without immunological testing [38].

In a randomized controlled trial (n=58) conducted in the USA the therapeutic effects of applying food sensitivity testing in dietary elimination was assessed in the management of irritable bowel syndrome (IBS) [35]. Individualized diet recommendations were provided based on the results of Leukocyte Activation Test. Participants were randomized to receive instructions to avoid the foods found to be reactive, or a control diet which included recommendations to include foods that were found to be reactive. Participants in the intervention arm reported a significantly greater increase in the IBS Global Improvement Scale at the end of the four-week intervention (-0.86 difference, p=0.04) and a significantly greater reduction in the IBS Symptom Severity Scale (-61.78 difference, p=0.04); improvements were maintained at eight-week follow-up. A decrease in neutrophil elastase was also associated with symptom reduction.

Dietary Education

Two studies (published in six papers) [40-45] assessed the impact of dietary education interventions. These trials included 115 participants and involved the group delivery of community-based educational programs. Topics included in the programs were nutritional guideline education, and exercises to develop skills related to cooking, grocery shopping, and reading food labels.

A randomized controlled trial involving Hispanic breast cancer survivors (n=70) delivered a culturally-based approach to diet change including nutrition education, cooking skills classes, and trips to grocery stores in a group setting [40]. Participants in the intervention group increased total targeted fruit and vegetable servings per day at month 3 compared to participants receiving written nutrition instructions alone (+2 vs +0.2, p=0.004) and the significant improvements were maintained at 6-month follow up (+2.7 vs +0.5, p=0.002). A similar difference was seen in favour of the intervention group for reduction in caloric intake at month 3 (-672.9 vs 92.4, p<0.001) and month 6 (-562.9 vs 61.6, p<0.001). A secondary analysis on serum biomarkers confirmed changes in reported fruit and vegetable consumption [41]. Several publications reported on long-term follow up and subsequent secondary analyses from this trial [41, 43-45].

Table 30.1 Clinical research investigating applied nutrition interventions conducted by naturopathic researchers

Author (year) [Country, World Region]	Design	Study Population	Intervention(s)	Concomitant therapies	Control or comparison group	No. Participants (Intervention/Control)	Outcome measure	Outcome
Ali, et al. (2011) [USA, AMRO] [15]	Randomized controlled trial (Crossover)	Metabolic syndrome (adults)	Encapsulated vegetable and fruit powder concentrate blends. Blend 1: vegetable, fruit, and berry; Blend 2: vegetable and fruit 3 capsules twice daily (1 capsule = 750mg) for 8 weeks, with 8-week washout period between crossing over to a new group	Nil	Placebo	64 (22/22/20)	Flow-mediated dilatation of the brachial artery [BL to Wk 8] [BL to Mth 6]	NS
							Plasma glucose (mg/dl) [BL to Wk 8]	NS
							Serum insulin (IU/l) [BL to Wk 8]	NS
							Serum lipids (mg/dl) [BL to Wk 8]	NS
							Body weight (kg) [BL to Wk 8]	NS
Ali, et al. (2017) [USA, AMRO] [35]	Randomized controlled trial	Irritable bowel syndrome	Dietary elimination based on leucocyte antigen test results (LATR); 4 weeks	Nil	Diet including reactive foods and exclusion of non-reactive foods (contrary to LATR)	58 (29/29)	IBS Global Improvement Scale [BL to Wk 4, Wk 8]	**Symptom improvement** Wk 4: -0.86 (p=0.04) Wk 8: -1.22 (p=0.04)
							IBS Symptom Severity Scale [BL to Wk 4, Wk 8]	**Reduced symptom severity** Wk 4: -61.78 (p=0.04) Wk 8: -66.42 (p=0.05)
							IBS Adequate Relief Scale [BL to Wk 4, Wk 8]	NS
							IBS-Quality of Life [BL to Wk 4, Wk 8]	NS
							Neutrophil elastase [BL to Wk 4, Wk 8]	**Reduced neutrophil elastase** Lower in strong responders
Ameya and Nair (2017) [India, SEARO] [27]	Case report	Acne vulgaris	Day 1 to 5: Diet plan including Holy Basil decoction, fresh carrot juice, mosambi (sweet lime) juice, non-spicy vegetable curry and bhakri (sorghum preparation). Day 6 to 16: Alternating daily between therapeutic fasting, and lemon honey juice and tender coconut water. Follow up on Day 14 and 30	Swedish massage, steam bath, warm water enema and hip bath. Yoga 45 minutes per day on non-fasting days	Nil	1	Acne lesions and inflammation [BL to Dy 30, 60]	**Reduced acne lesions** Dy 30: noticeable reduction in lesions, with no noticeable inflammation or swelling Dy 60: No relapse of symptoms reported.

Author (year) [Country, World Region]	Design	Study Population	Intervention(s)	Concomitant therapies	Control or comparison group	No. Participants (Intervention/ Control)	Outcome measure	Outcome
Aucoin and Bhardwaj (2016) [Canada, AMRO] [33]	Case report	Generalized anxiety disorder	Lower glycemic index diet by increasing protein, fibre, and unprocessed oils	Nil	4 weeks	1	Subjective anxiety symptom severity [BL to Wk 4]	**Reduced anxiety** Wk 4: (8/10 to 4 or 5/10)
							Subjective symptoms [BL to Wk 4]	**Increased energy at Wk 4, reduced frequency and intensity of hypoglycemic symptoms, reduced headaches (once per wk compared to everyday). Cessation of chronic vaginal discharge.**
Aucoin and Bhardwaj (2019) [Canada, AMRO] [38]	Case report	Major depressive disorder and Generalized anxiety disorder	2 years: 3 weeks of elimination diet containing hypoallergenic foods. Following elimination phase, reintroduction of one new food every 3 days, and introduction of nutritional products and exercise	Nutritional products: Omega-3 fish oil (EPA 1.3g, DHA, 200mg, Vitamin E, 6.7mg) daily; intramuscular vitamin B12 injections every 3 weeks; exercise daily	2 years	1	Subjective depression symptoms [BL to Yr 2]	**Reduced depression symptoms** Elimination phase: Fewer days of low mood, less episodes of crying, increase in interest in activities. Reintroduction phase: Dairy – Rapid onset (<24 hr) of low mood symptoms including feelings of sadness and increased crying Follow up phase: Maintenance of dietary change was intermittent, but consumption of dairy and gluten were associated with reduced mood while avoidance was associated with symptom improvement
							Other symptoms (subjective)	**Reduced symptoms** Elimination phase: Increased energy, mental clarity, frequency of bowel movements (once every 2 or 3 days), weight loss (-4.5kg), resolution of acne lesions Reintroduction phase: Dairy and gluten – headaches, gas, bloating,

Author (year) [Country, World Region]	Design	Study Population	Intervention(s)	Concomitant therapies	Control or comparison group	No. Participants (Intervention/ Control)	Outcome measure	Outcome
								abdominal discomfort Follow up phase: Maintenance of dietary change was intermittent, but consumption of dairy and gluten were associated with constipation and headaches while avoidance was associated with symptom improvement
Bishop, et al. (2015) [New Zealand, WPRO] [23]	Uncontrolled trial	Prostate cancer (males)	30 – 50 g of mixed, unsalted seeds and nuts daily; ⩾15 mL or more of extra virgin olive oil avoiding exposure of the oil to medium and high heat; reduce dairy intake to one portion daily; substitute butter and/or margarine with an olive oil-based spread; limit intake of red meat to less than 400g/wk and substitute with oily fish and white meat; avoid high temperature cooking of protein; avoid processed meats; and eat oily fish ⩾ once weekly. Light to moderate exercise was encouraged.	Exercise	Nil	20	Holman Bloodspot fatty acid profiles (mean %) [BL to 3 Mths]	**Reduced saturated fatty acids** Mean total SFA (-1.0, p=0.002) 18:0 stearic acid (-0.5, p=0.002) n6PUFA: n3PUFA (-0.6, p=0.019) AA: EPA (-1.6, p=0.030) Increased omega-3 fatty acids 22:5 n3 DHA (+0.5, p=0.01) EPA / DHA (+0.6, p=0.042) Modified WBS n3 index (+0.9, p=0.043)
							Alkaline Single-Cell Gel Electrophoresis (Comet) Assay [BL to 3 Mths]	**Reduced DNA damage** DNA damage inverse correlation with dietary adherence (p=0.013) whole blood MUFA (p=0.009) and oleic acid, high red meat (p=0.003) and dairy (p=0.008). Reduced DNA damage with adherence to diet (p=0.013), folate intake (p=0.023), vitamin C (p=0.007), legumes (p=0.004) and green tea (p=0.002). DNA damage positive correlation with intake of dairy products (p=0.043) red meat (p=0.007) and whole blood n6PUFA (p=0.015)

Author (year) [Country, World Region]	Design	Study Population	Intervention(s)	Concomitant therapies	Control or comparison group	No. Participants (Intervention/ Control)	Outcome measure	Outcome
Erdrich, et al. (2015) [New Zealand, WPRO] [24]							Body weight (kg) [BL to 3 Mths]	**Reduced body weight** - 2.3 kg, (p=0.0007)
							BMI [BL to 3 Mths]	**Reduced BMI** -0.85kg/m2, (p<0.001) BMI was inversely correlated to blood n3PUFA (p=0.046). Reduced BMI associated with increased blood PUFA (p=0.031) and LA (p=0.040).
							Changes in the sources of dietary fat [BL to 3 Mths]	**Increased dietary fat** olive oil (+14.2, p=0.0008) nuts (+2.9, p=0.0003) fish (+1.8, p=0.0005) Reduced dairy (-2.9, p=0.0025) and red meat (-2.0, p=0.0005)
							Holman Bloodspot fatty acid profiles (mean %) [BL to 3 Mths]	**Reduced saturated fatty acids** Mean total SFA (-1.0, p=0.002) 18:0 stearic acid (-0.5, p=0.002) n6PUFA: n3PUFA (-0.6, p=0.019) AA: EPA (-1.6, p=0.030) Increased omega-3 fatty acids 22:5 n3 DHA (+0.5, p=0.01) EPA / DHA (+0.6, p=0.042) Modified WBS n3 index (+0.9, p=0.043)
							C reactive protein [BL to 3 Mth, relative to Dietary Adherence Questionnaire]	NS
							Prostate-specific antigen [BL to 3 Mth, relative to Dietary Adherence Questionnaire]	NS

Author (year) [Country, World Region]	Design	Study Population	Intervention(s)	Concomitant therapies	Control or comparison group	No. Participants (Intervention/ Control)	Outcome measure	Outcome
Cohen, et al. (2017) [USA, AMRO] [30]	Uncontrolled trial	Low income, racially and ethnically diverse adults	Double up food bucks (DUFB) for a state-wide health food incentive	Nil	none	177	Use of DUFB and consumption of fruit and vegetables	**Increased fruit and vegetable intake** +0.66 servings ($p<0.001$). Sustained at 3 and 5mths ($p<0.001$). Participants more likely to report use of DUFB ($p<0.001$).
Faridi, et al. (2008) [USA, AMRO] [16]	Randomized controlled trial (crossover)	Healthy adults (overweight)	Phase 1: Solid dark chocolate (74g; equiv. 22g cocoa powder) Phase 2: Sugar-free cocoa (2 cups, equiv. 22g cocoa powder and vanillin, acesulfame-potassium, and aspartame) OR sugared cocoa (2 cups, equiv. 22g cocoa powder and 45.3g sugar)	Nil	Placebo Phase 1: 74g Phase 2: hot liquid	45	Flow-mediated dilation (%) [BL to immediately post-treatment]	**Increased** Chocolate: +4.3; Placebo: -1.8 Between group: $p<0.001$ Sugar-free: +5.7; Sugared: +2.0; Placebo: -1.5 Between group (Sugar-free vs placebo): $p<0.001$ Between group (Sugared vs placebo): $p<0.001$
							Stimulus-adjusted response measure [BL to immediately post-treatment]	**Increased** Chocolate: NS Sugar-free: +0.04; Sugared: +0.02; Placebo: -0.02 Between group (Sugar-free vs placebo): $p<0.001$ Between group (Sugared vs placebo): $p<0.001$
							Systolic blood pressure (mm Hg) [BL to immediately post-treatment]	**Reduced systolic BP** Chocolate: -3.2; Placebo: +2.7 Between group: $p<0.001$ Sugar-free: -2.1; Sugared: +0.9; Placebo: +3.2 Between group (Sugar-free vs placebo): $p<0.001$ Between group (Sugared vs placebo): NS
							Diastolic blood pressure (mm Hg) [BL to immediately post-treatment]	**Reduced diastolic BP** Chocolate: -1.4; Placebo: +2.7 Between group: $p<0.001$ Sugar-free: -1.2; Sugared: +1.7; Placebo: +2.8 Between group (Sugar-free vs placebo) $p<0.001$

Author (year) [Country, World Region]	Design	Study Population	Intervention(s)	Concomitant therapies	Control or comparison group	No. Participants (Intervention/ Control)	Outcome measure	Outcome
Greenlee, et al. (2007) [USA, AMRO] [31]	Randomized controlled trial	Healthy premenopausal woman	Group 1: Botanical formula 100mg Curcuma longa root extract standardized to 95% curcumin; 100 mg Cynara scolymus leaf 6:1 extract; 100 mg Rosmarinarus officinalis leaf 5:1 extract; 100 mg Silybin marinum seed extract standardized to 80% silybin, silichristin, silidianin, and silymarin; 100 mg Taraxacum officinalis root 4:1 extract; and 50 mg Schisandra. chinensis berry 20:1 extract Group 2: Dietary intervention 3 servings (1/2 cup each) per day of cruciferous vegetables, garlic, onions, beets, dark leafy greens; 30 grams of fiber per day; 1 to 2 liters of water per day; 1 cup per week or less of coffee and black tea (green tea was not limited); and 1 serving per week of alcohol and two grocery bags of organically grown vegetables weekly. Eight, 1 hr workshops with a nutritionist	1 month run-in phase followed by 12 weeks intervention (5 menstrual cycles)	placebo	40 (15/10/ 15)	Anthropometric [Early and late follicular phases from Cycle 1 to 5]	**Reduced** anthropometric -0.5 vs placebo +1.6 (p=0.05)
							Estrone (pg/ML) [Early and late follicular phases from Cycle 1 to 5]	NS
							Estrone sulfate (ng/mL) [Early and late follicular phases from Cycle 1 to 5]	NS
							Total estradiol (pg/mL) [Early and late follicular phases from Cycle 1 to 5]	NS
							Free estradiol (pg/mL) [Early and late follicular phases from Cycle 1 to 5]	NS
							SHBG (nmol/L) [Early and late follicular phases from Cycle 1 to 5]	NS
							2-Hydroxyestrone (ng/mg Cr) [Early and late follicular phases from Cycle 1 to 5]	NS
							16α-Hydroxyestrone (ng/ mg Cr) [Early and late follicular phases from Cycle 1 to 5]	NS
							2α-Hydroxyestrone /16α-hydroxyestrone ratio [Early and late follicular phases from Cycle 1 to 5]	NS
							DHEA (ng/mL) [Early and late follicular phases from Cycle 1 to 5]	**Reduced levels** early follicular -0.69 (p=0.016)
							DHEAS (ug/mL) [Early and late follicular phases from Cycle 1 to 5]	NS

Author (year) [Country, World Region]	Design	Study Population	Intervention(s)	Concomitant therapies	Control or comparison group	No. Participants (Intervention/ Control)	Outcome measure	Outcome
							Androstenedione (ng/mL) [Early and late follicular phases from Cycle 1 to 5]	NS
							Free testosterone (ng/mL) [Early and late follicular phases from Cycle 1 to 5]	NS
							Free testosterone (pg/mL) [Early and late follicular phases from Cycle 1 to 5]	NS
Greenlee, et al. (2013) [USA, AMRO] [29]	Randomized controlled trial	Breast cancer survivors (stage 0-IIIa minority groups)	Curves program for 6 months, 6 months observation (IA) (30min exercise circuit, a high vegetable/low fat/calorie- restricted diet – 1200kcal/day for 1-2 weeks; 45% protein, 30% carbohydrates, 25% fat)	90 minutes exercise per week encouraged	Wait list control arm (WCA): 6 Mth observation and 6 Mth curves program	42 (22/20)	Weight loss (kg) [BL to Mth 6 and 12]	**Reduced weight** Mth 6: IA, -3.3% ± 3.5; WC, +1.8% ± 2.9 (p=0.04) Mth 12: IA, regained some but not all of weight lost during first 6 months p=0.02
							Retainment	90.5% were retained for the full 12 months
Delgado-Cruzata, et al. (2015) [USA, AMRO] [28]	Secondary analysis of selected cohort (sub-analysis)				Nil	24	Anthropometric measures (mean change, %) [BL to Mth 6 and 12]	**Reduced weight** Mth 6: -1.9 (p=0.01), Mth 12: -2.1 (p=0.01) **Reduced waist circumference** Mth 6: -2.7 (p<0.01), Mth 12: -2.7 (p=0.01) **Reduced body fat** Mth 6: -2.4% (p=0.03), Mth 12: unavailable Hip circumference: NS Waist-to-hip ratio: NS
							Plasma insulin and HOMA-IR [BL to Mth 6 and 12]	**Reduced insulin resistance** Mth 12: Insulin, -10.6% (p<0.01) HOMA-IR, -11.4% (p<0.01)
							Adaption of Kaiser Physical Activity Survey [BL to Mth 6 and 12]	**Increased physical activity** Sports/exercise index Mth 6: +1.1 (p<0.001) Mth 12: +0.7 (p<0.001)

Author (year) [Country, World Region]	Design	Study Population	Intervention(s)	Concomitant therapies	Control or comparison group	No. Participants (Intervention/ Control)	Outcome measure	Outcome
							DNA methylation biomarkers [BL to Mth 6 and 12]	**Increased methylation** Mth 6: +4.2%; Mth 12: +3% (p<0.0001)
							Associations between changes in anthropometric measures, metabolic markers, diet, and physical activity and changes in markers of DNA methylation [BL to Mth 6 and 12]	**Increased diet quality** Weight loss: NS 10% body fat decrease: NS 10% caloric intake: -0.48% (CI:0.10-0.86) Physical activity: NS 10% increase in fruit and vegetable and protein: +0.85% (CI: 0.12-0.70)
Greenlee, et al. (2015) [USA, AMRO] [40]	Randomized controlled trial	Breast cancer survivors (stage 0-III)	Culturally based dietary interventions for Hispanic women *"¡ Cocinar Para Su Salud!"* (nine sessions on nutrition, education, cooking classes and food shopping field trips) 24 hours total over 12 weeks	Nil	Control – written dietary recommendations	70 (34/36)	Daily targeted fruit and vegetable intake (servings) [BL to Mth 3, Mth 6]	**Increased targeted fruit and vegetable intake** Total targeted fruits and vegetables Mth 3: +2.0 vs +0.2 (p=0.004) Mth 6: +2.7 vs +0.5 (p=0.002) Vegetables Mth 3: +1.2 vs -0.2 (p=0.001) Mth 6: +1.8 vs +0.6 (p=0.02) Fruits Mth 3: NS Mth 6: +0.8 vs -0.1 (p=0.04)
							Daily total fruit and vegetable intake (servings) [BL to Mth 3, Mth 6]	**Increased fruit and vegetable intake** Total fruits and vegetables Mth 3: +1.1 vs -0.3 (p=0.05) Mth 6: +2 vs -0.1 (p=0.005) Vegetables Mth 3: +1.0 vs -0.4 (p=0.004) Mth 6: +1.8 vs +0.2 (p=0.005) Fruits NS
							Daily total caloric intake (kcal) [BL to Mth 3, Mth 6]	**Reduced calorie intake** Mth 3: -672.9 vs -92.4 (p<0.001) Mth 6: -562.9 vs -61.6 (p<0.001)
							Calories from total fat (%) [BL to Mth 3, Mth 6]	NS

Author (year) [Country, World Region]	Design	Study Population	Intervention(s)	Concomitant therapies	Control or comparison group	No. Participants (Intervention/ Control)	Outcome measure	Outcome
Greenlee, et al. (2016) [USA, AMRO] [41]	Follow-up						Anthropometric data [BL to 3 Mths and 6 Mths]	**Reduced waist circumference** Waist circumference Mth 3: -1.6 vs +1.7 (p=0.05); Mth 6: NS Weight, BMI, hip circumference and waist hip ratio (NS)
							Daily targeted fruit and vegetable intake daily (servings) [BL to 12 Mths]	**Maintained increased targeted fruit and vegetable intake** Fruit: +2.3 vs.- 0.1 (p<0.01) Vegetables: 1.6 vs 0.1 (p<0.01)
							Daily total fruit and vegetable intake (servings) [BL to 12 Mths]	**Maintained increase total fruit and vegetable intake** Fruit: +2.0 vs.- 0.4 (p<0.01) Vegetables: 1.6 vs -0.2 (p<0.01)
							Fruit intake (subcategories) [BL to Mth 12]	**Reduced fruit juice intake** Fruit juice excluding citrus: -0.1 vs +0.3 (p=0.05) **Increased citrus fruit intake** Citrus fruit: -0.1 vs -0.2 (p=0.01) Fruit, excluding citrus; Avocado and similar; Fried fruits NS
							Vegetable intake (subcategories) [BL to Mth 12]	**Increased dark green vegetables** Dark green +0.5 vs -0.1 (p<0.01) Deep yellow; Tomato; White potatoes; Other starchy vegetables; Legumes and Other vegetables NS
							Daily total caloric intake (kcal) [BL to 12 Mths]	NS
							Calories from total fat (%) [BL to 12 Mths]	NS
							Inflammatory markers [BL to 12 Mths]	NS
							Anthropometric data [BL to 12 Mths]	NS

Author (year) [Country, World Region]	Design	Study Population	Intervention(s)	Concomitant therapies	Control or comparison group	No. Participants (Intervention/ Control)	Outcome measure	Outcome
Feathers, et al. (2015) [USA, AMRO] [43]	Secondary analysis						Association between access to produce and enrolment in program and consumption of produce	Non-significant trend between higher produce access and increased enrolment and produce (fruit/vegetable) consumption
Crookes, et al. (2016) [USA, AMRO] [44]	Secondary analysis						Social and family networks influence on diet	Participants more likely to share food- related activities rather than exercise with close networks. Spouses and children provide greater support for healthy eating than friends. Despite this support, family was a barrier to eating healthy for almost half of participants.
Shi, et al. (2018) [USA, AMRO] [45]	Secondary analysis						Analysis of covariance assessing intervention effects on psychosocial mediators [BL to Mth 6 and 12]	**Increased impact of intervention on mediators of behavioral change** 6 months: Stages of change: +0.9 ($p<0.001$) Self-efficacy: +0.6 ($p=0.009$) Snack preference: +0.2 ($p=0.045$) 12 months: Stages of change: +0.9 ($p<0.001$) Self-efficacy: +0.4 ($p=0.002$) Snack preference: +0.4 ($p=0.002$) Chance locus of control: -2.6 ($p=0.02$) Healthy food beliefs: NS Difficulty finding produce: NS Difficulty eating produce as snacks: NS Family opinions: NS Cancer worry: NS FACT-B: NS HADS: NS **Increased impact of intervention on mediators of produce intake**

Author (year) [Country, World Region]	Design	Study Population	Intervention(s)	Concomitant therapies	Control or comparison group	No. Participants (Intervention/ Control)	Outcome measure	Outcome
								6 month mediators on 12 month outcome Total effect: 2.2 ($p<0.001$) Direct effect: 2.2 ($p=0.002$) Indirect effect: NS 12 month mediators on 12 month outcome Total effect: 2.1 ($p<0.001$) Direct effect: 1.9 ($p=0.008$) Indirect effect: NS
Kennedy, et al (2014) [Canada, AMRO] [39]	Uncontrolled trial	Irritable bowel syndrome	Elimination/reintroduction diet based on the results of non-IgE mediated food allergy test; 4 weeks elimination, 5 x bi-weekly reviews	Nil	Nil	4	Non-IgE food allergy tests [BL to Wk 4]	NS
							Symptoms [BL to Wk 4]	NS
							IBS Symptom Severity Scale [BL to Wk 4]	NS
McDougall, et al. (2014) [USA, AMRO] [25]	Retrospective cohort	Mixed population (high cholesterol, hypertension, overweight)	10 days: Dietary counselling; low fat (<10% calories), minimally refined plant food diet; ad libitum to satiety; residential program	Nil	Nil	1615	Weight (kg) [BL to Dy 10]	**Reduced body weight** -1.4 ($p<0.001$)
							Total cholesterol (mg/dL) [BL to Dy 10]	**Reduced total cholesterol** -22 ($p<0.001$)
							Systolic and diastolic blood pressure (mm Hg) [BL to Dy 10]	**Reduced blood pressure** Systolic: -8 ($p<0.001$) Diastolic: -4 ($p<0.001$)
							Blood glucose (mg/dL) [BL to Dy 10]	**Reduced blood glucose** - 3 ($p<0.001$)
							Blood urea nitrogen (mg/dL) [BL to Dy 10]	**Reduced urea** -3 ($p<0.001$)
							Creatinine (mg/dL) [BL to Dy 10]	NS
							10-year risk of a cardiovascular event (%) [BL to Dy 10]	**Reduced cardiovascular risk** -1.0 ($p<0.001$)
Nagashree, et al. (2017) [India, SEARO] [17]	Randomized controlled trial	Healthy volunteers	90 days: Standardized diet based on yogic principles of food blended with modern medical nutrition plus fresh coconut (100g)	Nil	Standardised diet plus groundnuts (45g) and groundnut oil (22g)	58 (27/31)	Triglycerides (mg/dL) [BL to Dy 90]	NS
							Low density lipoprotein (LDL) cholesterol (mg/dL) [BL to Dy 90]	**Increased LDL cholesterol** Coconut: +12.06 ($p<0.001$) Groundnut: NS

Author (year) [Country, World Region]	Design	Study Population	Intervention(s)	Concomitant therapies	Control or comparison group	No. Participants (Intervention/ Control)	Outcome measure	Outcome
							High density lipoprotein (HDL) cholesterol (mg/dL) [BL to Dy 90]	**Increased HDL cholesterol** Coconut: +3.84 (p<0.01) Groundnut: -2.42 (p<0.001)
							Total cholesterol (mg/dL) [BL to Dy 90]	Coconut: NS Groundnut: -10.65 (p<0.01)
							Triglyceride-HDL ratio [BL to Dy 90]	NS
							Apolipoprotein A/ Apolipoprotein B ratio [BL to Dy 90]	NS
							Body weight (kg) [BL to Dy 90]	**Reduced body weight** Coconut: Reduced (p=0.04) Groundnut: NS
Nagasukeerthi, et al. (2017) [India, SEARO] [18]	Randomized controlled trial	Type II diabetes mellitus	Bell pepper *(Capsicum annuum var. grossum)* juice	Integrated approach of yoga therapy (IAYT)	Integrated approach of yoga therapy only	50 (25/25)	Fasting blood glucose [BL to Day 4]	NS
							Postprandial blood glucose (mg/dL) [BL to Day 4]	**Reduced postprandial glucose** IAYT+Juice: -68.3 (NS) IAYT only: -42.7 (NS) Between group: p<0.001
							Weight [BL to Day 4]	NS
							BMI [BL to Day 4]	NS
							Systolic blood pressure (mmHg) [BL to Day 4]	**Reduced systolic blood pressure** IAYT+Juice: -14.5 (p<0.05) IAYT only: -6.8 (p<0.05) Between group: p=0.002
							Diastolic blood pressure (mmHg) [BL to Day 4]	NS
							Pulse rate [BL to Day 4]	NS
							Mean arterial pressure [BL to Day 4]	NS
							Pulse pressure (mmHg) [BL to Day 4]	**Reduced pulse pressure** IAYT+Juice: -9.7 (p<0.05) IAYT only: +0.48 (NS) Between group: p=0.003

Author (year) [Country, World Region]	Design	Study Population	Intervention(s)	Concomitant therapies	Control or comparison group	No. Participants (Intervention/ Control)	Outcome measure	Outcome
							Rate pressure product [BL to Day 4]	**Reduced rate pressure product** IAYT+Juice: -19.7 ($p<0.05$) IAYT only: -8.7 ($p<0.05$) Between group: p=0.001
							Double product [BL to Day 4]	**Reduced double product** IAYT+Juice: -12.6 ($p<0.05$) IAYT only: -7.9 ($p<0.05$) Between group: p=0.03
Neuendorf, et al. (2019) [USA, AMRO] [36]	Randomized controlled trial	Overweight/ obese (adults)	Elimination of foods in response to IgG test result	Nil	Waitlist	30 (20/10)	Serum IgG titres [BL to Mth 3]	NS
Oates, et al. (2014) [Australia, WPRO] [22]	Randomized controlled trial (crossover)	Healthy adults	7 days: Diet containing at least 80% organic foods	Nil	Washout crossover	13	Urinary total dialkylphosphate metabolites [Day 8]	**Reduced levels** Organic: 0.032; Conventional: 0.294 Between group: -0.262 ($p=0.013$)
							Urinary dimethylphosphate metabolites [Day 8]	**Reduced levels** Organic: 0.011; Conventional: 0.252 Between group: -0.241 ($p=0.005$)
							Urinary diethylphosphate metabolites [Day 8]	NS
Oberg, et al. (2011) [USA, AMRO] [34]	Uncontrolled trial (pilot)	Type II diabetes mellitus (adults)	Nutrition program delivered as a combination of one-on-one naturopathic physician-delivered dietary counselling and bi-weekly educational sessions for the entire cohort conducted following potluck-style dinners.	Nil	Nil	12	Hemoglobin Alc (%) [BL to Wk 12]	**Reduced HbA1C** -0.4%, p=0.02
							Serum lipid profile [BL to Wk 12]	NS
							Blood pressure [BL to Wk 12]	NS
							Body Mass Index [BL to Wk 12]	NS
							Three-day diary [BL to Week 12]	**Increased diet quality** Adherence to healthy eating increased ($p=0.05$)

Author (year) [Country, World Region]	Design	Study Population	Intervention(s)	Concomitant therapies	Control or comparison group	No. Participants (Intervention/ Control)	Outcome measure	Outcome
							Summary of Diabetes Self-Care Activities [BL to Wk 12]	**Increased self-care behaviors** Healthy eating pattern (days in last week): +1.8 (p=0.05) Healthy eating pattern (days per week in last month): +1.2 (p=0.02) >5 fruits/vegetables per day (days in last week): +1.3 (p=0.01) Physical activity (days in last week): +3.4 (p=0.02) Blood glucose checking (% of time): +38% (p=0.05) Checked blood sugar as recommended (days in last week): +3.0 (p=0.04)
							Problem Areas in Diabetes [BL to Wk 12]	**Reduced problem areas** Feeling scared about living with diabetes: -1.8 (p=0.006) Feeling overwhelmed by diabetes: -1.9 (p=0.03) Feeling discouraged about diabetes treatment plan: NS Composite score: -18.9% (p=0.05)
							Perceptions about Nutritional counseling [BL to Wk 12]	**Reduced confidence** Average daily carbohydrate intake: NS Attention to type of dietary fat consumed: From 'Seldom' to 'Often' (p=0.04) Know how to follow dietary guidelines: From 'Definitely no' to 'Yes' (p=0.02) Feel in control of my diabetes: From 'Definitely no' to 'Yes' (p=0.01)

Author (year) [Country, World Region]	Design	Study Population	Intervention(s)	Concomitant therapies	Control or comparison group	No. Participants (Intervention/ Control)	Outcome measure	Outcome
							Seven Eating Styles Questionnaire [BL to Wk 12]	**Reduced eating behaviors** Emotional eating: -0.7 (p=0.02) Food fretting: NS Selecting fast food/fresh food: -0.8 (p=0.05) Attention to sensory/ spiritual dimensions of food: -1.2 (p<0.01) Task snacking: NS Attention to dining atmosphere: -0.6 (p=0.01) Attention to positive social settings: NS Integrated eating score: -3.7 (p=0.03)
Schumann, et al. (2018) [Germany, EURO] [21]	Randomized controlled trial	Irritable bowel syndrome	Low FODMAP diet (4 sessions of nutritional counselling including an educational group lecture, 2 individual counselling and 1 group counselling sessions; low-FODMAP recipes, lists of foods to avoid) for 12 weeks followed by reintroduction challenge of each food group	Nil	Yoga (75 minutes, 2x/ week)	59 (29/30)	IBS Symptom Severity Scale – Total [BL to Wk 12, 24]	**Decreased abdominal distension from low FODMAP diet** *Wk 12* – Total Score: FODMAP, -96.18 (p<0.001); Yoga: -66.16 (p<0.001); Between group: NS Abdominal distension: FODMAP: -29.96, p<0.001; Yoga, NS; Between group: -14.13 (p<0.04) Duration of pain: NS Severity of pain: NS Bowel satisfaction: NS Interference with life: NS *Wk 24* – NS
							IBS Quality of Life – Dysphoria [BL to Wk 12, 24]	**Decreased food avoidance in low FODMAP diet group** *Wk 12* – Food avoidance: FODMAP, NS; Yoga, NS; Between group, -17.1 (p=0.005) Dysphoria: NS

Author (year) [Country, World Region]	Design	Study Population	Intervention(s)	Concomitant therapies	Control or comparison group	No. Participants (Intervention/ Control)	Outcome measure	Outcome
								Interference with activity: NS Body image: NS Health worries: NS Social reaction: NS Sexual: NS Relationships: NS Overall: NS *Wk 24* – NS
							Perceived Stress Questionnaire [BL to Wk 12]	NS
							Cohen Perceived Stress Scale [BL to Wk 12]	NS
							Hospital Anxiety and Depression Scale [BL to Wk 12]	**Reduced anxiety in yoga group** Anxiety: Wk 12, -1.35 (p=0.03) Wk 24, NS Depression: Wk 12, NS Wk 24, NS
							Short Form-36 [BL to Wk 12]	NS
							Body Responsiveness Scale [BL to Wk 12]	NS
							Body awareness questionnaire [BL to Wk 12]	**Increased body awareness in yoga group** Wk 12: NS Wk 24: +7.6 (p=0.02)
Selvakumar, et al. (2017) [India, SEARO] [19]	Randomized controlled trial (pilot)	Type II diabetes mellitus (Adults)	Group 1: 250 ml bittergourd juice (30% concentrate) Group 2: 250 ml Knol-khol (80% concentrate) Group 3: 250 ml ashgourd juice (88% concentrate)	Nil	Nil	30 (Bittergourd: n=10, Ashgourd: n=10, Knol-khol: n=10)	Fasting plasma glucose [BL to 30 min, 60 min, 90 min and 120 min]	**Reduced plasma glucose** Bittergourd: NS Knol-khol: Reduced at 30, 90 and 120 min time points with effect seen over time (p=0.029, F=4.739). Ashgourd: NS
Sowmya (2018) [India, SEARO] [20]	Randomized controlled trial	Obesity	Group 1: Lemon juice with lemon seeds Group 2: Lemon juice only	Nil	7 days	30 (15/15)	C-Reactive Protein (mg/dL) [BL to Dy 7]	NS

Author (year) [Country, World Region]	Design	Study Population	Intervention(s)	Concomitant therapies	Control or comparison group	No. Participants (Intervention/ Control)	Outcome measure	Outcome
							Body mass index (kg/m^2) [BL to Dy 7]	**Reduced BMI** Lemon seeds: -2.0 Lemon juice only: -1.4 Between group: p=0.0001
							Weight (kg) [BL to Dy 7]	**Reduced body weight** Lemon seeds: -4.9 Lemon juice only: -3.3 Between group: p=0.0001
							Waist circumference (cm) [BL to Dy 7]	**Reduced waist circumference** Lemon seeds: -11.3 Lemon juice only: -3.4 Between group: p=0.004
							Hip circumference (cm) [BL to Dy 7]	**Reduced hip circumference** Lemon seeds: -3.53 Lemon juice only: -2.9 Between group: p=0.004
							Waist-hip ratio [BL to Dy 7]	NS
Telles, et al. (2009) [India, SEARO] [26]	Uncontrolled trial	Obesity	Low fat, high fiber, vegetarian diet	Yoga practice (5 hours daily)	Nil	47	Body mass index (kg/m^2) [BL to Dy 6]	**Reduced BMI** -0.57 ($p<0.01$)
							Waist circumference (cm) [BL to Dy 6]	**Reduced waist circumference** -1.72 ($p<0.01$)
							Hip circumference (cm) [BL to Dy 6]	**Reduced hip circumference** -1.69 ($p<0.01$)
							High density lipoprotein (HDL) cholesterol (mg/dl) [BL to Dy 6]	**Reduced HDL cholesterol** -2.88 ($p<0.01$)
							Fasting serum leptin (ng/ml) [BL to Dy 6]	**Reduced leptin levels** -23.75 ($p<0.01$)
							Total cholesterol (mg/dl) [BL to Dy 6]	NS
							Low-density lipoprotein (LDL) cholesterol (mg/dl) [BL to Dy 6]	NS

Author (year) [Country, World Region]	Design	Study Population	Intervention(s)	Concomitant therapies	Control or comparison group	No. Participants (Intervention/ Control)	Outcome measure	Outcome
							Serum triglycerides (mg/dl) [BL to Dy 6]	NS
							Hand grip strength (kg) [BL to Dy 6]	**Increased hand grip strength** Right: +2.09 ($p<0.001$) Left: +2.00 ($p<0.01$)
							Postural stability (sec) [BL to Dy 6]	**Increased postural stability** At 20 sec: +11.03 ($p<0.001$) At 40 sec: +24.41 ($p<0.001$) At 60 sec: +33.91 ($p<0.001$)
Tippens, et al. (2019) [USA, AMRO] [42]	Uncontrolled trial	Prediabetes (adults)	Naturopathic whole food nutrition education (12 weekly workshops)	Nil	Nil	45	High sensitivity c-reactive protein (mg/L) [BL to Wk 12, Mth 6, Mth 12]	**Reduced levels** Wk 12: -0.7 ($p<0.05$) Mth 6: -0.2 ($p<0.05$) Mth 12: -0.6 ($p<0.05$)
							Hemoglobin Alc (%) [BL to Wk 12, Mth 6, Mth 12]	**Reduced HbA1C** Wk 12: -0.0 (NS) Mth 6: -0.4 ($p<0.001$) Mth 12: -0.3 ($p<0.001$)
							Total cholesterol (mg/dL) [BL to Wk 12, Mth 6, Mth 12]	**Reduced total cholesterol** Wk 12: -7.6 (NS) Mth 6: -26.2 ($p<0.001$) Mth 12: -30.3 ($p<0.001$)
							High-density lipoprotein (HDL) – cholesterol (mg/dL) [BL to Wk 12, Mth 6, Mth 12]	**Reduced HDL cholesterol** Wk 12: -1.0 (NS) Mth 6: -11.4 ($p<0.001$) Mth 12: +6.2 ($p<0.01$)
							Low-density lipoprotein (LDL) – cholesterol (mg/dL) [BL to Wk 12, Mth 6, Mth 12]	**Reduced LDL cholesterol** Wk 12: -5.4 (NS) Mth 6: -6.0 (NS) Mth 12: -27.3 ($p<0.001$)
							Very-low-density lipoprotein (VLDL) – cholesterol (mg/dL) [BL to Wk 12, Mth 6, Mth 12]	**Reduced VLDL cholesterol** Wk 12: +0.1 (NS) Mth 6: -8.8 ($p<0.001$) Mth 12: -8.5 ($p<0.01$)

Author (year) [Country, World Region]	Design	Study Population	Intervention(s)	Concomitant therapies	Control or comparison group	No. Participants (Intervention/ Control)	Outcome measure	Outcome
							Triglycerides (mg/dL) [BL to Wk 12, Mth 6, Mth 12]	**Reduced triglycerides** Wk 12: +2.0 (NS); Mth 6: -38.7 (p<0.001) Mth 12: -37.6 (p<0.01)
							Fasting plasma insulin (uIU/mL) [BL to Wk 12, Mth 6, Mth 12]	**Increased insulin levels** Wk 12: +0.8 (NS) Mth 6: -3.9 (p<0.001) Mth 12: +4.9 (p<0.001)
							Fasting plasma glucose (mg/dl) [BL to Wk 12, Mth 6, Mth 12]	**Reduced fasting glucose levels** Wk 12: -6 (p<0.01) Mth 6: -11.5 (p<0.001) Mth 12: -13.9 (p<0.001)
							Healthy dietary behavior (food frequency questionnaire) [BL to Wk 12, Mth 6, Mth 12]	**Increased healthy diet** Processed and refined grains: reduced (p<0.001) More healthy oils: increased (p<0.05) Less healthy oils: reduced (p=0.02) Vegetables: NS Fruits: NS Grains: Wk 12, -0.7 (p<0.01); Mth 6, -0.8 (p<0.01); Mth 12, -0.4 (NS) Meat: Wk 12, -0.2 (NS); Mth 6, -0.5 (p<0.01); Mth 12, -0.1 (NS) Dairy: Wk 12, -0.4 (p<0.05); Mth 6, -0.5 (p<0.01); Mth 12, -0.3 (p<0.01) Fat: Wk 12, -0.3 (p<0.01); Mth 6, -0.4 (p<0.01); Mth 12, -0.4 (p<0.01)

Author (year) [Country, World Region]	Design	Study Population	Intervention(s)	Concomitant therapies	Control or comparison group	No. Participants (Intervention/ Control)	Outcome measure	Outcome
Virdee, et al. (2015) [USA, AMRO] [37]	Case report	Asthma	90 day elimination diet informed by individualized results of enzyme-linked immunosorbent assay (ELISA) for IgG antibody assessment. Trial period of complete avoidance of potential allergens while monitoring for symptom changes	Nil	Nil	2	Medication use [BL to Dy 21, 49 and 91]	**Reduced medication use** Patient A Fluticasone-salmeterol: twice daily vs none Albuterol: twice daily vs occasional use in cold weather Patient B: Montelukast sodium: At bedtime vs none Fluticasone-salmeterol: Twice a day (Wk 19) vs occasionally Albuterol: Every night vs at least every night Cetirizine hydrochloride: daily vs none
							Asthma attack frequency	**Reduced asthma frequency** Patient B: 2-3 attacks per week vs one in first 21 days of treatment and then none at Day 91
							Pulse Oxygen	**Reduced levels** Patient B: 86-95% vs 96%
							Physical exam	**Reduced wheezing** Patient B: audible wheezing vs clear lungs from 21 days
							Subjective asthma symptom severity	**Reduced** Patient A: 9/10 vs 0/10
Zick, et al. (2017) [USA, AMRO] [32]	Randomized controlled trial	Breast cancer survivors (stage 0 to III)	3 months: 'Fatigue reduction diet' (FRD) antioxidant-rich diet; rich in fruit/veg, whole grains, omega-3 fatty acids (with individualized counselling)	Nil	Control (general health curriculum with individualized counselling matched for time)	30 (15/15)	Brief fatigue Inventory (%) [BL to Mth 3]	**Reduced fatigue** -2.4 vs -0.77, ($p<0.01$)
							Pittsburgh Sleep Quality Index [BL to Mth 3]	**Increased sleep** -2.5 vs +0.9, ($p=0.03$)
							Serum fatty acids (%) [BL to Mth 3]	**Improved fatty acid profile** Reduced saturated fatty acid ($p=0.04$); Increased omega-3 ($p<0.01$), 3:6 omega ($p=0.02$)

Author (year) [Country, World Region]	Design	Study Population	Intervention(s)	Concomitant therapies	Control or comparison group	No. Participants (Intervention/ Control)	Outcome measure	Outcome
							Serum nutrient concentrations [BL to Mth 3]	**Increased carotenoid levels** Increase in FRD for total carotenoids ($p<0.01$), β-cryptoxanthin ($p=0.02$), lutein ($p=0.05$), zeaxanthin ($p=0.01$), lycopene ($p=0.05$). Control: increase γ-tocopherol ($p=0.03$)

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31 Clinical Nutrition

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HIGHLIGHTS

- Clinical nutrition is the use of nutritional and food-based products for therapeutic purposes including vitamins and minerals, amino acids, fish oils, probiotics, and others.
- Naturopaths/NDs are trained in and incorporate various clinical nutritional products into practice.
- Nutritional products can include single ingredients and/or multiple ingredients combined for a desired therapeutic effect.
- Clinical research by the naturopathic community has examined the use of essential fatty acids, multivitamins and/or mineral formulas, single vitamins, minerals, non-essential nutrients, medicinal food, and nutraceutical interventions.
- In line with the role of primary care, naturopathic researchers have investigated the effects of clinical nutrition on individuals with mental health conditions, complex immune conditions, neurological conditions, cancer, gastrointestinal conditions, and other conditions.

Naturopaths and naturopathic doctors commonly use nutritional interventions to support their patients [1], in part due to the fundamental importance of nutrition to the health and function of the body and in alignment with the naturopathic principle, *Treat the Cause*. Interventions involving nutrition include applied nutrition, which focuses on dietary assessment and recommendations and food as medicine (expanded upon in Chapter 30), and clinical nutrition [1, 2]. Clinical nutrition includes the use of therapeutic products (e.g., tablets, powders and liquids) of vitamins, minerals and food-based extracts with health-promoting, disease-preventing or medicinal properties for targeted clinical outcomes [2].

The naturopathic workforce employs clinical nutrition interventions to address identified nutritional insufficiencies (both confirmed and potential), or to initiate biochemical or physiological changes in response to a patient's specific health conditions or complaints [3]. The nutritional products used in this latter application of clinical nutrition can be referred to as 'nutraceuticals.' In addition to essential vitamins and minerals, nutraceuticals include nutrients that have physiological effects such as amino acids and other amino-based compounds (e.g. n-acetyl cysteine, glutathione, acetyl-l-carnitine, s-adenosyl methionine), food-based constituents (e.g. lycopene, lipoic acid, bromelain, quercetin, indole-3-carbinol), and other compounds that are important to foundational human biochemistry and physiology (e.g. essential fatty acids and fish oils, coenzyme Q10, probiotics, digestive enzymes).

The naturopathic workforce is trained to be discerning when prescribing nutritional supplements to patients. For example, they may prefer a partially metabolised or 'active' form of a vitamin if there are clinical concerns about a patient's ability to absorb or metabolize the more usual form (e.g., prescribing fulminic acid or methyltetrahydrofolate in place of folic acid). Similarly, a naturopath/naturopathic doctor may recommend different forms of a nutraceutical depending on a patient's needs (e.g., choosing zinc picolinate as a supplemental form of zinc instead of the more common zinc gluconate) and preferences (e.g., liquid instead of tablets/capsules; vegetarian instead of gelatine capsules). A naturopath's/naturopathic doctor's decision to employ nutraceutical interventions with any given patient will be determined with consideration of the patient's health status and the Naturopathic Therapeutic Order. Clinical nutrition can be used through a general approach to increasing levels of a wide range of vitamins and minerals (e.g., multivitamins); the application of specialized formulas developed for explicit health purposes and effects; or the use of single nutrients targeting specific patient needs. Naturopaths/naturopathic doctors may recommend or prescribe commercially-produced nutritional products,

or extemporaneously dispense compounded nutritional ingredients formulated by the naturopath/naturopathic doctor specifically for the individual patient [3, 4].

Overview of Studies

This chapter is dedicated to highlighting the original clinical research (n=58; published in 59 papers) naturopathic researchers undertook to examine the effectiveness of clinical nutrition. This research includes a total of 6,734 participants and was conducted in the United States (USA) (n=31), Canada (n=6), and Australia (n=22). The study designs include randomized controlled trials (RCT) (n=42), non-randomized controlled trials (n=1), uncontrolled trials (n=7) cohort studies (n=4), case reports (n=3), follow-up of a RCT (n=1) and one secondary analysis (n=1). The clinician nutrition interventions studied included single nutrients (n=28) and multi-nutrient combinations (n=25). In some studies (n=9) nutrients were combined with herbal medicines, while in others (n=10) different forms, doses or administration methods of the same nutrient were examined. Most interventions employed oral supplements, but studies also used intranasal (n=3), intravenous (n=2), and intramuscular (n=1) administration.

The populations treated with clinical nutrition included healthy adults (n=13), mental health conditions (n=9), complex immune conditions (n=8), neurological conditions (n=7), cancer (n=6), gastrointestinal conditions (n=4), and other conditions (n=8). Of all the naturopathic clinical studies employing clinical nutrition interventions, 62.5% reported a positive outcome in at least one primary or secondary outcome measure. Details of the studies are available in *Table 31.1 Clinical research investigating clinical nutrition interventions conducted by naturopathic researchers*. The body of naturopathic research on clinical nutrition is also supported by more than 50 observational studies and greater than 90 reviews or meta-analysis conducted by naturopathic researchers on this topic, as outlined in Chapter 40.

Implications

Naturopathic researchers have undertaken clinical research investigating clinical nutrition for a range of conditions, and for diverse nutritional interventions. Importantly, the clinical research undertaken by naturopathic researchers not only examines the effectiveness of single nutrients for specific populations, but also combinations of vitamins, minerals, non-essential nutrients, and other medicinal foods. Furthermore, the research examining clinical nutrition extends beyond efficacy compared with placebo to consider the clinical effect of different doses and forms of the same nutrient, and the safety of nutritional interventions in healthy populations. A similar topic focus is seen in other peer-reviewed publications authored by naturopaths/naturopathic researchers which consider the biochemistry and pharmacology [5-7], safety [8-11], and therapeutic benefits [7, 12-19] of a range of nutraceuticals for diverse health conditions. This broader research gaze highlights the degree to which naturopathic researchers seek to better understand their treatment options to ensure the safety and the best possible outcome for their patients.

With research suggesting that patients are more likely to disclose and discuss their nutritional product use with a naturopathic practitioner than other providers [20], and suggesting that naturopaths and naturopathic doctors are more knowledgeable about clinically significant interactions than other health professions such as conventional physicians and pharmacists [21], naturopaths/naturopathic doctors may be able to play a significant role in facilitating the safe and effective use of complementary medicine products such as nutritional products. Given the wide use of nutritional products in the community, both through self-prescription and under the guidance of different health professionals, insights from these studies have a wider benefit and significance to public health.

Studies investigating specific interventions:

Essential Fatty Acids

Fifteen studies published across 16 papers included omega-3 essential fatty acid products as at least one component of the clinical intervention [22-37]. The omega-3 fatty acids were most commonly derived from fish oil (n=12) [22, 23, 26, 27, 29, 31-37], although green-lipped mussel (n=3) [24, 25, 28], and algal sources (n=1) [30] were also reported. In ten of the included studies the omega-3 product was used in isolation in at least one arm of the study [23-26, 28-30, 34, 36, 37], while the remaining studies combined omega-3 with at least one other nutrient (e.g. vitamin E [22], lipoic acid [35]) or combined with other nutrients [31-33]. The conditions treated in the studies included multiple sclerosis [33, 34, 36], Alzheimer's disease [30, 35], knee osteoarthritis [24, 25], chronic work stress [23], breast cancer [26], ADHD [28], cardiovascular disease [29], acne vulgaris [31], and major depressive disorder [32]. One study also sampled a healthy adult population [22]. Although most studies used an omega-3 product in isolation, the specific doses, forms and health conditions varied substantially.

A randomized controlled trial conducted in Australia examined the clinical effect of a proprietary omega-3 anti-inflammatory extract of New Zealand green-lipped mussel (PCOS-524©) on symptoms of attention-deficit hyperactivity disorder (ADHD) among children (6 to 14 years old) (n=144). The interventional group was found to have improved mental performance (target memory

p=0.05; non-target memory p=0.02; picture recognition accuracy p=0.02) and significant improvements in six of fifteen symptoms in parent-reported outcome measures of the Computerized Mental Performance Assessment System [28]. An uncontrolled trial conducted in USA used a fish oil concentrate (9600mg containing 2.9g EPA and 1.9g DHA) in adults with relapsing-remitting multiple sclerosis (n=10) reported a 58% reduction in immune cell secretion of MMP-9 after 3 months (p<0.01) [34]. A further uncontrolled trial provided participants (n=26) with one of two different doses of DHA (260mg [n=21] or 520mg [n=5]) in adults with major depression disorder who were non-responsive to medication or psychotherapy [37]. This study reported 54% of participants had a ⩾50% reduction in Hamilton Depression Rating Scale (HAM-D) scores after the 8-week intervention (average reduction -10.33 points, p<0.001), and 45% were classified as 'in remission' (HAM-D⩽7). Also reported was a reduction in symptoms on the Clinical Global Impression Severity Scale (-1.28 points, p<0.05).

An uncontrolled trial conducted in Australia examined 3000mg of green-lipped mussel extract as a source of omega-3 fatty acids for the treatment of knee osteoarthritis [24]. The extract was provided twice daily (3 x 500mg BD) for 8 weeks. By the end of week 8, participants' scores for two separate instruments measuring arthritis symptoms had reduced (Lesquesne Index -4.03, p<0.001; Western Ontario McMaster Universities Arthritis Index -18.83, p<0.001), with one third of participants (7/21) not using rescue analgesic medication over the course of the study. The study also found participants had reduced gastrointestinal symptoms at week 8 (Gastrointestinal Symptom Rating Score -3.96, p=0.005).

Multivitamin and/or Mineral Formulas

Combination multivitamin and mineral formulas were examined in fifteen studies published in 16 papers [31-33, 38-50]. The studies focused either on healthy populations of adults (n=3) [45-47] and children (n=1) [50] or in populations with specific health conditions (n=11) (e.g. acne vulgaris (n=1) [31], chronic fatigue syndrome (n=1) [44], fibromyalgia (n=1) [38], AIDS/HIV (n=1) [39], cancer (n=3) [40, 42, 49], multiple sclerosis (n=1) [33], stress (n=1) [41], kidney disease (n=1) [43], major depressive disorder (n=1) [32]). The formulas used in populations with diagnosed health conditions included between 3 to 18 different micronutrients (median=8) as vitamins [32, 33, 38-44, 49, 50], essential minerals [31-33, 38, 39, 41-44, 50] and non-essential nutrients [31-33, 40, 44, 48].

A randomized controlled trial conducted in Australia sampled a healthy population for a 16-week placebo-controlled design to examine the effects of a multivitamin formula for either men or women on energy and mood in adults (n=116) [47]. The commercially available study product used a mix of essential vitamins, minerals and some herbal medicines in two combinations varied for either male or females. At the end of the intervention period, participants in the multivitamin arm reported a greater increase in energy and alertness (MV: 29.1% vs placebo: 11.9%; p=0.022) and improved mood (MV: 23.6% vs placebo: 8.5%; p=0.027) compared to the placebo group. A randomized controlled trial undertaken in the USA examined the effects of a multivitamin formula on behaviour in healthy children aged between 6 and 12 years (n=468) [50]. The study product contained 50% of the United States recommended daily allowance for vitamins and minerals and was administered over 4 months. At the end of the intervention period, participants in the multivitamin arm had a lower cumulative rate of rule violations per person compared to those receiving the placebo (MV: 1.0 vs placebo: 1.875; p=0.014)

A randomized controlled trial conducted in Australia which involved adults (n=71) who were newly diagnosed with cancer and had been prescribed one of three chemotherapeutic drug classes (taxanes, oxaliplatin, vincristine) employed a multi-nutrient B vitamin formula, compared to placebo [49]. The B complex provided a daily intake of thiamine (100mg), riboflavin (200mg), pantothenic acid (327mg), pyridoxine (60mg), folate (1000mcg), cyanocobalamin (1000mcg), biotin (1000mcg), choline (200mg), and inositol (1000mcg). The study measured several outcomes and although the primary outcome measure (Total Neuropathy Score) was non-significant, participants taking the B vitamin intervention reported improved sensory symptoms of peripheral neuropathy after 2 weeks (p=0.03) and extending to 24 (p=0.005) and 36 weeks (p=0.02) while no difference was reported in the placebo group.

An uncontrolled trial conducted in Australia involved 10 individuals with chronic fatigue syndrome (CFS) who were given a multi-nutrient formula designed to specifically address the pathology and symptomatology of CFS [44]. The formula contained 18 nutrients: ubiquinone (coenzyme Q10) – 200mg, alpha lipoic acid – 150mg, n-acetylcysteine – 2000mg, acetyl-l-carnitine – 1000mg, magnesium – 64mg, calcium ascorbate (vitamin C) – 242mg, cholecalciferol (vitamin D3) – 250IU, alpha-tocopherol (vitamin E) – 60IU, retinyl palmitate (vitamin A) – 3000IU, biotin – 600mcg, thiamine (vitamin B1) – 100mg, riboflavin (vitamin B2) – 100mg, nicotinamide (vitamin B3) – 200mg, calcium pantethonate (vitamin B5) – 100mg, pyridoxine hydrochloride (vitamin B6), folic acid – 800mg, and cyanocobalamin (vitamin B12) – 800mcg. Participants reported significant improvement in scores for the Chalder Fatigue Scales across 16 weeks (-9.4; p<0.001), as well as reduced insomnia (Insomnia Severity Index: -3.65; p=0.017) and improvement in overall symptoms (Clinical Global Impression Scale: -0.92; p=0.014).

Single Vitamins, Minerals and Non-essential Nutrients

Sixteen studies published in 17 papers investigated individual nutrients with direct or indirect antioxidant activity in the human body: glutathione (n=3) [51-53]; niacin (n=2) [54, 55]; folate (n=1) [56]; s-adenosyl methionine (SAMe) (n=1) [57]; chromium (n=2) [58, 59]; zinc (n=2) [60, 61], vitamin D (n=1) [62]; N-acetyl cysteine (n=1) [63]; lipoic acid (n=1) [64]; acetyl-l-carnitine (n=2) [65, 66] and one study investigating a variety of single nutrient antioxidants (vitamin C, vitamin E, selenium, zinc, carotenoids, betacarotene and lycopene) (n=1) [67]. The studies included populations diagnosed with Parkinson's disease (n=3) [52, 53, 68], major depressive disorder (n=1) [57], autism spectrum disorder (n=2) [69, 70], obsessive-compulsive disorder (n=1) [57], multiple sclerosis (n=1) [64], metabolic syndrome (n=1) [58], overweight (n=1) [59], cancer (n=2) [65, 67], dyspepsia (n=1) [55], and respiratory conditions (n=1) [51]. Six studies also involved healthy participants, children (n=1) [61] and adults (n=5) [54, 56, 60, 62, 71].

A randomized controlled trial conducted in the USA compared three different doses of lipoic acid with placebo in individuals with multiple sclerosis (n=37) [64]. Participants in the active arms were administered 600mg of lipoic acid twice per day, 1200mg once per day, or 1200mg twice per day. The researchers examined the impact of the different doses on serum lipoic acid levels as well as markers of disease progression. The study found a statistically significant increase in serum lipoic acid levels with increased dose ($p<0.05$). It also found a dose response relationship between lipoic acid and serum levels of both matrix metalloproteinase-9 (MMP-9): every lug/mL increase in serum lipoic acid correlated with 11.10 units of serum MMP-9 ($p=0.04$). A similar dose response relationship was found between serum lipoic acid and serum intercellular adhesion molecule-1 (ICAM-1) ($p=0.03$).

A randomized controlled trial undertaken in Australia compared 1600mg of SAMe per day with escitalopram (10mg/day) or placebo, for the treatment of adults with major depressive disorder (n=144) [57]. Participants in the SAMe arm had a similar reduction in depression symptoms, measured by the Hamilton Depression Score, as participants in the escitalopram arm (SAMe: -7.31; escitalopram: -6.69) and a significantly greater reduction in scores compared to placebo (-4.00; $p=0.018$). There was also a greater proportion of participants with a >50% reduction in their Hamilton Depression Score – considered a clinically significant reduction – in the SAMe arm compared to placebo (SAMe: 45%; placebo: 26%; $p=0.003$).

Two studies sampled healthy populations to investigated differences in zinc forms and dosages on markers of zinc sufficiency [60, 61]. A randomized controlled trial conducted in USA examined the effect of 50mg of elemental zinc per day as zinc picolinate, zinc citrate, zinc gluconate, or placebo over four weeks [60]. Each participant (n=15) crossed between each study arm throughout the total study period of 16 weeks (four weeks per arm). The researchers measured zinc levels in hair, urine, red blood cells and serum at the end of each four weeks. Significant increases in zinc levels were found in the zinc picolinate arm for hair (+7.8; $p<0.005$), urine (+0.26, $p<0.005$) and red blood cells (+1.82, $p<0.005$) but not serum. No other forms of zinc had an increase in any zinc levels. A randomized controlled trial from Canada involving healthy children (n=39) examined zinc gluconate providing 5mg, 10mg or 15mg of elemental zinc, or placebo, for 4 months [61]. The study found no change in zinc-based enzyme activity or other zinc and copper markers except for increase urine zinc/creatinine ratios at the end of the study period with highest levels for the 10mg group (5mg: +4mg; 10mg: +12mg; 15mg: -2mg; $p=0.02$). Participants in the zinc arms also had a greater gain in body weight gain ($p=0.03$) and weight-for-age ($p=0.02$) compared to placebo.

Medicinal Food and Nutraceutical Interventions

Medicinal food and nutraceutical interventions were investigated in ten studies [42, 72-80]. Four studies examined the effects of probiotics, either in isolation (n=2) [75, 76] or in combination with other treatments (n=2) [73, 77], while other studies investigated glucosamine and chondroitin (n=1) [42], methylsulfonylmethane (n=1) [80], l-theanine (n=1) [78], lactoferrin (n=1) [79] medium chain triglyceride oil (n=1) [72], and a proprietary blend of mixed tocopherals, phytonutrients, and fruit and vegetable powders [74]. The study populations included healthy individuals (n=2) [72, 80] as well as individuals with breast cancer (n=1) [42], gastrointestinal conditions (n=2) [73, 75], chronic fatigue syndrome [76], generalized anxiety disorder (n=1) [78], and frequent cold-related symptoms (n=1) [79].

A randomized controlled trial conducted in Australia compared a placebo with 400mg of bovine lactoferrin and 200mg of immunoglobulin-rich whey protein per day for 90 days [79]. The study measured the effect of the intervention on adults experiencing frequent cold-related symptoms (n=103). Participants in the intervention group had a reduced occurrence of the common cold in the first half (lactoferrin: 0.67 events per person; placebo: 1.40; $p<0.001$) and in the second half (lactoferrin: 0.38; placebo: 1.02; $p<0.001$) of the study. The average total of cold events for the entire study was less than half among the intervention group compared with the placebo group (lactoferrin: 0.93; placebo: 2.26; $p<0.001$). A second randomized controlled trial from Australia examined the

effect of probiotics in the prevention of gastrointestinal infection (n=19) [75]. The study employed a combination of two commercially available products; a combination of probiotic bacteria, and a probiotic yeast *(Sacchromyces boulardii)*. Compared to the placebo group, the study participants in the intervention arm had a reduced incidence of gastrointestinal infection at the completion of the 17-week study. They also had significantly increased levels of salivary alpha-amylase (probiotic: +16.2; placebo: +8.1; p=0.007).

A randomized controlled trial conducted in the USA compared the effects of canola oil or medium chain triglyceride (MCT) oil on plasma triglycerides in healthy men (n=20) 5-hours after ingestion [72]. The study found no difference after one hour, but significantly lower plasma triglycerides in the MCT group at 2 hours (MCT: 72.6; canola: 97.7; p=0.001), 3 hours (MCT: 68.6; canola: 114.5; p<0.001), 4 hours (MCT: 69.5; canola: 117.2; p,0.001), and 5 hours (MCT: 69.6; canola: 112.0; p=0.001).

Table 31.1 Clinical research investigating clinical nutrition interventions conducted by naturopathic researchers

Author (year) [Country, World Region]	Design	Study Population	Intervention(s)	Concomitant therapies	Control or comparison group	No. Participants (Intervention/Control)	Outcome measure	Outcome
Adams, et al. (2009) [USA, AMRO] [69] Adams, et al. (2009) [USA, AMRO] [70]	Randomized controlled trial	Autism spectrum disorders	Phase 1 & 2: dimercapto succinic acid (DMSA) 10 mg/kg TID or placebo	Nil	Placebo topical cream	106 Part A: 65 (31/33) Part B 2: 41 (26/15)	Urinary excretion of toxic metals after Phase 1 [BL to Dose 1, Dose 9]	**Increased excretion** Lead: Dose 1 +713% ($p<0.001$) Dose 9 +638% ($p<0.001$) Tin: Dose 1 +241% ($p<0.001$) Dose 9 +314% ($p<0.05$) Bismuth: Dose 1 NS Dose 9 +128% ($p<0.05$) Uranium: Dose 1 +0.021 (<0.001) Dose2 +0.016 ($p<0.05$) Mercury Dose 1 +70% (<0.01) Dose 9 NS Titanium: Dose 1 +67% ($p<0.001$) Dose 9 +42% ($p<0.01$) Antimony: Dose 1 +49% ($p<0.05$) Dose 9 NS Tungsten: Dose 1 +51% ($p<0.01$) Dose 9 +18% ($p<0.05$) Nickel: Dose 1 -18% ($p<0.05$) Dose 9 NS Cadmium: Dose 1 NS Dose 9 NS Arsenic: Dose 1 NS Dose 9 -19% ($p<0.05$)

Author (year) [Country, World Region]	Design	Study Population	Intervention(s)	Concomitant therapies	Control or comparison group	No. Participants (Intervention/ Control)	Outcome measure	Outcome
							Urinary excretion of toxic metals after Phase 2 [BL to Dose 1, Dose 9, Round 2, Round 4, Round 6]	**Increased excretion** Lead: Dose 1 +935% (p<0.001) Dose 9 +1562% (p<0.001) Round 2 +1001% (p<0.001) Round 4 +1063% (p<0.001) Round 6 +1005% (p<0.001) Tin: Dose 1 +118% (p<0.05) Dose 9 NS Round 2, 4 and 6 NS Bismuth: NS Uranium: NS Mercury: Dose 1, +120% (<0.05) Dose 9 NS Round 2 +98% Round 4 and 6 NS Titanium: Dose 1 +54% (p<0.01) Dose 9 +44% (p<0.05) Round 2, 4 and 6 NS Antimony: Dose 1 +49% (p<0.05) Dose 9 NS Round 2, 4 and 6 NS Tungsten: Dose 1 +51% (p<0.01) Dose 1 +18% (p<0.05) Round 2, 4 and 6 NS Nickel: Dose 1 -18% (p<0.05) Dose 9 NS Round 2, 4 and 6 NS Cadmium: Dose 1 NS Dose 9 -32% (p<0.05) Round 2, 4 and 6 NS Arsenic: Dose 1, NS Dose 9 -19% (p<0.05) Round 2 -39% (p<0.001) Round 4 -42% (p<0.001) Round 6 -31% (p<0.1)

Author (year) [Country, World Region]	Design	Study Population	Intervention(s)	Concomitant therapies	Control or comparison group	No. Participants (Intervention/ Control)	Outcome measure	Outcome
							Red blood cell (RBC) Glutathione [BL to Dose 1, Dose 9, Round 2, Round 4, Round 6]	**Normalized RBC glutathione**
							Platelet count [BL to Dose 1, Dose 9, Round 2, Round 4, Round 6]	**Normalized platelet counts**
							Pervasive Developmental Disorder Behavior Inventory (Maladaptive behaviors) [BL to Round 6]	**Reduced maladaptive behaviors** Sensory/Perceptual Approach Behaviors: 7 rounds -22% ($p<0.05$); 1 round -31% ($p<0.01$) Ritualisms/Resistance to Change: 7 rounds -28% ($p<0.01$); 1 round -23% ($p<0.01$) Arousal Regulation Problems: 7 rounds -22% ($p<0.01$); 1 round NS Specific fears: 7 rounds -22% ($p<0.01$); 1 round NS Aggressiveness: 7 rounds -27% ($p<0.05$); 1 round -26% ($p<0.05$) Social pragmatic problems: 7 rounds NS; 1 round -29% ($p<0.01$) Semantic/Pragmatic problems: NS Composite: 7 rounds -24% ($p<0.001$); 1 round -24% ($p<0.001$)

Author (year) [Country, World Region]	Design	Study Population	Intervention(s)	Concomitant therapies	Control or comparison group	No. Participants (Intervention/ Control)	Outcome measure	Outcome
							Pervasive Developmental Disorder Behavior Inventory (Adaptive behaviors) [BL to Round 6]	**Increased adaptive behaviors** Social approach behaviors: 7 rounds -11% ($p<0.05$); 1 round + 6% Express (Phonological and Semantic Pragmatic): 7 rounds +5%; 1 round +17% ($p<0.05$) Learning, Memory and Receptive Language: 7 rounds +12% ($p<0.05$); 1 round +14% ($p<0.05$) Composite: 7 rounds +12%; 1 round +11%
							Autism Treatment Evaluation Checklist [BL to Round 6]	**Reduced autism symptoms** SPLC: 7 rounds -21% ($p<0.001$); 1 round NS Sociability: 7 rounds -27% ($p<0.001$); 1 round -25% ($p<0.05$) Sensory/Cognitive Awareness: 7 rounds -27% ($p<0.001$); 1 round -26% ($p<0.05$) Health/Physical/ Behavior: 7 rounds -28% ($p<0.01$); 1 round NS Total: 7 rounds -26% ($p<0.001$); 1 round -19% ($p<0.01$)
							Severity of Autism Scale [BL to Round 6]	**Reduced severity** 7 rounds -19% ($p<0.001$); 1 round -18% ($p<0.01$)

Author (year) [Country, World Region]	Design	Study Population	Intervention(s)	Concomitant therapies	Control or comparison group	No. Participants (Intervention/Control)	Outcome measure	Outcome
							Autism Diagnostic Observation Schedule [BL to Round 6]	Communication: NS Sociability: 7 rounds -10% ($p<0.01$) 1 round NS Communication and sociability: 7 rounds -9% ($p<0.001$) 1 round NS Play: NS SBRI: NS
							Parent Global Impression [BL to Round 6]	NS
Ali et al. (2009) [USA, AMRO] [38]	Randomized controlled trial	Fibromyalgia syndrome	Intravenous micronutrient therapy (Myers' Cocktail): Magnesium chloride hexahydrate, 20% (5mL); Calcium gluconate, 10%) (3mL); Hydroxocobalamin, 1000u/mL (1mL); Pyridoxine hydrochloride, 100mg/mL (1mL); Dexpanthenol, 250mg/mL (1mL); B-complex 100 (1mL) containing thiamine HCl [100mg], riboflavin [2mg], pyridoxine HCl [2mg], panthenol [2mg], niacinamide [100mg + 2% benzyl alcohol], vitamin C [5mL of 500mg/mL], 20mL of sterile water.	Nil	Placebo	35 (17/18)	Tender Point Index [BL to Wk 8]	NS
							Visual Analog Scale [BL to Wk 8]	NS
							Fibromyalgia Impact Questionnaire [BL to Wk 8]	NS
							Beck Depression Inventory [BL to Wk 8]	NS
							Health Status Questionnaire [BL to Wk 8]	NS
Ali et al. (2011) [USA, AMRO] [58]	Randomized controlled trial (crossover)	Metabolic syndrome or impaired fasting glucose or impaired glucose tolerance (adults)	Chromium picolinate 500mcg or chromium picolinate 1000mcg (crossover)	Nil	Placebo	59 (30/29)	Serum fasting insulin (IU/l) [BL to Mth 6]	NS
							Homeostasis model assessment of insulin resistance [BL to Mth 6]	NS
							2-hour plasma glucose (mg/dl) [BL to Mth 6]	NS

Author (year) [Country, World Region]	Design	Study Population	Intervention(s)	Concomitant therapies	Control or comparison group	No. Participants (Intervention/ Control)	Outcome measure	Outcome
							Fasting plasma glucose (mg/dl) [BL to Mth 6]	NS
							2-hour insulin during oral glucose tolerance testing (IU/l) [BL to Mth 6]	NS
							Anthropometric measures [BL to Mth 6]	NS
							Blood pressure (mmHg) [BL to Mth 6]	NS
							Endothelial function [BL to Mth 6]	NS
							Hemoglobin A1c (%) [BL to Mth 6]	NS
							Urinary microalbumin (mg/dl) [BL to Mth 6]	NS
							Lipids (mg/dl) [BL to Mth 6]	NS
							Flow-mediated dilatation of the brachial artery [BL to Wk 8] [BL to Mth 6]	NS
							Plasma glucose (mg/dl) [BL to Wk 8]	NS
							Serum insulin (IU/l) [BL to Wk 8]	NS
							Serum lipids (mg/dl) [BL to Wk 8]	NS
							Body weight (kg) [BL to Wk 8]	NS
Allen and Bradley (2011) [USA, AMRO] [71]	Uncontrolled trial	Healthy adults	Glutathione (500mg twice daily)	Nil	Nil	40	Creatinine-standardized	NS
							Urinary F2-isoprostanes (F2-isoP)	NS

Author (year) [Country, World Region]	Design	Study Population	Intervention(s)	Concomitant therapies	Control or comparison group	No. Participants (Intervention/ Control)	Outcome measure	Outcome
							Urinary 8-hydroxy-2′-deoxyguanosine (8-OHdG)	NS
							Erythrocyte GSH concentrations	NS
Balfour, et al. (2014) [Canada, AMRO] [39]	Randomized controlled trial	Human immune-deficiency virus (Anti-retroviral treatment naive)	High-dose micronutrient, mineral and antioxidant preparation (K-PAX Ultra®)	Nil	100% recommended daily allowance (RDA) preparation of multivitamins and minerals.	127 (not reported as only presenting baseline data)	Baseline micronutrient deficiency	**Low baseline micronutrient levels** Carotene: 24% <1 nmol/L Vitamin D: 67% <75 nmol/L, 24% <40 nmol/L, 3.5% <20 nmol/L Serum folate: 20% <15 nmol/L Vitamin B12: 2.4% <133 pmol/L Lower baseline levels of B12 correlated with lower baseline CD4 count (r = 0.21, p= 0.02)
							Treatment adherence	Nineteen (15%) withdrew early from the study treatment. Mean treatment adherence was 88%. Subjective adherence was 81% and significantly correlated with pill count (r = 0.29, p <0.001). Adherence was <80% in 75% of participants.
Barrie, et al. (1987) [USA, AMRO] [60]	Randomized controlled trial (crossover)	Healthy adult students with no signs of zinc deficiency	Crossover four x four-week periods of zinc picolinate, zinc citrate, zinc gluconate (equivalent to 50 mg elemental zinc per day) and placebo	NS	Placebo	15	Hair zinc levels (ppm) [BL to Wk 16]	**Increased levels (with picolinate)** Picolinate: +7.8 (p<0.005) Placebo: NS Citrate: NS Gluconate: NS
							Urinary zinc levels [BL to Wk 16]	**Increased levels (with picolinate)** Picolinate: +0.26 (p<0.005) Placebo: NS Citrate: NS Gluconate: NS

Author (year) [Country, World Region]	Design	Study Population	Intervention(s)	Concomitant therapies	Control or comparison group	No. Participants (Intervention/ Control)	Outcome measure	Outcome
							Erythrocyte zinc levels [BL to Wk 16]	**Increased levels (with picolinate)** Picolinate: +1.82 ($p<0.005$) Placebo: NS Citrate: NS Gluconate: NS
							Serum zinc levels [BL to Wk 16]	Picolinate: NS Placebo: NS Citrate: NS Gluconate: NS
Bayes, et al. (2019) [Australia, WPRO] [56]	Randomized controlled trial	Healthy Individuals	4 weeks: folic acid (500 mcg), folinic acid (500 mcg) or 5-Methyltetrahydrofolate (500 mcg)	NS	Placebo	30 (5/5/5/15)	Serum folate [BL to Wk 4]	**Increased** Folic acid: Wk 2, +10.8; Wk 4, -39.9 Folinic acid: Wk 2, +17.1; Wk 4, +15.3 5-MTHF: Wk 2, +8.0; Wk 4, +9.1 Control: Wk 2, -1.3; Wk 4, -2.7 Between group: p=0.0113
							Serum folate, group comparison [BL to Wk 4]	Folinic acid vs other folate: NS MTHF vs other folate: NS
Bertinato, et al. (2013) [Canada, AMRO] [61]	Randomized controlled trial	Healthy children (males, 6-8 yrs)	4 months: Zinc (Zn) gluconate equivalent to elemental Zn (1) 5mg, (2) 10mg or (3) 15mg per day	Nil	Placebo	39 (5mg; 10, 10mg: 9, 15mg: 8, placebo: 10)	Erythrocyte Superoxide dismutase (SOD1) [BL to Mth 2, Mth 4]	NS
							Erythrocyte copper chaperone for copper-Zn superoxide dismutase (eCCS):-SOD1 ratio [BL, Mth 2, Mth 4]	NS
							Plasma zinc [BL, Mth 2, Mth 4]	NS
							Urine zinc/ creatinine ratio [BL, Mth 2, Mth 4]	**Increased zinc levels** Month 2: NS Month 4: 5mg, +4; 10mg, +12; 15mg, -2 Between group: p=0.02
							Plasma copper [BL, Mth 2, Mth 4]	NS

Author (year) [Country, World Region]	Design	Study Population	Intervention(s)	Concomitant therapies	Control or comparison group	No. Participants (Intervention/ Control)	Outcome measure	Outcome
							Plasma ceruloplasmin [BL, Mth 2, Mth 4]	NS
							Anthropometric measurements [BL, Mth 2, Mth 4]	**Increased body weight** Weight gain: Between groups, p=0.003 Weight-for-age: Between groups, p=0.02
Bradbury, et al. 2004) [Australia, WPRO] [22]	Randomized controlled trial	Healthy adults (moderately stressed)	6 weeks: 6000 mg tuna oil, with 60 mg d-alpha-Tocopherol containing DHA 1.512 g and EPA 3.6 g daily.	Nil	Placebo OR No treatment	93 (Omega-3: 16/Placebo: 14/ No treatment: 63)	Perceived Stress Scale [BL to Wk 6]	NS
Bradbury, et al. (2017) [Australia, WPRO] [23]	Randomized controlled trial	Chronic work stress	12 weeks: Fish oil 4000mg as 2.2 g EPA, and 0.44 g DHA per day.	Nil	Placebo	90 (45/45)	Perceived Stress Scale [BL to Wk 12]	NS
							Omega-3 index [BL to Wk 12]	**Improved fatty acid profile** Arachidonic acid (AA): Fish oil -22.6; Placebo -11.5 Between group (-8.7, p=0.002) EPA: Fish oil +7.3; Placebo -0.5 Between group (+9.6 ,p<0.001) DHA: NS AA:EPA (%): Fish oil -13.5; Placebo -0.8 Between group (-13.0, p<0.001) EPA:AA (%): Fish oil +0.28; Placebo +0.2 Between group, (+3.0, p<0.001)
							Plasma interleukin-1β [BL to Wk 12]	NS
							Plasma interleukin-6 [BL to Wk 12]	NS
							Plasma interleukin-10 [BL to Wk 12]	NS

Author (year) [Country, World Region]	Design	Study Population	Intervention(s)	Concomitant therapies	Control or comparison group	No. Participants (Intervention/ Control)	Outcome measure	Outcome
							Tumor necrosis factor-α [BL to Wk 12]	NS
							High-sensitivity c-reactive protein [BL to Wk 12]	NS
							Salivary cortisol/ DHEA ratio [BL to Wk 12]	NS
							Depression, Anxiety, Stress Scale [BL to Wk 12]	NS
							Occupational Stress Inventory Strain and Resources subscales [BL to Wk 12]	NS
							COPE Inventory [BL to Wk 12]	NS
							Copenhagen Burnout Inventory [BL to Wk 12]	NS
Braun, et al. (2013) [USA, AMRO] [40]	Cohort study (retrospective investigation)	Prostate cancer (post- treatment of radiation therapy with curative intent)	Individualized naturopathic and nutritional antioxidant supplementation (self-selected for naturopathic care. Most frequent green tea extract 750 BD, melatonin 20mg at bedtime, vitamin C 500-1000mg TD and vitamin E 200-400IU TD)	6-8 weeks of radiation, 24 month continuation	Usual care (self-selected for no naturopathic care)	134 (69/65)	Mean PSA (non-hormonal ablation) [⩾ 24 moths post-radiation]	NS
							Mean PSA (hormonal ablation) [⩾ 24 months post-radiation]	NS
Calabrese, et al. (1999) [USA, AMRO] [72]	Randomized controlled trial	Healthy men	5 hours: Sound Nutrition™ medium chain triglyceride (MCT) oil (71g)	Nil	HAIN™ canola oil (71g)	20 (10/10)	Plasma triglycerides (mg/dL) [BL to 1Hr, 2Hr, 3Hr, 4Hr, 5Hr]	**Reduced triglycerides** 1hr: NS 2hr: Canola 97.7; MCT 72.6 Between group -24.6 (p=0.001) 3hr: Canola 114.5; MCT 68.6 Between group -45.4 (p<0.001)

Author (year) [Country, World Region]	Design	Study Population	Intervention(s)	Concomitant therapies	Control or comparison group	No. Participants (Intervention/Control)	Outcome measure	Outcome
								4hr: Canola 117.2; MCT 69.5 Between group -46.6 ($p<0.001$) 5hr: Canola 112.0; MCT 69.6 Between group -42.05 ($p=0.001$)
Camfield, et al. (2013) [Australia, WPRO] [41]	Randomized controlled trial	Stress	Swisse Ultivite Formula 1® (Men's/Women's formula) multivitamin	Nil	Placebo	138 (68/70)	Perceived stress scale [BL to Wk 8, Wk 16]	NS
							Serum B6 [BL to Wk 8, Wk 16]	**Increased vitamin B6 levels** Wk 8: Between group ($p=0.003$) Wk 16: Between group ($p=0.009$)
							Serum B12 [BL to Wk 8, Wk 16]	**Increased vitamin B12 levels** Wk 8: Between group ($p=0.003$) Wk 16: Between group ($p=0.009$)
							Homocysteine [BL to Wk 8, Wk 16]	**Reduced homocysteine levels** Wk 8: Between group ($p=0.003$) Wk 16: Between group ($p=0.009$)
							Red cell folate [BL to Wk 8, Wk 16]	**Increased folate levels** Wk 8: NS Wk 16: Between group ($p=0.019$)
							Waking salivary cortisol [BL to Wk 8, Wk 16]	NS
							Evening salivary cortisol [BL to Wk 8, Wk 16]	NS
							Cortisol awakening response [BL to Wk 8, Wk 16]	NS

Author (year) [Country, World Region]	Design	Study Population	Intervention(s)	Concomitant therapies	Control or comparison group	No. Participants (Intervention/ Control)	Outcome measure	Outcome
Coulson, et al. (2012) [Australia, WPRO] [24]	Uncontrolled trial	Knee osteoarthritis	8 weeks: *Perna canaliculus* (green-lipped mussel) extract 1.5 g twice daily	Nil	Nil	21	Lesquesne Index [BL to Wk 4 and 8]	**Reduced arthritis symptoms** Wk 4: -2.86, (p=0.001) Wk 8: -4.03, (p<0.001)
							Western Ontario McMaster Universities Arthritis Index [BL Wk 4 and 8]	**Reduced arthritis symptoms** Wk 4 -11.63, (p=0.001) Wk 8 -18,833, (p<0.001)
							Gastrointestinal symptom rating score [BL Wk 4 and 8]	**Reduced gastrointestinal symptoms** Wk 4 -4.26 (p=0.004) Wk 8 -3.96 (p=0.005)
							Rescue medication use [BL Wk 4 and 8]	**Reduced rescue medication use** 14/21 used rescued medication
							Adverse symptoms [BL Wk 4 and 8]	**Mild adverse symptoms** Reflux (n=1), abdominal pain, reflux, and diarrhea (n=1), gout (n=2)
							Blood pressure [BL Wk 4 and 8]	NS
Coulson, et al. (2013) [Australia, WPRO] [25]	Randomized controlled trial	Knee osteoarthritis	12 weeks: *Perna canaliculus* (green-lipped mussel) extract 1.5 g twice daily	Nil	Glucosamine sulfate 1.5 g twice daily	38 (21/17)	Total fecal bacteria count, as well as levels of four genera of aerobic and six anaerobic bacteria as well as yeast [BL to Wk 12]	NS
							Lesquesne Index [BL to Wk 12]	NS
							Western Ontario McMaster Universities Arthritis Index [BL to Wk 12]	NS
							Gastrointestinal symptom rating score [BL to Wk 12]	NS

Author (year) [Country, World Region]	Design	Study Population	Intervention(s)	Concomitant therapies	Control or comparison group	No. Participants (Intervention/ Control)	Outcome measure	Outcome
							Adverse effects	NS
Greenlee, et al. (2012) [USA, AMRO] [67]	Cohort study (analysis of LACE cohort, PMID: 15986109)	Breast cancer stage I-III minimum 1 year since diagnosis	Antioxidants (AO) supplement (vitamin C, vitamin E, zinc, selenium, carotenoid, beta-carotene, lycopene), multivitamin	*Questionnaire and chart review follow up*	nil	2264 (1829 AO users)	All-cause mortality [compared to non-AO users]	**Reduced risk** Vitamin E (p=0.02) Increased risk Combination carotenoids (p=0.03)
							Deaths from breast cancer [compared to non-AO users]	NS for all **Increased risk** Combination carotenoids (p=0.02)
							Breast cancer recurrence [compared to non-AO users]	**Reduced risk** vitamin C – frequent users (p=0.01); vitamin E (p<0.01)
							AO users only	**Reduced risk** vitamin C – frequent users (p=0.03); vitamin E (p=0.02)
Greenlee, et al. (2013) [USA, AMRO] [42]	Uncontrolled trial	Breast cancer (postmenopausal women with joint pain/ stiffness)	24 weeks: Glucosamine-sulfate (1500mg/day) and chondroitin-sulfate (1200mg/day)	Nil	Nil	53 (39 evaluable at 24 weeks)	Outcome measure in Rheumatology Clinical Trials and Osteoarthritis Research society International (OMERACT-OARSI) [BL to Wk 12, Wk24]	**Improved outcomes** Wk 24: 46% (18/39) of patients met criteria
							WOMAC (0/100 scale) [BL to Wk 12, Wk24]	**Reduced pain** 12wks (-9.6, p=0.03) 24wks (-10.7, p=0.02) 51.4% reported ⩾20% reduction in hip and knee pain at 12wks,maintained at 24wks **Increased function** 12wks (-10.7, p=0.01) 24wks (-13.2, p<0.01).

Author (year) [Country, World Region]	Design	Study Population	Intervention(s)	Concomitant therapies	Control or comparison group	No. Participants (Intervention/Control)	Outcome measure	Outcome
							Modified score for Assessment and Quantification of Chronic Rheumatoid Affections of the hands and wrists (0/100 scale) [BL to Wk 12, Wk24]	**Reduced pain** 12wks (-14.4, p<0.001); 24wks (-13.8, p<0.001) 36.8% reported ≥20% reduction in pain severity; 43.6% reported ≥20% reduction in worst pain **Reduced stiffness** 12wks (-11.3, p=0.03); 24wks (NS) **Increased function** 12wks (-9.2, p=0.03); 24wks (-8.5, p=0.02)
							Beck Pain Inventory (0/100 scale) [BL to Wk 12, Wk24]	**Reduced pain severity** 12wks (-0.7, p=0.05) **Reduced pain interference** 24wks (-1.0, p<0.001) **Reduced worst pain** 12wks (-0.9, p=0.02); 24wks (-1.2, p=0.02)
Hershman, et al. (2013) [USA, AMRO] [65]	Randomized controlled trial	Breast cancer (stage I-III, prevention of chemotherapy-induced peripheral neuropathy (CIPN))	Acetyl l-carnitine (ALC) (3000mg per day)	24 weeks	Placebo	409 (208/201)	Functional Assessment of Cancer Therapy (FACT) – NTX (Taxane neurotoxicity) [BL to Wk 12 and 24]	**Reduced function (increased CIPN)** Wk 12: NS Wk 24: ALC -5.1, Placebo -3.8 Between group: p=0.01
							FACT – Taxane trial Outcome Index [BL to Wk 12 and 24]	**Reduced functional status** Wk 12: NS Wk 24: ALC -4.8, Placebo: -1.4 Between group: p=0.03
							FACT – Fatigue [BL to Wk 12 and 24]	NS
							Adverse events	NS

Author (year) [Country, World Region]	Design	Study Population	Intervention(s)	Concomitant therapies	Control or comparison group	No. Participants (Intervention/Control)	Outcome measure	Outcome
Hershman, et al. (2018) [USA, AMRO] [66]	Follow-up						FACT-NTX [BL to Wk 36, 52, and 104]	**Reduced function (increased CIPN)** Both groups, over time: p<0.001 Between group average: ALC -1.39 (p=0.01) Between group Wk 12: NS Between group Wk 24: ALC -1.68 (p=0.02) Between group Wk 36: ALC -1.37 (p=0.04) Between group Wk 52: ALC -1.83 (p=0.02) Between group Wk 104: NS
							FACIT Functional Assessment of Chronic Illness Therapy [BL to Wk 36, 52, and 104]	NS
							FACT-Taxane Trial Outcome Index [BL to Wk 36, 52, and 104]	NS
							Predictors of persistence CIPN	**Increased risk** Women <60 Wk 52: p=0.02, Wk 104: p=0.04 Weight (% per 5kg) Wk 52: p=0.001, Wk 104: p=0.001
Hershman, et al. (2015) [USA, AMRO] [26]	Randomized controlled trial	Stage I-III breast cancer (postmenopausal, Rx aromatase inhibitors)	Omega-3 fatty acid (3.3 g per day; 560mg eicosapentaenoic acid plus docosahexaenoic acid in a 40:20 ratio)	24 hours	placebo	249 (122/127)	Brief Pain Inventory – Short form [BL to Wks 6, 12 and 24]	NS

Author (year) [Country, World Region]	Design	Study Population	Intervention(s)	Concomitant therapies	Control or comparison group	No. Participants (Intervention/ Control)	Outcome measure	Outcome
							Western Ontario and McMaster Universities Osteoarthritis Index [BL to Wks 6, 12 and 24]	NS
							Modified Score for the Assessment and Quantification of Chronic Rheumatoid Affections of the Hands [BL to Wks 6, 12 and 24]	NS
							Functional Assessment of Cancer Therapy – Endocrine [BL to Wks 6, 12 and 24]	NS
							Lipid Profile (mg/dL) (Fasting serum) [BL to Wks 6, 12 and 24]	**Reduced triglycerides** Intervention: -22.1, Placebo: -10.3 Between group: p=0.01 Cholesterol: NS C-reactive protein: NS High density lipoprotein: NS Low density lipoprotein: NS
							Adverse events	NS
Shen, et al. (2018) [USA, AMRO] [27]	Secondary analysis (Participants with (BMI ⩾30) and without (BMI <30) obesity)						Brief Pain Inventory – short form [BL to Wk 6, 12 and 24]	**Reduced worst pain** BMI ⩾30, treatment compared to placebo Wk 12: NS, Wk 24: p=0.02 BMI <30, treatment compared to placebo Wk 12: NS, Wk 24: NS BMI-treatment group interaction: NS Reduced average pain BMI ⩾30, treatment compared to placebo

Author (year) [Country, World Region]	Design	Study Population	Intervention(s)	Concomitant therapies	Control or comparison group	No. Participants (Intervention/ Control)	Outcome measure	Outcome
								Wk 12: NS, Wk 24: p=0.002 BMI <30, treatment compared to placebo Wk 12: NS, Wk 24: NS BMI-treatment group interaction Wk 12: NS, Wk 24: p=0.005 Reduced pain interference BMI ⩾30, treatment compared to placebo Wk 12: NS, Wk 24: p=0.009 BMI <30, treatment compared to placebo Wk 12: NS, Wk 24: NS BMI-treatment group interaction Wk 12: NS, Wk 24: p=0.01
							Global Ratings of Change questionnaire [BL to Wk 6, 12 and 24]	**Reduced joint stiffness** BMI ⩾30, treatment compared to placebo Wk 12: p=0.02, Wk 24: NS BMI <30, treatment compared to placebo Wk 12: NS, Wk 24: NS BMI-treatment group interaction: NS Joint pain: NS
							Modified Score for the Assessment and Quantification of Chronic Rheumatoid Affections of the Hands [BL to Wk 6, 12 and 24]	**Reduced pain** BMI ⩾30, treatment compared to placebo Wk 12: NS, Wk 24: p=0.04 BMI <30, treatment compared to placebo Wk 12: NS, Wk 24: NS BMI-treatment group interaction: NS
							WOMAC [BL to Wk 6, 12 and 24]	**Reduced pain** BMI ⩾30, treatment compared to placebo Wk 12: NS,

Author (year) [Country, World Region]	Design	Study Population	Intervention(s)	Concomitant therapies	Control or comparison group	No. Participants (Intervention/ Control)	Outcome measure	Outcome
								Wk 24: p=0.01 BMI <30, treatment compared to placebo Wk 12: NS, Wk 24: NS BMI-treatment group interaction Wk 12: NS, Wk 24: p=0.02
							Lipid Profile (Fasting serum) [BL to Wk 6, 12 and 24]	**Increased high density lipoprotein** BMI ⩾30, treatment compared to placebo Wk 12: NS, Wk 24: NS BMI <30, treatment compared to placebo Wk 12: NS, Wk 24: p=0.002 BMI-treatment group interaction Wk 12: NS, Wk 24: p=0.003 **Reduced triglycerides** BMI ⩾30, treatment compared to placebo Wk 12: p=0.02, Wk 24: NS BMI <30, treatment compared to placebo Wk 12: p=0.02, Wk 24: NS BMI-treatment group interaction Wk 12: p=0.01, Wk 24: NS
Kean, et al. (2017) [Australia, WPRO] [28]	Randomized controlled trial	Attention deficit-hyperactivity disorder (6 to 14 years)	14 weeks: Omega-3 anti-inflammatory extract PCSO-524® (lipid extract of New Zealand green-lipped mussel)	Nil	Placebo	144 (74/70)	Test of Variables of Attention (TOVA) [BL to Wk 14]	NS
							Computerized Mental Performance Assessment System (COMPASS) [BL to Wk 14]	**Increased mental performance** PCSO: Improved target memory (p=0.05) PCSO: Improved non-target memory (p=0.02) PCSO: Improved picture recognition accuracy (p=0.02)

Author (year) [Country, World Region]	Design	Study Population	Intervention(s)	Concomitant therapies	Control or comparison group	No. Participants (Intervention/ Control)	Outcome measure	Outcome
							Brunel Mood Scale (BRUMS) for adolescents [BL to Wk 14]	**Increased fatigue** PCSO: increased fatigue (p=0.01) Placebo: reduced feelings of confusion (p=0.01)
							Conners Parent Rating Scales (CPRS) [BL to Wk 14]	**Reduced parent-reported symptoms** Aggression NS Peer relations NS Global ADHD index NS Impaired school life NS Impaired relationships NS Inattention NS Conduct disorder NS Oppositional defiant disorder NS Executive function NS ADHD probability: PCSO -28.3; Placebo -13.1 Between group p=0.04 Impaired home life: PCSO -0.52; Placebo +0.05 Between group p=0.02 Hyperactivity: PCSO -10.2; Placebo -3.3 Between group p=0.04 DSM inattention: PCSO -7.18; Placebo -3.3 Between group p=0.01 DSM hyperactivity: PCSO -13.8; Placebo -4.1 Between group p=0.04 Learning problems: PCSO -5.9; Placebo -2.8 Between group p=0.05
							Conners Parent Rating Scales (CPRS) [BL to Wk 14]	**Reduced maladaptive behaviors** Aggression NS Peer relations NS

Author (year) [Country, World Region]	Design	Study Population	Intervention(s)	Concomitant therapies	Control or comparison group	No. Participants (Intervention/ Control)	Outcome measure	Outcome
								Global ADHD index NS Impaired school life NS Impaired relationships NS Inattention NS Conduct disorder NS Oppositional defiant disorder NS Executive function NS ADHD probability: PCSO -28.3; Placebo -13.1 Between group p=0.04 Impaired home life: PCSO -0.52; Placebo +0.05 Between group p=0.02 Hyperactivity: PCSO -10.2; Placebo -3.3 Between group p=0.04 DSM inattention: PCSO -7.18; Placebo -3.3 DMS hyperactivity: PCSO -13.8; Placebo -4.1 Between group p=0.04 Learning problems: PCSO -5.9; Placebo -2.8 Between group p=0.05
Kim, et al. (2006) [USA, AMRO] [73]	Randomized controlled trial	Functional gastrointestinal disease	Probiotics & nutrients Group 1: 50million CFU x6 *spp* AND grass juice, fulvic acid derived minerals Group 2: 50million CFUx12 *spp* AND grass juice, fulvic acid derived minerals Group 3: C. 50million CFU x5 *spp* AND Mixed mushroom/ algae Group 4: 50million CFU x6 *spp* Group 5: Grass juice, fulvic acid derived minerals 12 weeks: 4-week run-in, 8 weeks of 4 cap TD	Grass juice, mixed mushroom/algae	Placebo	72 (12/12/12/ 12/12/12)	Gastrointestinal Quality of Life Index [BL to Wk 12]	NS
							Gastrointestinal Visual Analog Scales (bloating, gas, abdominal discomfort, indigestion, constipation, diarrhea) [BL to Wk 12]	NS
							Urinary lactulose-mannitol challenge test [BL to Wk 12]	NS

Author (year) [Country, World Region]	Design	Study Population	Intervention(s)	Concomitant therapies	Control or comparison group	No. Participants (Intervention/ Control)	Outcome measure	Outcome
Lamson and Brignall (2000) [USA, AMRO] [51]	Case study	Acute respiratory crisis secondary to emphysema and bronchial infection	Glutathione solution 60mg/ml	NS	NS	1	Signs of respiratory distress, lung sounds, use of oxygen, patient reported changes in breathing.	Following three days of treatment the patient no longer required a wheelchair or oxygen tank, had no signs of respiratory distress or adventitious lung sounds and reported his breathing was better than it had been in years
Lamson and Wright (2003) [USA, AMRO] [43]	Case study	Early renal functional impairment	Chinese herbal formula 500mg capsules, Ayurvedic herbal formula (includes Vitamin B6 25mg and magnesium aspartate 100mg), and Nutritional/ Botanical formula (vitamin A 5000IU, vitamin C 100mg, vitamin B6 10mg, potassium 99mg, raw kidney concentrate (bovine) 300mg, *Urtica dioca* 50mg, *Taraxacum officinale* root 50mg, parsley leaf 50mg)	Nil	Nil	1	Blood urea nitrogen (mg/dL) [BL to Yr 4]	**Reduced levels** -9
							Serum Creatinine (mg/dL) [BL to Dy 5]	**Reduced levels** -0.2
							24hrs Creatinine Clearance (mL/min)	**Increased clearance** +53
McEwen, et al. (2013) [Australia, WPRO] [29]	Non-Randomized controlled trial	History of cardiovascular disease (adults)	Omega-3 marine – derived PUFA 640 mg (DHA 520 mg and EPA 120 mg) daily	Nil	Healthy adults	56 (40/16)	Maximum slope – Healthy population [BL to Wk 4]	**Reduced** Adenosine phosphate -5.6 (p=0.014) Adrenaline NS Arachidonic acid NS Collagen (1.0 ug/mL) NS Collagen (1.0 ug/mL) NS C-reactive protein NS U46619 NS
							Maximum amplitude (%) – Healthy population [BL to Wk 4]	**Reduced** Adenosine phosphate -5.6 (p=0.014) Adrenaline -5.4 (p=0.013) Arachidonic acid NS Collagen (1.0 ug/mL) NS Collagen (1.0 ug/mL) NS C-reactive protein NS U46619 NS

Author (year) [Country, World Region]	Design	Study Population	Intervention(s)	Concomitant therapies	Control or comparison group	No. Participants (Intervention/ Control)	Outcome measure	Outcome
							Lag time (sec) – Healthy population [BL to Wk 4]	**Increased** Adenosine phosphate NS Adrenaline +10 (p=0.002) Arachidonic acid NS Collagen (1.0 ug/mL) NS Collagen (1.0 ug/mL) NS C-reactive protein NS U46619 +5 (p<0.001)
							Maximum slope – CVD population [BL to Wk 4]	**Increased** Adenosine phosphate NS Adrenaline NS Arachidonic acid +8.4 (p=0.009) Collagen (1.0 ug/mL) NS Collagen (1.0 ug/mL) NS C-reactive protein NS U46619 NS
							Maximum amplitude (%) – CVD population [BL to Wk 4]	**Increased** Adenosine phosphate NS Adrenaline NS Arachidonic acid NS Collagen (1.0 ug/mL), NS Collagen (1.0 ug/mL), NS C-reactive protein +5.9 (p=0.012) U46619 NS
							Lag time (sec) – CVD population [BL to Wk 4]	**Increased** Adenosine phosphate NS Adrenaline +10 (p=0.002) Arachidonic acid NS Collagen (1.0 ug/mL) NS Collagen (1.0 ug/mL) NS C-reactive protein, NS U46619 +13 (p=0.0018)
							Platelet activation [BL to Wk 4]	**Reduced in health population** Healthy: -15%; CVD: NS

Author (year) [Country, World Region]	Design	Study Population	Intervention(s)	Concomitant therapies	Control or comparison group	No. Participants (Intervention/ Control)	Outcome measure	Outcome
Menon, et al. (2017) [Australia, WPRO] [44]	Uncontrolled trial	Chronic Fatigue Syndrome	16 weeks – Ubiquinone (Co Q10) 200 mg; alpha lipoic acid 150 mg; N-acetylcysteine (NAC) 2000 mg; Acetyl l-carnitine (ALC) 1000 mg; magnesium (as orotate 500 mg) 64 mg; calcium ascorbate dehydrate (equiv. ascorbic acid 200 mg) 242 mg; cholecalciferol (equiv. vitamin D3 250 IU); 12.5 ug; a-tocopherol (equiv. natural vitamin E 50 IU) 60 IU; Retinyl palmitate (equiv. vitamin A 3000 IU) 900 ug REIU; and vitamin B co-factors: biotin (vitamin H) (600 ug), thiamine hydrochloride (100 mg), riboflavin (100 mg), nicotinamide (200 mg), calcium pantothenate (100 mg), pyridoxine hydrocholoride (100 mg), folic acid (800 mg), cyanocobalamin (vitamin B12) (800 mcg)	Nil	Nil	10	Chalder Fatigue Scale [BL to Wk 16]	**Reduced fatigue** -9.4 ($p<0.001$).
							Montgomery – Asberg Depression Rating Scale [BL to Wk 16]	NS
							Insomnia Severity Index [BL to Wk 16]	**Reduced insomnia** -3.65 ($p=0.017$)
							Patient Global Impression Scale [BL to Wk 16]	NS
							Clinical Global Impression Scale [BL to Wk 16]	**Reduced symptoms** Severity: NS; Improvement: -0.92 ($p=0.014$)
							Work and Social Adjustment Scale [BL to Wk 16]	NS
							Short-Form Health Survey [BL to Wk 16]	NS
Mills, et al. (2003) [Canada, AMRO] [54]	Randomized controlled trial	Healthy adults	90 minutes: Immediate-release niacin 500 mg	Nil	Placebo	68 (33/35)	Tolerability (no. %) [BL to 90min]	**Reduced tolerability** Niacin: No effect 0.0; Easy to tolerate 6.1; Mildly unpleasant 42.4; Unpleasant 33.3; Intolerable 18.2 Placebo: No effect 97.1; Easy to tolerate 2.9; Mildly unpleasant 0.0; Unpleasant 0.0; Intolerable 0.0
							Adverse events	**Increased adverse events** Composite of pruritis: Niacin 75%; Placebo 0% Between group $p<0.001$

Author (year) [Country, World Region]	Design	Study Population	Intervention(s)	Concomitant therapies	Control or comparison group	No. Participants (Intervention/ Control)	Outcome measure	Outcome
								Composite of tingling: Niacin 30%; Placebo 0.0% Between group p<0.001 Unpleasant warmth or flushing: Niacin 100%; Placebo 3% Between group p<0.001 Nausea: Niacin 30%; Placebo 3% Between group p=0.005 Vomiting: Niacin 12%; Placebo 3% Between group p=0.005 Vertigo: Niacin 12%; Placebo 3% Between group p=0.005 Chills: Niacin 52%; Placebo 0% Between group p<0.001 Heart palpitations: Niacin 15%; Placebo 3% Between group p=0.0228
Mischley, et al. (2015) [USA, AMRO] [68]	Randomized controlled trial	Parkinson's Disease (Hoehn Yahr stage <3)	12 weeks: Intranasal reduced glutathione (GSH) 300mg and 600mg	Stable medication (not defined) Supplements (not defined), diet and exercise (30 days)	Control (saline) and placebo (watchful waiting)	34 (10/10/10/4)	Complete blood count [BL to Wk 12]	NS
							Alanine aminotransferase (ALT) [BL to Wk 12]	NS
							Aspartate aminotransferase (AST) [BL to Wk 12]	NS
							Blood urea nitrogen (BUN) [BL to Wk 12]	NS
							Creatine [BL to Wk 12]	NS
							Urinalysis [BL to Wk 12]	NS
							Monitoring of Side Effects Scale [BL to Wk 12]	NS

Author (year) [Country, World Region]	Design	Study Population	Intervention(s)	Concomitant therapies	Control or comparison group	No. Participants (Intervention/ Control)	Outcome measure	Outcome
							SinuNasal Outcome Test (SNOT-20) [BL to Wk 12]	NS
							Unified Parkinson's Disease Rating Scale (UPDRS) [BL to Wk 12]	Mild clinical improvements in both treatment arms compared to placebo (NS)
Mischley, et al. (2016) [USA, AMRO] [52]	Cohort	Parkinson's disease	45 minutes: Intranasal reduced glutathione (GSH) 200mg	Nil	Nil	15	GSH and GSH/ Cr concentrations (H-MRS) [BL to Min 45]	**Increased levels** GSH/Cr: +269% ; GSH: +240% 7.5 min: +0.03 (0.008-0.06) 19.9 min: +0.04 (0.01-0.08) 32.0 min: +0.04 (0.01-0.08) 44.7 min: +0.05 (0.01-0.11)
Mischley et al. (2017) [USA, AMRO] [53]	Randomized controlled trial	Parkinson's Disease (Hoehn Yahr stage 1-3)	12 weeks: Intranasal reduced glutathione (GSH) 300mg and 600mg	Stable medication (not defined) previous 30 days	Control (saline)	39 (11/14/14)	Unified Parkinson's Disease Rating Scale (UPDRS) [BL to and Wk 4, 8, 12 and 16 (at same appointment time for each participant)]	NS
							GSH and GSH/ Cr concentrations (H-MRS) [BL to and Wk 4, 8, 12 and 16]	NS trend toward increasing brain GSH concentrations in the 600 mg/d cohort
Myers, et al. (2010) [Australia, WPRO] [74]	Uncontrolled trial	Healthy adults	5 weeks: Titrated dosing schedule containing (per capsule) 18 mg vitamin E as mixed tocopherols (as d-alpha, d-beta, d-delta and d-gamma tocopherols); 113 mg of an antioxidant blend (quercetin dihydrate; grape skin extract; green tea extract; *Terminalia ferdinandiana* [Australian bush plum powder], 331 mg of a proprietary blend of plant polysaccharide and fruit and vegetable powders	Nil	Nil	21	Serum oxygen radical absorbance capacity (ORAC) [BL to Wk 5]	**Increased oxygen levels** Non-smoker: +58 Smoker: +92 (p=0.040)

Author (year) [Country, World Region]	Design	Study Population	Intervention(s)	Concomitant therapies	Control or comparison group	No. Participants (Intervention/ Control)	Outcome measure	Outcome
			(aloe vera inner leaf gel, gum acacia, xanthan gum, gum tragacanth, gum ghatti, broccoli, brussel sprouts, cabbage, carrot, cauliflower, garlic, kale, onion, tomato, turnip, papaya and pineapple (Ambrotose AO®)					
Pipingas, et al. (2013) [Australia, WPRO] [45]	Randomized controlled trial	Healthy adults	16 weeks: Swisse Ultivite F1® (Men's/Women's formula) multivitamin (MV). Includes B vitamins as well as vitamins C, D and E, together with select mineral chelates and small quantities of select botanicals.	Nil	Placebo	138 (68/70)	General health questionnaire [BL to Wk 16]	NS
							Profile of Mood states [BL to Wk 16]	NS
							Chalder Fatigue scale [BL to Wk 16]	NS
							State-Trait Anxiety Inventory [BL to Wk 16]	NS
							Bond-Lader and visual analog scales [BL to Wk 16]	NS
							Pennebaker Inventory of Limbic languidness [BL to Wk 16]	NS
							Multi-tasking framework [BL to Wk 16]	NS
Pipingas, et al. (2014) [Australia, WPRO] [46]							Cognitive tasks: Swinburne University Computerized Cognitive Assessment Battery [BL to Wk 16]	**Improved cognition** Simple reaction: NS Complex reaction: NS Stroop congruent: Multivitamin, -12; Placebo, +15 Between group: p=0.01
							Immediate and delayed recognition memory, contextual	NS

Author (year) [Country, World Region]	Design	Study Population	Intervention(s)	Concomitant therapies	Control or comparison group	No. Participants (Intervention/Control)	Outcome measure	Outcome
							recognition memory, working memory, arrow flankers [BL to Wk 16]	
							Serum homocysteine [BL to Wk 16]	**Reduced homocysteine levels** Multivitamin: -16%; Placebo: -14% Between group: p<0.0001
							Serum vitamin B6 (nmol/L) [BL to Wk 16]	**Increased vitamin B6 levels** Multivitamin: +391%; Placebo: +12% Between group: p<0.0001
							Serum vitamin B12 (nmol/L) [BL to Wk 16]	**Increased vitamin B12 levels** Multivitamin: +33%; Placebo: +3% Between group: p<0.0001
							Red blood cell folate [BL to Wk 16]	**Increased folate levels** Multivitamin: +30%; Placebo: +11% Between group: p<0.0001
Prousky and Seely (2011) [Canada, AMRO] [55]	Randomized controlled trial	Non-ulcer dyspepsia	4 weeks: inositol hexaniacinate (IHN) (540mg crystalline niacin and 54mg inositol)	Nil	Placebo	62 (36/26)	Gastrointestinal Symptom Questionnaire [BL to Wk 4]	NS
							Gastro-test® pH [BL to Wk 4]	NS
Pumpa et al. (2019) [Australia, WPRO] [75]	Randomized controlled trial	Prevention of gastrointestinal Infection	27 weeks: Probiotics (Ultrabiotic 60 and SB Floractiv)	Nil	Placebo	19 (11/8)	Incidence of GI infection [BL to Wk 17]	**Reduced incidence**
							Salivary Immunoglobulin A (U/mL) [BL to Wk 17]	NS

Author (year) [Country, World Region]	Design	Study Population	Intervention(s)	Concomitant therapies	Control or comparison group	No. Participants (Intervention/Control)	Outcome measure	Outcome
							Salivary alpha-amylase (U/mL) [BL to Wk 27]	**Increased levels** Wk 10: NS Wk 17: NS Wk 27: Probiotic +16.2; Placebo +8.1 Between group p=0.007
							Salivary cortisol (ug/dL) [BL to Wk 27]	**Increased** Wk 10: NS Wk 17: Probiotic, +0.02; Placebo -0.01 Between group p=0.02 Wk 27: Probiotics -0.01; Placebo -0.05 Between group p=0.001
Quinn, et al. (2010) [USA, AMRO] [30]	Randomized controlled trial	Alzheimer's disease (mild to moderate)	18 months: Algal-derived DHA 2g daily	Nil	Placebo	402 (238/164)	Alzheimer's Disease Assessment Scale [BL to Mth 18]	NS
							Clinical Dementia Rating [BL to Mth 18]	NS
							Mini-Mental State Examination [BL to Mth 18]	NS
							Alzheimer's Disease Cooperative Study activity of daily living scale [BL to Mth 18]	NS
							Neuropsychiatric inventory [BL to Mth 18]	NS
							Adverse events [BL to Mth 18]	NS
Rao, et al. (2009) [Canada, AMRO] [76]	Randomized controlled trial (pilot)	Chronic Fatigue Syndrome	8 weeks: Probiotics (24 billion CFU of *Lactobacillus casei* strain Shirota per day)	Nil	Placebo	35 (19/16)	Stool, total aerobes [BL to Wk 8]	**Increased aerobes** Placebo: -0.16; Probiotics: +0.43
							Stool, total anaerobes [BL to Wk 8]	**Increased anaerobes** Placebo: +0.03; Probiotics: +0.26

Author (year) [Country, World Region]	Design	Study Population	Intervention(s)	Concomitant therapies	Control or comparison group	No. Participants (Intervention/Control)	Outcome measure	Outcome
							Stool, bifidobacteria [BL to Wk 8]	**Increased bifidobacteria** Placebo: -0.36; Probiotics: +0.66
							Stool, lactobacillus [BL to Wk 8]	**Increased lactobacillus** Placebo: +0.15; Probiotics: +1.12
							Beck Depression Inventory [BL to Wk 8]	NS
							Beck Anxiety Inventory [BL to Wk 8]	NS
Ross, et al. (2008) [USA, AMRO] [77]	Retrospective cohort study	Eating disorders	3 days: Various integrative therapies for insomnia and constipation: insomnia was treated with instructions on sleep hygiene as well as an herbal product (containing valerian root extract, *Rhodiola rosea* root extract, Hops strobiles extract, *Passiflora incarnata* aerial parts extract, and German chamomile flower extract) and/or 5-hydroxytryptophan (the metabolic precursor to serotonin) were prescribed. Constipation was treated with plant-based digestive enzymes at mealtimes and a daily probiotic supplement containing *Lactobacillus rhamnosus*	Herbal product (containing valerian root extract, *Rhodiola rosea* root extract, Hops strobiles extract, *Passiflora incarnata* aerial parts extract, and German chamomile flower extract)	Placebo	38	Medications used for sleep [After Dy 3]	NS
							Sleep medications [After Dy 3]	NS
							Constipation medications [After Dy 3]	NS
Rubin, et al. (2008) [Canada, AMRO] [31]	Case studies	Acne vulgaris	2 months: 1000 mg of EPA (from sardines and anchovies), zinc gluconate 15mg, selenium 200 mcg, chromium 200 mcg and epigallocatechin-3-gallate (EGCG) 200 mg (from green tea extract)	Nil	Nil	5	Inflammatory acne lesions [BL to Mth 2]	**Reduced lesions** Lesions (average): -40 Inflammatory papule lesions (average): -15
							Arizona Integrative Outcomes Scale [BL to Mth 2]	**Increased outcomes** +24% average across domains

Author (year) [Country, World Region]	Design	Study Population	Intervention(s)	Concomitant therapies	Control or comparison group	No. Participants (Intervention/ Control)	Outcome measure	Outcome
Sarris, et al. (2012) [Australia, WPRO] [47]	Randomized controlled trial	Healthy adults	16 weeks: Swisse Men's Ultivite F1®/Swisse Women's Ultivite F1®(SMV)	Nil	Placebo	116 (56/60)	More energetic and/ or alert [BL to Wk 16]	**Increased energy/ alertness** MV: 29.1%; Placebo: 11.9% (p=0.022)
							Better mood and emotional state [BL to Wk 16]	**Improved mood** MV: 23.6%; Placebo: 8.5% (p=0.027)
							Negative experiences [BL to Wk 16]	NS
Sarris, et al. (2014) [Australia, WPRO] [57]	Randomized controlled trial	Major depressive disorder	Week 12: SAMe 1600mg/day Or Escitalopram 10mg/day	Nil	Placebo	102 (32/35/35)	Hamilton depression score [BL to Wk 12]	**Reduced depression** SAMe: -7.31; Escitalopram: -6.69; Placebo: -4.00 Between group (placebo v SAMe): p=0.018
							>50% reduction of Hamilton depression score [BL to Wk 12]	**Increased clinically important reduction in depression** SAMe: 45%; Escitalopram: 31%; Placebo: 26% Between group (placebo v SAMe): p=0.003
Sarris, et al (2015) [Australia, WPRO] [63]	Randomized controlled trial	Obsessive-compulsive disorder (OCD)	N-acetyl cysteine (NAC)	16 weeks: Week 1 1000mg Week 2 2000mg Week 3 3000mg	placebo	35 (20/15)	Yale – Brown Obsessive Compulsive Scale (YBOCS) [BL to Wk 4, 8, 12 and 16]	**Reduced compulsion** NAC [BL to week 12] (p=0.013 (dissipating at week 16)
							Hamilton Anxiety Rating Scale [BL to Wk 4, 8, 12 and 16]	NS
							Montgomery-Asberg Depression Rating Scale [BL to Wk 4, 8, 12 and 16]	NS

Author (year) [Country, World Region]	Design	Study Population	Intervention(s)	Concomitant therapies	Control or comparison group	No. Participants (Intervention/Control)	Outcome measure	Outcome
							Clinical Global Impression Scales – Severity and Improvement [BL to Wk 4, 8, 12 and 16]	NS
							General health (GHQ-28) [BL to Wk 4, 8, 12 and 16]	NS
Sarris, et al. (2018) [Australia, WPRO] [48]	Randomized controlled trial	Major Depressive Disorder	8 weeks: S-adenosylmethionine (SAMe) (800 mg/day); Folinic acid (500 mcg/day) and co-factor vitamin B12 (200 mcg/day)	Nil	Placebo	107 (55/52)	Montgomery-Asberg Depression Rating Scale [BL to Wk 8]	NS
							Beck Depression Inventory-II [BL to Wk 8]	NS
							Hamilton Anxiety Rating Scale [BL to Wk 8]	NS
							Short Form-12 [BL to Wk 8]	NS
							Leeds Sleep Evaluation Questionnaire [BL to Wk 8]	NS
							Clinical global impression scales severity and improvement [BL to Wk 8]	NS
Sarris, et al. (2019) [Australia, WPRO] [78]	Randomized controlled trial	Generalized Anxiety Disorder	10 weeks: L-theanine 450mg per day then titrated up to 900mg per day if required	Nil	Placebo	46 (22/24)	Hamilton Anxiety Rate Score [BL to Wk 10]	NS
							Insomnia severity index [BL to Wk 10]	NS

Author (year) [Country, World Region]	Design	Study Population	Intervention(s)	Concomitant therapies	Control or comparison group	No. Participants (Intervention/ Control)	Outcome measure	Outcome
Sarris et al. (2019) [Australia, WPRO] [32]	Randomized controlled trial	Major Depressive Disorder	8 weeks: SAMe (800 mg), folinic acid (500mcg), vitamin B12 (200mcg). Capsules: omega-3 fatty acid concentrate (EPA-esters 1000 mg/day, DHA-esters 656 mg), 5-HTP (200 mg), zinc picolinate (30 mg elemental/ day), vitamin B6 (100 mg), vitamin C (60 mg), magnesium (amino acid chelate, elemental 40 mg), vitamin E (40IU).	Nil	Placebo	158 (81/77)	Montgomery-Asberg Depression Rating Scale [BL to Wk 10]	NS
Schloss, et al. (2017) [Australia, WPRO] [49]	Randomized controlled trial	Newly diagnosed cancer (breast, lymphoma or lung, undergoing chemotherapy)	B-group vitamin complex, initiated 1 week pre-chemotherapy, continued for 12 weeks post-chemotherapy	36 weeks (B1 50 mg, B2 20 mg, B3 100 mg, P5 164 mg, B6 30 mg, folate 500 mcg, B12 500 mcg, biotin 500 mcg, choline 100 mg, inositol 500 mcg)	Placebo	71 (38/33)	Total Neuropathy Score [BL to Wk 12, 24 and 36]	NS
							MD Anderson Brief Pain Inventory [BL to Wk 12, 24 and 36]	NS
							European Organization for the Research and Treatment of Cancer – Quality of Life [BL to Wk 12, 24 and 36]	NS
							Patient Neurotoxicity Questionnaires – sensory, motor or other neuropathy [BL to Wk 12, 24 and 36]	**Reduced sensory neuropathy** Intervention: Wk 2: p=0.03 Wk 24: p=0.005 Wk 36: p=0.021 Placebo: NS Motor and other: NS
Schoenthaler, et al. (2000) [USA, AMRO] [50]	Randomized controlled trial	Healthy children (6-12 yrs)	4 Months: Daily vitamin-mineral supplement containing 50% of the U.S. recommended daily allowance	Nil	Placebo	468 (234/234)	Violations per person [BL to Mth 4]	**Reduced violations per person** MV: 1.0; Placebo: 1.875 p=0.014

Author (year) [Country, World Region]	Design	Study Population	Intervention(s)	Concomitant therapies	Control or comparison group	No. Participants (Intervention/ Control)	Outcome measure	Outcome
Shinto, et al. (2008) [USA, AMRO] [33]	Randomized controlled trial	Multiple sclerosis	6 months: Naturopathic treatments plus usual care – daily supplementation of the following: multivitamin/ mineral without iron, vitamin C, vitamin E, fish oil, and α-lipoic acid (Pure Encapsulations, Sudbury, MA) and intramuscular vitamin B12 once a week (Apothecure, Dallas, TX).	Dietary therapy (4 levels). Level 1: limit *trans* fatty acids, decrease intake of artificial sweeteners, decrease intake of coffee and alcohol, decrease cigarette use, increase intake of water to 6-8 cups per day; Level 2: Level 1 intervention plus reduced intake of red meat to two 4-6 oz servings per week; Level 3: Level 2 plus no refined sugar, no fried foods, no processed/ packaged foods, no coffee or alcohol; Level 4: hypoallergenic diet (Brennamen's food elimination and challenge)	MS-focused educational visits with a nurse plus usual care	45 (15/15/15)	Short Form-36 [BL to Mth 6]	NS
							Modified Fatigue Impact Scale [BL to Mth 6]	NS
							Beck Depression inventory [BL to Mth 6]	NS
							Stroop test [BL to Mth 6]	NS
							Paced Auditory Serial Addition Test-3 [BL to Mth 6]	NS
							Expanded Disability Status Scale [BL to Mth 6]	NS
Shinto, et al. (2009) [USA, AMRO] [34]	Uncontrolled trial	Multiple sclerosis (relapsing-remitting)	6 months (including 3 months wash out): Omega-3 fatty acids in the form of fish oil concentrate (9.6 g/day containing 2.9 g EPA and 1.9g DHA)	Nil	Nil	10	Immune cell secretion of matrix metalloproteinase-9 (MMP-9) [BL to Mth 3]	**Reduced MMP-9 levels** -58% after 3 months ($p<0.01$)
							Red blood cell omega-3 fatty acid [BL to Mth 3]	**Increased omega-3 levels** Increased (x6.3 times) ($p=0.001$)

Author (year) [Country, World Region]	Design	Study Population	Intervention(s)	Concomitant therapies	Control or comparison group	No. Participants (Intervention/ Control)	Outcome measure	Outcome
Shinto, et al. (2014) [USA, AMRO] [35]	Randomized controlled trial	Alzheimer's disease	12 months: omega-3 fish oil concentrate containing a daily dose of 675mg DHA and 975mg EPA OR omega-3 fish oil concentrate plus alpha-lipoic acid (ALA) 600 mg/day	Nil	Placebo	39 (13/13/13)	Peripheral F2-isoprostane levels [BL to Mth 12]	NS
							Mini-Mental State Examination [BL to Mth 12]	**Improved mental state** omega-3: -4.3; omega-3 + ALA: -1.0; Placebo: -4.6 Between group (Placebo vs ALA): p<0.01
							Activities of Daily Living [BL to Mth 12]	NS
							Instrumental Activities of Daily Living [BL to Mth 12]	**Increased activities of daily living** Omega-3: -0.7; Omega-3 + ALA: -0.9; Placebo: -4.2 Between group (Placebo vs ALA): p<0.01 Between group (Placebo vs Omega-3): p<0.01
							Alzheimer's Disease Assessment Scale-cognitive subscale [BL to Mth 12]	NS
Shinto, et al. (2016) [USA, AMRO] [36]	Randomized controlled trial	Multiple sclerosis (with major depressive disorder)	3 months: omega-3 fatty acids in the form of fish oil at a daily dose of 5.81g (1.95 grams of EPA and 1.35 grams of DHA)	Nil	Placebo	39 (21/18)	Montgomery-Asberg Depression Rating scale [BL to Mth 3]	NS
Smith, et al. (2017) [Australia, WPRO] [37]	Uncontrolled trial	Major Depressive Disorder	8 weeks: DHA (260 mg or 520 mg/day)	Nil	Nil	26 (21/5)	Hamilton Depression Rating Scale (HAM-D) [BL to Wk 8]	**Reduced depression** -10.33, (p<0.001)

Author (year) [Country, World Region]	Design	Study Population	Intervention(s)	Concomitant therapies	Control or comparison group	No. Participants (Intervention/ Control)	Outcome measure	Outcome
							⩾50% reduction on HAM-D [BL to Wk 8]	**Increased clinically important reduction in depression** Clinical response to treatment: 54% In remission: 46% (p<0.0001)
							Clinical Global Impression Severity Scale [BL to Wk 8]	**Reduced symptom severity** -1.28 (p<0.05)
							Epsworth sleepiness scale [BL to Wk 8]	NS
Traub, et al. (2014) [USA, AMRO] [62]	Randomized controlled trial	Healthy adults with low serum 25-hydroxycholecalciferol (25(OH)D)	12 weeks: 10,000 IU Vitamin D3 daily 1. Chewable tablet 2. Liquid drop 3. Capsule	Nil	Nil	66 (22/23/21)	Total serum 25(OH) D/mcg [BL to Wk 12]	**Increased vitamin D levels** Tablet: +33.3; Liquid: +34.4; Capsule: +53.6 Between groups: p=0.04
							Difference in proportion of D3 between interventions [BL to Mth 12]	Drops had greater increase than tablets (p<0.05). Tablet not different to capsule
							Patients reaching sufficiency [BL to Mth 12]	Tablet: 100%; Drop: 80%; Capsule: 100% (p=0.03)
							Mean change in serum 1,25 (OH)D [BL to Mth 12]	NS
Vitetta, et al. (2013) [Australia, WPRO] [79]	Randomized controlled trial	Adults experiencing frequent cold-related symptoms	Bovine lactoferrin (Lf) 400mg and whey protein Ig rich fraction (IgF) 200mg daily for 90 days	Nil	Placebo	105 (53/52)	Total cold events [BL to Dy 45, Dy 90]	**Reduced occurrence of common cold** Dy 1-45: Lactoferrin 0.67; Placebo 1.40 Between group p<0.001 Dy 46-90: Lactoferrin 0.38; Placebo 1.02 Between group p<0.001 Dy 1-90: Lactoferrin 0.93; Placebo 2.26 Between group p<0.001

Author (year) [Country, World Region]	Design	Study Population	Intervention(s)	Concomitant therapies	Control or comparison group	No. Participants (Intervention/ Control)	Outcome measure	Outcome
							Total number of cold-associated symptoms [BL to Dy 90]	**Reduced cold-associated symptoms** Lactoferrin, 208; Placebo, 288 Between group p<0.05
							Cold duration [BL to Dy 90]	NS
							Cold severity [BL to Dy 90]	NS
Withee, et al. (2017) [USA, AMRO] [80]	Randomized controlled trial	Healthy adult runners	21 days (+2 days post-race): Methylsulfonylmethane (MSM) as OptiMSM® 3g/day prior to half-marathon	Nil	Placebo	22 (11/11)	VAS for muscle pain [BL to Dy 23]	NS
							VAS for joint pain [BL to Dy 23]	NS
							8-hydroxy-2'-deoxyguanosine [BL to Dy 23]	NS
							Malondialdehyde [BL to Dy 23]	NS
							Serum creatine kinase [BL to Dy 23]	NS
							Lactate dehydrogenase [BL to Dy 23]	NS
Yadav, et al. (2005) [USA, AMRO] [64]	Randomized controlled trial	Multiple Sclerosis	14 days: Lipoic acid (a) 600mg twice per day; (b) 1200mg once per day; (c) 1200mg twice per day	Nil	Placebo	37 (10/9/9/9)	Serum lipoic acid [BL to Dy 14]	**Increased levels** Variable levels across all participants 600mg: 0.2ug/mL 1200mg: 4.8ug/mL 2400mg: not reported Placebo: 0.1 ug/mL Between group p<0.05
							Matrix metalloproteinase-9 (MMP-9) [BL to Dy 14]	**Increased MMP-9** +1ug/mL serum lipoic acid correlated with -11.10 units of serum matrix metalloproteinase-9 (p=0.04)
							Serum intercellular adhesion molecule-1 [BL to Dy 14]	**Increased levels** Dose response with lipoic acid (p=0.03)

Author (year) [Country, World Region]	Design	Study Population	Intervention(s)	Concomitant therapies	Control or comparison group	No. Participants (Intervention/Control)	Outcome measure	Outcome
Yazaki, et al. (2010) [USA, AMRO] [59]	Randomized controlled trial	Overweight	6 months: 1000 mg of chromium picolinate/day	Nil	Placebo	80 (40/40)	Body mass index [BL to Mth 6]	NS
							Body fat (%) [BL to Mth 6]	NS
							Fasting glucose (mg/dl) [BL to Mth 6]	NS
							Fasting serum insulin (u/ml) [BL to Mth 6]	NS
							Cholesterol (mg/dl) [BL to Mth 6]	NS
							High-sensitivity C-reactive protein (mg/dl) [BL to Mth 6]	NS

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32 Herbal Medicine

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HIGHLIGHTS

- Herbal medicine is one of the most common therapies used globally and is a core aspect of naturopathic care.
- Naturopathic training includes a wide range of herbs and integrates herbs common to each Region.
- Clinical research by the naturopathic community has examined the application of single herbs, complex herbal formulations, essential oils, and topical herbal medicine applications.
- In line with the role of primary care, naturopathic researchers have investigated the effects of herbal medicine on individuals with mental health conditions, women's health conditions, gastrointestinal conditions, cardiovascular conditions, musculoskeletal conditions, skin conditions, cancer, complex immune conditions, and a range of other health conditions.

Herbal medicine (also known as botanical medicine or phytotherapy) involves the use of plants, lichen, fungi, and algae in the prevention and treatment of human disease. The naturopathic profession has always included herbal medicine as a pre-eminent modality, strongly influenced by Sebastian Kneipp who identified phytotherapy as one of the "five pillars" of treatment [1-4]. A 2020 international naturopathic survey confirmed the significant importance of herbal medicine in current naturopathic practice with more than half of naturopathic visits including some form of herbal prescription [5]. Hence, the chapter on complex naturopathic interventions (Chapter 29) also includes research on herbal medicine.

The use of herbal medicine in naturopathic practice ranges from herbs as food, the prescription of single herbs (either in whole form or various extracts or use of unaltered constituents from these sources) and compounded formulations with more than one herbal remedy. Herbs may be prescribed as pre-formulated proprietary products (i.e., commercially produced formulas), or dispensed extemporaneously (i.e., compounded onsite for the specific needs of the individual patient). Herbs can be prescribed internally as part of diet, as teas, tinctures, essential oils, or tablets/capsules, and can also be used topically in creams, oils and in poultices and compresses.

Naturopaths and naturopathic doctors are trained to use a wide range of herbs from mild herbs such as *Allium sativum* (garlic), *Zingiber officinale* (ginger), *Salvia rosmarinus* (rosemary), and *Avena sativa* (oats) to extremely powerful herbs that arguably are the basis of modern pharmacological medicine, such as *Digitalis purpurea* (foxglove) yielding digoxin, *Atropa belladonna* (deadly nightshade) yielding atropine, *Pausinystalia johimbe* (yohimbe) yielding yohimbine, *Rauvolfia serpentina* (Indian snakeroot) yielding reserpine, and *Papaver somniferum* (opium poppy) yielding morphine. The range of herbs employed by naturopaths/naturopathic doctors, and the form and dosage, vary based on access to specific herbal medicines in a region as well as the education and scope of practice in a jurisdiction. The integrated nature of naturopathic care supports the use of indigenous herbs in each WHO Region. Hence, the specific herbs studied and prescribed in North America, for example, would likely vary somewhat from those used by naturopaths and naturopathic doctors in Africa or Europe.

Overview of Studies

This chapter is dedicated to highlighting the original clinical research (n=46, published papers 48) naturopathic clinicians undertook in the field of herbal medicine. This research includes a total of 2,745 participants and was conducted in the United States of America (USA) (n=25), Australia (n=13), Canada (n=6), Germany (n=2), India (n=1) and Puerto Rico (n=1). The study designs include randomized controlled trials (RCT) (n=23), case reports (n=14), uncontrolled trials (n=7), retrospective cohort studies (n=2) and secondary analysis (n=2). The

studied interventions evaluated either single herbal remedies (n=27), complex herbal formulations (n=17), topical uses of herbs (n=4) and essential oils (n=2). The conditions treated with herbal medicine ranged from mental health conditions (anxiety (n=4), depression (n=4), ADHD (n=1)); women's health conditions (menopausal symptoms (n=3), candidiasis (n=1), ovarian cysts (n=1), pregnancy issues (n=1)); gastrointestinal conditions (IBS/IBD (n=4)), cardiovascular conditions (heart failure (n=2), leg ulcers (n=2)), musculoskeletal conditions (osteoarthritis (n=1)); skin conditions (dermatitis (n=1), plantar warts (n=1), psoriasis (n=1), vitiligo (n=1)), cancer (breast cancer (n=2), colorectal cancer (n=2), prostate cancer (n=1), general cancer (n=1)), complex immune conditions (human immunodeficiency virus (HIV) (n=2), hepatitis C (n=1)) and other conditions (kidney disease (n=1), asthma (n=2), insomnia (n=2)). Studies were also conducted to determine the impact on healthy volunteers for tasks such as improved driving (n=2).

The studies on naturopathic herbal interventions were completed in a wide range of settings, including naturopathic medical schools and research institutes, private naturopathic practices, and conventional hospitals, clinics, and research centers. While most studies looked at treatment of established conditions, three were conducted principally to determine the safety of various herbal medicines. Of all the naturopathic clinical studies employing herbal medicine interventions, 71.7% reported a positive outcome in at least one primary or secondary outcome measure. Details of the studies are available in *Table 32.1: Clinical research investigating herbal medicine interventions conducted by naturopathic researchers.* This body of naturopathic research on herbal medicine is also supported by more than 30 observational studies and more than 120 reviews or meta-analysis conducted by naturopathic researchers on this topic, as outlined in Chapter 40.

Implications

As indicated by the naturopathic research, a wide range of herbs are used in naturopathic practice in a diverse range of conditions. Naturopathic researchers have investigated whole plants, extracts, and isolated constituents as well as single and combination herbs used internally and topically. The research in herbal medicine indicates that herbal medicine interventions provide significant outcomes in most conditions.

Herbal medicines are one of the most common forms of treatment globally, historically through traditional practices but increasingly via integration into developed health systems, with the World Health Organization *2019 Global Report on Traditional and Complementary Medicine* noting that at least 34 countries include herbal medicines in their essential medicines lists [6]. However, the same report identified regulatory issues in the herbal medicine sector which impacted on the safety, quality, and efficacy of herbal medicines. Naturopaths/naturopathic doctors are one profession which has been identified as having a high level of knowledge about regulatory, clinical and safety issues surrounding herbal medicines [7]. This knowledge is formed from a focused education including pharmacognosy and integrated pharmacology, leading to naturopaths/naturopathic doctors playing leading research and clinical roles in identifying and managing drug-herb interactions in primary health care [8, 9]. As such, naturopaths/naturopathic doctors are particularly well-equipped to assist patients manage their use of herbal medicines in conjunction with other therapies [10]. These qualities, in addition to evidence of beneficial application of herbal medicines by the naturopathic community, suggest a greater role of naturopaths/naturopathic doctors in maximizing the benefits of herbal medicine use and minimizing potential harms is warranted.

Studies investigating specific interventions:

Single Herb Interventions

The 26 studies investigating single herbs included the following 18 herbs: two using standard extracts of *Aesculus hippocastanum* for venous insufficiency [11, 12]; *Allium sativum* in the treatment of candidiasis [13]; *Andrographis paniculata* in the treatment of HIV [14]; one using *Artemisia annua* in prostate cancer patients [15]; one using *Bacopa monnieri*, with adults with anxiety and depression [16]; a study using standardized extracts of *Camellia sinensis* in the treatment of breast cancer [17, 18]; a study on *Crataegus laevigata* for heart failure [19, 20]; *Curcuma longa* was studied in children with Crohn's or ulcerative colitis [21]; *Echinacea purpurea* for upper respiratory tract infections [22], *Ginkgo biloba* in the treatment of vitiligo [23]; there were three studies of *Hypericum perforatum*, one in the treatment of depression [24]; one which included *Piper methysticum* in the treatment of anxiety [25] and one with children and adolescents for the treatment of ADHD [26]. ; the safety of *Larrea tridentata* on liver function was studied [27]; one study on *Matricaria chamomilla* for insomnia [28]; one study of *Panax quinquefolius* for upper tract infections in children [29]; *Piper methysticum* impact on driving ability was measured in healthy adults [30]; *Silybum marianum* in the treatment of hepatitis C [31]; *Trigonella foenum-graecum* in the treatment of menopausal symptoms [32]; *Vitex agnus-castus* fruit extract along with vaginal Progesterone for history of spontaneous abortions [33]; three studies on *Zingiber officinale*, two in the treatment of colorectal cancer [34, 35] and one in the management of chemotherapy induced nausea and vomiting [36].

A randomized double-blind, placebo-controlled trial conducted in Australia (n=60) with adult participants with more than one month of generalized anxiety on the Hamilton Anxiety Scale (HAS) were prescribed placebo or *Piper methysticum*, 5 tablets containing 250 mg/d kavalactones [37]. There was a significant reduction in anxiety based on the HAS -10.3, p<0.001, the Beck anxiety index (BAI) score, -8.1, p<0.001, and the Montgomery Asberg Depression Rating Score, -7.6 p=0.003. The aqueous extract was safe with no serious adverse effects or clinical hepatotoxicity.

A randomized placebo control trial conducted in the USA involving 48 adult participants with anxiety and depression found that *Bacapa monnieri* standardized to 50% bacosides A and B, 300mg once daily resulted in significant improvements both at 6 weeks and 12 [16]. The results at 12 weeks were increased learning based on the Rey Auditory Verbal Learning Test (*B.monnieri*, +1.2; placebo +.01; p=0.03), reduced depression based on the Center for Epidemiological Studies Depression scale (*B.monnieri*, -0.9; placebo, +0.8; p=0.05), reduced anxiety based on the State-Anxiety Inventory (*B.monnieri*, -1.6; placebo, +1.1; p=0.04), reduced stroop task reaction time (*B.monnieri*, -2.9; placebo, -0.4; p=0.003) and reduced heart rate (*B.monnieri*, -1.1; placebo, +5.1; p=0.01).

An uncontrolled trial conducted in Canada with twelve participants (ages 12 – 35 years) with confirmed vitiligo, were given standardized *Ginkgo biloba* extract, 60mg BID for 12 weeks [23]. Eleven completed the trial with 85% or more compliance. The progression of vitiligo stopped in all subjects, the vitiligo lesion area scoring index for affected areas decreased (-0.05, p=0.021), the vitiligo European Task Force scale showed reduced disease activity (-3.9, p<0.001), and there were no significant changes in blood clotting markers. Another uncontrolled trial conducted in Canada (n=11) prescribed *Echinacea purpurea* for ten days in children (2-5 years old [n=7] and 6-12 years old [n=4]) for the treatment of upper respiratory tract infections (URTI) [22]. Improvement was seen on all measures assessed: children experiencing sneezing decreased from 5 to 1, nasal secretions 5 to 2, cough 7 to 2, difficulty breathing 5 to 2 and difficulty swallowing 2 to 0.

Complex Herbal Formulations

Naturopaths/naturopathic doctors often prescribe complex herbal formulations as part of a multi-faceted naturopathic treatment. This section focuses on the 17 studies where complex herbal formulations were the primary focus of the study. The complex herbal formulations included between two and eleven different herbs. The conditions treated with herbal complexes included PCOS [38], two studies on depressive with anxiety [16, 25, 39], dermatitis [40], HIV [41], two studies on asthma [42, 43], facial rash [44], IBS [45], cervical cancer [46], chronic kidney disease [47], plantar warts [48], menopausal symptoms [49, 50], sleep difficulties [51] and quality of life in breast cancer [52].

Four of the complex intervention studies assessed the safety and risk of adverse events using several measurements including laboratory testing of liver enzymes and reporting of symptoms compared to a control group [38, 39, 50, 53]. One additional study described the safety profile and adverse effects associated with some herbal medicines as observed by naturopaths/naturopathic doctors in clinical practice [54].

A randomized controlled trial conducted in Australia with women (n=104) experiencing menopausal symptoms scoring greater than 'mild' on MENQOL examined the effects of a multi-botanical capsule comprising of 100mg *Tinospora cardiofolia* (stem), 100mg *Asparagus racemosus* (root), 100mg *Withania somnifera* (root) and 225mg *Commiphora mukul* (gum exudate) [50]. Throughout the study period of 12 weeks, participants in the intervention group (n=54) ingested one capsule twice daily and the placebo group (n=50) were given an identical capsule containing maltodextrin. A change from baseline at Week 4, 8 and 12 for all symptom domains of the MENQOL questionnaire was used to measure study outcomes. A statistically significant difference in change in symptom scores for each domain was reported between groups, with a greater reduction in symptoms reported for the intervention group compared to placebo (p≤0.002). The study also measured changes from baseline in the 7-day incidence of hot flushes, night sweats and total vasomotor symptoms at Week 4, 8 and 12. The intervention group reported a reduction in hot flushes (-30%), night sweats (-50%), and total vasomotor symptoms (-43%) at Week 4, and these reductions increased in magnitude through to Week 12 (Hot flushes: -64%; night sweats: -71%; total flushes: -67%). The difference in change in 7-day incidence of vasomotor symptoms between the intervention and placebo groups was statistically significant across all time points for all symptom categories (p<0.001). Safety data collected in this study found no difference between groups.

A randomized controlled trial conducted in Australia sampled women (n=122) between 18 and 44 years old with PCOS diagnosis confirmed according to the Rotterdam criteria [38]. The study compared a lifestyle intervention with a combined lifestyle and herbal intervention for three months. The lifestyle intervention consisted of lifestyle counselling, inclusive of dietary and exercise behaviours, delivered through a structured personalized plan and fortnightly follow-up support. The herbal medicine intervention constituted administration of two herbal medicine products: (1) Three tablets administered daily containing combined extracts equivalent to 750mg *Glychyrrhiza glabra* (root), 750mg *Paeonia lactiflora* (root), 750mg *Cinnamomum verum* (stem bark) and 750mg *Hypericum perforatum* (flowering herb); (2) Three tablets per day for ten consecutive days – commencing either

on Day 5 of the menstrual cycle of women with oligomenorrhea or within one week of trial commencement for women with amenorrhea-containing a single herbal extract equivalent to 13 500mg *Tribulus terrestris* (aerial parts) standardized to 100mg furostanol saponins (protodioscin). There were 60 participants in the herbal and lifestyle (HL) intervention arm and 62 participants in the lifestyle only (LO) arm. At the end of the 3-month study period, a significant ($p<0.01$) difference in number of days between menstrual periods (Mean difference: -42.9 days), body weight (-2.95 kg), body mass index (-1.0), waist circumference (-3.41 cm) in favor of the HL group compared to LO was reported. Comparatively greater reductions in luteinizing hormone (-1.82 IU/L), fasting insulin (-0.44 mU/L) and systolic (-3.6 mmHg) and diastolic (-5.13 mmHg) blood pressure, as well as increased estradiol (+68.9 pmol/L) were also reported in the HL group. The quality-of-life scores, as measured by the Polycystic Ovarian Syndrome Questionnaire (PCOSQ), were also lower in the HL group compared with the LO group, indicating an improved quality of life in participants receiving HL ($p<0.01$). Depression, anxiety, and stress levels were also significantly reduced for participants in the HL group compared to those receiving LO ($p<0.01$). Pregnancy rates were higher (RR 3.9) for women in the HL group compared with the control, but no difference in the proportional rates of miscarriage was reported between groups.

An uncontrolled trial (n=31) conducted in Australia compared two herbal formulae in the treatment of irritable bowel syndrome (IBS) [45]. The first formula DA-IBS contained dried bilberries (*Vaccinium myrtillus*) 20g, Slippery elm (*Ulmus fulva*) 9g, Cinnamon (*Cinnamomum zeylanicum*) 3g, and Agrimony (*Agrimonia eupatoria*) 6g. The second formulae C-IBS formula contained Lactulose 6g, Slippery elm (*Ulmus fulva*) 14g, Licorice (*Glycyrrhiza glabra*) 3g, and Oat bran (*Avena sativa*) 4g. Twenty-one of the participants received DA-IBS and 10 received C-IBS at a dosage of twice daily in 250 ml of apple juice for three weeks. At the end of the intervention there was an overall reduction in symptoms compared to baseline DA-IBS -0.4 ($p=0.002$) and C-IBS -0.71 ($p=0.0005$). The reduction in diarrhea was greater in the DA-IBS (-0.19 $p=0.03$), reduction in straining was greater in C-IBS (DA-IBS -0.19, $p=0.004$ vs C-IBS -0.74, $p<0.0001$), both formulae resulted in a reduction in pain (DA-IBS -0.19, $p=0.006$ vs C-IBS -0.20, $p=0.03$) and bloating (DA-IBS -0.32, $p<0.0001$ vs C-IBS -0.19, $p=0.03$) and the reduction in flatulence was greater in the DA-IBS formula -0.25 ($p=0.0001$) versus no significant change on this scale with the C-IBS formula.

Essential Oils

There were two studies that involved essential oils. One focused on peppermint oil in the treatment of IBS and SIBO [55], and the other on caraway oil in the treatment of IBS [56]. A case report conducted in Canada examined peppermint oil in a case involving a patient with small intestine bowel overgrowth symptoms based on the lactulose hydrogen breath test. The results indicated a marked reduction in hydrogen production (-22ppm) after a twenty-day treatment with enteric coated peppermint oil (*Mentha x piperita*). The patient in this study also reported decreased bloating, pain, eructation and improvement in bowel function [55].

Topical Applications

Five studies examined the use of herbal remedies topically and were conducted in Germany [56, 57], the USA [40, 46] and India [58]. The studies investigated caraway (*Carum carvi*) oil in a hot abdominal poultice [56], the use of cabbage leaf wraps for osteoarthritis of the knee [57], a starch-fortified turmeric bath for psoriasis [58], and *Calendula officinalis* applied as part of a multi-faceted naturopathic approach for poison oak dermatitis [40] and as part of an integrative treatment for class IV carcinoma in situ of the cervix [46].

A randomized controlled trial conducted in Germany involved participants (n=48) with IBS who were either treated with poultices of hot caraway (*Carum carvi*) oil, hot olive (*Olea europea*) oil, or non-heated olive oil in a cross-over design [56]. During the three-week trial, the reduction of IBS symptoms based on the IBS Symptom Severity Scale was -35.4 during caraway oil treatment, -20.0 during hot olive oil treatment and -4.3 during unheated olive oil treatment.

A randomized clinical trial conducted in India (n=60) assessed the effectiveness of a starch-fortified turmeric bath along with general naturopathic care on patients with psoriasis over a period of ten days [58]. Based on the Psoriasis Area and Severity Index those receiving the turmeric bath reported a reduction in severity of -13.9 whereas those receiving only standard naturopathic care reported a reduction of -0.15 ($p<0.01$).

Table 32.1 Original research on herbal medicine interventions conducted by naturopathic researchers

Author (year) [Country, World region]	Design	Study Population	Intervention	Concomitant therapies	Control or Placebo	No. Participants (Intervention/ Placebo)	Measure of Outcome	Outcome
Arentz, et al. (2017) [Australia, WPRO] [38]	Randomized controlled trial	Polycystic ovarian syndrome (Women, 18 – 44 years, BMI >24.5 kg/m^2)	Herbal medicine: Tableted extracts of *Glycyrrhiza glabra* root 2.25 g, *Paeonia lactiflora* root without bark 2.25 g, *Cinnamomum verum* bark 2.25 g, *Hypericum perforatum* flowering tops 2.25 g (throughout the cycle), *Tribulus terrestris* aerial parts (standardized to 110 mg protodioscin/tablet) 40.5 g (follicular phase of menstrual cycle only) once per day.	Lifestyle change: calorie-controlled, low-glycemic, nutrient-dense diet; 150 min exercise per week including 90 min aerobic activity (60 – 90% of maximum heart rate) with optional occasional supervised exercise sessions	Lifestyle change only	122 (60/62)	Time between menstrual periods (days) [BL to Mth 3]	**Reduced time between menstrual periods** Herbal and Lifestyle: 63.7; Lifestyle only: 106.6 Between group: p<0.01
							Women with normal menstrual cycle length defined as 20 – 34 days (%) [BL to Mth 3]	**Increased proportion** Herbal and Lifestyle: 55%; Lifestyle only: 24.2% Between group: p<0.01
							Body weight (kg) [BL to Mth 3]	**Reduced body weight** Herbal and Lifestyle: 90.2; Lifestyle only: 97.2 Between group: p<0.01
							Body mass index (kg/m^2) [BL to Mth 3]	**Reduced BMI** Herbal and Lifestyle: 33; Lifestyle only: 35 Between group: p<0.01
							Waist-to-hip ratio [BL to Mth 3]	NS
							Serum luteinizing hormone (LH) level (IU/L) [BL to Mth 3]	**Reduced LH** Herbal and Lifestyle: 5.84; Lifestyle only: 7.4 Between group: p=0.04
							Serum FSH (IU/L) [BL to Mth 3]	NS
							Serum oestradiol (pmol/L) [BL to Mth 3]	**Increased oestradiol** Herbal and Lifestyle: 217; Lifestyle only: 148.1 Between group: p=0.03
							Serum testosterone, total (nmol/L) [BL to Mth 3]	NS
							Serum sex hormone- binding globulin (nmol/L) [BL to Mth 3]	NS
							Serum fasting glucose (nmol/L) [BL to Mth 3]	NS

Author (year) [Country, World region]	Design	Study Population	Intervention	Concomitant therapies	Control or Placebo	No. Participants (Intervention/ Placebo)	Measure of Outcome	Outcome
							Serum insulin (mU/L) [BL to Mth 3]	**Reduced insulin levels** Herbal and Lifestyle: 12.3; Lifestyle only: 20.3 Between group: p=0.02
							Blood pressure (BP), systolic (mmHg) [BL to Mth 3]	**Reduced systolic BP** Herbal and Lifestyle: 114.3; Lifestyle only: 118 Between group: p=0.01
							Blood pressure (BP), diastolic (mmHg) [BL to Mth 3]	**Reduced diastolic BP** Herbal and Lifestyle: 69.3; Lifestyle only: 74.6 Between group: p<0.01
							Impact on health-related quality of life (total PCOS score) [BL to Mth 3]	**Reduced quality of life** Herbal and Lifestyle: 81.5; Lifestyle only: 109.3 Between group: p<0.01
							Depression, Anxiety and Stress Scale [BL to Mth 3]	**Reduced depression** Herbal and Lifestyle: 3.5; Lifestyle only: 7.5 Between group: p<0.01 Reduced anxiety Herbal and Lifestyle: 2.4; Lifestyle only: 6.3 Between group: p<0.01 Reduced stress Herbal and Lifestyle: 4.9; Lifestyle only: 9.6 Between group: p<0.01
Aucoin (2017) [Canada, AMRO] [39]	Case study	Major depressive disorder and social anxiety disorder	Herbal formula (*Hypericum perforatum* 60mg, *Passiflora incarnata* 32mg, *Valeriana officinalis* 28mg)	Breakfast smoothies, increased vegetable intake, 45 min exercise twice weekly. Supplement: fish oil (EPA 750mg: DHA 500mg)	Nil	1	Subjective mood and anxiety symptoms [BL to Wk 4]	**Improved mood at each return visit, increased tolerance to anxiety provoking situations, increased energy, and no headaches**

Author (year) [Country, World region]	Design	Study Population	Intervention	Concomitant therapies	Control or Placebo	No. Participants (Intervention/ Placebo)	Measure of Outcome	Outcome
				iron ferrous bisglycinate 36mg, methyl cobalamin 300µg, L-5-methyltetrahydrofolate 400µg, pyridoxal 5'-phosphate 5mg, vitamin C 15mg, 1 capsule daily methyl cobalamin 1mg daily sublingual.				
Aucoin (2018) [Canada, AMRO] [33]	Case study	Recurrent pregnancy loss (Female, 29 years)	*Vitex agnus-castus* fruit extract 166.6 mg, 2 capsules per day (fifth and six pregnancies) Progesterone 200 mg vaginal pessary twice daily (from week 5 to week 10 of fifth pregnancy only)	Nil	First pregnancy on presentation (fourth pregnancy in case received no treatment)	1	Serum β-human chorionic gonadotropic (HcG)(IU/ml)	**Increased HcG** 4th pregnancy: 459 5th pregnancy: 1200 6th pregnancy: Not reported
							Serum progesterone (nmol/ml)	**Increased progesterone** 4th pregnancy: 22.1 5th pregnancy: 85.0 6th pregnancy: Not reported
							Pregnancy outcome	**Live births** 4th pregnancy: spontaneous abortion at 5 weeks, 6 days 5th pregnancy: full-term live birth 6th pregnancy: 38 weeks' pregnancy with normal, live, singleton expected

Author (year) [Country, World region]	Design	Study Population	Intervention	Concomitant therapies	Control or Placebo	No. Participants (Intervention/ Placebo)	Measure of Outcome	Outcome
Bares, et al. (2008) [USA, AMRO] [31]	Uncontrolled trial	Hepatitis C (chronic)	12 weeks: Standardized silybin and soy phosphatidylcholine complex (IdB 1016) 314mg with 120mg silybin per capsule Dose 1: 314mg tds Dose 2: 628mg tds Dose 3: 942mg tds	Nil	Nil	37	Serum iron (ug/dL) [BL to Wk 12]	NS
							Total Iron binding capacity (ug/dL) [BL to Wk 12]	NS
							Transferrin-iron saturation (%) [BL to Wk 12]	NS
							Serum ferritin, by dose (ug/L) [BL to Wk 12]	**Reduced ferritin levels** All participants: -30 (p=0.0005) Dose 1: -51 (p=0.004) Dose 2: -13 (p=0.03) Dose 3: NS
							Serum ferritin, by stage of fibrosis (ug/L) [BL to Wk 12]	**Reduced ferritin levels (Stage III and IV)** Stage II: NS Stage III: -36 (p=0.005) Stage IV: -16 (p=0.01)
							Liver enzymes [BL to Week 12]	NS
Calabrese, et al. (2000) [USA, AMRO] [14]	Uncontrolled trial	Human immunedeficiency virus (Adults, >18 years)	Andrographolide (from *Andrographis paniculata*) 5 or 10 mg/kg tid (planned 20 mg/kg tid dose not administered due to adverse effects). Isolated herbal constituent	Nil	HIV negative patients	18 (HIV+, 13/HIV-, 5)	Adverse effects including allergy (including anaphylaxis), fatigue, headache, rash, diarrhea, nausea, abnormal taste, and others [BL to Wk 6]	**Adverse effects** HIV+: 12/13 (92%), one experienced anaphylaxis requiring hospitalization HIV-: 4/5 (80%)
							Serum AST [µL] [BL to Wk 6]	NS
							Serum ALT [µL] [BL to Wk 6]	**Increased ALT** HIV+: Wk 3, +22.3 (p<0.005); Wk 6, +20.6 (p<0.005); Wk 9, NS HIV-: NS
							Serum CD4 count [cell/mm3] [BL to Wk 6]	**Increased CD4 count** HIV+: Wk 3, NS; Wk 6, 501.1 vs 404.8 (p=0.002); Wk 9, NS HIV-: NS

Author (year) [Country, World region]	Design	Study Population	Intervention	Concomitant therapies	Control or Placebo	No. Participants (Intervention/ Placebo)	Measure of Outcome	Outcome
							HIV-1 RNA [log copies/ ml] [BL to Wk 6]	NS
Calabrese, et al. (2008) [USA, AMRO] [16]	Randomized controlled trial	Anxiety and depression (adults ⩾65 years old, without signs of dementia)	*Bacopa monnieri* aerial parts dry methanol extract tablet, standardized to 50% bacosides A and B, 300 mg once daily	Nil	Placebo	48 (24/24)	Rey Auditory Verbal Learning Test delayed recall (# of words) [BL to Wk 6 and 12]	**Increased learning** Wk 6: Bacopa, +0.2; placebo, -0.2 Wk 12: Bacopa, +1.2; placebo, +.01 Between group: p=0.03
							Rey Auditory Verbal Learning immediate reaction times [BL to Wk 6 and 12]	NS
							Center for Epidemiologic Studies Depression scale [BL to Wk 6 and 12]	**Reduced depression** Wk 6: Bacopa, -0.1; placebo, +1.8 Wk 12: Bacopa, -0.9; placebo, +0.8 Between group: p=0.05
							State-Trait Anxiety Inventory [BL to Wk 6 and 12]	**Reduced anxiety** Wk 6: Bacopa, -2.0; placebo, +2.7 Wk 12: Bacopa, -1.6; placebo, +1.1 Between group: p=0.04
							Stroop task reaction time (seconds) [BL to Wk 6 and 12]	**Reduced** Wk 6: Bacopa, -3.8; placebo, -0.6 Wk 12: Bacopa, -2.9; placebo, -0.4 Between group: p=0.003
							Stroop task errors (seconds) [BL to Wk 6 and 12]	NS
							Divided attention task score [BL to Wk 6 and 12]	NS
							Wechsler Intelligence Scale digit task [BL to Wk 6 and 12]	NS

Author (year) [Country, World region]	Design	Study Population	Intervention	Concomitant therapies	Control or Placebo	No. Participants (Intervention/ Placebo)	Measure of Outcome	Outcome
							Profile of Mood States [BL to Wk 6 and 12]	NS
							Heart rate [bpm] [BL to Wk 6 and 12]	**Reduced** Wk 6: Bacopa, -1.4; placebo, +2.8 Wk 12: Bacopa, -1.1; placebo, +5.1 Between group: p=0.01
							Blood pressure [mmHg] [BL to Wk 6 and 12]	NS
Canavan and Yarnell (2005) [USA, AMRO] [40]	Case report	Dermatitis not responsive to topical steroids (51-year-old white healthy female)	(1) Initial treatment: chlorine/water wash (2) Second treatment: *Calendula officinalis* and *Ocimum tenuiflorum* ointment, homeopathic rhus tox 30C (3) Third treatment: topical corticosteroid (specific drug and concentration unknown), homeopathic causticum 30C and arsenicum 30C (4) Fourth treatment: *Impatiens capensis* tincture and *Calendula officinalis* cream topically, homeopathic sulfur 30C (5) Fifth treatment: *Grindelia* spp tincture topically and *Grindelia* spp/*Calendula officinalis* cream	Homeopathic sulfur 30C	Nil	1	Skin area affected by rash, self- and physician-assessed	**Reduced rash** 1: reduction on left arm, no change on right 2: spread from arms to supra-pubic region, lower legs, and forearms 3: stable 4: stable 5: rash area stopped oozing and shrank gradually to total resolution
Crew, et al. (2012) [USA, AMRO] [17]	Randomized controlled trial	Breast cancer stage I-III hormone receptor negative, completed adjuvant treatment (survivors)	Oral Green tea (Poly E) – Sinecatechins, a combination of four catechin flavonoids from *Camellia sinensis*	Nil	Placebo	34 (26/8)	Dose-limiting toxicity	1 at 400mg (grade III rectal bleeding) 3 at 600mg (grade II weight gain, grade III indigestion and insomnia) 1 at 800mg (grade III liver functional abnormality)
							Maximum tolerated dose	600mg twice daily (BID)

Author (year) [Country, World region]	Design	Study Population	Intervention	Concomitant therapies	Control or Placebo	No. Participants (Intervention/ Placebo)	Measure of Outcome	Outcome
Crew, et al. (2015) [USA, AMRO] [18]	Secondary analysis						Hepatocyte Growth factor (HGF) [BL to Mth 2, 4 and 6]	**Reduced HGF** Poly E 2mths: 12.7% compared to placebo, 6.3% (p=0.04) 4 Mths and 6 mths: NS
							VEGF [BL to Mth 2, 4 and 6]	NS
							Lipids [BL to Mth 2, 4 and 6]	NS
							Oxidative damage [BL to Mth 2, 4 and 6]	NS
							Inflammatory biomarkers [BL to Mth 2, 4 and 6]	NS
D'Adamo (1992) [USA, AMRO] [41]	Case series	Human immunodeficiency virus/ Autoimmune deficiency syndrome	*Chelidonium majus* 175 mg, *Sanguinaria canadensis* 5 mg, *Ulmus rubra* 20 mg, 1 – 3 tid; concomitant use of *Glycyrrhiza glabra* solid extract (dose not stated). Capsules of freeze-dried extracts. (RZ_2)	Nil	Nil	13, 8 on anti-retroviral drugs; 5 not	Lymphadenopathy (n=8) [unknown]	8/8 had diminished node size and tenderness, 3/8 had total or near total resolution after 3 weeks of RZ2
							Serum CD8 lymphocyte count (n=11) [unknown]	1/11 mild increase (⩽7%), 5/11 no change, 4/11 mild decrease (⩽7%), 1/11 large decrease (>7%)
							Serum CD4 lymphocyte count (n-11) [unknown]	4/11 mild increase (⩽7%), 4/11 no change, 3/11 mild decrease
							Self-assessed energy level (n=8) [unknown]	6/8 energy increased, 2/8 no improvement
Frances (1998) [USA, AMRO] [42]	Case series	Asthma	Concomitant therapeutics highly variable but included: *Passiflora incarnata* tincture, *Piper methysticum* tincture, *Verbascum thapsus* spp tincture, *Eriodictyon* spp tincture, *Aspidosperma quebracho* tincture, *Oplopanax horridus* tincture, *Eleutherococcus senticosus* tincture, *Glycyrrhiza glabra* glycerite, *Echinacea* spp tablets, *Astragalus propinquus*	B complex, antioxidants, nutrients and homeopathic remedies	Nil	6	Beta-agonist inhaler use [unknown]	Elimination or substantial reduction in use

Author (year) [Country, World region]	Design	Study Population	Intervention	Concomitant therapies	Control or Placebo	No. Participants (Intervention/ Placebo)	Measure of Outcome	Outcome
			tincture, *Eupatorium perfoliatum* tincture, *Chelidonium majus* tincture, *Taraxacum officinale* tincture, *Silybum marianum* tincture, *Cynara scolymus* tincture, *Bupleurum falcatum* tincture, *Berberis* spp tincture, *Althaea officinalis* tincture, *Foeniculum vulgare* tincture, *Hypericum perforatum* tincture, *Actaea racemosa* tincture, *Panax ginseng* tincture, *Trifolium pratense* tincture					
Gerontakos and Casteleijn (2018) [Australia WPRO] [44]	Case study	Facial skin condition (unknown aetiology) association to nervous system	Herbal medicine *(Avena sativa, Cynara scolymus, Passiflora incarnata, Asparagus racemosus. Zingiber officinale, Gentian lutea, Ulmus rubra)*	Daily meditation and Australian Bush Flower Essence	6-10 weeks	1	Presentation of skin condition; digestion (presence of constipation and/or bloating); mental well-being (perceived stress levels)	**Reduced skin condition** At 10 weeks there was no return of skin condition. Improved digestive symptoms at 4 weeks. Self-reported association with stress and mental and physical wellbeing.
Greenlee, et al. (2007) [USA, AMRO] [53]	Randomized controlled trial	Healthy menstruating women (21 to 45 years)	12 weeks: Curcumin 95% 100 mg, *Cynara scolymus* leaf extract 100 mg, *Salvia rosmarinus* leaf extract 100 mg, silymarin 80% 100 mg, *Taraxacum officinalis* root extract 100 mg, *Schisandra chinensis* fruit extract 50 mg per capsule, 4 capsules twice daily	Nil	Dietary changes OR placebo	40 (15/10/15)	Adverse effects [BL to Wk 12]	Indigestion: Botanical, 5/15; Dietary, 1/10; Placebo, 0/15 Between group, p=0.014
							Serum estrogen fractions, any phase [% change] [BL to Wk 12]	NS
							Serum sex hormone-binding globulin, any phase [nmol/L] [BL to Wk 12]	NS
							Urine estrogen metabolites, late follicular (% change) [BL to Wk 12]	NS
							Body weight [BL to Wk 12]	NS

Author (year) [Country, World region]	Design	Study Population	Intervention	Concomitant therapies	Control or Placebo	No. Participants (Intervention/ Placebo)	Measure of Outcome	Outcome
							Serum dehydroepiandrosterone, early follicular phase [% change] [BL to Wk 12]	**Reduced DHEA** Botanical: -13.22; Diet: -18.03; Placebo: +8.66 Between group (botanical vs diet): NS Between group (botanical vs placebo): p=0.016
							Serum androgens, all others, any phase [% change] [BL to Wk 12]	NS
Hawrelak and Meyers (2010) [Australia, WPRO] [45]	Uncontrolled trial	Irritable bowel syndrome	DA-IBS Formula: Dried bilberries *(Vaccinium myrtillus)* 20g, Slippery elm *(Ulmus fulva)* 9g, Cinnamon *(Cinnamomum zeylanicum)* 3g, Agrimony *(Agrimonia eupatoria)* 6g. C-IBS formula: Lactulose 6g, Slippery elm *(Ulmus fulva)* 14g, Licorice *(Glycyrrhiza glabra)* 3g, Oat bran *(Avena sativa)* 4g.	Twice daily in 250 ml apple juice for 3 weeks	Nil	31 (21/10)	Bowel movements per day [BL to Wk 3]	**Reduced (Diarrhea subtype)** DA-IBS: -0.19 (p=0.03) **Increased (Constipation subtype)** C-IBS: +0.22 (p=0.02)
							Consistency of stool [BL to Wk 3]	**Increased (Constipation subtype)** DA-IBS: NS; C-IBS: +0.67 (p<0.0001)
							Sense of straining [BL to Wk 3]	**Reduced straining** DA-IBS: -0.19 (p=0.004); C-IBS: -0.74 (p<0.0001)
							Sense of urgency [BL to Wk 3]	DA-IBS: NS C-IBS: NS
							Abdominal pain [BL to Wk 3]	**Reduced pain** DA-IBS: -0.19 (p=0.006); C-IBS: -0.20 (p=0.03)
							Bloating severity [BL to Wk 3]	**Reduced bloating** DA-IBS: -0.32 (p<0.0001); C-IBS: -0.19 (p=0.03)
							Flatulence severity [BL to Wk 3]	**Reduced (Diarrhea subtype)** DA-IBS: -0.25 (p=0.0001); C-IBS: NS
							Global symptom severity [BL to Wk 3]	**Reduced overall symptoms** DA-IBS: -0.40 (p=0.002); C-IBS: -0.71 (p=0.0005)

Author (year) [Country, World region]	Design	Study Population	Intervention	Concomitant therapies	Control or Placebo	No. Participants (Intervention/ Placebo)	Measure of Outcome	Outcome
Heron and Yarnell (2001) [USA, AMRO] [27]	Case reports	All adults who took *Larrea tridentata* tincture in a naturopathic practice between Jan 1997 and Oct 1998	*Larrea tridentata* aerial parts tincture in various herbal formulas, 32 – 240 ml over several months	Nil	Nil	12	Signs and symptoms of liver damage (n=12)	Nil
							Serum aminotransferases	NS
							Lactate dehydrogenase	NS
							Total bilirubin	NS
							Alkaline phosphatase	NS
Hudson (1991) [USA, AMRO] [46]	Case reports	Cervical cancer (Class IV)	9 weeks: Escharotic treatment to the cervix: bromelain powder was applied to the cervix for 15 min followed removal with *Calendula officinalis* succus, *Sanguinaria canadensis* tincture 75% and zinc chloride 90 g/60 ml sterile water 25% was applied to cervix for 1 min then removed with *Calendula officinalis* succus, vaginal suppositories containing magnesium, iron, *Hydrastis canadensis*, vitamin A, *Melaleuca alternifolia* volatile oil, *Citrus x aurantium* volatile oil, and *Thuja occidentalis* volatile oil placed for 24 hours, then vinegar vaginal douche. Repeated twice weekly for five weeks. During treatment, oral supplements: vitamin C 6 – 10 g, beta-carotene 120,000 – 180,000 IU, selenium 400 mcg, *Taraxacum officinale* root and *Arctium lappa* root capsules 2 – 6 each daily, vegan diet, constitutional homeopathic remedy. After treatment: vitamin A emulsion on a tampon	During treatment, oral supplements: vitamin C 6 – 10 g, beta-carotene 120,000 – 180,000 IU, selenium 400 mcg; vegan diet, constitutional homeopathic remedy; After treatment: vitamin A emulsion on a tampon (for one week) applied each night, then rotated again for two more weeks.	Nil	7	Pap smear [BL to Wk 10, Mth 3, 6 and 12]	**Reduced pap smear** BL: class IV (7) Wk 10: class I (4), class II (1), class IV (2 – 1 regression of dysplasia on ectocervix to class I) Mth 3: class I continued remission (1-4), regression of endocervix in subject 6 to class II, class II (subject 5), class IV (subject 7 – continue to show regression of dysplasia on ectocervix to complete remission) Mth 6: complete remission (1-4), class II (subject 5) class IV (subject 6 despite cryosurgery) class I complete remission (subject after conization) Mth 12: remission (1-4), partial relapse class II-III (Subject 5). Complete remission (subjects 6-7)

Author (year) [Country, World region]	Design	Study Population	Intervention	Concomitant therapies	Control or Placebo	No. Participants (Intervention/ Placebo)	Measure of Outcome	Outcome
			(for one week) or *Ulmus rubra* suppositories (for one week) were applied each night, then rotated again for two more weeks.					
Jiang, et al. (2013) [USA, AMRO] [34]	Randomized controlled trial	Colorectal cancer	*Zingiber officinalis (radix)* (250mg capsules total of 2g daily)	Nil	Placebo	50 normal risk (14/16) increased risk (10/10)	Colonic COX-1 protein level [BL to Dy 28]	**Risk reduced in high-risk patients** Ginger, -23.8%; Placebo, 18.9%, (p=0.03) Normal risk CRC (NS)
							15-PGDH protein level [BL to Dy 28]	NS
Lamson and Wright (2003) [USA, AMRO] [47]	Case study	Early renal functional impairment	Capsule one: *Rehmannia glutinosa (rehmannia)* prepared root, *Dioscorea oppositifolia* (Chinese yam) rhizome, *Cornus officinalis* (cornelian cherry) fruit, *Wolfiporia cocos* (hoelen) sclerotium, Alisma plantago-aquatica (water plantain) rhizome, *Cinnamomum cassia* (cassia cinnamon) bark, *Aconitum carmichaeli* (aconite) prepared root. Dose: 1 g TID Capsule two: *Didymocarpus pedicellata* (shilapushpa) leaf, *Bergenia ligulata* (pashanbhed) root, *Rubia cordifolia* (Indian madder) root, *Ocimum tenuifolium* (holy basil) leaf, *Achyranthes aspera* (chaff flower) leaf, *Cyperus rotundus* (Java grass) rhizome, *Crataeva religiosa* (sacred garlic pear) bark, vitamin B6, magnesium aspartate, Arctostaphylos uva ursi (uva ursi) leaf. Dose: 1150 mg tid Capsule three: vitamin	Chinese herbal formula 500mg capsules, Ayurvedic herbal formula (includes vitamin B6 25mg and Magnesium aspartate 100mg) and Nutritional/ Botanical formula (vitamin A 5000IU, vitamin C 100mg, vitamin B6 10mg, Potassium 99mg, Raw kidney concentrate (bovine) 300mg, *Urtica dioca* 50mg, *Taraxacum officinale* root	Nil	1	Blood urea nitrogen (mg/dL) [BL to Yr 4]	**Reduced urea** -9
							Serum Creatinine (mg/dL) [BL to Dy 5]	**Reduced creatinine** -0.2
							24 hrs Creatinine Clearance mL/min	**Increased creatinine clearance** +53

Author (year) [Country, World region]	Design	Study Population	Intervention	Concomitant therapies	Control or Placebo	No. Participants (Intervention/ Placebo)	Measure of Outcome	Outcome
			A, vitamin C, vitamin B6, potassium, raw bovine kidney concentrate, *Urtica dioica* (stinging nettle) leaf, *Taraxacum officinale* (dandelion) root, *Petroselinum crispum* (parsley) leaf. Dose: 1300 mg tid	50mg, Parsley leaf 50mg)				
Lauche, et al. (2015) [Germany, EURO] [56]	Randomized controlled trial (crossover)	Irritable bowel syndrome	3 weeks: 2% Caraway oil hot poultice (topical oils) applied to abdomen once daily for 20 – 30 mins	Nil	1. Hot olive oil poultice 2. Cold olive oil poultice	48	IBS Symptom Severity Score [BL to Wk 3]	**Reduced severity** *All types:* Caraway oil -35.4; Olive oil (hot) -20.0; Olive oil (cold) -4.3 Between Group Caraway and Olive Oil (hot) NS Between Group Caraway and Olive Oil (cold) -38.4 (p=0.03) *IBS Mixed type:* Between Group Caraway and Olive Oil (hot) -43.2 (p=0.02) Between Group Caraway and Olive Oil (cold) -55.8 (p=0.009) *IBS-C NS* *IBS-D NS*
							European Quality of Life (5 Domain) [BL to Wk 3]	Index NS Visual analog score NS
							Irritable Bowel Syndrome Quality of Life [BL to Wk 3]	All domains: NS
							Hamilton Anxiety and Depression Scale [BL to Wk 3]	NS
Lauche, et al. (2016) [Germany EURO] [57]	Randomized controlled trial	Osteoarthritis (knee)	Cabbage leaf wraps (CLW) (1-2 leaves applied as a poultice) 4 weeks: 2hrs per day	Nil	Diclofenac gel (TPG) and usual care (UC)	81 (27/27/27)	Pain intensity, Visual Analog Scale [BL to Wk 4, Wk 12]	**Reduced pain** UC Wk 4: Between group -12.2 pts (p=0.033) Wk 12: NS TPG Wk 4: NS Wk 12: NS

Author (year) [Country, World region]	Design	Study Population	Intervention	Concomitant therapies	Control or Placebo	No. Participants (Intervention/ Placebo)	Measure of Outcome	Outcome
							Western Ontario and McMaster Universities Arthritis Index [BL to Wk 4, Wk 12]	**Reduced disability** Pain Wk 4: Cabbage leaf -1.3; Usual care +0.2 Between group (UC) -1.3 (p=0.002) Between group (TPG) NS Wk 12: Cabbage leaf -1.0; Usual care +0.2 Between group (UC) -1.1 (p=0.009) Between group (TPG) NS Stiffness Wk 4: Cabbage leaf -1.0; Usual care +0.3 Between group (UC) -1.1 (p=0.031) Between group (TPG) NS Wk 12: Cabbage leaf -1.0; Usual care +0.4 Between group (UC) -1.1 (p=0.039) Between group (TPG) NS Physical function Wk 4: Cabbage leaf -0.9; Usual care +0.3 Between group (UC) -1.2 (p=0.002) Between group (TPG) NS Wk 12: Cabbage leaf -0.8; Usual care +0.3 Between group (UC) -1.0 (p=0.017) Between group (TPG) NS

Author (year) [Country, World region]	Design	Study Population	Intervention	Concomitant therapies	Control or Placebo	No. Participants (Intervention/ Placebo)	Measure of Outcome	Outcome
							Short Form 36 [BL to Wk 4, Wk 12]	**Increased Quality of Life** Physical component Wk 4: Cabbage leaf +4.1; Usual care +1.3; Diclofenac -0.9 Between group (UC) NS Between group (TPG) +5.0 (p=0.004) Wk 12: Cabbage leaf +4.5; Usual care +0.1; Diclofenac -2.2 Between group (UC) +4.3 (p=0.007) Between group (TPG) +7.8 (p=0.0001) Physical functioning Wk 4: Cabbage leaf +7.2; Usual care -2.5 Between group (UC) +9.4 (p=0.004) Between group (TPG) NS Wk 12: Cabbage leaf +8.3; Usual care -0.9; Diclofenac -0.9 Between group (UC) +9.0 (p=0.019) Between group (TPG) +12.0 (p=0.026) Physical role functioning Wk 4: NS Wk 12: Cabbage leaf +5.5; Diclofenac -16.4 Between group (UC) NS Between group (TPG) +22.1 (p=0.024) Bodily pain Wk 4: NS Wk 12: Cabbage leaf +9.0; Usual care -1.2; Diclofenac -1.7

Author (year) [Country, World region]	Design	Study Population	Intervention	Concomitant therapies	Control or Placebo	No. Participants (Intervention/ Placebo)	Measure of Outcome	Outcome
								Between group (UC) +10.7 (p=0.007) Between group (TPG) +13.7 (p=0.003) General health perception Wk 4: NS Wk 12: Cabbage leaf +3.7; Diclofenac -5.0 Between group (UC) NS Between group (TPG) +8.9 (p=0.024) Mental component: NS Vitality: NS Social role functioning: NS Emotional role functioning: NS Mental health: NS
							Arthritis-Specific Self-Efficacy Short-Form Scale [BL to Wk 4, Wk 12]	NS
							Physical Function (30s Chair Stand Test) [BL to Wk 4]	**Reduced Pain** Number of sit ups: NS Pain: Cabbage leaf -1.2 Usual care -0.4 Between group (UC) -1.4 (p=0.003) Diclofenac -0.1 Between group (TPG) -1.3 (p=0.033)
							Pressure Pain Sensitivity Threshold [BL to Wk 4]	**Increased threshold to pressure pain** Maximum: NS Quadriceps muscle: Cabbage leaf, +16.5; Usual care -64.1; Diclofenac -53.2

Author (year) [Country, World region]	Design	Study Population	Intervention	Concomitant therapies	Control or Placebo	No. Participants (Intervention/ Placebo)	Measure of Outcome	Outcome
								Between group (UC) +77.8 (p=0.010) Between group (TPG) +90.2 (p=0.039) Pes anserinus: Cabbage leaf +59.1; Usual care -31.3 Between group (UC) +127.1 (p=0.010) Between group (TPG) NS Lateral joint line: NS
Leach, et al. (2006) [Australia, WPRO] [11]	Randomized controlled trial	Chronic venous ulcers	12 weeks: Horse-chestnut *(Aesculus hippocastanum)* seed extract (HSCE) 375mg HCSE, standardized to 75mg aecin	Standardized wound dressing protocol	Placebo + Standardized wound dressing protocol	54 (27/27)	Healed leg ulcers (%) [BL to Wk 4, 8, 12]	NS
							Change in wound dimension [BL to Wk 4, 8, 12]	NS
							Symptoms of chronic venous insufficiency [BL to Wk 4, 8, 12]	NS
							Changes in wound topography [BL to Wk 4, 8, 12]	**Reduced wound slough** Between groups: p=0.045
							Frequency of dressing changes [BL to Wk 4, 8, 12]	**Reduced frequency of dressing changes** Wk 12: HSCE 1.11 (p=0.009); Placebo 2.48 Between group (p=0.009)
							Recurrent episodes [BL to Wk 4, 8, 12]	NS
Leach (2014) [Australia, WPRO] [12]	Case series (prospective)	Chronic venous ulcers	8 -12 weeks: *Aesculus hippocastanum* seed extract 375 mg (standardized to contain 75 mg aescin), 1 tablet twice daily	Standardized wound dressing protocol	None	2	Factors associated with healing [BL to Wk 4 and 8]	Smaller wound volume, mild-to-moderate chronic venous insufficient, improvement in underlying chronic venous insufficient
							Factors associated with non-healing [BL to Wk 4 and 8]	*Pseudomonas aeruginosa* infection of ulcer, larger wound volume, severe chronic venous insufficient that does not improve

Author (year) [Country, World region]	Design	Study Population	Intervention	Concomitant therapies	Control or Placebo	No. Participants (Intervention/ Placebo)	Measure of Outcome	Outcome
Logan and Beaulne (2002) [Canada, AMRO] [55]	Case report	Irritable bowel syndrome	20mL; Enteric-coated peppermint oil (Herbal/ aromatherapy), 0.2mL three times daily	Nil	Nil	1	Lactulose Hydrogen Breath Test [BL to Day 20+6]	**Reduced levels** *Hydrogen* – Fasting: -6ppm; 20 min: -19ppm; 60 min: -22ppm *Methane* – Fasting: -0.0ppm; 20 min: -2.0ppm; 60 min: -0.0pm
							Self-reported symptoms [BL to Day 20]	**Decreased bloating, pain, eructation, improved frequency of bowel function**
Nelson, et al. (2017) [USA, AMRO] [48]	Case report	Plantar warts of the left hallux unresponsive to cryotherapy (24-year-old white man)	63 days (+ 30 days follow-up): *Hypericum perforatum* aerial parts 2.5%, *Lavandula officinalis* leaf 10%, *Glycyrrhiza glabra* root 2.5%, *Melissa officinalis* leaf 6%, *Eleutherococcus senticosus* root 4%, and *Sarracenia* spp. aerial parts 25% gel with allantoin applied 1 – 2 times daily after application of a pumice stone to the lesions	Nil	Nil	1	Extent of visible lesion	**Reduced lesions** *Day 5:* 'remarkable' reduction *Day 17:* return of epidermal ridges in the affected toe *Day 27:* no further progress *Day 36:* no further progress *Day 46:* appearance of keratotic debris and superficial epidermal necrosis *Day 56:* same as day 46 *Day 63:* changes from day 46 resolved, wart largely resolved; benign, painless petechial hemorrhages on medial margin *Day 90:* total resolution
Newton, et al. (2006) [USA, AMRO] [49]	Randomized controlled trial	Menopausal hot flushes	(1) *Actaea racemosa* root 160 mg standardized to 2.5% triterpenes daily (capsule) + diet counselling (1 phone call; fruit and vegetable booklet (2) Multibotanical: *Actaea racemosa* root 200mg, *Medicago sativa* aerial parts 400 mg, boron 4 mg, *Vitex agnus-castus* fruit 200 mg, *Angelica sinensis* processed root 400 mg, *Chamaelirium luteum* root 200 mg, *Glycyrrhiza*	Diet counselling	Lactose capsules plus dietary counselling (1 phone call from a clinical dietician and a 34-page booklet reinforcing fruit and vegetable	351 (257/77) 1: n=77 2: n=74 3: n=77 4: n=29	Frequency of vasomotor symptoms [BL to Mth 3, 6, 12]	**Reduced in Group 4** Group 1, 2 and 3: NS Group 4: Mth 3, -4.55 ($p<0.001$) Mth 6, -3.86 ($p<0.001$) Mth 12, -3.76 ($p<0.001$) Overall, -4.06 ($p<0.001$)
							Intensity of vasomotor symptoms [BL to Mth 3, 6, 12]	Group 1, 2, 3 and 4: NS

Author (year) [Country, World region]	Design	Study Population	Intervention	Concomitant therapies	Control or Placebo	No. Participants (Intervention/ Placebo)	Measure of Outcome	Outcome
			glabra root 200 mg, *Avena sativa* seed 400 mg, *Punica granatum* fruit 400 mg, *Eleutherococcus senticosus* root extract standardized to 0.8% eleutherosides E and B, 400 mg daily + diet counselling (1 phone call; fruit and vegetable booklet). (3) Multibotanical + soy diet counselling: 5 phone calls from a clinical dietician and a 34-page booklet recommending 2 soy food servings daily (equivalent to 12 – 20 g soy protein) (4) Conjugated equine estrogen 0.625mg; + medroxyproges-terone acetate (2.5mg) for women with a uterus + diet counselling (1 phone call; fruit and vegetable booklet)		intake).		Wiklund Menopause Symptom Scale score [BL to Mth 3, 6, 12]	**Reduced in Group 4** Group 1, 2 and 3: NS Group 4: Mth 3, -2.60 ($p<0.001$) Mth 6, -1.78 ($p<0.001$) Mth 12, -1.77 ($p<0.001$) Overall, -2.05 ($p<0.001$)
Rodriguez Malavé (1991) [Puerto Rico, AMRO] [43]	Case series	Asthma (patients of various ages seen in a single naturopathic clinic)	Bromelain (>20 yr only): 250 mg TID, Ma huang compound (>20 yr only): extracts of *Ephedra sinica* 200 mg (standardized to 12 mg ephedrine), *Zingiber officinale* 65 mg, *Glycyrrhiza glabra* 50 mg (standardized to 5% glycyrrhizic acid), *Althaea officinalis* 50 mg (standardized to mucilage content of 30 – 40%) 50 mg, *Drosera rotundifolia* 40 mg, *Euphorbia hirta* 40 mg, *Polygala senega* 40 mg, *Hydrastis canadensis* 20 mg (standardized to 5% total alkaloids, 1 tablet QID	Bromelain, constitutional homeopathic remedy	Nil	6 (1) 51 yrs, (2) 27 yrs, (3) underage, (4) 21 yrs, (5) 24 yrs, (6) >20 yrs	Number of subjects improved	**Increased** <21 yr: 16/17 (94%) >20 yr: 25/29 (86.2%)

Author (year) [Country, World region]	Design	Study Population	Intervention	Concomitant therapies	Control or Placebo	No. Participants (Intervention/ Placebo)	Measure of Outcome	Outcome
			Compound herbal cough elixir (<21 yr only): *Glycyrrhiza glabra* root, *Inula helenium* root, *Trifolium pratense* flower, *Prunus serotina* bark, *Marrubium vulgare* aerial parts, *Grindelia robusta* aerial parts, *Lobelia inflata* leaf and seed, *Foeniculum vulgare* fruit, *Lomatium dissectum* root, *Pinus strobus* bark, *Populus* spp. bud, 10 or 30 drops four times daily Constitutional homeopathic remedy: individualized.					
Sarris, et al. (2009) [Australia WPRO] [25]	Randomized controlled trial (crossover)	Adults (age 18-65) with Massive Depressive Disorder and comorbid anxiety (minimum score of 10 on Beck Anxiety Inventory)	*Hypericum perforatum* (St. John's wort (SJW) 1.8g (standardized 990mcg of hypericin, and 1500 mcg of flavone glycoside) and *Piper methysticum* (Kava) 2.66g (standardized to 50 mg of kavalactones) (8 weeks)	Nil	Placebo	28	Beck Depression Inventory (BDI-II) [Wk 2 to Wk 6 and 10]	**Reduced depression** Intention-to-treat Over time: p=0.047 Between group: p=0.023 Completer analyses Over time: p=0.008 Between group: p=0.003
							Beck Anxiety Inventory [Wk 2 to Wk 6 and 10]	NS
							WHO Quality of Life Survey (WHOQOL) [Wk 2 to Wk 6 and 10]	NS
Sarris, et al. (2009) [Australia, WPRO] [37]	Randomized controlled trial	Generalized anxiety (adults (18-65 years with > 1 month of > 10 on Beck Anxiety Inventory)	Tablet from pressed, dried aqueous extract of *Piper methysticum* (Kava) standardized to 50mg kavalactones per tablet		placebo	60	Hamilton Anxiety Scale (HAM-A) [BL to Wk 1 and phase 1 and 2]	**Reduced anxiety** Phase 1: −9.9 vs −0.8, (p<0.0001) Phase 2; −10.3 vs. +3.3, (p<0.0001) Increased pooled effect in kava across phases (p<0.0001)

Author (year) [Country, World region]	Design	Study Population	Intervention	Concomitant therapies	Control or Placebo	No. Participants (Intervention/ Placebo)	Measure of Outcome	Outcome
							Beck Anxiety Inventory (BAI) [BL to Wk 1 and post treatment 1 and 2]	**Reduced anxiety** Phase 1: −7.2 vs −1.6, (p=0.001) Phase 2: −8.1 vs. +1.4, (p=0.001) Increased pooled effect in kava (p=0.001)
							Montgomery – Asberg Depression Rating Scale (MADRS) [BL to Wk 1 and post treatment 1 and 2]	**Reduced depression** Phase 1: −5.9 vs −1.1, (p=0.003) Phase 2: −7.6 vs. +3.3, (p=0.003)
Sarris, et al. (2012) [Australia, WPRO] [24]	Randomized controlled trial	Major Depressive Disorder (adults)	26 weeks: St John's wort (SJW) (Hypericum perforatum) versus sertraline and placebo (SJW (LI-160, 900 – 1500 mg, standardized for between 0.12 – 0.28 % hypericin) vs sertraline (50 – 100 mg))	Nil	placebo	124 (35/49/ 40)	Hamilton depression rating scale (HAM-D) [Wk 10 to 26]	NS
							Beck Depression inventory (BD) and improvement (CGI-I) [Wk 10 to 26]	NS
							Global Assessment of Functioning (GAF) [Wk 10 to 26]	NS
							Clinical Global Impressions Scales for Severity (CGI-S) [Wk 10 to 26]	NS
Sarris, et al. (2013) [Australia, WPRO] [30]	Randomized controlled trial	Driving ability	Pressed dried aqueous extract of kava standardized to contain 60mg of kavalactones per tablet (total acute dose of 180mg of kavalactones – 3 tablets) administered 90 min before 15min driving simulation	Nil	Oxazepam (30mg) or placebo	22	Braking reaction time (ms) [post intervention]	**Faster braking reaction time** Kava, 104; Oxazepam, 116; placebo, 101 Between group (p<0.001)
							Deviation of lateral position [post intervention]	NS
							Speed deviation [post intervention]	NS
							Concentration lapse [post intervention]	**Reduced concentration lapse** Kava, 1.55; Oxazepam, 2.73 (p=0.033)

Author (year) [Country, World region]	Design	Study Population	Intervention	Concomitant therapies	Control or Placebo	No. Participants (Intervention/ Placebo)	Measure of Outcome	Outcome
							Crashes [post intervention]	NS
							Bon-Lader mood visual analogue scale [post intervention]	Treatment and time interaction (p=0.032) Alertness subscale reduced in oxazepam (p<0.01)
							Safety (Fatigue) [post intervention]	NS
Saunders, et al. (2007) [Canada, AMRO] [22]	Uncontrolled trial	Upper respiratory tract infections (URTI) in children	10 days: *Echinacea purpurea* aerial	One child received vitamin A, C and E and zinc	Nil	11	URTI symptoms [BL to day 13]	**Reduced symptoms** Sneezing 5/11 – 1/11 Nasal secretions 5/11 -2/11 Cough 7/11 – 2/11 Difficulty breathing 5/11 – 2/11 Difficulty swallowing 2/11 – 0/11
							Other symptoms [BL to day 13]	Eye discharge 1/11 – 0/11 Lung rattling 1/11 – 0/11 Abdominal tenderness 1/11 – 1/11 Ear cerumen 2/11 – 0/11 Tonsil enlargement 2/11 – 1/11 Lymph enlargement 9/11 – 7/11
Scholey, et al. (2017) [Australia, WPRO] [51]	Randomized controlled trial	Sleep difficulties	3 weeks: Sour date *(Zizyphus jujube var. spinosa)* ext. equiv. to dry seed 4.5g; Hops *(Humulus lupulus)* ext. equiv. to dry flower 500mg	Lactium™ (hydrolyzed milk protein; alpha casozepine enriched) 75 mg; magnesium oxide (equivalent magnesium) 81.7 mg (52.5 mg); vitamin B6; pyridoxine hydrochloride	2 Weeks (+ 1 week run-in)	170	Pittsburgh Sleep Quality Index (PSQI) [BL to Wk 3]	NS
							Leeds Sleep Evaluation Questionnaire [BL to Wk 3]	NS
							Epworth Sleepiness Scale [BL to Wk 3]	NS
							Insomnia Severity Index [BL to Wk 3]	NS
							Consensus Sleep Diary [BL to Wk 3]	NS

Author (year) [Country, World region]	Design	Study Population	Intervention	Concomitant therapies	Control or Placebo	No. Participants (Intervention/ Placebo)	Measure of Outcome	Outcome
				(equivalent pyridoxine) 10 mg (8.23 mg)			Burckhardt Quality of Life Scale [BL to Wk 3]	NS
							Chalder Fatigue Scale [BL to Wk 3]	NS
							Bond-Lader Visual Analog Scale [BL to Wk 3]	NS
							State-Trait Anxiety Inventory State subscale [BL to Wk 3]	NS
							Stress and Fatigue Visual Analog Mood Scales [BL to Wk 3]	NS
							Multi-tasking Framework [BL to Wk 3]	NS
Shathirapathiyet al. (2015) [India, SEARO] [58]	Randomized controlled trial	Psoriasis	10 days: Starch-fortified turmeric bath with naturopathy interventions	Massage, yoga, hydrotherapy, diet therapy	Naturopathy interventions only (massage, yoga, hydrotherapy, diet therapy	60 (30/30)	Psoriasis Area and Severity Index [BL to Dy 10]	**Reduced psoriasis severity** Turmeric Bath: -13.9; Naturopathy only: -0.15 Between group: p<0.01
Steels, et al. (2017) [Australia, WPRO] [32]	Randomized controlled trial	Menopausal symptoms	12 weeks: *Trigonella foenum-graecum* L. de-husked seed extract 300 mg extract equivalent to 9.9 g dry herb, standardized to minimum 50% furostanol saponins, 1 capsule twice daily	Nil	Placebo: Maltodextrin in identical capsule	104 (54/50)	Vasomotor symptoms (Menopause-Specific Quality of Life Questionnaire – MENQOL) [BL to Wk4, Wk8, Wk12]	**Reduced vasomotor symptoms** Herbal: Wk 4, -1.3; Wk 8, -1.7; Wk 12, -2.1 Placebo: Wk 4, +0.3; Wk 8, +0.2; Wk 12, +0.2 Between group, p<0.001
							Psychosocial symptoms (MENQOL) [BL to Wk4, Wk 8, Wk 12]	**Reduced psychosocial symptoms** Herbal: Wk 4, -0.7; Wk 8, -1.1; Wk 12, -1.0 Placebo: Wk 4, +0.1; Wk 8, -0.1; Wk 12, -0.1 Between group, p<0.001

Author (year) [Country, World region]	Design	Study Population	Intervention	Concomitant therapies	Control or Placebo	No. Participants (Intervention/ Placebo)	Measure of Outcome	Outcome
							Physical symptoms (MENQOL) [BL to Wk4, Wk 8, Wk 12]	**Reduced physical symptoms** Herbal: Wk 4, -0.7; Wk 8, -1.0; Wk 12, -1.0 Placebo: Wk 4, -0.2; Wk 8, -0.4; Wk 12, −0.3 Between group, p<0.001
							Sexual symptoms (MENQOL) [BL to Wk4, Wk 8, Wk 12]	**Reduced sexual symptoms** Herbal: Wk 4, -0.8; Wk 8, -1.4; Wk 12, -1.4 Placebo: Wk 4, +0.1; Wk 8, -0.3; Wk 12, -0.2 Between group, p<0.001
							Impact on Total Quality of Life (MENQOL) [BL to Wk4, Wk 8, Wk 12]	**Reduced quality of life** Herbal: Wk 4, -3.5; Wk 8, -5.2; Wk 12, -5.4 Placebo: Wk 4, -0.3; Wk 8, -0.6; Wk 12, -0.4 Between group, p<0.001
Steels, et al. (2018) [Australia, WPRO] [50]	Randomized controlled trial	Menopausal hot flushes	*Tinospora cordifolia* stem 100 mg, *Asparagus racemosus* rhizome 100 mg, *Withania somnifera* root 100 mg, *Commiphora mukul* gum exudate 225 mg, 1 capsule twice daily	Nil	Placebo: Maltodextrin in identical capsule	104 (54/50)	Vasomotor symptoms [Menopause-Specific Quality of Life Questionnaire – MENQOL] [BL to Wk4, Wk 8, Wk 12]	**Reduced vasomotor symptoms** Herbal: Wk 4, -1.4; Wk 8, -1.9; Wk 12, -1.6 Placebo: Wk 4, +0.3; Wk 8, +0.2; Wk 12, +0.2 Between group, p<0.001
							Psychosocial symptoms [MENQOL] [BL to Wk4, Wk 8, Wk 12]	**Reduced psychosocial symptoms** Herbal: Wk 4, -0.9; Wk 8, -1.1; Wk 12, -0.9 Placebo: Wk 4, +0.3; Wk 8, -0.1; Wk 12, -0.1 Between group, p<0.001
							Physical symptoms [MENQOL] [BL to Wk4, Wk 8, Wk 12]	**Reduced physical symptoms** Herbal: Wk 4, -0.8; Wk 8, -1.2; Wk 12, -0.9 Placebo: Wk 4, -0.2; Wk 8, -0.4; Wk 12, -0.3 Between group, p=0.002

Author (year) [Country, World region]	Design	Study Population	Intervention	Concomitant therapies	Control or Placebo	No. Participants (Intervention/ Placebo)	Measure of Outcome	Outcome
							Sexual symptoms [MENQOL] [BL to Wk4, Wk 8, Wk 12]	**Reduced sexual symptoms** Herbal: Wk 4, -0.7; Wk 8, -1.0; Wk 12, -1.3 Placebo: Wk 4, +0.1; Wk 8, -0.3; Wk 12, -0.2 Between group, p<0.001
							Impact on Total Quality of Life [MENQOL] [BL to Wk4, Wk 8, Wk 12]	**Reduced quality of life** Herbal: Wk 4, -3.8; Wk 8, -5.2; Wk 12, -4.8 Placebo: Wk 4, +0.3; Wk 8, -0.6; Wk 12, -0.4 Between group, p<0.001
							7-day incidence of daytime hot flushes [BL to Wk4, Wk 8, Wk 12]	**Reduced hot flushes** Herbal: Wk 4, -8 (-30%); Wk 8, -14 (-50%); Wk 12, -18 (-64%) Placebo: Wk 4, -1 (-6%); Wk 8, -0.0 (0%); Wk 12, +4 (+22%) Between group, p<0.001
							7-day incidence of night sweats [BL to Wk4, Wk 8, Wk 12]	**Reduced night sweats** Herbal: Wk 4, -7 (-50%); Wk 8, -7 (-50%); Wk 12, -10 (-71%) Placebo: Wk 4, -4 (-36%); Wk 8, -3 (-27%); Wk 12, -1 (-9%) Between group, p<0.001
							7-day incidence of total flushes [BL to Wk4, Wk 8, Wk 12]	**Reduced total flushes** Herbal: Wk 4, -18 (-43%); Wk 8, -22 (-52%); Wk 12, -28 (-67%) Placebo: Wk 4, -17 (-19%); Wk 8, -17 (-19%); Wk 12, +1 (+3%) Between group, p<0.001

Author (year) [Country, World region]	Design	Study Population	Intervention	Concomitant therapies	Control or Placebo	No. Participants (Intervention/ Placebo)	Measure of Outcome	Outcome
							Safety measurements – Blood pressure, weight (kg), fasting blood glucose, serum cholesterol, red cell count, hamatocrit, mean cell volume, mean cell hemoglobin, total protein, albumin [BL to Wk4, Wk 8, Wk 12]	NS
Suskind, et al. (2013) [USA, AMRO] [21]	Uncontrolled trial	Inflammatory Bowel Disorder (IBD) (Pediatric)	Curcumin 500mg	Standard therapy	Nil	11	Pediatric Ulcerative Colitis Index (<30) [BL to Wk 3]	**Reduced symptoms** -20 pts in 2 patients (=remission)
							Pediatric Crohn's Disease Activity Index (<34) [BL to Wk 3]	**Reduced symptoms** -5 (to 0) in 1 patient
Szczurko, et al. (2011) [Canada, AMRO] [23]	Uncontrolled trial	Vitiligo vulgaris (12 – 35 yo)	12 weeks: *Ginkgo biloba* 60mg (standardized to 15mg gingkoflavonglycosides and 4mg terpene lactones per pill), 1 capsule twice per day	Nil	Nil	12	Vitiligo Area Scoring Index [BL to Wk 12]	**Reduced affected area** Total: -0.05 (p=0.021)
							Vitiligo European Task Force Score [BL to Wk 12]	**Reduced disease activity** Area: NS Staging: NS Disease activity: -3.9 (p<0.001)
Vohra, et al. (2007) [Canada, AMRO] [29]	Randomized controlled trial	Children (3 to 12 years) with spontaneous upper respiratory tract infections	Group 1: *Panax quinquefolius* root extract aqueous solution: 26 mg/kg day 1 (max 1800 mg), 17 mg/kg day 2 (max 1200 mg), 9 mg/kg day 3 (max 600 mg) day 3 (all in three equally divided doses) Group 2: same product as above at half the doses stated Treatment was started within 24 hours of onset of upper respiratory tract infection symptoms in all groups	unspecified	Placebo	45 (15/15/15)	Adverse events	NS
							Canadian Acute Respiratory Infection Flu Scale [days to drop to 25% below onset of infection] (compared to controls)	NS
							Use of antipyretics, antibiotics, or any other treatments for respiratory infections (compared to controls)	NS

Author (year) [Country, World region]	Design	Study Population	Intervention	Concomitant therapies	Control or Placebo	No. Participants (Intervention/ Placebo)	Measure of Outcome	Outcome
Watson, et al. (2014) [Australia, WPRO] [13]	Randomized controlled trial	Candidiasis	14 days: *Allium sativum* bulb 350 mg with allicin potential 3200 mg, 3 tablets twice daily	Nil	Placebo: tablets containing lactose, povidone, maize starch, talc, magnesium stearate	59 (29/30)	Proportion of 'cases' (women with colony counts of candida >100 CFU/ml in any given day during the last 7 days before menstruation) [BL to Wk4, Wk 8, Wk 12]	NS
							Vaginal quantative counts (daily swabs for 2 weeks prior to menstruation) [BL to Wk4, Wk 8, Wk 12]	NS
							Vaginal itch (moderate to severe, compared to mild) [BL to Wk4, Wk 8, Wk 12]	NS
							Abnormal discharge (yes/no) [BL to Wk4, Wk 8, Wk 12]	NS
							Self-reported change in experience of symptoms of vaginitis (same, better or worse than usual) [BL to Wk4, Wk 8, Wk 12]	NS
Weber, et al. (2008) [USA, AMRO] [26]	Randomized controlled trial	Attention-Deficit Hyperactivity Disorder (Children and young adults 6 to 17yo DSM IV Edition criteria for ADHD	8 weeks: 300mg of *Hypericum perforatum* standardized to 0.3% hypericin TID	Nil	Nil	54 (27/27)	ADHD Rating Scale – IV [BL to Wk 8]	NS
							Clinical Global Impression Improvement Scale [BL to Wk 8]	NS
							Adverse events	NS
Yarnell and Heron (2000) [USA, AMRO] [54]	Retrospective cohort	Any patient prescribed at least 960 ml (32 oz) of the intervention	*Gentiana lutea* root 52.5%, *Taraxacum officinale* leaf 15.5%, *Taraxacum officinale* root 11%, *Achillea millefolium* aerial parts 11%, *Artemisia absinthium* root 11% tincture, 1 tsp TID	Nil	Nil	27 (Complete data: 9 Incomplete data: 18)	Symptoms reported historically to be due to *Artemisia absinthium* toxicity	Nil

Author (year) [Country, World region]	Design	Study Population	Intervention	Concomitant therapies	Control or Placebo	No. Participants (Intervention/ Placebo)	Measure of Outcome	Outcome
		herbal formula in a nine-month period					Serum alanine amino transferase levels (ALT) (U/L) (n=9) [BL to Mth 9]	**Variable change** Reduced: 2 of 3 patients with baseline elevated levels Increased: (within normal range) 4 patients
							Serum aspartate amino transferase levels (U/L) [BL to Mth 9]	**Variable change** Reduced: In 1 of 1 patient with baseline elevated level Increased (within normal range): 3 patients
Yarnell (2015) [USA, AMRO] [15]	Case series	Prostate cancer	Artemisinin (from *Artemisia annua*) 300 or 400 mg three times daily for 7 days followed by 7 days without	All patients were additionally treated with extensive personalized lifestyle, diet, herbal, and dietary supplement protocols	Nil	15 (Prior prostatectomy: 5; No prior conventional therapy: 10)	Serum prostate-specific antigen doubling time >1 year [BL to 14 days]	Prior prostatectomy: 2/5 (1 unknown) No prior conventional therapy: 5/10 (4 unknown)
							Phase angle, improvement [BL to 14 days]	Prior prostatectomy: 1/5 (4 unknown) No prior conventional therapy: 2/10 (7 unknown)
							Metastasis (of prostate cancer) or mortality (all-cause) [BL to 14 days]	Prior prostatectomy: 0/5 No prior conventional therapy: 0/10
							Adverse effects [BL to 14 days]	Prior prostatectomy: 0/5 No prior conventional therapy: 0/10
Yu, et al. (2011) [USA, AMRO] [35]	Randomized controlled trial and uncontrolled trial	Healthy adults (Trial 2: with normal risk of colorectal cancer Trial 3: with high risk of colorectal cancer)	*Zingiber officinale (ginger)* dry rhizome extract 250 mg containing 6.6 mg [6]-gingerol, 1.58 mg [8]-gingerol, 3.05 mg [10]-gingerol, and 5.63 mg [6]-shogaol per capsule Trial 1: 2 g single dose Trials 2 and 3: 2 g daily for 28 days	Nil	Trial 1: none Trials 2 and 3: placebo	Trial 1: 9 Trial 2: 30 (14/16) Trial 3: 20 (10/10)	Single-dose pharmacokinetics in serum, area under the curve (mcg h/ml), half-life (in h), maximum serum concentration (mcg/ml)	**Metabolized to** [10]-gingerol and [6]-shogaol [6]-gingerol: nd [8]-gingerol: nd [10]-gingerol: 0.008, 1.79, 0.009 [6]-shogaol: 0.024, 1.32, 0.011
							Multi-dose pharmacokinetics in serum, 24 hours after last dose	**No serum accumulation of constituents** [6]-gingerol: nd; [8]-gingerol: nd; [10]-gingerol: nd; [6]-shogaol: nd

Author (year) [Country, World region]	Design	Study Population	Intervention	Concomitant therapies	Control or Placebo	No. Participants (Intervention/ Placebo)	Measure of Outcome	Outcome
							Multi-dose pharmacokinetics in colon tissue (ng/mL), 24 h after last dose	**Accumulation of** [10]-gingerol glucuronide and [10]-gingerol sulfate in colon tissue [6]-gingerol: nd; [8]-gingerol: nd; [10]-gingerol: nd; [10]-gingerol glucuronide: 1.72; [10]-gingerol sulfate: 2.76; [6]-shogaol: nd
Zick, et al. (2006) [USA, AMRO] [52]	Retrospective cohort study	Breast cancer associated quality of life	*Arctium lappa* root, *Rheum palmatum* root, *Rumex acetosella* aerial parts, *Ulmus rubra inner bark (Essiac formula)* tea, mean 43 ml per day (range 12 – 114 ml) or those herbs plus *Nasturtium officinale* aerial parts, *Laminaria digitata thallus, Cnicus benedictus* aerial parts, *Trifolium pratense* flower in various doses (reported use since diagnosis)	Nil	Non-users within cohort	510 (41/469)	Functional Assessment of Cancer Therapy – Breast [between group assessment]	**Increased impact on Physical wellbeing** +1.7 (p=0.02) Associated with: Younger age (p<0.001) Advanced cancer stage (p<0.05) Fewer social supports (p<0.05) **Increased impact on Relationship with doctor:** +0.2 (p=0.047) Associated with: Fewer social supports (p<0.05)
							Profile of Mood Syndromes (compared to controls)	NS
Zick, et al. (2008) [USA, AMRO] [19]	Randomized controlled trial	Heart Failure	*Crataegus laevigata* (hawthorn) leaf and flower extract WS 1442 (containing 84.3 mg proanthocyanins) (Crataegus Special Extract WS1442 (CSE)) 450mg BID for 6 months	Concomitant medications: angiotensin-converting enzyme inhibitor or angiotensin receptor antagonist, beta blocker, and diuretic	Placebo	120 (60/60)	Progression to Heart failure [BL to Mth 6]	**Increased progression to heart failure** CSE resulted in 3.9 times risk of progression. Association of increased risk with LVEF <35%
							Six-minute walk distance	NS
							Peak exercise oxygen consumption	NS
							Anaerobic threshold	NS

Author (year) [Country, World region]	Design	Study Population	Intervention	Concomitant therapies	Control or Placebo	No. Participants (Intervention/ Placebo)	Measure of Outcome	Outcome
Zick, et al. (2009) [USA, AMRO] [20]	Secondary analysis						Cardiovascular deaths, cardiac events, hospitalizations due to CHF [BL to Mth 6]	NS
							Quality of life, assessed by multiple measures	NS
							Exercise capacity – 6 min walk test	NS
							Blood pressure and heart rate	NS
							Minnesota Living with Heart Failure Questionnaire	NS
							EuroQoL-5D	NS
							Left ventricular ejection fraction (LVEF) (%)	**Increased LVEF** Hawthorn, +0.4 (p=0.004)
Zick, et al. (2009) [USA, AMRO] [36]	Randomized controlled trial	Chemotherapy induced nausea and vomiting	*Zingiber officinale* (ginger) rhizome ethanol extract (containing 5% total gingerols) lg OR 2g per day, for 3 days	Anti-nausea medications (Apripetant, Dolasetron, Granistron, Ondansetron, Palonosetron)	Placebo	162 (53/52/ 57)	Acute or delayed nausea or vomiting, prevalence [BL to Dy 3]	NS
							Severity of nausea or vomiting [BL to Dy 3]	**Increased severity of nausea and vomiting** High-dose ginger: p=0.03 Concomitant aprepitant and ginger: p=0.01
							Adverse effects [BL to Dy 3]	NS
Zick, et al. (2011) [USA, AMRO] [28]	Randomized controlled trial	Insomnia	*Matricaria chamomilla* (chamomile) flower extract (containing 4.3% apigenin and 2% (−)-α-bisabolol) 270 mg twice daily (between lunch and dinner time and 1 hour before bed) for 28 days	Nil	Placebo	34 (17/17)	Total sleep time, sleep efficiency [BL to Dy 28]	NS
							Sleep latency, wake after sleep onset, number of night awakenings, sleep quality [BL to Dy 28]	NS
							Insomnia Severity Index [BL to Dy 28]	NS
							Pittsburgh Sleep Quality Index [BL to Dy 28]	NS
							Daytime fatigue [BL to Dy 28]	NS

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33 Lifestyle Modification

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HIGHLIGHTS

- A person's lifestyle is an important determinant of their level of health.
- Assessing for various lifestyle factors and lifestyle counselling are considered core elements of naturopathic care.
- The naturopathic workforce is known for increasing health literacy and for teaching patients and their community how to achieve a healthy lifestyle.
- Naturopaths/NDs can play an essential role in addressing non-communicable diseases and other diseases that are strongly influenced by lifestyle factors.
- Clinical research by the naturopathic community has examined the application of lifestyle interventions and lifestyle-based risk factor identification.
- In line with the role of primary care, naturopathic researchers have investigated the effects of lifestyle modification on individuals with depression, metabolic syndrome, obesity, and type II diabetes mellitus.

The appreciation for lifestyle factors as critical elements determining wellbeing stems from the knowledge imparted by notable physicians including Hippocrates, through to Sebastian Kniepp and Henry Lindlar of 19th century Europe [1]. These physicians promoted specific therapies, including walking barefoot in the forest and water therapies (hydrotherapy), as well as general factors including the pursuit of 'cleanliness', eating healing foods, regular movement and relaxation. A student of Kniepp, Benedict Lust, embraced these approaches as he brought naturopathy from Europe to North America [1].

Early naturopaths were among the first health professionals to formally acknowledge lifestyle modification as an important element of treatment, which aligned with their focus on prioritizing drugless approaches to healing [2, 3]. The importance of lifestyle counselling in naturopathic practice continues, and is considered one of the core therapeutic elements in naturopathic practice [4]. There is an increasing awareness of the negative implications of modernity on lifestyle factors. Concerns include alterations to the sleep/wake cycle, increased social competition causing less intimate engagement with the family unit, sedentary lifestyle, poorer diets, social isolation, and substance/alcohol misuse. These factors may have implications on both mental and physical health [5].

The therapeutic application of lifestyle modifications is regarded as 'lifestyle medicine.' This approach consists of the application of environmental, psychological, and behavioural principles to enhance wellbeing. This is increasingly regarded as a potentially preventive approach to illness [6], and is one with long-standing strong alignment with naturopathic practices and theories of diagnosis, treatment and management [7]. In practice, these principles may be applied through exercise prescription and postural awareness; the modification of diet; advocation for minimized exposure to tobacco smoking, alcohol, and other illicit substances; and guidelines for the regulation of the sleep-wake cycle through addressing work-rest balance and recreation [8]. Significant considerations of note also include activity scheduling, which encourages meaningful social engagement [9]. Environmental factors are also significant considerations and may be targeted by advocating for reduced exposure to air, water, and noise pollution, and encouraging time spent in nature.

Overview of Studies

This chapter is dedicated to highlighting the original clinical research (n=3) naturopathic clinicians undertook in the field of lifestyle and exercise. It is important to note that lifestyle interventions are typically included in complex naturopathic interventions which are covered in Chapter 29 and in dietary interventional studies (applied nutrition) which are covered in Chapter 30. The naturopathic research on lifestyle and exercise includes a total

of 85,012 participants and was conducted in Australia (n=1), the United States of America (USA) (n=1) and the United Kingdom (n=1). The study designs include randomized controlled trial (n=1), an uncontrolled trial (n=1) and a cohort study (n=1). The populations treated included depression (n=1), metabolic syndrome and/or obesity along with chronic mental illness (n=1), and type II diabetes mellitus (T2DM) (n=1). Of all the naturopathic clinical studies employing lifestyle interventions, 100% reported a positive outcome in at least one primary or secondary outcome measure. Details of the studies are available in *Table 33.1 Clinical research investigating lifestyle interventions conducted by naturopathic researchers.*

Implications

The studies indicate that naturopathic interventions focused on modifying lifestyle factors have positive impacts on health. Other cross-sectional data has concurred with these findings and has shown that women who consult a naturopath/naturopathic doctor report relatively more positive lifestyle behaviours than those who do not [10]. These findings indicate that lifestyle factors are potentially able to be modified significantly within a therapeutic setting, though due to the cross-sectional nature of the above analysis, it is possible that patients seeing naturopaths/naturopathic doctors may already be predisposed to a healthier lifestyle. However, observational findings from naturopathic practice have also found that positive lifestyle modifications are generally sustained after naturopathic intervention [7, 11].

More research is required to discern the specific implications of lifestyle modifications on health outcomes. Data discerning the key elements which may modify successful lifestyle change, time restrictions and motivational issues, and financial limitations is also required [12]. This may assist naturopaths/naturopathic doctors with sustaining long-term behavioural change through treatment strategies which take cognisance of the above factors. Accordingly, the treatment approach should be offered in a manner which is achievable for the patient and personalized appropriately [13]. Such an approach is best enacted through supported individualized formats that are adaptable to participant needs, which being the basis of naturopathic practice should be translatable in naturopathic settings. With lifestyle medicine being increasingly identified as a tool to improve health outcomes and reduce health burdens [14], further attention on the role of a profession with extensive experience in the application of translation of lifestyle medicine – such as naturopathy – is warranted.

Studies investigating specific interventions:

Lifestyle interventions

Two studies focused on exercise-based interventions [15, 16]. A randomized controlled trial (n=20) conducted in the USA measured the outcome of medical Qigong on stress and depression in T2DM patients [15]. Participants either engaged in Yi Ren Medical Qigong for 60 minutes per week with 30 minutes of home practice twice per week for 12 weeks or in progressive resistance training for 60 minutes per week with 30 minutes of home practice twice a week for 12 weeks. These two forms of exercise were matched to a usual care group for T2DM. The study indicated a reduction in stress in the Qigong group as measured by the Perceived Stress Scale (Qigong -29.3%, $p<0.05$ vs no change with progressive resistance or usual care) and a reduction in depression as measured by the Beck Depression Inventory in the progressive resistance group (progressive resistance -50% $p<0.03$, no change in Qigong or usual care group).

An uncontrolled trial conducted (n=10) in Australia involved a 12 week lifestyle program for patients with a mental illness and co-morbidities of metabolic syndrome or diabetes [16]. The Australian study involved a naturopath-initiated 'Healthy Body Healthy Mind (HBHM)' program which integrated meditation and mindfulness, comprehensive psychoeducation, and educational and practical exercise and nutrition guidance to improve the mental and physical health of participants with a serious mental health diagnosis [16]. Pilot data reported from this study concerned two points: 1) Qualitative data obtained from the patients and clinicians involved in a 2012 unstructured program exploring its acceptance and utility; and 2) Mental health and biometric data collected from the 10 participants involved in the modified and enhanced 12-week 2016 HBHM program. Results revealed a decrease in body mass index (BMI) of approximately one point ($0.96 kg/m^2$; $p=0.019$), coupled with a significant reduction in abdominal circumference (2.55cm; $p=0.046$). Results also indicated that a significant weight loss of 2kg was achieved at the end of the program ($p=0.023$). However, there were no significant alterations in any biometrics, including blood levels, or mental health parameters.

Lifestyle-based risk factor identification

The cohort study was a cross-sectional and longitudinal analysis (n=84,860) conducted in the United Kingdom. This study assessed the relationships between six key lifestyle factors and mood status in individuals with a history or current diagnosis of major depressive disorder

(MDD), and healthy controls (HC) [17]. The study revealed that tobacco smoking and higher levels of sedentary screen-time were both associated with a higher frequency of depressed mood (both $p<0.0001$; ORs 1.09 to 1.36). The study also indicated that optimal sleep duration, healthy diet, and physical activity were associated with a lower frequency of depressed mood (all $p<0.001$; ORs 0.62 to 0.94). The longitudinal analyses revealed that optimal screen time (MDD: OR=0.71, $p<0.001$; HC: OR=0.80, $p<0.001$) and sleep duration (MDD: OR=1.10, $p<0.001$; HC: OR=1.08, $p<0.001$) were both indicative of lower frequencies of depressed mood in both groups. Analyses also revealed a significant interaction between MDD diagnosis and healthy diet ($p=0.024$). In HCs, a higher-quality diet was revealed to alleviate depressed mood (OR=0.92, $p=0.045$), but was not associated with depressive mood in people with MDD.

Table 33.1 Clinical research investigating lifestyle interventions conducted by naturopathic researchers

Author (year) [Country, World Region]	Design	Study Population	Intervention(s)	Concomitant therapies	Control or comparison group	No. Participants (Intervention/Control)	Outcome measure	Outcome
Murphy, et al. (2019) [Australia, WPRO] [16]	Uncontrolled trial (pilot study)	Mental illness and co-morbid metabolic syndrome or obesity (stabilized with psychotropic medication for ⩾4 weeks)	Lifestyle program 'Healthy Body Healthy Mind (HBHM)': exercise (theory and practicals), lifestyle psychoeducation, motivation and goal setting skills, and mindfulness techniques (12 week program of weekly 6 hour sessions)	Diet and nutrition (theory and practical skills)	Nil	10	Weight (kg) [BL to Wk 12]	**Reduced body weight** Wk 12: -2.00 (p=0.023)
							Abdominal circumference (cm)	**Reduced abdominal circumference** Wk 12: -2.55 (p=0.046)
							Body mass index (BMI) (kg/m^2)	**Reduced BMI** Wk 12: -0.96 (p=0.019)
							Waist to hip ratio	NS
							Blood pressure	NS
							Fasting glucose	NS
							High-density lipoprotein cholesterol	NS
							Low-density lipoprotein cholesterol	NS
							Total fasting cholesterol	NS
							Triglycerides	NS
							Depression Anxiety Stress Scales	NS
Putiri, et al (2012) [USA, AMRO] [15]	Randomized controlled trial	Type II diabetes mellitus, psychological factors (adults)	Yi Ren Medical Qigong (60 min per wk, with 30 min home practice twice per wk, for 12 wks)	Nil	Progressive resistance training (60 min per wk, with 30 min home practice twice per wk, for 12 wks), Usual care control	20 (7/5/8)	Perceived stress scale [BL to Wk 12]	**Reduced** Qigong: -29.3%, (p<0.05) Progressive resistance: NS Usual care: NS
							Beck Depression Inventory [BL to Wk 12]	**Reduced** Qigong: NS Progressive resistance: -50% (p<0.03) Usual care: NS
Sarris et al. (2020) [UK, EURO] [17]	Cohort study	Major depressive disorder (MDD)	Lifestyle behaviors (physical activity, dietary patterns, sleep, screen time, alcohol intake)	Nil	Healthy control (no history of depressive disorder)	84,860 (18,793/66,067)	Physical activity: metabolic equivalent of task, minutes per week [association with depressive mood at BL, BL to follow-up] (time to follow-up not reported)	**Reduced depressive mood** MDD group: BL, OR 0.94 (p<0.0001); Follow-up, NS Control group: BL, OR 0.94 (p<0.0001); Follow-up, OR 0.92 (p=0.045)

Author (year) [Country, World Region]	Design	Study Population	Intervention(s)	Concomitant therapies	Control or comparison group	No. Participants (Intervention/Control)	Outcome measure	Outcome
							Healthy diet Food Frequency Questionnaire [association with depressive mood at BL, BL to follow-up] (time to follow-up not reported)	**Reduced depressive mood** MDD group: BL, OR 0.91 (p=0.0026); Follow-up, NS Control group: BL, OR 0.88 (p<0.0001); Follow-up, NS
							Sleep (hours per 24 hours) [association with depressive mood at BL, BL to follow-up] (time to follow-up not reported)	**Reduced depressive mood (optimal sleep)** MDD group: BL, OR 0.62 (p<0.0001); Control group, BL: OR 0.65 (p<0.0001) Increased depressive mood (non-optimal sleep) MDD group: Follow-up: OR 0.71 (p<0.0001) Control group: Follow-up: OR 0.80 (p<0.0001)
							Tobacco smoking status (current smoker) [association with depressive mood at BL, BL to follow-up] (time to follow-up not reported)	**Increased depressive mood** MDD group: BL, OR 1.36, (p<0.0001); Follow-up, NS Control group: BL, OR 1.32 (p<0.0001); Follow-up, NS
							Sedentary screen time (hours per week) [association with depressive mood at BL, BL to follow-up] (time to follow-up not reported)	**Increased depressive mood** MDD group: BL: OR 1.13 (p<0.0001); Follow-up: OR 1.10 (p=0.0001) Control group: BL: OR 1.09 (p<0.0001); Follow-up: OR 1.08 (p<0.0001)
							Alcohol frequency (6-point Likert scale) [association with depressive mood at BL, BL to follow-up] (time to follow-up not reported)	**Reduced depressive mood** MDD group: BL: OR 0.91 (p<0.0001); Follow-up: NS Control group: NS

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34 Mind-Body Medicine Counselling

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HIGHLIGHTS

- Mind-body medicine (MBM) recognizes the significant role that the mind can have on health outcomes.
- Research indicates that MBM practices are effective in addressing a wide range of conditions including decreasing pain, improvements in blood pressure and digestive symptoms, in reducing stress, anxiety and depression and others.
- Naturopaths/NDs incorporate various MBM practices into patient care.
- Clinical research by the naturopathic community has examined the application of mindfulness-based stress reduction, meditation and other MBM interventions.
- In line with the role of primary care, naturopathic researchers have investigated the effects of MBM practices on individuals with chronic pain, mental health conditions, complex immune conditions, neurological conditions, cancer, and other conditions.

Mind-body medicine (MBM) comprises a variety of practices designed to enhance the mind's positive impact on the body and vice versa, including behavioural, psychological, social, artistic and spiritual approaches [1, 2]. MBM practices, such as yoga, *tai chi*, or meditation have been part of traditional medicine for several hundreds to thousands of years and continue to be part of many practices within traditional and complementary medicine.

In 1979 mindfulness-based stress reduction (MBSR) was introduced as a form of stress reduction, but MBSR technique has evolved to encompass a number of health related conditions [3]. The naturopathic profession formally documented the importance of the mind-body connection in its earliest writings [4]. Others, such as biofeedback, are newer developments that evolved from technological progress. MBM counselling methods, especially counselling on health-related lifestyle factors, has been a substantial component of naturopathic practice from its inception and continues to be an integral aspect of naturopathic care. In a 2019 international practice survey of naturopaths/naturopathic doctors globally, MBM was incorporated as part of the therapeutic intervention with one fifth of all naturopathic patients [5].

MBM is prescribed and practiced by the naturopathic workforce with patients of all ages presenting with functional disorders (e.g., gastrointestinal, endocrine, neurological or cardiovascular conditions), structural disorders (e.g., musculoskeletal conditions, chronic pain), psychological conditions (anxiety, depression, ADHD), and as part of preventive and palliative care. MBM embraces the naturopathic philosophy of Holism and the principle of *Treat the Whole Person*. The practice of MBM is based on the understanding that the mind influences the physical body and conversely the physical influences the state of the mind. MBM is often included as part of a complex naturopathic intervention (see Chapter 29) and as an integral element of yoga therapy (see Chapter 38). This chapter focuses only on those studies where MBM was used as a standalone naturopathic intervention.

Overview of Studies

This chapter is dedicated to highlighting the original clinical research (n=9) naturopathic clinicians conducted investigating MBM. This research includes a total of 531 participants and was conducted in the USA (n=7) and Australia (n=2). The study designs include randomized controlled trials (n=4), uncontrolled trials (n=3), non-randomized controlled trials (n=1) and case reports (n=1). The mind-body medicine techniques studied include the use of mind-body stress reduction (MBSR) (n=2), meditation (n=2), videoconference delivery of mind-body group therapy (n=1), group counselling (n=1), music therapy (n=1), narrative therapy (n=1) and healing touch (n=1).

The conditions treated with MBM included one study each for chronic pain, mental health concerns, work stress, multiple sclerosis, headache, migraine, autism, breast cancer and hospital patients with various ailments. Of all the naturopathic clinical studies employing MBM counselling interventions, 88.9% reported a positive

outcome in at least one primary or secondary outcome measure. Details of the studies are available in *Table 34.1: Clinical research investigating mind-body medicine interventions conducted by naturopathic researchers.*

Implications

The studies indicate that, while MBM is a broad category of diverse therapeutic options, it may have clinical benefit in several different conditions. Naturopathic researchers have employed MBM interventions for diverse populations and with a focus on changes to participant health behaviours, symptoms, and perceived wellbeing.

One notable consideration in the application of MBM by naturopaths/naturopathic doctors is that in many instances it has functioned as a very practical approach to counselling, facilitating behavioural change and improved symptom management even after the intervention has ceased. While there has been some criticism of MBM such as mindfulness approaches as being ineffective if not being appropriately patient-centered or too focused on the intervention rather than facilitating change [6], these results suggest that when applied in naturopathic clinical settings and in accordance with naturopathic philosophies and principles there can be improved health outcomes. These results are most likely due to the historical and philosophical role of naturopathic practice in acknowledging the importance of mind-body approaches to health as being a core foundation of optimizing patient health. Further attention on the role of naturopaths/naturopathic doctors in the integration and application of MBM to improve health outcomes is warranted.

Studies investigating specific interventions:

Mindfulness-Based Stress Reduction and Meditation

Three studies (total n=81) assessed mindfulness-based stress reduction (MBSR) in somatic illness [7-9]. The MBSR programs were delivered as structured 8-week programs consisting of weekly 2.5-hour group sessions and an all-day silent retreat. Key components of the MBSR program include sitting meditation; walking meditation; hatha yoga and body scan. Another key component is the incorporation of mindfulness into everyday life. The studies investigating MBSR interventions included populations with chronic pain (n=1) [7], stress, anxiety and depression (n=1) [8], and migraine [9].

An uncontrolled trial (n=18) conducted in the USA assessed the effects of MBSR on chronic pain and functional syndromes in adolescents and found reduced disability and symptom impact, stress and anxiety but no effect on quality of life [7]. The reduction in anxiety was measured based on the Multidimensional Anxiety Scale for Children and indicated child reports: Wk 8, -7.5 (p=0.03); Wk 12, -10.1 (p=0.047) and parent reports: Wk 8, -10.0 (p=0.03); Wk 12, -16.2 (p=0.004). A randomized controlled trial (n=62) investigated the feasibility of MBSR compared to education in multiple sclerosis and found the intervention to be feasible. No effects were found on the secondary outcomes stress, anxiety, depression, fatigue, pain, resilience, and information processing [10].

A randomized controlled trial (n=178) conducted in Australia compared the effects of "mental silence" Sahaja meditation to relaxation and a wait-list control group [8]. The 8-week intervention consisted of twice weekly 90-minute sessions and twice daily 10 to 20-minute home practice and employed a series of silent yoga-based affirmations to reach "thoughtless awareness". The meditation intervention resulted in a greater reduction of stress as measured by the Psychological Strain Questionnaire (meditation: -37.0; relaxation: -22.30; no treatment: -17.5 (p=0.026)) and depression as measured by the Profile of Mood States, Depression-dejection subscale (meditation: -3.0; relaxation: no change; no treatment: no change (p=0.019)), but not anxiety.

A case report conducted in the USA assessed effects of an 8-week self-directed variation of the MBSR program (based on a book and recorded meditations without group sessions and retreat) in a 45-year-old female migraine patient with hypertension, pre-diabetes and a BMI of 30 kg/m2 [9]. At the 11-week follow-up there was a significant decrease in both systolic (-34.7, p<0.0001) and diastolic (-29.3, p<0.0004) blood pressure, migraine frequency and use of associated medication.

Other MBM Interventions

Five studies examined a range of other MBM interventions including music therapy [11], healing touch [12], narrative therapy [13], mind-body group therapy [14] and group counselling [15]. The populations for these studies were individuals with breast cancer risk (n=1) [15], autism (n=1) [13], mental health diagnoses (n=1) [14], and chronic headache (n=1) [12]. One study also included hospital inpatients in a family medicine ward (n=1) [11].

A randomized controlled trial (n=90) conducted in the USA used mixed-methods to assess the effectiveness of music therapy compared to massage and usual care in inpatients with mixed internal medicine diagnoses [11]. In the first phase of the music therapy intervention, a customized music playlist was created and provided for use in the hospital and after discharge. Follow-up visits included music-facilitated relaxation and meditation, songwriting, and singing, amongst other. The study

found no significant effects on patients' hospital experience using quantitative measures, but favourable subjective effects on hospital experience, pain management and therapist connectedness were reported in qualitative interviews.

An uncontrolled trial conducted as a qualitative study (n=13) in the USA assessed the subjective effects of healing touch in chronic headache [12], and found the intervention was associated with subjective symptom improvements as well as general changes in patients' views on their lives and health. The intervention consisted of 3 to 6 weekly sessions, consisting of "Mind Clearance", "Full Body Connection", and further energy work based on the therapists' perceptions of the patient's individual state.

An uncontrolled trial (n=10) conducted in Australia evaluated the effects of narrative therapy for young people with autism, and found no effects on the primary outcome parent-rated strength and difficulties [13]. Positive results were found on the child-reported outcome distress but not on hopelessness or salivary cortisol. Narrative therapy consisted of five 1-hour sessions over 10 weeks and was based on the work of Michael White and David Epston, highlighting the individual construction of meaning. A controlled trial (n=9) conducted in the USA included participants with mixed mental health diagnoses and found that compared to a wait-list control, participants who underwent the mind-body group therapy program reported increased wellbeing in the mental (+2.56, $p=0.004$) and physical (+5.0, $p<0.001$) subscales of the Mental, Physical and Spiritual Wellbeing Scale [14]. The 8-week intervention used videoconference technology and was weekly focusing on one of the "7 Foundations of Health and Happiness" (Rest/Relaxation, Movement, Nutrition, Self, Relationships, Work, Meaning), and a final week on Behaviour Change.

A randomized controlled trial (n=150) conducted in the USA included sexual minority women who received 2 hour group breast cancer counselling sessions for four weeks compared to a wait-list control group [15]. The counselling consisted of a personalized assessment of actual risk for breast cancer at three future time points (5 years, 10 years, and at age 79) along with sessions on breast self-exam techniques, problem-solving exercises to identify and overcome barriers to mammography, stress management and social support. The intervention significantly reduced perceived personal cancer risk ($p<0.001$) and cancer worry ($p<0.001$) and increased cancer screening behaviour ($p<0.05$) and mental health-related quality of life ($p<0.01$).

Table 34.1 Clinical research investigating mind-body medicine interventions conducted by naturopathic researchers

Author (year) [Country, World Region]	Design	Study Population	Intervention	Concomitant therapies	Control or comparison group	No. Participants (Intervention/Control)	Outcome measure	Outcome
Ali, et al. (2017) [USA, AMRO] [7]	Uncontrolled trial	Chronic pain and other functional somatic syndromes (adolescents and their parents)	Mindfulness-based stress reduction (8-week program of weekly 1.5-hour group sessions and one 4-hour retreat)	Nil	Nil	18	Functional Disability Inventory (reported by child) [BL to Wk 8, Wk 12]	**Reduced disability** Wk 8: -6.8 (p=0.026) Wk 12: NS
							Fibromyalgia Impact Questionnaire – Revised / Symptom Impact Questionnaire (reported by child) [BL to Wk 8, Wk 12]	**Reduced impact** Wk 8: -11.0 (p=0.03) Wk 12: NS
							Pediatric Quality of Life Inventory (reported by child) [BL to Wk 8, Wk 12]	NS
							Perceived Stress Scale (reported by child) [BL to Wk 8, Wk 12]	**Reduced stress** Wk 8: NS Wk 12: -6.2 (p=0.01)
							Multidimensional Anxiety Scale for Children, Second Edition (reported by child and parent) [BL to Wk 8, Wk 12]	**Reduced anxiety** Child reports: Wk 8, -7.5 (p=0.03); Wk 12, -10.1 (p=0.047) Parent reports: Wk 8, -10.0 (p=0.03); Wk 12, -16.2 (p=0.004)
Bowen, et al. (2006) [USA, AMRO] [15]	Randomized controlled trial	Breast cancer risk	Group psychological counselling (Four weekly 2-hour sessions)	Nil	Waitlist control	150 (81/69)	Breast cancer screening – mammography [BL to Mth 24]	**Increased screening** Mth 24 ⩾40 years old: +12% (p<0.05)
							Breast cancer screening – breast (self-exam) [BL to Mth 6, Mth 24]	**Increased screening** Mth 6: +17% (p<0.01) Mth 24: +13% (p<0.05)
							Perception of lifetime personal breast cancer risk [BL to 6mth, 24mth]	**Reduced perception of risk** Mth 6: -20%; Mth 24: -21% Over time: p<0.001 Between group: p<0.001

Author (year) [Country, World Region]	Design	Study Population	Intervention	Concomitant therapies	Control or comparison group	No. Participants (Intervention/ Control)	Outcome measure	Outcome
							Cancer Worry Scale [BL to 6mth, 24mth]	**Reduced worry** Mth 6: -0.7; Mth 24: -0.7% Over time: p<0.001 Between group: p<0.001
							Short Form-36 Health Survey [BL to 6mth, 24mth]	**Increased quality of life** Mth 6: +4.6; Mth 24: +5.1 Over time: p<0.001 Between group: p<0.01
Cashin, et al. (2013) [Australia, WPRO] [13]	Uncontrolled trial	Autism (adolescents and their parents)	Narrative therapy (five 1-hour sessions over 10 weeks)	Nil	Nil	10	Strengths and Difficulties Questionnaire [BL to Wk 9 (Session 5)] (reported by parent)	**Reduced emotional symptoms** Emotional symptoms scale: -2.0 (p=0.042) Conduct problem: NS Hyperactivity scale: NS Peer problem scale: NS Pro-social scale: NS Total difficulties: NS
							Kessler-10 (Scale of Psychological Distress) [BL to Wk 9 (Session 5)] (reported by child)	**Reduced distress** Wk 9: -7.5 (=-0.017)
							Beck Hopelessness Scale [BL to Wk 9 (Session 5)] (reported by child)	NS
							Salivary cortisol: DHEA ratio [Wk 1 (Session 1) to Wk 9 (Session 5)] (for child)	NS
Heermann, et al. (2017) [USA, AMRO] [14]	Non-Randomized controlled trial	Mental health diagnoses	Videoconference delivery of mind-body group therapy (8 sessions)	Nil	Waitlist control	9 (3/6)	Mental, Physical and Spiritual Wellbeing Scale [BL to Session 8]	**Increased wellbeing** Mental subscale: +2.56 (p=0.004) Physical subscale: +5.0 (p<0.001) Spiritual subscale: NS Between groups: NS
							Arizona Integrative Outcomes Scale [BL to Session 8]	NS

Author (year) [Country, World Region]	Design	Study Population	Intervention	Concomitant therapies	Control or comparison group	No. Participants (Intervention/Control)	Outcome measure	Outcome
Manocha, at al. (2011) [Australia, WPRO] [8]	Randomized controlled trial	Stress, anxiety and depressed mood (full time workers)	"Mental silence" Sahaja yoga meditation (two 1-hour sessions per week and 10-20 minutes daily practice at home for 8 weeks,)	Nil	Active control: relaxation. No treatment control: waitlist	178 (59/56/63)	Psychological Strain Questionnaire [BL to Wk 8]	**Reduced strain** Meditation: -37.0; Relaxation: -22.30; No treatment: -17.5 (p=0.026)
							State/Trait Anxiety Inventory for Adults [BL to Wk 8]	NS
							Profile of Mood States, Depression-dejection subscale [BL to Wk 8]	**Reduced depression** Meditation: -3.0; Relaxation: no change; No treatment: no change (p=0.019)
Oberg, et al. (2013) [USA, AMRO] [9]	Case report	Migraine	Mindfulness meditation (self-directed 8-week program of 45 min sessions)	Nil	Nil	1	Blood pressure (BP), systolic/diastolic (pre- and post-meditation) [Weekly from Wk 1 to Wk 11]	**Reduced BP** Wk 1 BP: 149.2/97.3 vs. 132/84.6; Wk 11 BP: 114.5/68 vs. 112.7/72.7. Systolic -34.7 and -19.3 (p<0.0001) Diastolic -29.3 and -11.9 (p<0.0004)
							Migraine frequency (subjective) [BL to Wk 11]	**Reduced migraine frequency** Reduction until week 17 of migraine headache and use of associated medication
Roseen, et al. (2017) [USA, AMRO] [11]	Randomized controlled trial	Hospital inpatients (family medicine)	Music therapy (10-40 min daily sessions during hospital stay)	Usual inpatient care	Control: Usual care alone Comparison: Massage therapy	90 (30/30/30)	Hospital Consumer Assessment of Healthcare Providers and Systems survey [within 7 days of discharge]	NS
							Qualitative telephone survey [within 7 days of discharge] (not administered to control group)	**Improved experience of hospital stay and pain management** Subjective reports of interventions improving patient experience

Author (year) [Country, World Region]	Design	Study Population	Intervention	Concomitant therapies	Control or comparison group	No. Participants (Intervention/ Control)	Outcome measure	Outcome
Senders, et al. (2019) [USA, AMRO] [10]	Randomized controlled trial	Multiple sclerosis	Mindfulness-based stress reduction (8 weekly 2 hr classes and one 6-hour retreat)	Nil	Control: Multiple Sclerosis Education protocol (matched to intervention for time and attention, with no overlap in content)	67 (33/34)	Feasibility	**Confirmed** 85% participated in at least 6/8 classes. Practiced on 55% of assigned home practice days, (median duration of 38 min)
							Perceived Stress Scale [BL to post-intervention, 12 Mth]	NS
							Short Form 36 health survey [BL to post-intervention, 12 Mth]	NS
							Patient-Reported Outcomes Measurement Information System (PROMIS) Anxiety [BL to post-intervention, 12 Mth]	NS
							PROMIS Depression [BL to post-intervention, 12 Mth]	NS
							PROMIS Fatigue [BL to post-intervention, 12 Mth]	NS
							PROMIS Pain [BL to post-intervention, 12 Mth]	NS
							Connor-Davidson Resilience Scale [BL to post-intervention, 12 Mth]	NS
							Paced Auditory Serial Addition Test [BL to post-intervention, 12 Mth]	NS
Sutherland, et al. (2009) [USA, AMRO] [12]	Uncontrolled trial (pilot study)	Chronic headache	Healing Touch (three to six 30-40 min sessions, weekly)	Nil	Nil	13	Qualitative interviews [BL, session 3, session 6, post-treatment Mth 3)	**Reduced symptoms** Subjective symptom reduction (frequency, intensity or duration of headaches) and reports of shifts in self-awareness.

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35 Naturopathic Physical Medicine

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HIGHLIGHTS

- Naturopathic physical medicine emphasizes the importance of addressing various structural aspects – including posture, gait, movement and symptoms related to joint and muscle health – as part of naturopathic care.
- Naturopathic practice includes a diverse range of bodywork therapies ranging from exercise recommendations, muscle release techniques, manipulation, yoga, and others depending on the country and jurisdictional regulations.
- There is therapeutic value to incorporating physical medicine techniques in naturopathic care.
- Clinical research by the naturopathic community has examined the application of massage and other manual therapies to improve a range of health conditions.
- In line with the role of primary care, naturopathic researchers have investigated the effects of naturopathic physical medicine on individuals with neck pain, asthma, traumatic brain injury, and knee osteoarthritis as well as medicals inpatients including those receiving hospice/palliative care and undergoing cardiac surgery.

Naturopathic philosophy views the health of the structure of the body including muscles, joints, posture, gait and movement as a primary component of the triad of health. For this reason, bodywork – also known as naturopathic physical medicine – is considered an essential aspect of naturopathic care. Naturopathic physical medicine has always been one of the core foundations of naturopathic practice and remains one of the major treatment modalities employed by the naturopathic community globally [1].

Naturopathic physical medicine has been described as a modality that "integrates both scientific knowledge in physical medicine and the principles of naturopathic medicine into a distinct approach to physical medicine practice." Addressing or correcting structural integrity is considered an essential stage of the Naturopathic Therapeutic Order [2, 3] as naturopaths/naturopathic doctors recognize that there is a correlation between an individual's alignment and structure, the functioning of internal organs and a person's psychological state. A core naturopathic principle is *tolle totum* (Treat the Whole Person): as such, it is not always just the patient's structural issues that are treated through naturopathic physical medicine, as working on the structure can have far-reaching benefits on all aspects of a patient.

Naturopathic practice includes forms of bodywork ranging from muscle release and massage techniques, naturopathic manipulation, and other bodywork techniques. Naturopaths/naturopathic doctors may also employ yoga and acupuncture in their clinical practice, and while these therapies can also be considered within the broad category of naturopathic physical medicine, the clinical studies produced by naturopathic researchers that examines these therapies are presented separately (see *Chapter 37: Acupuncture* and *Chapter 38: Yoga*). Some naturopaths/naturopathic doctors provide naturopathic physical medicine as part of their practice directly with patients while others work with various bodywork practitioners to provide patients with a holistic and an integrated approach to healthcare.

Overview of Studies

This chapter is dedicated to highlighting the original clinical research (n=9) naturopathic clinicians undertook in the field of naturopathic physical medicine. This research includes a total of 595 participants and was conducted in USA (n=4), Germany (n=3) and Australia (n=2). The study designs include randomized controlled trials (RCT) (n=5) and case reports (n=2) with two additional papers presenting the results of secondary analysis from RCTs (n=2). The aspects of naturopathic physical medicine studied include massage therapy (n=5), craniosacral therapy (n=3) and breathing exercises (n=1).

The conditions treated with naturopathic physical medicine included neck pain (n=2), hospice / palliative care (n=2) and one study for asthma, pre- and post-cardiac

surgery, traumatic brain injury, osteoarthritis of the knee and medical inpatients. Of all the naturopathic clinical studies employing naturopathic physical medicine interventions, 66.7% reported a positive outcome in at least one primary or secondary outcome measure. Details of the studies are available in *Table 35.1 Clinical research investigating naturopathic physical medicine interventions conducted by naturopathic researchers*. This body of naturopathic research on naturopathic physical medicine is also supported by more than 20 observational studies and seven reviews or meta-analyses conducted by naturopathic researchers on this topic, as outlined in Chapter 40.

Implications

The naturopathic studies on naturopathic physical medicine imply that there is therapeutic value in bodywork including massage and craniosacral therapy for a range of conditions. Where comparative studies have not been done, there are indications that naturopathic physical medicine may be as effective as mind-body therapies such as music therapy or guided meditation. The results also suggest that the therapeutic value of a treatment is partially dependent on the patient's desire for the therapy, which may position therapeutically eclectic naturopaths/naturopathic doctors, as they are more likely able to provide alternatives to those patients who prefer bodywork therapies.

The degree to which naturopaths/naturopathic doctors apply bodywork practices themselves, or recommend their patients receive treatment or support from other bodywork practitioners varies regionally based on historical and educational factors. For example, in Australia, massage (including Swedish massage) has been included in naturopathic curricula for over 20 years [4]. In North America, naturopathic manipulation and acupuncture is generally part of the scope of practice [5]. Furthermore, in the UK and Australia there has been a historical connection between osteopathy (a profession that is commonly trained in cranio-sacral therapy and other bodywork techniques) and naturopathy which resulted in an extension of naturopaths/naturopathic doctors training and skills in physical medicine [6, 7]. In India, naturopathy and yoga are combined within the naturopathic program and yoga is an integral part of naturopathic care [8].

The 2015 survey conducted by the WNF also found that the naturopathic workforce frequently work in integrated clinics [9] and, as such, they may be referring patients to other practitioners for bodywork therapies through clinical relationships developed through these settings or through external referral networks [10]. With physical therapies increasingly being promoted as non-pharmacological alternatives for conditions that previously required high-level intervention, and the naturopathic philosophical approach centered on low-level interventions as a priority, naturopaths/naturopathic doctors may have an important role in expanding non-pharmacological physical medicine interventions. Given the historic and contemporary focus on bodywork modalities by the global naturopathic profession, more research in the field of naturopathic physical medicine is warranted.

Studies investigating specific interventions:

Massage

The most common intervention studied was therapeutic massage, with five trials involving post-surgery cardiothoracic patients [11], hospice or palliative care patients [12, 13] or hospital inpatients [14] and osteoarthritis of the knee [15]. A randomized controlled trial (n=152) conducted in Australia compared Swedish massage therapy with rest for post-surgery cardiothoracic patients [11]. The results of the study included significant reduction in pain, anxiety and muscular tension and increase in relaxation and satisfaction based on the visual analog scale for those receiving massage. Another randomized controlled trial (n=90) conducted in the USA involving medical inpatients compared massage therapy (inclusive of Swedish and acupressure techniques), music therapy and usual care [14]. Both those patients receiving massage and music therapy reported an overall improvement in their hospital experience and a reduction in pain.

A randomized controlled trial (n=167) conducted in the USA of hospice or palliative care patients compared therapeutic massage, guided meditation/visualization or friendly visits [12]. Neither massage nor guided meditation, delivered up to twice per week, had specific treatment effects when compared with friendly visits from hospice-trained volunteers. In a follow-up publication, the authors found that there was an increase in quality of life when participants were assigned to their preferred treatment group ($p=0.047$), an increase in benefit from the treatment intervention ($p=0.001$) and an increase in days of participation in the study ($p=0.18$) [13]. Much of the apparent benefit of massage over the other two therapies resulted from prior preference for massage; an insight that suggests matching of available treatments to those actively preferred and requested by patients is critical in gaining benefit from such treatments and should lead to a re-evaluation of the appropriateness of randomized controlled trials for end-of-life research.

Other Manual Therapies

Naturopathic research also included manual therapy (osteopathy) combined with breathing training in asthma patients [16] and craniosacral therapy (CST) for

the management of chronic non-specific neck pain [17] and for symptoms associated with post-operative meningioma and traumatic brain injury [18]. One randomized controlled trial (n=54) conducted in Germany investigated CST [17] for the treatment of chronic non-specific neck pain. The CST intervention for this study involved one 45-minute treatment per week for eight weeks. This was compared with a sham intervention through which the participant received light touch applied to standardized anatomical areas for two minutes each time, once per week. Both groups were also followed up at 20 weeks after baseline measurements. The primary study outcomes identified reductions at Week 8 and Week 20 in pain on movement (Wk 8: -18.6, p=0.001; Wk 20: -11.4, p=0.020), pain intensity (Wk 8: -21.0, p=0.001; Wk 20: -16.8, p=0.003) and neck disability (Wk 8: -8.2, p=0.010; Wk 20: -6.5, p=0.006) in the CST intervention group compared to the sham control. They also reported increased physical quality of life (Wk8: +8.0, p=0.010; Wk 20: +6.5, p=0.006). Subsequent secondary analysis [19] examined the applicability of the sham control and found it to be an appropriate control.

A case study conducted in Germany with a patient suffering with headaches, vertigo and chronic neck pain as a result of a traumatic brain injury included five 1-hour sessions of CST into a complex naturopathic plan that involved auricular acupuncture, hydrotherapy, exercise, nutritional therapy, mindfulness exercises and other treatments [18]. The patient reported a decrease in headache intensity, vertigo symptoms, and cervicobrachial and hand numbness (measured by visual analog scales), subjective and objective improvements in neck mobility, muscle tension, sleep quality and general wellbeing.

Table 35.1 Clinical research investigating naturopathic physical medicine interventions conducted by naturopathic researchers

Author (year) [Country, World Region]	Design	Study Population	Intervention	Concomitant therapies	Control or comparison group	No. Participants (Intervention/ Control)	Outcome measure	Outcome
Braun, et al. (2012) [Australia, WPRO] [11]	Randomized controlled trial	Post-surgery cardiothoracic patients	Swedish Massage therapy		Active control: rest	146 (75/71)	Anxiety, Visual Analog Scale [pre and post intervention]	**Reduced anxiety** Massage: -1.72; Rest: -0.041 Between group: p<0.001
							Muscular tension, Visual Analog Scale [pre and post intervention]	**Reduced muscular tension** Massage: -1.70; Rest: -0.61 Between group: p=0.002
							Relaxation, Visual Analog [pre and post intervention]	**Increased relaxation** Massage: + 2.11; Rest: 0.74 Between group: p<0.0001
							Satisfaction, Visual Analog Scale [pre and post intervention]	**Increased satisfaction** Massage: +0.31; Rest: -0.28 Between group: p=0.016
							Heart rate (beats/sec) [pre and post intervention]	NS
							Respiratory rate (breaths/min) [pre and post intervention]	NS
							Blood pressure (mmHg) [pre and post intervention]	NS
							Anxiety, Visual Analog Scale [pre and post intervention]	**Reduced anxiety** Massage: -1.72; Rest: -0.041 Between group: p<0.001
Courtney, et al. (2019) [Australia, WPRO] [16]	Case reports	Asthma (dysfunctional breathing)	Combined manual therapy and standardized breathing retraining protocol	Not specified	Nil	6	Simplified manual assessment of respiratory motion (MARM) [pre and post treatment to Wk 4]	**Improved respiratory motion** Reduced in 5/6 patients
							Chest expansion (cm) [pre and post treatment to Wk 4]	**Increased chest expansion** Increased xiphoid expansion 3/6 patients Increased axilla expansion 2/6 patients

Author (year) [Country, World Region]	Design	Study Population	Intervention	Concomitant therapies	Control or comparison group	No. Participants (Intervention/ Control)	Outcome measure	Outcome
							Dysfunctional breathing symptoms questionnaires – Self-Evaluation of Breathing Questionnaire (SEBQ) [pre- and post-treatment to Wk 4]	**Reduced dysfunctional breathing** Reduced post treatment 6/6 patients Reduced wk 4 5/5 patients Further reduced from BL 4/5 patients
							Dysfunctional breathing symptoms questionnaires Nijmegen questionnaire (NQ) [pre- and post-treatment to Wk 4]	**Reduced dysfunctional breathing** Reduced post treatment 6/6 patients Reduced wk 4 5/5 patients Further reduced from BL 4/5 patients
							End Tidal CO2 measures (mmHg) [pre- and post-treatment]	**Reduced end tidal CO2 measures** ETCO2 <35 mmHg (hyperventilation) 4/6 patients ETCO2 >35 mmHg 1/6 patients (3)
							Lung function measures (predicted change %)	**Increased lung function measures** Increased FEV1 1/6 patients (3) (29% – 39%) Increased FVC 1/6 patients (3) Reduced FVC 1/6 patients (5)
							Asthma Related Quality of Life Questionnaire (AQLQ) [pre- and post-treatment to Wk 4]	NS
							Perceived Control of Asthma Questionnaire (PCAQ) [pre- and post-treatment to Wk 4]	**Increased control of asthma** Post-treatment and Wk 4 5/6 patients
							Hospital anxiety and depression scale [pre and post treatment to Wk 4]	**Reduced anxiety and depression** Anxiety Score >7 pre: 4/6 post 3/6 Depression score >7 pre: 3/6 post 3/6

Author (year) [Country, World Region]	Design	Study Population	Intervention	Concomitant therapies	Control or comparison group	No. Participants (Intervention/ Control)	Outcome measure	Outcome
Downey, et al. (2009) [USA, AMRO] [12]	Randomized controlled trial	Hospice or palliative care patients	Therapeutic massage – light back-and neck massage in a position of the patient's choosing, followed by effleurage and goodbye holding (35+10min)		Guided meditation/visualization or Friendly visits	167 (56/56/55)	Quality of Dying and Death Instrument [BL to Wk 10]	NS
							Expected number of weeks of good-quality life over a 10-week period [BL to Wk 10]	NS
							Memorial Symptom Assessment Scale Pain distress over a 10-week period [BL to Wk 10]	NS
							Study partners' reports of quality of life of 106 deceased patients [BL to Wk 10]	NS
Downey, et al. (2009) [USA, AMRO] [13]	Secondary analysis					108 (37/34/37)	Rating scale by surrogate of patient benefit from study treatment	Patient benefit from study treatment when assigned to preferred treatment group (p=0.001)
							Baseline QoL according to patient's treatment preference assignment	Increased baseline QoL when assigned to preferred treatment (p=0.047)
							Days of participation in the study before withdrawal according to patient's treatment preference assignment	Increase in days of participation in study when assigned to preferred treatment (p=0.18)
Haller, et al. (2015) [Germany, EURO] [18]	Case report	Traumatic Brain Injury (headaches, vertigo, and chronic neck pain)	Five 1-hour craniosacral therapy (CST) sessions	Auricular acupuncture, cupping massage, hydrotherapy (cold affusions), thermotherapy (hot and cold cataplasms), exercise, nutritional therapy, and	Nil	1	VAS for headache intensity [BL to Wk 2]	**Reduced headache intensity** Symptom improvement after treatment
							VAS for vertigo symptoms [BL to Wk 2]	**Reduced vertigo symptoms** Symptom improvement after treatment
							Neck mobility and muscle tension [BL to Wk 2]	**Increased mobility and reduced tension** Subjective improvements after treatment

Author (year) [Country, World Region]	Design	Study Population	Intervention	Concomitant therapies	Control or comparison group	No. Participants (Intervention/ Control)	Outcome measure	Outcome
				phytotherapy with *Bryophyllum sp.* and *Avena sativa.* Relaxation, stress reduction, mindfulness, and cognitive re-structuring training			VAS for cervicobrachial and hand numbness [BL to Wk 2]	**Reduced numbness** Symptom improvement after treatment
							Interview for sleep quality [BL to Wk 2]	**Increased sleep quality** Improvement after treatment
							Interview for general well-being [BL to Wk 2]	**Increased general wellbeing** Improvement after treatment
Haller, et al. (2016) [Germany, EURO] [17]	Randomized controlled trial	Neck pain (chronic)	8 weeks: Craniosacral therapy (CST) 45 minutes, once per week	Pain medication, massage and acupuncture	Sham: light touch applied to standardized anatomic areas for 2 minutes each time, once per week	54 (27/27)	Pain on Movement Questionnaire [BL, Wk 8, Wk 20]	**Reduced pain on movement** Wk 8: CST, -28.8; Sham, -11.2 Between group -18.6 (p=0.001) Wk 20: CST, -31.2; Sham, -21.1 Between group -11.4 (p=0.020)
							Pain intensity, Visual Analog score [BL, Wk 8, Wk 20]	**Reduced pain intensity** Wk 8: CST, -32.4; Sham, -16.6 Between group -21.0 (p=0.001) Wk 20: CST, -32.5; Sham, -21.1 Between group -16.8 (p=0.003)
							Pressure pain sensitivity test [BL, Wk 8, Wk 20]	Point of max. pain: NS M. levator scapulae: NS M. trapezius: NS M. semispinalis capitis: NS
							Neck Disability Index [BL, Wk 8, Wk 20]	**Reduced neck disability** Wk 8: CST, -14.8; Sham, -4.5 Between group -8.2 (p=0.010) Wk 12: CST, -13.9; Sham, -5.4 Between group, -6.5 (p=0.006)
							Short Form-12, Physical [BL, Wk 8, Wk 20]	**Increased quality of life** Physical Wk 8: CST, +9.2; Sham, +2.1 Between group +8.0 (p=0.010) Wk 12: CST, +10.5; Sham, +2.0 Between group +6.5 (p=0.006)
							Short Form-12, Mental [BL, Wk 8, Wk 20]	NS

Author (year) [Country, World Region]	Design	Study Population	Intervention	Concomitant therapies	Control or comparison group	No. Participants (Intervention/ Control)	Outcome measure	Outcome
Haller, et al. (2014) [Germany, EURO] [19]	Secondary analysis						Questionnaire for Assessing Subjective Physical Wellbeing [BL, Wk 8, Wk 20]	NS
							Hospital Anxiety and Depression Scale [BL, Wk 8, Wk 20]	**Reduced Anxiety** Wk 8: CST, -1.6; Sham, -0.1 Between group -1.0 (NS) Wk 20: CST, -1.9; Sham, +0.7 Between group -2.1 (p=0.020) Depression: NS
							Perceived Stress Questionnaire [BL, Wk 8, Wk 20]	NS
							Emotional/Rational Disease Acceptance Questionnaire [BL, Wk 8, Wk 20]	NS
							Scale of Body Connection [BL, Wk 8, Wk 20]	NS
							Global Impression of Improvement [BL, Wk 8, Wk 20]	**Increased impression of improvement** Wk 8: CST, 2.2; Sham, 3.3 Between group -1.0 (p<0.001) Wk 20: CST, 2.3; Sham, 3.1 Between group -0.7 (p=0.029)
							Credibility/ Expectancy Questionnaire and Helping Alliance/ Satisfaction Questionnaire	NS
							Helping Alliance Questionnaire	**Sham treatment is an appropriate control**

Author (year) [Country, World Region]	Design	Study Population	Intervention	Concomitant therapies	Control or comparison group	No. Participants (Intervention/ Control)	Outcome measure	Outcome
Perlman, et al. (2012) [USA, AMRO] [15]	Randomized controlled trial (dose-finding)	Osteoarthritis of the knee	Swedish massage (30-60 min, once or twice per wk, for 8 wks)	Not specified	Group 1: 30 mins once per wk, Group 2: 30 mins twice per wk Group 3: 60 mins once per wk Group 4: 60 mins twice per week Control: Usual care	125 (25/25/25/25/25)	Western Ontario and McMaster Universities Arthritis Index (WOMAC) [BL to Wk 8]	**Reduced symptoms** Pain: Group 1, NS; Group 2, NS; Group 3, -27.2; Group 4, -27.7; Usual care, -5.6 Between group (1&2 vs UC), NS Between group (3&4 vs UC), p<0.05 Functionality: Group 1, NS; Group 2, NS; Group 3, -21.2; Group 4, -22.0; Usual care, -6.6 Between group (1&2 vs UC), NS Between group (3&4 vs UC), p<0.05 Global: Group 1, NS; Group 2, NS; Group 3, -24.0; Group 4, -24.0; Usual care, -6.3 Between group (1&2 vs UC), NS Between group (3&4 vs UC), p<0.05 Stiffness: NS
							Visual Analog Scale [BL to Wk 8]	**Reduced pain** Group 1, NS; Group 2, NS; Group 3, -39.8; Group 4, -31.2; Usual care, -9.8 Between group (1&2 vs UC), NS Between group (3&4 vs UC), p<0.05
							Knee range of motion (flexion) [BL to Wk 8]	NS
							Time to walk 50 feet (15m) [BL to Wk 8]	NS
Roseen, et al. (2017) [USA, AMRO] [14]	Randomized controlled trial	Hospital inpatients (family medicine)	Massage therapy (Swedish and acupressure techniques) 10-40 min therapy session each day.	Usual inpatient care	Control: Usual care alone Comparison: Music therapy	90 (30/30/30)	Hospital Consumer Assessment of Healthcare Providers and Systems survey [within 7 days of discharge]	NS

Author (year) [Country, World Region]	Design	Study Population	Intervention	Concomitant therapies	Control or comparison group	No. Participants (Intervention/ Control)	Outcome measure	Outcome
							Qualitative telephone survey [within 7 days of discharge] (not administered to control group)	**Improved hospital stay experience and pain management** Subjective reports of interventions improving patient experience

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36 Hydrotherapy

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HIGHLIGHTS

- Hydrotherapy – the application of water for therapeutic purposes – has been used for thousands of years and has been part of naturopathic care since its inception.
- Hydrotherapy can be used externally (baths, compresses and sprays) and internally (inhalation and colon therapy).
- Hydrotherapy is a low cost, effective and safe therapy that can be easily integrated into practice.
- Clinical research by the naturopathic community has examined the application of hydrotherapy baths, topical compresses, and complex hydrotherapy involving multiple hydrotherapy techniques.
- In line with the role of primary care, naturopathic researchers have investigated the effects of hydrotherapy on individuals with primary dysmenorrhoea, anemia, chronic neck pain, migraine, and hepatic cirrhosis.

Hydrotherapy (formerly 'hydropathy') is the application of water for therapeutic purposes. Hydrotherapy can be used externally, which includes compresses, baths (balneotherapy or thalassotherapy) and sprays; and internally, which includes inhalations and colon hydrotherapy [1]. Hydrotherapy is considered a core aspect of nature cure [2] and it is taught in over 80% of naturopathic educational programs globally. It is also included as part of the treatment modalities offered by naturopaths and naturopathic doctors in most countries [3].

As a healing force in the natural environment, water is used to stimulate both the healing power of nature and the self-healing processes within the body [4]. It is a completely drugless therapy that supports the body's healing processes primarily through the manipulation of blood circulation through thermic and mechanical means. Some therapies also use water as a medium for transfer of minerals, herbal remedies or other therapeutic agents. The treatment effect of hydrotherapy is based on the specific application of either cold or hot water or the alternating of cold and hot water compresses and is designed to generally be sedative in acute disease and stimulative in chronic [5].

Although the healing power of water has been used by humans for tens of thousands of years, modern hydrotherapy originated with Vincent Priessnitz in the mid-1820s who is credited with opening the first hydropathic center. Hydrotherapy was further promoted by Sebastian Kneipp with "Kneippism," and his book *My Water Cure* published in 1886, in which he wrote: "Health depends on a normal and regular circulation of blood which is achieved by hydrotherapy, nutrition and herbalism" [6]. Kneipp, a German hydrotherapist, health promotor, herbalist and nutritionist was a pioneer in the naturopathic movement, and an inspiration and mentor to other important naturopaths such as Benedict Lust, Henry Lindlahr and John Scheel, who further entrenched hydrotherapy as a key component of naturopathic treatment [2]. In the early 1900s, Otis G. Carroll, a naturopathic doctor from the United States of America (USA) developed constitutional hydrotherapy which is the alternating of hot and then cold wet towels on the trunk and back of the body followed by wrapping the person in blankets [2].

Today hydrotherapy forms one of the seven core therapeutic modalities used as part of naturopathic treatment and it is applied in practice to stimulate the *vis medicatrix naturae,* or the natural healing ability of the body [2]. Although readily employed in both inpatient and outpatient settings, it is particularly prevalent in countries where naturopathy/naturopathic medicine has retained a focus on inpatient delivery through naturopathic hospitals such as India.

Overview of Studies

This chapter is dedicated to highlighting the original clinical research (n=17) naturopathic clinicians undertook in the field of hydrotherapy. This research includes a total 483 participants and was conducted in India (n=15), Canada (n=1) and the United States (n=1). The study designs include uncontrolled trials (n=5), randomized controlled trials (n=4), randomized crossover trials (n=3), comparative trials (n=2), case studies (n=2) and

non-randomized controlled study (n=1). The location of the clinical research studies was strongly weighted to India and were conducted primarily in inpatient settings in naturopathic hospitals or residential educational institutions. The studies in North America were conducted in outpatient clinics in the community. The hydrotherapy interventions were diverse, and included external applications of plain water (i.e., not spring or sea water), ice, mud and the use of saunas. Hydrotherapy treatments included constitutional hydrotherapy, cold applications including cold packs, or cold baths; hot applications including hot packs or hot baths; and other hydrotherapy techniques including neutral temperature baths, water spray, ice bag, simultaneous applications of hot and cold water, alternating hot and cold baths, ionic foot baths, saunas, and the application of mud.

The conditions treated with hydrotherapy included the effects of hydrotherapy on the blood pressure and heart function of healthy adults (n=5), and one study each for the conditions of heel pain, chronic neck pain, chronic migraine, primary dysmenorrhea, HIV, diabetes, bronchial asthma, anemia, and hepatic cirrhosis. Of all the naturopathic clinical studies employing hydrotherapy interventions, 84.2% reported a positive outcome in at least one primary or secondary outcome measure. Details of the studies are available in *Table 36.1: Clinical research investigating hydrotherapy interventions conducted by naturopathic researchers.*

Implications

The practice of hydrotherapy encompasses a broad range of treatment modalities which could potentially be applied in many therapeutic settings for both preventive and curative approaches. The results indicate that hydrotherapy may be effective in low lowering of blood pressure, blood sugar and inflammation. For some chronic conditions, such as rheumatoid arthritis or liver disease, hydrotherapy can form an integral part of an inpatient treatment program of naturopathic therapies. Importantly, although most studies were performed in inpatient hospital settings, many of these applications are readily translatable to low resource settings or self-management due to limited equipment required [7].

Due to multiple physiological actions, hydrotherapy has a wide range of therapeutic applications and may offer a low-cost treatment option which can play a major part in naturopathic practice, both in a clinic setting and for home use. Although most studies have been performed in inpatient settings in India, hydrotherapy remains taught and practiced by naturopaths/naturopathic doctors globally [7-9], highlighting the need for further research in these locations. The results of the research and the lack of repetition of studies for the same condition warrant the need for more research in hydrotherapy, but also point to its potential as a low-cost, effective tool for integrating naturopaths/naturopathic doctors.

Studies investigating specific interventions:

Hydrotherapy Baths

Hydrotherapy baths involve immersing parts of the body in water with a controlled temperature, or alternating temperatures. Water bath exposures included those for the hip [10-12], spine [13, 14], foot [15], pelvis (sitz) [11], foot and arm [16], immersion [11, 12, 17] and a mud bath [18]. The populations involved in the studies had primary dysmenorrhea (n=1) [10], anemia (n=1) [11], chronic neck pain (n=1) [12], migraine (n=1) [16], and hepatic cirrhosis (n=1) [17]. Four studies also sampled health populations (n=4) [13-15, 18].

An uncontrolled clinical trial (n=17) conducted in India with women aged 18 to 35 with primary dysmenorrhea [10] included a hot hip sitz bath for 10 minutes with a simultaneous cold compress on the head after drinking a glass of cold water daily, from day 20 of their menstrual cycle until the start of the menstruation. Pain intensity on Day 1 of menstruation decreased (Mth 1: -2.7 ($p=0.03$); Mth 2: -2.8 ($p=0.04$); Mth 3: -3.2 ($p=0.01$)). Participants also reported decreased use of analgesics and absenteeism decreased significantly (Mth 1: -7 ($p < 0.01$); Mth 2: -8 ($p<0.01$); Mth 3: -8 ($p<0.01$)) [7].

A randomized controlled trial conducted in India with chronic migraine patients (n=40) compared conventional medication as needed (n=20), with conventional medication as needed plus hydrotherapy treatments [16]. The hydrotherapy treatments consisted of applying hot compresses to the arm, a hot foot bath (103°F to 110°F) and an ice massage to the head daily for 20 min for 45 days. There was a significant decrease in headache impact test score (34.25±6.74 in the hydrotherapy group versus 9.45±1.42 for pharmacotherapy only group, $p<0.001$ between groups). A decrease in the frequency (hydrotherapy group: -8.65 and pharmaceutical only group: -3.15, between group: $p<0.001$), and intensity of headaches (hydrotherapy group: -6.85 and pharmaceutical only group: -2.05, between group: $p<0.001$) based on the visual analog scale was found. There was also significant improvement in heart rate variability (HRV) parameters in the hydrotherapy group, including a significant decrease in heart rate ($p=0.017$), as well as an increase in parasympathetic activity as measured by an increase in high frequency power ($p=0.014$) and a significant decrease in sympathovagal balance as measured by a decrease in LF/HF ratio ($p=0.004$) [13].

Topical Compresses

Compresses are an alternative way to apply water to specific parts of the body, typically using cloths soaked in cold or hot water. Eleven studies measured the effect of hydrotherapy compresses using alternating hot and cold compress on legs and heels [19] or neck [12], cold compress on the head [10], cold pack on the abdomen [20], cold chest pack [21], hot chest pack [22] ice bag on head [23] or ice massage [24]; and abdominal mud pack [11, 17] and eyes [11, 25]. The participants in these studies were sampled for primary dysmenorrhea (n=1) [10], anemia (n=1) [11], chronic neck pain (n=1) [12], heel pain (n=1) [19], type 2 diabetes mellitus (n=1) [20], and bronchial asthma (n=1) [21]. Four studies sampled healthy populations (n=4) [22-25].

An uncontrolled trial (n=20) conducted in India studied the impact of a 20-minute cold abdominal pack (CAP) on males taking medication for type II diabetes [20]. The parameters studied included blood pressure, pulse rate, variables calculated from those measurements, HRV and blood glucose. Measurements before and after the intervention of a 20-minute CAP showed a significant reduction in blood glucose (154.35±4.09 mg/dL vs. 149.55±33.25 mg/dL, p=0.011). Improvements in cardiovascular and HRV parameters, including pulse rate, systolic blood pressure, mean arterial pressure, but not in diastolic blood pressure or pulse pressure.

A controlled trial (n=20) conducted as a pilot study in India used alternating hot and cold compresses on individuals with heel pain. Patients were assigned to standard naturopathic physiotherapy care (NPC) with two adjuvant therapy groups: a control group (therapeutic ultrasound, n=10), or alternating compresses (n=10) [19]. In this study, alternating compress was the application of hot and cold-water packs, where the hot moist sponge cloth was applied first for 15 to 20 minutes, followed by a cold moist sponge cloth for 30 seconds to 1 minute. The Foot Function Index (FFI) was used to measure changes. The FFI reduced from 46.97 to 31.98 (p=0.005) among standard protocol patients, and from 49.72 to 21.35 (p=<0.001) among the alternating compress protocol patients. Average pain intensity in the seven days of treatment decreased from 3.53 to 2.53 cm on the visual analogue scale (p=<0.001) among patients receiving NPC, and from 4.09 to 2.61 cm (p=<0.001) amongst those receiving NPC plus alternating compresses. There was no significant difference in pain score reduction between the two groups (p=0.206), but patients with alternating compresses as part of their treatment had significant improvements in foot functionality (p=0.007).

Complex Hydrotherapy

Complex hydrotherapy uses an alternating sequence of different hydrotherapy techniques to effect changes in multiple areas. Two studies [12, 17] used multiple hydrotherapy techniques; and a further clinical trial measured the outcome of constitutional hydrotherapy in HIV positive adults [26].

A case study conducted in India with a 39-year-old male with hepatic cirrhosis received various forms of hydrotherapy over a 4-week period of time that included abdominal mud packs, hot and cold kidney packs, neutral baths and alternating hot and cold baths along with yoga and breathing exercises [17]. At the end of the 4 weeks there was a reduction in weight (17 kg) and body mass (6.25 kg/m^2), a reduction in both systolic and diastolic blood pressure (10 mm Hg and 12 mm Hg), reduction in total bilirubin (0.6 mg/dL), reduction in AST by 16 u/L and ALT by 17 u/L and improvement in kidney function as measured by a reduction in urea by 8 mg/dL.

Table 36.1 Clinical research investigating hydrotherapy interventions conducted by naturopathic researchers

Author (year) [Country, World Region]	Design	Study Population	Intervention(s)	Concomitant therapies	Control or comparison group	No. Participants (Intervention/Control)	Outcome measure	Outcome
Arankalle, et al. (2016) [India, SEARO] [19]	Non-randomized controlled trial (pilot study)	Heel pain	Alternating hot and cold compresses (AC)	Naturopathic physical care (NPC)	Control: NPC plus ultrasound 'placbo'	20 (10/10)	Visual analog scale [BL to Dy 6]	**Reduced pain** AC: -1.48 (p<0.001); NPC: -1.0 (p<0.001) Between group: NS
							Foot Functional Index [BL to Dy 6]	**Increased function** AC: -18.47 (p-0.001); NPC: -14.99 (p=0.005) Between group: p=0.007
Bharthis, et al. (2012) [India, SEARO] [10]	Uncontrolled trial (pilot study)	Primary dysmenorrhea	Hot hip bath with cold compress on the head (10 min daily for 3 menstrual cycles)	Nil	Nil	17	Absenteeism due to pain (days) [BL to Mth 5]	**Reduced absenteeism** Mth 1: -7 (p < 0.01); Mth 2: -8 (p<0.01); Mth 3: -8 (p<0.01)
							Pain before onset of menstruation, Visual Analog Scale [BL to Mth 1, Mth 2, Mth 3]	NS
							Pain on first day of menstruation, Visual Analog Scale [BL to Mth 1, Mth 2, Mth 3]	**Reduced pain on first day of menstruation** Mth 1: -2.7 (p=0.03); Mth 2: -2.8 (p=0.04); Mth 3: -3.2 (p=0.01)
							Conventional analgesic medication use [BL to Mth 3]	**Reduced medication use**
Corroon et al. (2018) [USA, AMRO] [26]	Uncontrolled trial (pilot study)	HIV+ adults	Constitutional hydrotherapy (Two treatments per week for 6 weeks + 1 week follow-up)	Nil	Nil	15	Adverse events [BL to Wk 8]	None serious
							Viral load (cp/mL) [BL to Wk 8]	NS
							TNF-alpha (pg/mL) [BL to Wk 8]	NS
							Erythrocyte sedimentation rate (pg/mL) [BL to Wk 8]	NS
							High sensitivity C-reactive protein (mg/L) [BL to Wk 8]	NS

Author (year) [Country, World Region]	Design	Study Population	Intervention(s)	Concomitant therapies	Control or comparison group	No. Participants (Intervention/ Control)	Outcome measure	Outcome
							Blood pressure (mmHg) [BL to Wk 8]	NS
							Body mass index (kg/m^2) [BL to Wk 8]	NS
							Mean body fat (%) [BL to Wk 8]	**Reduced body fat** -1.6 ($p < 0.0001$)
							Red blood cell (x106/uL) [BL to Wk 8]	NS
							Hemoglobin (g/dL) [BL to Wk 8]	NS
							Hematocrit (%) [BL to Wk 8]	NS
							CD3 (cells/ul) [BL to Wk 8]	NS
							CD4 (cells/ul) [BL to Wk 8]	NS
							CD8 (cells/ul) [BL to Wk 8]	NS
							Sodium (mmol/L) [BL to Wk 8]	**Reduced sodium levels** -2.08 ($p = 0.005$)
							Potassium (mmol/L) [BL to Wk 8]	NS
							BUN ratio	NS
							Creatinine (mg/dL) [BL to Wk 8]	NS
							Aspartate transferase (IU/L) [BL to Wk 8]	NS
							Alanine transferase (IU/L) [BL to Wk 8]	NS
							Bilirubin (mg/dL) [BL to Wk 8]	NS

Author (year) [Country, World Region]	Design	Study Population	Intervention(s)	Concomitant therapies	Control or comparison group	No. Participants (Intervention/ Control)	Outcome measure	Outcome
							Short Form-36 health survey [BL to Wk 8]	**Increased energy** Total: NS Energy/Fatigue: +2.5 (p = 0.03) Physical functioning: NS Pain: NS General health: NS
Das, et al. (2018) [India, SEARO] [20]	Uncontrolled trial	Type II diabetes mellitus (adults, male)	Cold abdominal pack (15 – 16°C) (single application, 20 minutes)	Nil	Nil	20	Random blood glucose (mg/dL) [BL to 20 min]	**Reduced blood glucose** -4.8 (p=0.011)
							Systolic blood pressure (mmHg) [BL to 20 min]	**Reduced systolic blood pressure** -2.35 (p=0.023)
							Diastolic blood pressure (mmHg) [BL to 20 min]	NS
							Pulse rate (beats/minute) [BL to 20 min]	**Reduced pulse rate** -1.6 (p=0.028)
							Pulse pressure (mmHg) [BL to 20 min]	NS
							Mean arterial pressure (mmHg) [BL to 20 min]	**Reduced mean arterial pressure** -1.55 (p=0.010)
							Rate pressure product (units) [BL to 20 min]	**Reduced rate pressure product** -3.77 (p=0.006)
							Double product (units) [BL to 20 min]	**Reduced double product** -2.72 (p=0.003)
Gnanadeep, et al. 2016 [India, SEARO] [18]	Randomized controlled trial	Healthy adults (young males)	Mud bath (single session, 45 min)	Nil	Cold wet wrap (single session, 45 min)	60 (30/30)	Heart rate variability [5 min pre- and post-intervention]	NS
							Pulse rate [5 min pre- and post- intervention]	NS
							Respiratory rate [5 min pre- and post-intervention]	NS
							Blood pressure [5 min pre- and post-intervention]	NS
							Body temperature [5 min pre- and post-intervention]	NS

Author (year) [Country, World Region]	Design	Study Population	Intervention(s)	Concomitant therapies	Control or comparison group	No. Participants (Intervention/ Control)	Outcome measure	Outcome
Goley et al. (2018) [India, SEARO] [13]	Randomized comparative trial (pilot study)	Healthy adults	Neutral spinal bath (NSB) or Neutral spinal spray (single session, 15 min)	Nil	Nil	30 (15/15)	Blood pressure (BP), systolic (mmHg) [BL to 5 min post-intervention]	**Reduced systolic BP** NSB group: NS NSS group: -5.2 (p=0.037)
							Blood pressure (BP), diastolic (mmHg) [BL to 5 min post-intervention]	**Reduced diastolic BP** NSB group: -7.47 (p=0.008) NSS group: NS
							Pulse pressure (mmHg) [BL to 5 min post-intervention]	**Reduced pulse pressure** NSB group: NS NSS group: -7.34 (p=0.017) Between group: (p=0.039)
							Mean arterial pressure (mmHg) [BL to 5 min post-intervention]	**Reduced mean arterial pressure** NSB group: -5.6 (p=0.008) NSS group: NS
							Heart rate variability (HRV) (RR intervals) [BL to 5 min post-intervention]	**Increased heart rate variability** NSB group: +44.25 (p=0.002) NSS group: +45.92 (p=0.009)
							Heart rate (beats per min) [BL to 5 min post-intervention]	**Reduced heart rate** NSB group: -4.89 (p=0.002) NSS group: -4.96 (p=0.004)
							Low frequency (LF) band HRV (0.04-0.15Hz) [BL to 5 min post-intervention]	NS
							High frequency (HF) band HRV (0.15-0.4 Hz) [BL to 5 min post-intervention]	NS
							HF/LF ratio [BL to 5 min post-intervention]	**Reduced HF/LF ratio** NSB group: -0.7 (p=0.041) NSS group: NS Between group: (p=0.026)

Author (year) [Country, World Region]	Design	Study Population	Intervention(s)	Concomitant therapies	Control or comparison group	No. Participants (Intervention/Control)	Outcome measure	Outcome
Jainraj, et al. (2016) [India, SEARO] [14]	Uncontrolled trial	Healthy adults	Cool spinal bath (single session, 26°C, 15 min)	Nil	Nil	50	Blood pressure (BP), systolic (mmHg) [BL to post-intervention]	**Reduced systolic BP** -7.62 (p=<0.001)
							Blood pressure (BP), diastolic (mmHg) [BL to post-intervention]	**Reduced diastolic BP** -6.39 (p=<0.001)
							Breathing rate [BL to post-intervention]	NS
							Pulse rate (beats/min) [BL to post-intervention]	**Reduced pulse rate** -6.18 (p=<0.001)
							Body temperature (% change) [BL to post-intervention]	**Reduced body temperature** -2% (p=0.001)
Jogdand, et al. (2018) [India, SEARO] [25]	Randomized controlled trial (pilot study)	Healthy adults	Mud pack (over eyes, 30 min, 15 sessions)	Nil	Wet pack (over eyes, 30 min, 15 sessions)	60 (30/30)	Mindfulness Attention Awareness Scale (6 point Likert scale) [BL to post-intervention]	**Increased mindfulness** Mud pack: +15.76 (p<0.001) Wet pack: NS
							Perseverative Thinking Questionnaire of negative thinking (5 point Likert scale) [BL to post-intervention]	**Reduced obsessive negative thinking** Mud pack: -9.04 (p<0.05) Wet pack: -8.32 (p<0.01)
							Positive and Negative Affect Schedule – positive score [BL to post-intervention]	NS
							Positive and Negative Affect Schedule – negative score [BL to post-intervention]	**Reduced negative effect** Mud pack: -4.08 (p<0.05) Wet pack: 3.6 (p<0.05)
Kennedy, et al. (2011) [Canada, AMRO] [15]	Comparative trial (proof-of-principle)	Healthy adults	Ionic footbath (70/30 mix positive/negative polarity, 30 min, 4 sessions)	Nil	Footbath without active participant (2 sessions)	6	Concentration of elements in water (difference between pre- and post-footbath, 28 individual elements, grouped as 'Array components', 'Essential elements' and 'Potentially toxic elements (PTEs)'	**Increased concentration of elements in water** Without feet: Total, +103% (p=0.01) Array, +8,271% (p=0.01); Essential, NS; PTEs, NS With feet: Total, +99% (p<0.0001); Array, +10,830% (p<0.0001);

Author (year) [Country, World Region]	Design	Study Population	Intervention(s)	Concomitant therapies	Control or comparison group	No. Participants (Intervention/ Control)	Outcome measure	Outcome
							[pre- and post-intervention]	Essential, NS; PTEs, +19% (p=0.042) Between group: Total, NS; Array, p=0.005; Essential, NS; PTEs, NS
Manjunath, et al. (2006) [India, SEARO] [21]	Uncontrolled trial	Bronchial asthma (unmedicated adults)	Cold chest pack (30 min daily for 21 days)	Naturopathic care (hydrotherapy, fasting, diet therapy, magnet and colour therapy, acupuncture, mud packs, massage therapy, yoga therapy)	Nil	15	Peak Expiratory Flow Rate (l/min) [BL to Dy 21]	**Increased peak expiratory flow** Day 21: +65.3 (p<0.002)
							Symptom presence/ absence (score out of 3 for breathlessness, cough with expectoration, and wheezing) [BL to Dy 21]	**Reduced symptoms** Day 21: -2.2 (p<0.05)
Manjuladevi, et al (2017) [India, SEARO] [22]	Randomized crossover trial	Healthy adults (young females)	Hot chest pack (HCP) (40°C, 20 min)	Nil	Supine rest (SR) (20 min)	30	Blood pressure (BP), systolic (mmHg) [BL to post-intervention]	**Reduced systolic BP** HCP: -4.4 (p<0.001); SR: -2.8 (p=0.02) Between group: NS
							Blood pressure (BP), diastolic (mmHg) [BL to post-intervention]	**Reduced diastolic BP** HCP: -3.1 (p=0.009); SR: NS Between group: NS
							Pulse rate (beats per min) [BL to post-intervention]	**Reduced pulse rate** HCP: -2.34 (p=0.032); SR: NS Between group: NS
							Pulse pressure (mmHg) [BL to post-intervention]	NS
							Peak Expiratory Flow Rate (l/min) [BL to post-intervention]	**Increased peak expiratory flow** HCP: +22.34 (p<0.001); SR: NS Between group: NS
							Mean arterial pressure (mmHg) [BL to post-intervention]	**Reduced arterial pressure** HCP: -3.51 (p<0.001); SR: NS Between group: NS

Author (year) [Country, World Region]	Design	Study Population	Intervention(s)	Concomitant therapies	Control or comparison group	No. Participants (Intervention/ Control)	Outcome measure	Outcome
							Rate pressure product (myocardial workload) [BL to post-intervention]	**Reduced rate pressure product** HCP: -6.08 ($p<0.001$); SR: NS Between group: $p=0.043$
							Double product (myocardial oxygen consumption) [BL to post-intervention]	**Reduced double product** HCP: -4.79 ($p<0.001$); SR: NS Between group: $p=0.04$
Mooventhan, et al (2016) [India, SEARO] [23]	Randomized crossover trial	Healthy adults (young males, with average adipose tissue)	Ice bag (1 – 2°C, applied to head and spine while prone, 20 min)	Nil	Tap water bag (24 – 25°C, applied to head and spine while prone, 20 min). Control (lying prone on massage table, 20 min)	28	Blood pressure (BP), systolic (mmHg) [BL to post-intervention]	**Reduced systolic BP** Ice bag: -1.93 ($p<0.05$); Tap water: -2.46 ($p<0.05$); Control: NS
							Blood pressure (BP), diastolic (mmHg) [BL to post-intervention]	**Reduced diastolic BP** Ice bag: -2.75 ($P<0.01$); Tap water: NS; Control: NS
							Pulse rate (beats per min) [BL to post-intervention]	**Reduced pulse rate** Ice bag: -5.0 ($p<0.001$); Tap water: -2.22 ($p<0.05$); Control: NS
							Pulse pressure (mmHg) [BL to post-intervention]	NS
							Mean arterial pressure [BL to post-intervention]	**Reduced mean arterial pressure** Ice bag: -2.48 ($p<0.01$); Tap water: NS; Control: NS
							Rate pressure product (myocardial workload) [BL to post-intervention]	**Reduced rate pressure product** Ice bag: -6.55 ($p<0.001$); Tap water: -4.04 ($p<0.05$); Control: NS
							Double product (myocardial oxygen consumption) [BL to post-intervention]	**Reduced double product** Ice bag: -5.53 ($p<0.001$); Tap water: -2.78 ($p<0.05$); Control: NS

Author (year) [Country, World Region]	Design	Study Population	Intervention(s)	Concomitant therapies	Control or comparison group	No. Participants (Intervention/ Control)	Outcome measure	Outcome
Mooven-than, et al. (2016) [India SEARO] [24]	Randomized crossover trial	Healthy adults (unmedicated young males)	Ice massage (with bag of ice, 1 – 2°C, applied to head and spine while prone, 20 min)	Nil	Tap water massage (with bag of water, 24 – 25°C, applied to head and spine while prone, 20 min). Control (lying prone on massage table, 20 min)	30	Heart rate variability (HRV) (RR intervals) [BL to post-intervention]	**Increased heart rate variability** Ice massage: +52.99 (p=0.001); Tap water: +34.15 (p=0.004); Control: NS
							Heart rate (beats per min) [BL to post-intervention]	**Reduced heart rate** Ice massage: -4.02 (p=0.001); Tap water: -2.43 (p=0.008); Control: NS
							Heart rate variability – parasympathetic branch (Root mean square of the successive differences) [BL to post-intervention]	**Increased parasympathetic HRV** Ice massage: +13.67 (p=0.013); Tap water: NS; Control: +8.5 (p=0.027)
							Heart rate variability – successive variation (NN50) [BL to post-intervention]	**Increased successive variation HRV** Ice massage: +24.56 (p=0.17); Tap water: NS; Control: NS
							Heart rate variability – proportionate (PNN50) [BL to post-intervention]	**Increased proportionate HRV** Ice massage: +9.58; Tap water: NS; Control: NS
							Low frequency (LF) band HRV (0.05-0.15Hz) [BL to post-intervention]	NS
							High frequency (HF) band HRV (0.15-0.5 Hz) [BL to post-intervention]	NS
							HF/LF ratio [BL to post-intervention]	NS
Nair, et al. (2015) [India, SEARO] [11]	Case report	Anemia (female)	Mud pack (lower abdomen, eyes), sitz bath/hip bath, spinal spray, emersion bath, enemas, abdominal cold water wrap (90 min sessions, daily, for 6 days)	Swedish massage, vibro (talcum) massage, electrotherapy	Nil	1	Hemoglobin (gm/dL) [BL to Dy 6]	**Increased hemoglobin** Dy 6: +1.2
							Resting blood pressure [BL to Dy 6]	No change
							Pulse rate [BL to Dy 6]	No change
							Respiratory rate [BL to Dy 6]	No change

Author (year) [Country, World Region]	Design	Study Population	Intervention(s)	Concomitant therapies	Control or comparison group	No. Participants (Intervention/Control)	Outcome measure	Outcome
Pullan, et al. (2016) [India, SEARO] [12]	Randomized controlled trial	Chronic neck pain	Moist heat; bath (steam baths, neutral bath – immersion, hip, spinal or half); compress/pack/revulsive (alternating hot and cold) compress (neck, kidney) (10 days)	Naturopathy (hydrotherapy, massage, diet, yoga)	Acupuncture (ACU) (with naturopathy)	60 (30/30)	Pain, Visual Analog Scale [BL to Dy 10]	NS
							Neck Disability Index [BL to Dy 10]	NS
							State Trait Anxiety Inventory [BL to Dy 10]	**Reduced anxiety** Between group: p=0.02
							Short Form-36 (SF-36) health survey – Physical functioning [BL to Dy 10]	NS
							SF-36 – limitations, physical health [BL to Dy 10]	NS
							SF-36 – limitations, emotional problems [BL to Dy 10]	**Reduced emotional problems** Between group: p=0.01
							SF-36 – emotional wellbeing [BL to Dy 10]	NS
							SF-36 – social functioning [BL to Dy 10]	NS
							SF-36 – energy/fatigue [BL to Dy 10]	NS
							SF-36 health survey – bodily pain [BL to Dy 10]	NS
							SF-36 – general health [BL to Dy 10]	NS
Revadi, et al. (2018) [India, SEARO] [17]	Case report	Hepatic cirrhosis with portal hypertension and ascites (male, 39 years)	Naturopathic hydrotherapy (abdominal mud packs, hot and cold kidney packs, neutral baths 34 – 35°C, alternate hot and cold baths. Varied daily treatments for 4 weeks)	Yogic meditation and breathing exercises (2 hrs per day during 3rd and 4th weeks), bodywork to legs (15 min daily for 3rd week), vegetarian diet (4 weeks)	Nil	1	Weight (kg) [BL to Wk 4]	**Reduced body weight** Wk 4: -17
							Body Mass Index (kg/m^2) [BL to Wk 4]	Reduced BMI Wk 4: -6.25
							Abdominal girth (inches) [BL to Wk 4]	**Reduced abdominal girth** Wk 4: -12
							Blood pressure (BP), systolic (mmHg) [BL to Wk 4]	**Reduced systolic BP** Wk 4: -10
							Blood pressure (BP), diastolic (mmHg) [BL to Wk 4]	**Reduced diastolic BP** Wk 4: -12

Author (year) [Country, World Region]	Design	Study Population	Intervention(s)	Concomitant therapies	Control or comparison group	No. Participants (Intervention/ Control)	Outcome measure	Outcome
							Breath holding capacity (secs) [BL to Wk 4]	**Increased breath holding capacity** Wk 4: +6
							Hemoglobin (gm %) [BL to Wk 4]	**Increased hemoglobin** Wk 4: +4.2
							Liver function – bilirubin (mg/dL, total, direct and indirect) [BL to Wk 4]	**Reduced bilirubin** Wk 4 total: -0.6 Wk 4 direct: -0.2 Wk 4 indirect: -0.4
							Liver function – aspartate amino transferase enzyme (u/L) [BL to Wk 4]	**Reduced AST** Wk 4: -16
							Liver function – alanine aminotransferase enzyme (u/L) [BL to Wk 4]	**Reduced ALT** Wk 4: -17
							Liver function – serum albumin (g/dL) [BL to Wk 4]	**Increased serum albumin** Wk 4: +1.3
							Renal function – serum creatinine (mg/dL) [BL to Wk 4]	**Reduced creatinine** Wk 4: -0.4
							Renal function – blood urea (mg/dL) [BL to Wk 4]	**Reduced urea** Wk 4: -8
Sujan, et al. (2016) [India SEARO] [16]	Randomized controlled trial	Chronic migraine	Hot arm and foot bath (103°F – 110°F), ice massage to head (20 min, five days per week, for 45 days)	Pharmaceutical medication	Pharmaceutical medication only	40 (20/20)	Headache Impact Test [BL to Dy 45]	**Reduced impact** Hydrotherapy: -34.3; Pharmaceutical: -9.5 Between group: p<0.001
							Pain frequency (daily diary) [BL to Dy 45]	**Reduced pain frequency** Hydrotherapy: -8.65; Pharmaceutical: -3.15 Between group: p<0.001
							Visual Analog Scale (pain intensity) [BL to Dy 45]	**Reduced pain intensity** Hydrotherapy: -6.85; Pharmaceutical: -2.05 Between group: p<0.001

Author (year) [Country, World Region]	Design	Study Population	Intervention(s)	Concomitant therapies	Control or comparison group	No. Participants (Intervention/ Control)	Outcome measure	Outcome
							Heart rates (beats per min) [BL to Dy 45]	**Reduced heart rates** Hydrotherapy: -5.9; Pharmaceutical: +2.4 Between group: p<0.05
							Standard Deviation of NN interval [BL to Dy 45]	NS
							Root mean square of the successive differences [BL to Dy 45]	NS
							Heart rate variability – total frequency (ms^2) [BL to Dy 45]	NS
							Low-frequency (LF) power (ms^2) [BL to Dy 45]	**No change in low frequency power** Hydrotherapy: -0.97; Pharmaceutical: -2.62 Between group: p<0.05
							High-frequency (HF) power (ms^2) [BL to Dy 45]	**Increased high-frequency power** Hydrotherapy: +1.3; Pharmaceutical: -0.8 Between group: p<0.05
							LF/HF ratio [BL to Dy 45]	**Reduced LF/HF ratio** Hydrotherapy: -0.27; Pharmaceutical: -0.09 Between group: p<0.01

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37 Acupuncture

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HIGHLIGHTS

- Acupuncture is practiced in over 180 countries and has been incorporated into diverse disciplines, including naturopathy.
- The practice of acupuncture includes needling, auricular acupuncture, electroacupuncture, cupping, and others.
- Naturopaths/NDs often combine acupuncture with other therapies and practices.
- Clinical research by the naturopathic community has examined the application of combination acupuncture interventions, standalone acupuncture, standalone cupping therapy and other forms of standalone acupuncture-related treatments.
- In line with the role of primary care, naturopathic researchers have investigated the effects of acupuncture and acupuncture-related treatments on individuals with musculoskeletal conditions, cancer, endocrine conditions, complex immune conditions, neurological conditions, women's health conditions, cardiovascular conditions, mental health conditions and other conditions as well as in healthy individuals.

Acupuncture is particularly associated with and prominent in Traditional Chinese Medicine (TCM) [1], yet it also has a long history in other Asian, European and American traditional medical systems [2, 3]. Acupuncture has been practiced for over 3000 years for a wide range of conditions [4], from headaches to musculoskeletal pain to gastrointestinal complaints to anxiety and depression, among others [1]. Acupuncture is practiced in over 180 countries worldwide [5] and practitioners from diverse disciplines, including traditional healers, medical doctors, physiotherapists as well as naturopaths and naturopathic doctors have incorporated acupuncture into their practice. The education and licensure requirements to practice acupuncture differ by profession and jurisdictions [6].

Acupuncture, as a drugless therapy, fits well into the Naturopathic Therapeutic Order as it involves four of the seven stages outlined in the Naturopathic Therapeutic Order: establishing the conditions for health (level 1); stimulation of the healing power of nature (level 2); supporting and balancing physiological and bioenergetic systems (level 3); and addressing pathology using specific natural modalities (level 5) [7]. Acupuncture, along with the study of TCM is included in the curriculum in some naturopathic educational programs and is part of the scope of naturopathic care in some countries such as Canada, the USA, South Africa, India, Germany, Switzerland, and Brazil [6, 8].

Acupuncture is practiced in several different ways including needling, electroacupuncture, auricular acupuncture, acupressure, cupping and moxibustion to name a few. Needle acupuncture includes the insertion of needles along meridian channels on the body based on TCM philosophy. Auricular acupuncture, first described in 1950 in France [9], is another modality within acupuncture whereby points in the ear are needled or where acupuncture 'seeds' or tiny needles (often resembling a small circular bandage) are applied to specific points on the ear. In 1958 electroacupuncture was introduced whereby a small electric current is connected to pairs of needles which have been inserted into the skin [10]. Acupressure uses the same philosophical basis as acupuncture, but instead of needles, pressure, either with a finger or with a device, is applied to acupuncture points. Specific acupressure points are sometimes taught to patients as a way of managing conditions such as headaches. Acupressure also allows practitioners who cannot use needling techniques, due to regulatory restrictions, to still practice a form of acupuncture. Cupping dates back to Egyptian, Chinese and Middle Eastern cultures and involves the application of suction using various devices on a specific area of skin using cups of various sizes for a short period of time [11]. Cupping traditionally uses continuous suction, but modern devices also allow for pulsating suction or the sliding of cups along the skin. Other techniques that fall under TCM and are included

in this chapter include moxibustion which is the burning of herbs near or on the body, Tui na, a therapeutic type of TCM massage, and *Gua sha* therapy, a TCM healing method which involves scraping the skin. A stimulation pad or device is another modern means of using the principles of acupuncture for pain relief that may be safely applied at home.

Overview of Studies

This chapter is dedicated to highlighting the original clinical research (n=32) conducted by naturopathic researchers investigating acupuncture and its related practices. This research includes a total of 2,522 participants and was conducted in Germany (n=10), United States of America (USA) (n=9), India (n=9), Canada (n=3) and Australia (n=1). The study designs include randomized controlled trials (RCTs) (n=23) and case reports (n=5), uncontrolled trials (n=3), a secondary analysis (n=1) and a pooled, secondary analysis (n=1). The studied interventions include practitioner-administered acupuncture (n=12), home-based acupuncture (n=5), electroacupuncture (n=4), acupressure (n=3), auricular acupuncture along with acupuncture of the body (n=2), cupping (n=7) and *Gua sha* Therapy (n=1).

The conditions where acupuncture was used as an intervention include chronic neck pain (n=7) or back pain (n=2), breast cancer (n=5), type II diabetes mellitus (T2DM) (n=1), human immunodeficiency virus (HIV) (n=2), and one study in each area of Parkinson's disease, systemic lupus erythematosus (SLE), fibromyalgia, menopause, primary dysmenorrhea, osteoarthritis of the knee, rheumatoid arthritis, acute inpatient care, hypertension, rhinosinusitis, transverse myelitis, secondary dysfunction, cigarette smoking, anxiety, and healthy volunteers.

Finding an adequate way to perform sham acupuncture in blinding the patient to the lack of treatment while having no physiological effect has long been a controversial issue [12]. Two forms of sham acupuncture were used in these trials, either a sham acupuncture device (n=390) [13, 14], where the needle looks as if it is being pushed into the skin but retracts inside the device, or shallow needling in areas which are not true acupuncture points [15-18]. Sham adhesives were used for ear acupuncture [16], and one study used a sham cupping device (n=141) [19]. Using a waitlist to compare those having treatment with those not having treatment is another way to create a control group, but in this type of trial the patients are not blinded to the treatment. Seven trials (n=688) used a waitlist [16, 20-25] and one (n=46) used slow breathing as an alternative to acupuncture [26]. Of all the naturopathic clinical studies employing acupuncture interventions, 84.8% reported a positive outcome in at least one primary or secondary outcome measure. Details of the studies are available in *Table 37.1: Clinical research investigating acupuncture interventions conducted by naturopathic researchers*. This body of naturopathic research on acupuncture is also supported by ten observational studies and 15 reviews or meta-analyses conducted by naturopathic researchers on this topic, as outlined in Chapter 40.

Implications

Acupuncture has been studied within naturopathic clinical settings to treat a broad range of conditions. Most studies were one-off studies, except for pain associated with breast cancer in postmenopausal women. The breast cancer studies indicated that acupuncture reduced pain of breast cancer in postmenopausal, but not in premenopausal women. Studies on cupping and use of a needle stimulation pad were focused on pain in musculoskeletal complaints, although cupping in TCM has a broader range of therapeutic applications that may be applicable to naturopathic practice.

Given the lack of replication of studies in conditions such as hot flushes and dysmenorrhea, hypertension or sexual dysfunction, more research is needed to establish robust evidence for the use of acupuncture in those conditions by naturopaths/naturopathic doctors. In most cases, acupuncture used by naturopaths and naturopathic doctors was aligned with the TCM paradigm, suggesting that the evidence base for acupuncture treatments applied by naturopaths/naturopathic doctors may be broader than those listed in this chapter, and comparable to the evidence base for acupuncture. Even in countries where acupuncture is not formally integrated into naturopathic training, naturopaths/naturopathic doctors provide a significant level of acupuncture services [27], or a significant amount possess additional qualifications in acupuncture [28], suggesting that acupuncture is a tool that is suitable for and readily accepted in naturopathic applications. Further research is warranted to examine the role of acupuncture in naturopathic practice.

Studies investigating specific interventions:

Combination Acupuncture Interventions

Seven studies investigated a combination of acupuncture-related treatments including needle acupuncture (n=6) [15, 23, 29-32], electroacupuncture (n=3) [30-32], auricular acupuncture (n=4) [15, 23, 29, 30], cupping (n=1) [23], moxibustion (n=1) [30], and tui na massage (n=1) [30]. One study did not report the specific styles of acupuncture treatments as they were substantially varied to suit the requirements of the individual (n=1) [33]. In addition to the acupuncture treatments, one study also

provided yoga, lifestyle counselling and a naturopathic dietary prescription [31], while a second study provided concomitant massage and hydrotherapy interventions [32]. The populations included in these studies encompassed individuals with breast cancer (n=2) [15, 29] , anxiety (n=1) [23], HIV (n=1) [30], transverse myelitis (n=1) [31], and rheumatoid arthritis (n=1) [32], as well as inpatients admitted to hospital for acute care (n=1) [33].

A randomized controlled pilot trial conducted in Canada [23] investigated personalized acupuncture interventions for children and adolescents with anxiety (n=19), compared to a waitlist control. Participants received individualized acupuncture treatments that included needle acupuncture, cupping and auricular acupuncture to stimulate a range of acupuncture points (e.g., LI4, DU4, DU20, HT7, PC6, CV4, CV6, UB14, BL15, BL23, BL25, TW5, Yin Tang, CV12, SP6, SP20, ST36, KI3, KI7). Participants received 30-minute treatments once per week for five weeks. Following treatment, participants had lower anxiety scores on the Multidimensional Anxiety Scale for Parents (-15.4, p=0.025).

An uncontrolled trial conducted in the USA [30] reported the outcomes associated with individualized acupuncture treatments for individuals who were HIV positive (n=27). Participants received a personalized combination of auricular and body acupuncture, moxibustion, electroacupuncture, and *tui na* massage based on their unique tongue and pulse assessments. They were observed for four months prior to receiving the intervention, which they then received for six months. While participants did not identify any significant change in the two validated scales used as outcome measures, in the qualitative post-intervention interviews conducted by the research team 96% of participants reported relief of symptoms and complaints, 89% reported an improved sense of wellness and emotional wellbeing and 48% reported an increased ability to work more with reduced financial worries.

A case report conducted in India [31] with a 32-year-old male patient with transverse myelitis reported on the outcomes of 15 30-minute needle acupuncture and electroacupuncture treatments across a range of acupuncture points (needle: GB34, GB39, ST32, ST36, ST37, ST39, ST41, UB40, UB62, HT7, LI11, LI4, DU14, SP6, UB36, Ex21, Ex36; electro: LI11, LI4, GB36, ST36, SP6) for three weeks. The acupuncture was also combined with yoga, lifestyle counselling and a naturopathic dietary prescription. The participant demonstrated significant improvement over 21 days in the WHO Brief Quality of Life Questionnaire (WHOQOL) in physical, psychological, social and environmental health. There was also improvement in quality of sleep based on the Pittsburg Sleep Quality Index (PSQI) (18 to 8) and reduction for pain intensity (8 to 1) as measured by visual analog scale (VAS).

Another case report conducted in India, this time with a 48-year-old female with rheumatoid arthritis who underwent 3 weeks of acupuncture and electroacupuncture across a range of points (needle: GV20, EX28, EX36; electro: GV20, LI4, LI11, BL11, GB34, SP6, KI3, ST44. The individual received treatments for 30-minutes in total including 20-minutes of electro-stimulation, in 14 sessions over three weeks. She was also administered massage, mud therapy and sauna therapies. At the end of the treatment period she showed a significant reduction in depression, anxiety and stress based on the Depression Anxiety and Stress Scales (depression 31 to 8, anxiety 21 to 8, stress 23 to 6) [32]. There was also improvement on the PSQI scale (11 to 7), the VAS (8.2 to 1.9) and the Short-form 36 Version-2 Health Survey from 12 on day 1 to 63 on day 22.

Standalone Acupuncture

There were ten studies investigating needle-based acupuncture as a standalone intervention in individuals with cancer (n=1) [16]; menopausal hot flushes (n=1) [13] and primary dysmenorrhea (n=1) [25]; sexual dysfunction (n=1) [34]; hypertension (n=1) [26], chronic rhinosinusitis [35], SLE (n=1) [36], HIV [37] and T2DM (n=1) [17]. One further study evaluated the health effects of standalone acupuncture on a healthy population [18].

A randomized controlled trial (n=60) conducted in India investigated the outcomes of acupuncture, compared with usual care, on females from age 17-23 diagnosed with primary dysmenorrhea [25]. The acupuncture intervention included 12 pre-determined acupuncture points: KI3, SP8, ST25, ST29, ST30, ST36, CV4, CV6, BL62, HT7, LI4, and PC6. The acupuncture points were stimulated during 15 sessions, lasting 20-minutes each, per month for three months. The acupuncture was initiated on the sixty day of each participant's menstrual cycle and was not performed during menstruation. Compared to usual care, the acupuncture intervention demonstrated a significant reduction in pain intensity ($p<0.05$) menstrual cramping ($p<0.05$), dizziness (p,0.05), diarrhea ($p<0.05$), faint feeling ($p<0.05$), negative mood ($p<0.05$), tiredness ($p<0.05$), nausea ($p<0.05$) and vomiting ($p<0.05$) at all time points (Day 30, 60 and 90). Headaches were also reduced at Day 90 ($p<0.05$) in the group undergoing acupuncture but not at earlier time points.

An uncontrolled trial (n=35) was conducted in India [34] to investigate the effects of an acupuncture protocol on secondary sexual dysfunction associated with antidepressant medication. The participants received stimulation of five acupuncture points (KI3, GV4, BL23, HT7, PC6) aimed at addressing Heart *Yin* deficiency and Kidney *Qi* deficiency. Acupuncture stimulation was administered weekly for 15 minutes, over 12 weeks with a 4-week follow up. At the end of treatment, participants reported reduced anxiety (Beck Anxiety Inventory: -2.8, p=0.01), increased sexual function (VAS Sexual

Function, total: +62.28, p<0.01) and a reduced impact on their sexual experience (Arizona Sexual Experience Questionnaire, total: -1.59, p=0.027).

A case report was prepared from a patient in India with SLE [36]. The patient received 20-minute sessions of acupuncture daily for 30 days, with a 7-day rest period after 15 sessions. The acupuncture needles were inserted into six acupuncture points: GV20, GV6, LI11, HT7, GB34, KI3. At the end of the treatment period, the patient reported reduced pain (VAS: -4.8), reduced daytime sleepiness (Epworth Sleepiness Scale: -8), reduced sleep problems (PSQI: -8) and increased quality of life (across numerous scales of the Short Form-36).

A second case study conducted in Canada [37] with a patient with Guillain-Barre syndrome associated with HIV underwent acupuncture treatment (points: GB34, GB39, PC6, KI3, BL40, GV4, GV3, BL23) for 30-minutes weekly for seven weeks, then monthly for ten months. The acupuncture intervention was administered alongside dietary changes eliminating reactive foods, weekly vitamin B12 intramuscular injections and a calcium-rich multi-nutrient supplement. The patient experienced 90% recovery of function after 1 year of treatment.

Standalone Cupping Therapy

There were six studies that investigated cupping therapy as an intervention, either as dry (n=5) [19, 20, 22, 24, 38] or wet (n=1) [39]. The studies investigated cupping for the treatment of chronic non-specific low back (n=2) [20, 24] and neck pain (n=3) [22, 39], and fibromyalgia (n=1) [19]. One additional publication presented the pooled analysis of previously unpublished results of four studies examining 2-year follow up outcomes for a range of cupping techniques in individuals with chronic non-specific neck pain [40].

One randomized controlled trial (n=50) [24] conducted in Germany for chronic non-specific neck pain compared dry cupping treatments with a waitlist control. Participants in the treatment phase received 10-minute cupping treatments twice per week for three weeks (five treatments in total). The treatment involved dry cupping massage along the spine and trapezius massage. The results indicated significant reduction in neck pain on movement (-11.7, p=0.019), pain intensity (-14.3; p=0.037) and neck disability (-4.1; p<0.001). They also experienced an increased quality of life in the domains of bodily pain (+16.7, pp=0.002) and mental health (+8.5, p=0.003).

A randomized controlled trial (n=50) [39] conducted in Germany investigated the impact of wet cupping on participants with chronic non-specific neck pain. In those receiving the wet cupping (n=25) superficial incisions were made at areas of pain and covered with double-walled glass cups using flame-generated vacuum for 15 min with 3-day washout. As measured by the VAS, the wet cupping group reported reduced pain at rest (-17.9 p=0.003) and reduced maximum pain on movement (-19.7 p=0.003) compared to the waitlist group. The treatment group also reported increased quality of life based on the Short Form-36 survey.

Other Forms of Standalone Acupuncture-related Treatments

Seven studies investigated other acupuncture-related treatments as standalone interventions. These included electroacupuncture (n=2) [14, 41], self-administered needle pads (n=2) [21, 42], acupressure (n=2) [43, 44], *gua sha* therapy (n=1) [45], and auricular acupuncture (n=1) [46].

A randomized controlled trial conducted in the USA [46] investigated auricular acupuncture to assist with smoking cessation. The study compared auricular acupuncture with an educational smoking cessation program, with a third study arm combining auricular acupuncture and the education program. The auricular acupuncture was used to stimulate acupuncture points commonly used in chemical dependency including four bilateral ear points (Sympathetic, LU, KI, LV) and two wrist points (LI4, HT7). The 30-minute treatments were administered five times per week for four weeks. Compared to the other two groups, a greater proportion of the group receiving auricular acupuncture and education had ceased smoking (p=0.023) or decreased the number of cigarettes smoked (p=0.003) at the end of the intervention.

A randomized controlled trial conducted in Germany [45] investigated *gua sha* therapy for the treatment of chronic non-specific low back pain (n=50). The *gua sha* was applied as paravertebral between cerebral vertebrae 7 (C7) and lumbar vertebrae 5 (L5) and horizontal strokes across the back below C7 and above L5. Paravertebral strokes were also applied between cerebral vertebrae 1 or 2 and C7, with additional strokes along the dorsal surface of gluteus maximus. The treatment was administered twice, with seven days between treatments. Compared to the waitlist control, participants receiving *gua sha* had reduced pain on movement at the end of the study period (Pain on Movement Questionnaire: -24.55 vs -12.3, p<0.001).

A randomized controlled trial conducted in the USA [44] examined the effects of acupressure massage on breast cancer survivors, more than 12 months after cancer treatment. Participants were allocated to receive either relaxing or stimulating acupressure massage, or usual care. The relaxing acupressure intervention was applied to Yin Tang acupuncture points, and bilaterally to Anmian, HT7, SP6 and LV3. The stimulating acupressure treatment was used on Du20, CV6 and bilateral points for LI4, ST36, SP6 and KI3. Each acupuncture point was

massaged daily for 3 minutes in both acupressure groups, for six weeks with an additional follow up conducted four weeks after treatment concluded. Participants in both groups reported improvements in fatigue ($p<0.001$), sleep quality ($p<0.05$) somatic function ($p<0.05$) and fitness ($p<0.05$) compared to the usual care control.

A case study conducted in India with a patient undergoing treatment for Parkinson's disease was treated with 30-minute sessions of electro-acupuncture six times a week, for 5 weeks. The acupuncture included points on the torso and the scalp [41]. The study indicated improvement on all scales assessed and included a decrease in resting heart rate and blood pressure, improvement in balance based on the Berg Balance Scale and improvement in the Parkinson's Disease Questionnaire-39.

Table 37.1 Clinical research investigating acupuncture interventions conducted by naturopathic researchers

Author (year) [Country, World region]	Design	Study Population	Intervention	Concomitant therapies	Control or comparison group	No. Participants (Intervention/ Control)	Outcome measure	Outcome
Arankalle and Nair (2013) [India, SEARO] [41]	Case Report	Parkinson's disease (stage III, male)	Electroacupuncture on GV20, BL11, LI11, HT7, LI4, SI19, ST36, GB34 + Scalp acupuncture (motor area and Chorea tremor control area) (24 sessions over 4 wks with 7-day rest period after 12 sessions)	Dietary and lifestyle advice emphasizing water intake and regular physical activity	Nil	1	Resting Heart rate (bpm) [BL to Wk 4]	**Reduced** - 4bpm
							Blood pressure (mmHg) [BL to Wk 4]	**Reduced** Systolic: -20
							Berg Balance Scale [BL to Wk 4]	**Increased** +2
							Parkinson's Disease Questionaire-39 impact on quality of life [BL to Wk 4]	**Reduced impact on quality of life** -10
Bier, et al. (2002) [USA, AMRO] [46]	Randomized controlled trial	Smoking cessation	Auricular acupuncture bilaterally at five ear points and one wrist point commonly used in treatment of chemical dependency: HT7, Sympathetic, LU, KI, LV, LI4 (30 min, 5 sessions per wk for 4 wks)	Educational smoking cessation program (Acupuncture plus)	Comparison: Acupuncture alone. Control: Educational smoking cessation program with sham acupuncture (Sham plus)	141 (38/45/58)	Smoking cessation (smoking or not) [BL to Mth 1, Mth 3, Mth 6, Mth 12, Mth 15, Mth 18]	**Increased cessation Mth 1** Acupuncture alone: +10% Acupuncture plus: +40% Sham plus: +22% Between group: p=0.023
							Percentage decrease in cigarettes smoked [BL to Mth 1, 3, 6, 12, 15, 18]	**Reduced smoking Mth 1** Acupuncture alone: -49% Acupuncture plus: -53% Sham plus: 40% Between group: p=0.003
							Craving intensity [BL to Mth 1, 3, 6, 12, 15, 18]	NS
							Beck Depression Inventory [BL to Mth 1, 3, 6, 12, 15, 18]	NS
							Zung Anxiety Scale [BL to Mth 1, 3, 6, 12, 15, 18]	NS

Author (year) [Country, World region]	Design	Study Population	Intervention	Concomitant therapies	Control or comparison group	No. Participants (Intervention/ Control)	Outcome measure	Outcome
Cramer, et al. (2011) [Germany, EURO] [20]	Randomized controlled trial	Chronic non-specific neck pain	Pneumatic pulsation therapy: pulsating cupping applied to neck and shoulder areas where manual pressure and lifting of the skin caused the most discomfort (5 treatments over 2 wks)	Nil	Standard care: self-directed standard medical care, including physiotherapy, sports activities, and analgesics as needed	50 (25/25)	Pain intensity (numerical rating scale) [BL to Wk 2.5]	**Reduced pain intensity** Acupuncture: -1.4; Standard care: +0.24 Between group: p=0.001
							Total pain at motion (visual analogue scale) [BL to Wk 2.5]	**Reduced total pain at motion** Acupuncture: -8.1; Standard care: +4.1 Between group: p < 0.001
							Maximum pain at motion (visual analogue scale) [BL to Wk 2.5]	**Reduced maximum pain at motion** Acupuncture: -2.5; Standard care: -0.26 Between group: p=0.004
							Functional disability (Neck Disability Index) [BL to Wk 2.5]	**Reduced functional disability** Acupuncture: -5.5; Standard care: -0.3 Between group: p=0.025
							Short Form-36 (SF-36) health survey – physical component [BL to Wk 2.5]	**Increased physical function** Acupuncture: +3.7; Standard care: -1.2 Between group: p=0.002
							SF-36 health survey – mental component [BL to Wk 2.5]	NS
Crew et al. (2007) [USA, AMRO] [29]	Randomized controlled trial (cross-over)	Breast cancer stage I-IIIa hormone receptor positive – joint pain associated with adjuvant aromatase inhibitor therapy	Acupuncture on TW5, GB41, GB34, LI4, ST41, KD3, auricular acupuncture (Shen Men, kidney, liver, upper lung, and sympathetic), and joint-specific protocols (shoulder (LI-15, SJ-14, SI-10); wrist (SJ-4, LI-5); fingers (SI-5, SI3, Ba Xie, LI-3); lumbar (Du-3, Du-8, UB-23); hip (GB-30, GB-39); and knee (SP-9, SP-10, ST-34)) (30 min, twice per wk for 6 wks)	Non-narcotic, non-steroidal pain medications as needed	Observation with non-narcotic, non-steroidal pain medications as needed	19	Brief Pain Inventory – short form [BL to Wk 6]	**Reduced pain** Pain scores: -3.1 (p=0.01) Pain severity: -2.7 (p=0.02) Functional interference: -1.4 (p=0.02)
							Western Ontario and McMaster Universities Osteoarthritis index [BL to Wk 6]	**Reduced impact on quality of life** Total score: -33.6 (p=0.04) Impact on function: -165.2 (p=0.02) Pain, stiffness: NS

Author (year) [Country, World region]	Design	Study Population	Intervention	Concomitant therapies	Control or comparison group	No. Participants (Intervention/ Control)	Outcome measure	Outcome
							Functional Assessment of Cancer Therapy – General [BL to Wk 6]	**Increased wellbeing** Physical: +3.5 (p=0.03) Social/family, emotional and functional: NS
							Inflammatory markers (TNF-α, IL-1β) [BL to Wk 6]	NS
Crew et al. (2010) [USA, AMRO] [15]	Randomized controlled trial	Breast cancer stage I-IIIa hormone receptor positive – aromatase inhibitor induced joint pain	Standardized full body and auricular acupuncture (shoulder (LI-15, SJ-14, SI-10); wrist (SJ-4, LI-5); fingers (SI-5, SI3, Ba Xie, LI-3); lumbar (Du-3, Du-8, UB-23); hip (GB-30, GB-39); and knee (SP-9, SP-10, ST-34)) (30 min, twice per wk for 6 wks)	Non-narcotic, non-steroidal pain medications as needed	Sham acupuncture control (superficial needle insertion at body locations not recognised as true acupoints)	38 (20/18)	Brief Pain Inventory – short form [BL to Wk 6]	**Reduced worst pain** Acupuncture: -3.7, Sham: -0.11 Between group: p=0.002 **Reduced pain severity** Acupuncture: -3.34, Sham: +0.10 Between group: p<0.001 **Reduced interference** Acupuncture: -1.99, Sham: -0.02 Between group: p=0.002
							Western Ontario and McMaster Universities Osteoarthritis index [BL to Wk 6]	**Reduced total score** Acupuncture: -96, Sham: +3 Between group: p<0.01 **Reduced pain** Acupuncture: -160, Sham: -14 Between group: p<0.01 **Reduced stiffness** Acupuncture: -69, Sham: +12 Between group: p<0.01 **Reduced functional impact** Acupuncture: -506, Sham: -149 Between group: p=0.01

Author (year) [Country, World region]	Design	Study Population	Intervention	Concomitant therapies	Control or comparison group	No. Participants (Intervention/ Control)	Outcome measure	Outcome
							Modified Score for the Assessment of Chronic Rheumatoid Affections of the hand (M-SACRAH) [BL to Wk 6]	**Reduced total score** Acupuncture: -87, Sham: -28 Between group: p<0.01 **Reduced pain** Acupuncture: -59, Sham: -13 Between group: p<0.01 **Reduced stiffness** Acupuncture: -55, Sham: -40 Between group: p=0.01 **Reduced functional impact** Acupuncture: -213, Sham: -31 Between group: p=0.02
							Functional Assessment of Cancer Therapy – General [BL to Wk 6]	**Increased physical wellbeing** Acupuncture: +5.7, Sham: -0.7 Between group: p=0.03
Ee, et al. (2016) [Australia, WPRO] [13]	Randomized, controlled trial	Menopause	Standardized needle acupuncture to treat kidney yin deficiency on KI6, KI7, SP6, HT6, CV4, LR3 (8 wk protocol: twice per wk for 2 wks, then weekly for 6 wks)	Unspecified non-HRT vasomotor symptom treatments	Non-insertive sham acupuncture at body locations not recognised as true acupoints	327 (163/164)	Hot flush score (mean) [BL to Wk 8]	NS
							Hospital Anxiety and Depression Scale [BL to Wk 8]	NS
							Menopause-Specific Quality of Life [BL to Wk 8]	NS
Greenlee et al. (2016) [USA, AMRO] [14]	Randomized controlled trial (pilot)	Breast cancer (stage I-III, prevention of chemotherapy-induced peripheral neuropathy)	Electroacupuncture (EA) on GB34, St36, LI4, LI10, Huatuojiaji (L3, L5, C5, C7), Bafeng, Baxie (weekly for 12 wks, within 2 days of weekly chemotherapy infusion)	Nil	Sham acupuncture control	63 (31/32)	Brief Pain Inventory – short form [BL to Wk 6, 12, 16]	**Increased pain** Wk 6, Wk 12: NS Wk 16, between group: p=0.03
							Functional Assessment of Cancer Therapy [BL to Wk 6, 12, 16]	NS
							Neuropathic Pain Scale [BL to Wk 6, 12, 16]	**Increased pain** Wk 6, Wk 12: NS Wk 16, between group: p=0.03

Author (year) [Country, World region]	Design	Study Population	Intervention	Concomitant therapies	Control or comparison group	No. Participants (Intervention/ Control)	Outcome measure	Outcome
Hershman et al. (2018) [USA, AMRO] [16]	Randomized controlled trial	Breast cancer (Stage I-III hormone receptor positive – aromatase inhibitor induced joint pain)	Acupuncture joint specific protocol (Acu) (30 – 45 min, twice per wk, for 6 wks)	Nil	Sham acupuncture control, Waitlist (WL) control.	226 (110/59/ 57)	Brief Pain Inventory – Short Form [BL to Wk 6, Wk 12]	**Reduced worst pain** Wk 6 Acu: -2.05, Sham: -1.07, WL: -0.99 Between group: Sham p=0.01, WL p=0.01 Wk 12 Acu: -2.31, Sham: -1.51, Waitlist: -0.19 Between group: Sham NS, Waitlist p<0.001 **Reduced average pain** Wk 6 Acu: -1.45, Sham: -0.76, WL: -0.81 Between group: Sham p=0.04, WL p=0.01 Wk 12 Acu: -1.95, Sham: -1.07, WL: -0.62 Between group: Sham p=0.02, WL: p<0.001 **Reduced pain interference** Wk 6 Acu: -1.69, Sham: -0.82, WL: -0.94 Between group: Sham p=0.02, Waitlist NS Wk 12 Acu: -1.8, Sham: -1.45, WL: -0.7 Between group: Sham NS, Waitlist p=0.003 **Reduced pain severity** Wk 6 Acu: -1.5, Sham: -1.00, WL: -0.82 Between group: Sham p=0.05, WL p=0.01 Wk 12 Acu: -1.82, Sham: -1.34, WL: -0.39 Between group: Sham NS, Waitlist p<0.001
Hohmann et al. (2012) [Germany, EURO] [21]	Randomized controlled trial	Chronic neck pain (CNP) or lower back pain (LBP) (non-specific)	Home-based, self-administered needle stimulation pad: applied to both hands (CNP group) or both feet (LBP group), then to the painful area (neck or back) uncovered. (10 min per day hands or feet, 30 min per day neck or back, for 2 wks).	Nil	Waitlist control	78 (CNP: 17/18, LBP: 21/21)	Pain, Numeric Rating Scale [BL to Dy 14]	**Reduced pain** CNP: -1.6 (p=0.021) LBP: -2.3 (p<.001)
							Mechanical Detection Threshold [BL to Dy 14]	NS
							Vibration Detection Threshold [BL to Dy 14]	NS

Author (year) [Country, World region]	Design	Study Population	Intervention	Concomitant therapies	Control or comparison group	No. Participants (Intervention/ Control)	Outcome measure	Outcome
							Pressure Pain Threshold (area of maximum pain) [BL to Dy 14]	**Increased pressure pain threshold** CNP: +0.106 (p = .032) LBP: +0.082 (p = .013)
							Pressure Pain Threshold (10cm close to area of maximum pain) [BL to Dy 14]	**Increased pressure pain threshold** CNP: NS LBP: +0.073 (p = .018)
							Neck Pain Questionnaire [BL to Dy 14]	**Reduced neck pain** CNP: -7.4 (p = 0.028)
							Oswestry Disease Index [BL to Dy 14]	NS
Huff, Cooley & Waller (2008) [Canada, AMRO] [37]	Case Report	Guillain-Barre syndrome associated with Human Immunodeficiency Virus (HIV)	Acupuncture (GB34, GB39, PC6, KI3, BL40, GV4, GV3, BL23) (30 min weekly for 7 weeks, then monthly for 10 mths (16 treatments total)	Dietary elimination, weekly B12 injections, calcium-rich multinutrient formula	Nil	1	Perceived Sensation, Coordination, Balance, Mobility [BL to 12 mths]	**Increased sensation** **Increased coordination and balance, and confidence in mobility** **90% recovery of functions**
Jisha Mol, et al. (2017) [India, SEARO] [35]	Randomized controlled trial	Chronic rhinosinusitis	Acupuncture (bilateral LI4, LI20, ST2 and ST36; unilateral EX-1 and GV23) (20 min daily for 10 days)	Nil	Steam inhalation (20 min daily: four cycles of steam (3 min) and withdraw (1-2 min)	60 (30/30)	Sino-Nasal Outcome Test [BL to Dy 10]	**Reduced symptoms** Inhalation: -4.83 (p=0.05) Acupuncture: -3.47 (p=0.005)
							Symptom frequency [BL to Dy 10]	**Reduced symptom frequency** Inhalation: -1.03 (p=0.05) Acupuncture: -1.20 (p=0.001)
Khamba, et al. (2013) [Canada, AMRO] [34]	Uncontrolled trial	Secondary sexual dysfunction associated with antidepressant medication	Acupuncture (Kd3, GV4, UB23, Ht7, PC6). Intervention delivered as protocol for Heart *Yin* Deficiency and Kidney *Qi* Deficiency (15 min, weekly for 12 wks with 4 wk follow-up)	Nil	Nil	35	Beck Anxiety Inventory [BL to Wk 12, 1 Mth follow-up]	**Reduced anxiety** Wk 12: -2.8 (p=0.01) 1 Mth follow-up: NS
							Beck Depression Inventory, Second Edition [BL to Wk 12, 1 Mth follow-up]	NS

Author (year) [Country, World region]	Design	Study Population	Intervention	Concomitant therapies	Control or comparison group	No. Participants (Intervention/ Control)	Outcome measure	Outcome
							The Sexual Function Visual Analogue Scale [BL to Wk 12, 1 Mth follow-up]	**Increased sexual function** Wk 12 Total: +62.28 (p<0.01) Desire/Libido: +13.9 (p=0.030) Erection: +12.0 (p=0.012) Ejaculation delay: +19.2 (p=0.03) Orgasm delay: +17.0 (p=0.025) Frequency of sex: +12.4 (p=0.04) 1 Mth follow-up: NS
							The Arizona Sexual Experience Questionnaire [BL to Wk 12, 1 Mth follow-up)	**Reduced impact on sexual experience** Wk 12 Total: -1.59 (p=0.027) Drive: -0.6 (p=0.014) Arousal: NS Erection: -0.5 (p=0.015) Ability to reach orgasm: -0.5 (p=0.027) Satisfaction from orgasm: NS 1 Mth follow up: NS
Kumar et al. (2017) [India, SEARO] [17]	Randomized controlled trial	Type II diabetes mellitus	Acupuncture on CV12 (30 min)	Nil	Sham acupuncture at non-acupuncture point 1 cun lateral to CV-12 (30 min)	40 (20/20)	Random blood glucose (mg/dL) [BL to 30 mins]	**Reduced blood glucose** Acupuncture: -12.25 (p < 0.001) Sham: NS Between group: NS
Lauche et al. (2011) [Germany, EURO] [38]	Randomized controlled trial (pilot)	Chronic non-specific neck pain	Dry cupping therapy: performed according to patient pain diagram and physical examination to determine areas of muscle tension and myogeloses (10-20 min, every 3-4 days for five treatments)	Nil	Waitlist control	50 (25/25)	Pain at rest, Visual Analog Scale [BL to Dy 18]	**Reduced pain at rest** Cupping: -19.4, Waitlist: +4.8 Between group: p<0.001
							Pain at movement, Visual Analog Scale [BL to Dy 18]	**Reduced pain at movement** Cupping: -33, Waitlist: -13 Between group: p=0.01
							Neck Disability Index [BL to Dy 18]	**Reduced neck disability** Cupping: -6.4, Waitlist: +0.1 Between group: p=0.002

Author (year) [Country, World region]	Design	Study Population	Intervention	Concomitant therapies	Control or comparison group	No. Participants (Intervention/ Control)	Outcome measure	Outcome
							Short Form-36 (SF-36) health survey [BL to Dy 18]	**Increased quality of life** Bodily pain related quality Cupping: +13.4, Waitlist: +2.9 Between group: p=0.006 Vitality Cupping: +8.9, Waitlist: +0.5 Between group: p=0.006 Social function Cupping: +11.9, Waitlist: +4.7 Between group: p=0.04 Mental health Cupping: +30.6, Waitlist: +20.4 Between group: p=0.01 Physical functioning: NS Role physical: NS General health: NS Role emotional: NS Physical component score: NS Mental component score: NS
							Mechanical-detection, pressure-pain and vibration-detection thresholds [BL to Dy 18]	**Increased pressure-pain threshold** Maximum pain Cupping: +0.05, Waitlist: -0.04 Between group: p=0.026 Adjacent pain Cupping: +0.04, Waitlist: -0.07 Between group: p=0.001 Hand pain Cupping: +0.01, Waitlist: -0.09 Between group: p=0.034 Foot pain Cupping: +0.19, Waitlist: +0.06 Between group: p=0.004 Mechanical detection: NS Vibration detection: NS

Author (year) [Country, World region]	Design	Study Population	Intervention	Concomitant therapies	Control or comparison group	No. Participants (Intervention/ Control)	Outcome measure	Outcome
Lauche et. al. (2012) [Germany, EURO] [39]	Randomized controlled trial (pilot)	Chronic non-specific neck pain	Wet cupping therapy: superficial incisions made at areas of pain, and covered with double-walled glass cups using flame- generated vacuum (15 min with 3 day washout)	Nil	Waitlist control	50 (25/25)	Pain at rest, Visual Analog Scale [BL to 15 min]	**Reduced pain at rest** Cupping: -16.4; Waitlist: +3.1 Between group: -17.9 (p=0.003)
							Maximal pain related to movement, Visual Analog Scale [BL to Dy 3]	**Reduced maximum pain at movement** Cupping: -24.8; Waitlist: -11.8 Between group: -19.7 (p = 0.003)
							Neck Disability Index [BL to Dy 3]	NS
							Short Form 36 health survey [BL to Dy 3]	**Increased quality of life** Physical functioning Cupping: +5.5; Waitlist: -1.1 Between group: +7.5 (p = 0.017) Bodily pain Cupping: +15.3; Waitlist: -0.4 Between group: +14.9 (p = 0.007) Physical component score Cupping: +5.5; Waitlist: +1.1 Between group: +5.0 (p = 0.008) Role physical: NS General health perception: NS Vitality: NS Social function: NS Role emotional: NS Mental health: NS Mental Component Score: NS
Lauche, et. al. (2013) [Germany, EURO] [40]	Secondary analysis (pooled)	Chronic non-specific neck pain	Wet cupping treatment (single application), Dry cupping (5 applications), Pulsating cupping (5 applications), of cupping massage (5 applications) (2 year follow-up post-intervention, pooled across four studies)	Not reported	Nil	133	Pain intensity, Visual Analog Scale [BL to Mth 24]	NS
							Neck disability index [BL to Mth 24]	**Reduced disability** -3.5 (p=0.025)

Author (year) [Country, World region]	Design	Study Population	Intervention	Concomitant therapies	Control or comparison group	No. Participants (Intervention/ Control)	Outcome measure	Outcome
							Short Form-36 health survey [BL to Mth 24]	**Increased quality of life** Bodily pain +14.6 ($p<0.001$) Physical component study +3.0 ($p=0.004$)
Lauche, et. al. (2013) [Germany, EURO] [22]	Randomized controlled trial	Chronic non-specific neck pain	Self-directed partner-delivered cupping massage (10-15 min, twice per wk, for 12 wks, with initial 1 hr workshop training)	Nil	Progressive muscle relaxation (PMR) (20 min, twice per wk, for 12 wks)	61 (30/31)	Pain intensity, Visual Analog Scale [BL to Wk 12]	NS
							Pain on motion, Visual Analog Scale [BL to Wk 12]	NS
							Pain Description List [BL to Wk 12]	NS
							Neck Disability Index [BL to Wk 12]	NS
							Hospital Anxiety and Depression Scale [BL to Wk 12]	NS
							Short Form 36 [BL to Wk 12]	NS
Lauche, et. al. (2016) [Germany, EURO] [19]	Randomized controlled trial	Fibromyalgia syndrome	Cupping therapy on upper and lower back (30 min, 5 sessions over 18 days)	Nil	Sham cupping control, Usual care (as waitlist control)	141 (47/48/46)	Pain (Visual Analog Scale) [BL to Dy 18]	**Reduced intensity** Usual care: -12.4 ($p<0.001$), Sham: NS Between group: **Reduced pain** Cupping: 25.5%; Sham: 18.8%; Usual care: 2.2% Between group: $p=0.006$ >50% reduction: NS
							Fibromyalgia Impact Questionnaire [BL to Dy 18]	NS
							Short Form-36 health survey [BL to Dy 18]	**Increased quality of life** Bodily pain Between group: +4.7 Vitality Between group: +6.3 Social role functioning:

Author (year) [Country, World region]	Design	Study Population	Intervention	Concomitant therapies	Control or comparison group	No. Participants (Intervention/Control)	Outcome measure	Outcome
								Between group: +7.1 Mental health Between group: +4.5 Mental component Between group: +3.4 Physical functioning: NS Physical role functioning: NS General health: NS Emotional role: NS Physical component: NS
							Pain perception [BL to Dy 18]	NS
							Multidimensional Fatigue Inventory [BL to Dy 18]	**Reduced** Reduced motivation Between group -1.2 General fatigue: NS Physical fatigue: NS Reduced activity: NS Mental fatigue: NS
							Pittsburgh Sleep Quality Inventory [BL to Dy 18]	NS
Leung, et al. (2018) [Canada, AMRO] [23]	Randomized controlled trial (pilot)	Anxiety (children and adolescents)	Personalized acupuncture and cupping and/or ear seeds, examples of points included: LI4, Du20, He7, Pe6, CV4, CV6, CV, AB14, B15, Du4, TW5, Yin Tang, CV12, Sp6, St36, Sp20, Ki3, Ki7, B23 and B25 (30 min, weekly for 5 wks)	Nil	Waitlist control	19 (10/9)	Hamilton Anxiety Rating Scale [BL to Wk 5]	**Reduced** Acupuncture: -11.1 ($p<0.001$) Waitlist control: NS Waitlist post-treatment: +10.38 ($p=0.007$) Between group at endpoint: NS
							Multidimensional Anxiety Scale for Children (MASC-2) [BL to Wk 5]	**Reduced** Acupuncture: NS Waitlist control: NS Waitlist post-treatment: -8.37 ($p=0.022$) Between group at endpoint: NS

Author (year) [Country, World region]	Design	Study Population	Intervention	Concomitant therapies	Control or comparison group	No. Participants (Intervention/ Control)	Outcome measure	Outcome
							MASC-Parent [BL to Wk 5]	**Reduced** Acupuncture: -9.5 (p=0.008) Waitlist: NS Waitlist post-treatment: -5.13 (p=0.048) Between group at endpoint: Acupuncture -15.4 (p=0.025)
Louie, et al (2010) [USA, AMRO] [30]	Uncontrolled trial	Human Immunodeficiency Virus (HIV) positive	Individualized acupuncture treatment based on tongue and pulse assessments including: ear and body acupuncture, moxibustion, electroacupuncture, *tui na* massage (6 mths treatment, 4 mths pre-intervention observation)	Nil	Nil	27 (27/0)	Memorial Symptoms Assessment Scale [BL to 6 Mth post-treatment]	NS
							WHO Quality of Life scale [BL to 6 Mth post-treatment]	NS
							Qualitative outcomes (from exit interviews regarding effect of treatment on physical symptoms, ART side effects and quality of life)	Relief of symptoms and complaints: reported by 96% Improved sense of wellness and emotional wellbeing: reported by 89% Increased ability to work more with reduced financial worries: reported by 48%
Mohanty, et al. (2016) [India, SEARO] [18]	Randomized controlled trial (pilot)	Blood glucose levels (healthy young adults)	Acupuncture on CV12 (20 min, single session)	Nil	Control: needling 1 cun lateral to CV12 (no known acupuncture point)	36 (18/18)	Random blood glucose [BL to post-intervention]	NS
Mohanty and Shrestha (2017) [India, SEARO] [31]	Case Report	Transverse myelitis (adult male)	Traditional Chinese acupuncture on GB34, GB39, St32, St36, St37, St39, St41, UB40, UB62, HT7, LI11, LI4, Du14, Sp6, UB36, Ex21, Ex36. Electroacupuncture on LI11, LI4, GB36, ST36, SP6 (30 min, 15 treatments over 3 wks)	Yoga, lifestyle counselling, naturopathic diet	Nil	1	Resting heart rate (beats/min) [BL to Dy 21]	**Reduced** Dy 21: -4
							Blood pressure (mmHg) [BL to Dy 21]	**Reduced** Systolic: -8 Diastolic: -2
							Visual Analog Scale, pain intensity [BL to Dy 21]	**Reduced** Dy 21: -7

Author (year) [Country, World region]	Design	Study Population	Intervention	Concomitant therapies	Control or comparison group	No. Participants (Intervention/Control)	Outcome measure	Outcome
							World Health Organization Brief Quality of Life [BL to Dy 21]	**Increased quality of life** Physical health: +61 Psychological health: +43 Social health: +6 Environmental health: +49
							Pittsburgh Sleep Quality Index [BL to Dy 21]	**Reduced sleep problems** Day 21: -9
Mooventhan and Nivethitha (2014) [India, SEARO] [36]	Case Report	Systemic lupus erythematosus (adult female)	Acupuncture on GV20, GV6, LI11, Ht7, GB34, Kd3 (20 min, daily for 30 days with 7 day rest period after 15 sessions)	Nil	Nil	1	Visual Analog Scale, pain [BL to post-intervention]	**Reduced** -4.8
							Epworth Sleepiness Scale [BL to post-intervention]	**Reduced daytime sleepiness** -8
							Pittsburgh Sleep Quality Index [BL to post-intervention]	**Reduced sleep problems** -8
							Short form-36 health survey [BL to post-intervention]	**Increased quality of life** Physical functioning: +40 Role physical: +43.75 Role emotional: +58.33 Energy/fatigue: +50 Emotional wellbeing: +60 Social functioning: +37.5 Bodily pain (function): +45 General health: +35
Painovich and Herman (2011) [USA, AMRO] [33]	Randomized controlled trial	Inpatient acute care (hospital)	Personalized acupuncture of varied styles (20 – 30 min, daily during stay)	Usual care	Usual care only	431 (288/143)	Length of hospital stay (days)	**Increased length of stay** Acupuncture: +0.8 (p=0.047)
Saha, et al. (2016) [Germany, EURO] [42]	Uncontrolled trial	Chronic low back pain	Mechanical needle stimulation pad (45 min per day, for 14 wks)	Nil	Nil	91	Visual Analog Scale, pain [BL to Wk 2, Wk 14]	NS
							Oswestry Disability Index [BL to Wk 2, Wk 14]	**Reduced disability** Wk 2: -4.6 (p<0.001) Wk 14: -4.3 (p<0.001)

Author (year) [Country, World region]	Design	Study Population	Intervention	Concomitant therapies	Control or comparison group	No. Participants (Intervention/ Control)	Outcome measure	Outcome
							Short form-36 health survey [BL to Wk 2, Wk 14]	**Increased quality of life** Physical component: Wk 2, +3.8 (p<0.001); Wk 14, +2.5 (p=0.008) Physical functioning: Wk 2, +6.4 (p=0.001); Wk 14, +5.6 (p=0.002) Vitality: Wk 2: +3.3 (p=0.045); Wk 14: NS Mental component: NS Physical role functioning: NS Bodily pain: NS General health perception: NS Social role functioning: NS Emotional role functioning: NS Mental health: NS
							Fear avoidance behavior [BL to Wk 2, Wk 14]	NS
							Days under medication per wk [BL to Wk 2, Wk 14]	**Reduced medication use** Wk 2: -1.2 (p=0.015) Wk 14: NS
Saha, et al. (2017) [Germany, EURO] [24]	Randomized controlled trial	Non-specific chronic neck pain	Cupping massages, along spine and trapezius muscles (10 min, twice per wk for 3 wks, 5 treatments in total)	Nil	Waitlist control	50 (25/25)	Pain on Movement Questionnaire [BL to Wk 3]	**Reduced pain on movement** Cupping: -10.4; Waitlist: -2.7 Between group: -11.7 (p=0.019)
							Visual Analogue Scale, pain intensity [BL to Wk 3]	**Reduced pain intensity** Cupping: -29.9; Waitlist: -2.3 Between group: -14.3 (p=0.037)
							Neck Disability Index [BL to Wk 3]	**Reduced disability** Cupping: -3.6 Waitlist: -0.3 Between group: -4.1 (p<0.001)

Author (year) [Country, World region]	Design	Study Population	Intervention	Concomitant therapies	Control or comparison group	No. Participants (Intervention/ Control)	Outcome measure	Outcome
							Short Form 36 [BL to Wk 3]	**Increased quality of life** Bodily pain: Cupping, +15.6 Waitlist, +0.5 Between group, +16.7 points (p=0.002) Mental health: Cupping, +7.7 Waitlist, -0.5 Between group, +8.5 (p=0.003) Mental component: Cupping, +4.3 Waitlist, +0.4 Between group, +4.3 (p=0.036) Physical component: NS Physical functioning: NS Physical role functioning: NS General health perception: NS Vitality: NS Social role functioning: NS Emotional role functioning: NS
							Pressure-pain threshold [BL to Wk 3]	**Increased pressure-pain threshold** Between group: improvement at site of maximal pain (p=0.022)
							Mechanical detection threshold [BL to Wk 3]	NS
							Vibration detection threshold [BL to Wk 3]	NS
							2-point discrimination threshold [BL to Wk 3]	NS

Author (year) [Country, World region]	Design	Study Population	Intervention	Concomitant therapies	Control or comparison group	No. Participants (Intervention/ Control)	Outcome measure	Outcome
Saha, et al. (2019) [Germany, EURO] [45]	Randomized controlled trial	Non-specific chronic low back pain	*Gua sha* Therapy: paravertebral strokes applied from C7 to L5, horizontal strokes between C7 and L5, additional strokes along dorsal surface of gluteus maximus, paravertebral strokes applied to the neck from C1/2 to C7 (2 treatments, 7 days apart)	Nil	Waitlist control	50 (25/25)	Pain on Movement Questionnaire [BL to Day 12]	**Reduced pain on movement** Gua sha: -24.55; Waitlist: -12.3 Between group: ($p<0.001$)
							Oswestry Low Back Pain Disability Questionnaire [BL to Day 12]	NS
							Pressure-pain threshold [BL to Day 12]	NS
							Mechanical detection threshold [BL to Day 12]	NS
							Vibration detection threshold [BL to Day 12]	NS
Shetty, et al. (2015) [India, SEARO] [32]	Case Report	Rheumatoid arthritis (female)	Acupuncture on GV20, LI4, Li11, BL11, GB34, SP6, KI3, ST44, EX28, EX36. Electroacupuncture at all points except GV20, EX28, EX36. (30 min total, 20 min for electro-stimulation, 14 sessions over 3 wks)	Massage, mud and sauna therapies	Nil	1	Visual Analog Scale, pain [BL to Dy 22]	**Reduced pain** -6.3
							10-meter walk test (m/sec) [BL to Dy 22]	**Increased velocity** -0.28
							Isometric hand grip test (mmHg) [BL to Dy 22]	**Increased grip strength** Right hand: +6 Left hand: +6
							Pittsburgh Sleep Quality [BL to Dy 22]	**Reduced sleep problems** -4
							Depression, Anxiety and Stress Scales [BL to Dy 22]	**Reduced depression, anxiety and stress** Depression: -23 Anxiety: -13 Stress: -17
							Short Form-36 health survey [BL to Dy 22]	**Increased quality of life** Total score: +50.97 Physical functioning: +45 Role physical: +62.5 Role emotional: +58.33 Energy/fatigue: +37.5 Emotional wellbeing: +50 Social functioning: +50 Bodily pain function: +55 General health: +60
							Blood analysis [BL to Dy 22]	**Increased blood cell counts** White blood cell total: +2100 **Reduced inflammation** ESR: -45

Author (year) [Country, World region]	Design	Study Population	Intervention	Concomitant therapies	Control or comparison group	No. Participants (Intervention/ Control)	Outcome measure	Outcome
							Urine analysis (per hpf) [BL to Dy 22]	**Reduced urinary bacteria** Pus-cells: -21 Epithelial cells: -4
Shetty, et al (2018) [India, SEARO] [25]	Randomized controlled trial	Primary dysmenorrhea (young adult females)	Acupuncture (KI-3, SP-8, ST-25, ST-29, ST-30, ST-36, CV-4, CV-6, BL-62, HT-7, LI-4, and PC-6) (20 min, 15 sessions per mth, initiated on 6th day of menstrual cycle [not performed during menstruation])	Nil	Usual care	60 (30/30)	Pain intensity (10-point numerical rating scale) [BL to Dy 30, 60, 90]	**Reduced pain intensity** Dy 30: Acupuncture -2.86; Control -0.39 Between group, p<0.05 Dy 60: Acupuncture -4.75; Control -0.34 Between group, p<0.05 Dy 90: Acupuncture -4.76; Control +0.05 Between group, p<0.05
							Muscle/menstrual cramping (4-point numerical rating scale) [BL to Dy 30, 60, 90]	**Reduced cramping** Dy 30: Acupuncture -1.20; Control +0.10 Between group, p<0.05 Dy 60: Acupuncture 1.43; Control +0.17 Between group, p<0.05 Dy 90: Acupuncture -1.60; Control +0.10 Between group, p<0.05
							Headache (4-point numerical rating scale) [BL to Dy 30, 60, 90]	**Reduced headache** Dy 30: NS Dy 60: NS Dy 90: Acupuncture -0.30; Control -0.03 Between group, p<0.05
							Dizziness (4-point numerical rating scale) [BL to Dy 30, 60, 90]	**Reduced dizziness** Dy 30: Acupuncture -0.84; Control -0.10 Between group p<0.05 Dy 60: Acupuncture -1.00; Control +0.03 Between group p<0.05 Dy 90: Acupuncture -1.00; Control +0.06 Between group p<0.05

Author (year) [Country, World region]	Design	Study Population	Intervention	Concomitant therapies	Control or comparison group	No. Participants (Intervention/ Control)	Outcome measure	Outcome
							Diarrhea (4-point numerical rating scale) [BL to Dy 30, 60, 90]	**Reduced diarrhea** Dy 30: Acupuncture -0.46; Control +0.20 Between group p<0.05 Dy 60: Acupuncture -0.53; Control +0.07 Between group p<0.05 Dy 90: Acupuncture -0.56; Control +0.20 Between group p<0.05
							Faint (4-point numerical rating scale) [BL to Dy 30, 60, 90]	**Reduced faint feeling** Dy 30: Acupuncture -0.40; Control -0.03 Between group p<0.05 Dy 60: Acupuncture -0.40; Control -0.16 Between group p<0.05 Dy 90: Acupuncture -0.43; Control +0.10 Between group p<0.05
							Mood changes (4-point numerical rating scale) [BL to Dy 30, 60, 90]	**Reduced negative mood** Dy 30: Acupuncture -1.00; Control -0.04 Between group p<0.05 Dy 60: Acupuncture -0.90; Control -0.17 Between group p<0.05 Dy 90: Acupuncture -0.97; Control -0.10 Between group p<0.05
							Tiredness (4-point numerical rating scale) [BL to Dy 30, 60, 90]	**Reduced tiredness** Dy 30: Acupuncture -1.00; Control -0.04 Between group p<0.05 Dy 60: Acupuncture -1.27; Control -0.04 Between group p<0.05 Dy 90: Acupuncture -1.27; Control -0.24 Between group, p<0.05

Author (year) [Country, World region]	Design	Study Population	Intervention	Concomitant therapies	Control or comparison group	No. Participants (Intervention/ Control)	Outcome measure	Outcome
							Nausea (4-point numerical rating scale) [BL to Dy 30, 60, 90]	**Reduced nausea** Dy 30: Acupuncture -0.70; Control -0.07 Between group p<0.05 Dy 60: Acupuncture -0.73; Control +0.13 Between group p<0.05 Dy 90: Acupuncture -0.87; Control +0.16 Between group, p<0.05
							Vomiting (4-point numerical rating scale) [BL to Dy 30, 60, 90]	**Reduced vomiting** Dy 30: Acupuncture -0.47; Control +0.03 Between group p<0.05 Dy 60: Acupuncture -0.47; Control +0.07 Between group p<0.05 Dy 90: Acupuncture -0.47; Control -0.00 Between group, p<0.05
Sriloy, et al. (2015) [India, SEARO] [26]	Randomized controlled trial (parallel)	Hypertension (acupuncture naïve)	Acupuncture, unilateral on left, seeking *de qi*, on GV20, ST36, LV3, HT7 with manual stimulation to all points except GV20 (20 min, single session)	Nil	Slow breathing (abdominal, alternate nostril and sectional breathing) (20 min, seated)	37 (18/19)	Blood pressure – systolic (mmHg) [BL to post-test]	**Reduced systolic BP** Acupuncture: NS Slow breathing: p=0.007
							Blood pressure – diastolic (mmHg) [BL to post-test]	**Reduced diastolic BP** Acupuncture: p=0.02 Slow breathing: NS
Zick, et al. (2011) [USA, AMRO] [43]	Randomized controlled trial	Persistent cancer-related fatigue (adults, >12 wks post cancer treatment)	Stimulatory acupressure on CV6, GV20 and bilaterally on ST36, SP6, KI13, LI3: high (HIS, 2 x per day) or low (LIS, 3 2 per wk) dose; Relaxation acupressure (RA, 2 x per day) on Yin Tang and bilaterally on Anmian, HT7, LV3, SP6 (30 min, 12 wks, self-administered)	Nil	Nil	43 (15/14/ 14)	Brief Fatigue Inventory [BL to Wk 12]	**Reduced Fatigue severity** HIS: -2.2 LIS: -2.7 RA: -4.0 Between group: p=0.027 Adjusted: p=0.013

Author (year) [Country, World region]	Design	Study Population	Intervention	Concomitant therapies	Control or comparison group	No. Participants (Intervention/ Control)	Outcome measure	Outcome
Zick, et al. (2016) [USA, AMRO] [44]	Randomized controlled trial	Breast cancer stage 0-IIII (female survivors, >12 months post cancer treatment)	Relaxing acupressure (RA) on Yin Tang and bilaterally on Anmian, HT7, SP6, LV3; Stimulating acupressure (SA) on Du20, CV6 and bilaterally on LI4, ST36, SP6, KI3 (3 min each point, daily, for 6 wks with 4 wk follow-up)	Nil	Usual care control	270 (94/90/ 86)	Brief Fatigue Inventory (BFI) [BL to Wk 6, Wk 10]	**Reduced fatigue** Wk 6 RA: -2.6, SA: -2.0, Control -1.1 Between group: p<0.001 Wk 10 RA: -2.3, SA: -2.0, Control: -1.0 Between group: p<0.001 BFI score <4 (Wk 6) RA: 66.2%; SA: 60.9%, Control: 31.3% Between group: p<0.001
							Pittsburg Sleep Quality Index [BL to Wk 6, Wk 10]	**Reduced sleep problems** Wk 6 RA: -2.0, SA: -1.4, Control: 0.6 Between group: p<0.05 Wk 10: NS
							Long-Term Quality of Life (LTQL) Instrument – Somatic [BL to Wk 6, Wk 10]	**Increased somatic function** Wk 6 RA: +3.3, SA: +2.0, Control: +0.2 Between group: p<0.05 Wk 10 RA: +3.5, SA: +1.2, Control: +0.6 Between group: p<0.05
							LTQL – Fitness [BL to Wk 6, Wk 10]	**Increased fitness** Wk 6 RA: +1.4, SA: +0.5, Control: -0.1 Between group: p<0.05 Wk 10 RA: +2.2, SA: +0.9, Control: +0.4 Between group: p<0.05
							LTQL – Social support [BL to Wk 6, Wk 10]	**Increased social support** Wk 6 RA: +0.1, SA: -0.4, Control: -0.8 Between group: p<0.05 Wk 10 RA: 0.0, SA: -0.8, Control: -0.7 Between group: p<0.05
							Adverse events	**Non-serious** 6 cases of mild bruising at acupressure sites

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38 Yoga

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HIGHLIGHTS

- Yoga is practiced around the world and is an integral aspect of naturopathic care.
- Yoga practice includes the integration of breath work, specific exercises, dietary recommendations, and mindfulness or meditation.
- Clinical research by the naturopathic community has examined the application of combined yoga practices, yoga breathing, and yoga meditation.
- In line with the role of primary care, naturopathic researchers have investigated the effects of yoga on individuals with cancer, musculoskeletal conditions, endocrine conditions, mental health conditions, neurological conditions, skin conditions gastrointestinal conditions, women's health conditions, and a range of other conditions.

Originating in ancient India, yoga refers to a philosophically based practice and a blend of physical and mental disciplines. Practiced under proper guidance, yoga can be systematically and methodically applied therapeutically in different health conditions and diverse cultures as it adopts a holistic approach to health and life and acknowledges the interconnectedness between the mental, physical, emotional, social, and spiritual dimensions of health and being. Traditionally yoga incorporates physical *asanas* (postures) and practices, but also *pranayama* (breathing exercises), *nidra* (chanting), *kriyas* (cleansing activities), and *dhyana* (meditation), as well as other meditation, spirituality, and dietary and lifestyle modifications that support harmony and balance within the whole person. The term yoga refers to both the entire process of these practices and the goal or end-point philosophically [1].

Outside of India the term yoga is often synonymous with physical exercise and *asanas* in particular can become the singular focus [2]. Interest in yoga from Western scholars and practitioners has been documented since the mid-19th century [3], with the earliest scientific yogic claims such as voluntary control over involuntary body functions through the practice of yoga occurring in the mid-19th century [4]. The Yoga Institute in India was established by Yogendra in 1918 to seek scientific evidence of the potential health benefits of yoga, followed by the first peer-reviewed yoga research journal (Yoga Mimamsa) in 1924 [5]. Since this time there has been a steadily growing body of research examining the effectiveness of yoga in promoting health and wellbeing [6]. In particular, the systematic and methodic therapeutic application of yoga under clinical guidance appears to benefit individuals with various health conditions.

In India, yoga and naturopathy were famously integrated by Mahatma Gandhi. Gandhi studied naturopathy during his time in the United Kingdom, refining his practice in South Africa to then combine yoga and nature cure as core therapeutic elements within the Indian naturopathic profession [7]. Mahatma Gandhi popularized yoga in his many writings on naturopathy, in his practice, and in the naturopathic hospitals and the National Institute of Naturopathy which he helped to establish in India that combine yoga and naturopathy even today [8, 9]. Yoga and naturopathy have a long history outside of India, with the global naturopathic community having a significant role in promoting yoga to new audiences [10]. Yoga articles by Indian authors such as Shri Yogendra and Paramahansa Yogananda appear in early American, Australian and British naturopathic journals. The articles introduce yogic philosophy and practices which were aligned with naturopathic concepts such as *holism* and physical culture [11, 12].

Whilst undergraduate training combining naturopathy and yoga is most developed in India, where a combined naturopathy and yoga degree is awarded [13, 14], the application of yoga within naturopathic practice is seen globally, with practice surveys of Australian naturopaths, for example, indicating that 75% of naturopathic practitioners in that country prescribe yoga to patients [9]. The clinical application of yoga within naturopathic

practice is dependent on the practitioner's training and may include the prescription of physical and mental practices, and the integration of yoga philosophy into the practitioner's understanding of health and disease.

Overview of Studies

This chapter is dedicated to highlighting the original clinical research (n=52, published in 58 papers) conducted by naturopathic researchers investigating yoga. The naturopathic research examining yoga includes a total of 5,474 participants and was conducted in India (n=49) and Germany (n=9). The study designs include randomized controlled trials (n=37), controlled trials (n=6), uncontrolled trials (n=5), secondary analyses (n=5), case reports (n=4), and a follow-up study (n=1). Study settings varied from hospital and out-patient settings, private class practice, home practice, residential programs and schools. The aspects of yoga studied include physical postures/*asanas* (n=47), breath control/*pranayama* (n=47), chanting/meditation (n=42) and cleansing activities/*kriyas* (n=7).

There were various conditions treated with yoga including breast cancer (n=12), neck pain (n=5), type 2 diabetes mellitus (T2DM) (n=5), depression (n=4), migraine (n=3), sleep disorders (n=2), mood disorders (n=2), one study each for individuals with acne, menopause, colorectal cancer, obesity, ulcerative colitis, schizophrenia, uterine bleeding, anorexia, anxiety, tuberculosis, urinary incontinence, and hepatic cirrhosis. Yoga interventions also included healthy volunteers evaluating changes in cognitive function (n=8) and/or changes in autonomic and respiratory or cardiovascular function (n=6). Of all the naturopathic clinical studies employing yoga interventions, 86.3% reported a positive outcome in at least one primary or secondary outcome measure. Details of the studies are available in *Table 38.1 Clinical research investigating yoga interventions conducted by naturopathic researchers.* This body of naturopathic research on yoga is supported by more than 20 observational studies and more than 50 reviews or meta-analysis conducted by naturopathic researchers on this topic, as outlined in Chapter 40.

Implications

The research to date indicates naturopaths/naturopathic doctors use a variety of yogic practices, such as *asanas, pranayama* and meditation, to achieve demonstrable improvements in patient health and wellbeing. The varied application of treatment modalities shown in the research reflects the holistic ontology of naturopathic practitioners, validates the effectiveness of this approach, and supports the role of naturopaths/naturopathic doctors in facilitating yoga-based interventions to improve healthcare. While further research is needed to confirm findings of the uncontrolled studies and case reports presented in this review, and to fully ascertain the physiological mechanisms of action of some yoga practices, the evidence demonstrates the alignment of yoga practices and philosophy with naturopathy/naturopathic medicine and its effectiveness as a treatment modality within naturopathic practice for a diverse range of health conditions.

It is important to note that while yoga may be viewed as largely a form of exercise rather than healing modality in many parts of the world, several of the studies by naturopathic researchers highlight the importance of non-physical aspects of yoga, such as breathwork and meditation. As yoga utilization increases globally, so too do injuries and adverse events most often due to physical over-extension and inappropriate, unsupervised and/or unguided practice [15-17]. The long-standing and complex relationship between naturopathy/naturopathic medicine and yoga positions indicated that naturopaths/naturopathic doctors are well suited to facilitate integration of yoga into primary health care in a critically applied manner that advocates evidence-based applications and safe, therapeutic outcomes whilst respecting yoga's culture and traditions.

Studies investigating specific interventions:

Combination Yoga Practices

The majority of original clinical research studying yoga and conducted by naturopathic researchers have used interventions that combine different elements of yogic practice such as asanas, pranayama, and meditation (n=39; 46 papers published) [18-64]. The studies investigated yoga for populations of individuals with breast cancer (n=9; 12 published papers) [19, 35-41, 48-51], chronic neck pain (n=4; 5 published papers) [34, 56-59], major depressive disorder (n=1; 4 published papers) [21-24], T2DM (n=5) [31, 32, 52, 53, 55], migraine (n=3) [25, 27, 44], one study each investigated yoga practices for menopausal symptoms in breast cancer survivors [60], abdominal obesity [62], colorectal cancer [61], liver cirrhosis [42], anorexia [64], schizophrenia [26] ulcerative colitis [63], acne [18], uterine bleeding [33], urinary incontinence [54]. A further eight studies tested the effects of yoga on various outcomes for healthy volunteers [20, 28-30, 43, 45, 46, 65]. While not always specified in the study methods, the interventions included *asanas* (postures) (n=25) [18-21, 26-35, 43-48, 51-53, 55, 64] *pranayama* (breathing) (n=30) [18-21, 26-36, 38, 39, 41, 43-48, 52, 53, 55, 61, 64], *dhyana* (meditation) (n=22) [19, 20, 28-30, 32-35, 38, 39, 41, 43, 45, 46, 48, 51, 52, 55, 60, 61, 64], relaxation techniques (n=19) [20, 28-31, 33-36, 38, 39, 41, 43-48, 51], *kriyas* (cleansing) (n=8) [18, 20, 28, 29, 46, 47, 55], *nidra* (chanting) (n=7) [19, 21, 26, 31, 44, 51,

61], lectures or counselling on yogic theory (n=10) [21, 30, 32, 34, 40, 46, 51-53, 55] and prescribed home practice (n=10) [19, 21, 35, 36, 44, 48, 57, 59, 63, 64].

An age-matched controlled trial conducted in India with healthy participants examined the effect of an integrated yoga intervention on psychomotor performance and self-efficacy of school children less than 17 years old (n=420) [20]. The intervention included *asana* postures, *pranayama* breathing, meditation *(dhyana)*, relaxation techniques, cleansing *(kriyas)*, and reciting hymns from traditional yoga text, music, yoga games and 'happy assembly'. The intervention was delivered for 10 hours per day for 10 days. The children in the intervention group achieved improved scores on two psychomotor tests *(Trail Making Task A* and *B)*, including reduced wrong attempts (A: p<0.001; B: p<0.001) and increased right attempts (A: p<0.001; B: p<0.001). Participants in the yoga arm also demonstrated a greater increase in self-efficacy at study completion compared to the age-matched control (Self-efficacy Questionnaire for Children: p<0.001).

A randomized controlled trial conducted in India involving adults with elevated blood glucose (n=41) examined the impact of integrated yoga on T2DM risk factors [31]. The yoga intervention required participants to complete 75-minute yoga classes that included a combination of *asana* postures, *pranayama* breathing, loosening exercises, guided relaxation and chanting. This intervention was compared with 30-minute counselling sessions that discussed healthy lifestyle changes (diet, physical activity and smoking) and walking. Both groups attended 3-6 classes of their respective interventions per week for 8 weeks. There was no difference in change from baseline of blood glucose levels, insulin levels or lipid markers for either group, however, participants in the yoga group recorded a greater reduction in body weight (-0.8kg vs +1.4kg, p=0.02), body mass index (-0.2kg/m^2 vs +0.6kg/m^2, p=0.05) and waist circumference (-0.8cm vs +1.4cm, p<0.01) compared to the control group.

One randomized controlled trial conducted in India [19] involved breast cancer patients (n=68) undergoing radiotherapy or adjuvant chemotherapy, and employed a combination of guided meditation, *asana* postures, *pranayama* breathing, *nidra* chanting for 90-minutes per week over six weeks. Participants were also encouraged to practice at home over the study period. The yoga intervention was compared to supportive psychotherapy and was found to have a greater reduction in anxiety (p<0.001), depression (p<0.001), and stress (p<0.001). A second randomized controlled trial conducted in India [36] allocated individuals recently diagnosed with stage II and III breast cancer (n=69) to receive an integrated yoga intervention or supportive counselling sessions and post-operative exercise rehabilitation. The integrated yoga intervention involved *pranayama* breathing and yogic relaxation techniques. In addition, both groups received surgery and related usual care. Participants practiced the interventions for 30-minute daily sessions at home for three weeks. Yoga group participants reported a significant reduction in state (p=0.04) and trait (p=0.004) anxiety, and depression (p=0.01) compared to controls. They also reported a greater reduction in symptom severity (p=0.01) and symptom distress (p<0.01) as well as improvement in quality of life (=0.01). Secondary analysis of this same study [37] examined post-operative outcomes and wound healing. It found reduced drain retention (p=0.001) and interval for suture removal (p=0.031). Duration of hospital stay was also shorter among yoga participants compared to control (p=0.003).

A randomized controlled trial conducted in Germany examined individuals with chronic neck pain (n=51) attending yoga classes compared to self-directed evidence-based exercise routines [57]. The weekly Iyengar classes focused on the precision and alignment of specific yoga postures and included 90-minute classes offered over 9 weeks. Participants in the Iyengar group were also encouraged to undertake 10 minutes home practice daily. The control group was provided with a self-directed evidence-based exercise manual and were also asked to undertake 10 minutes home practice per day. The yoga group demonstrated significantly reduced neck pain (-13.9, p=0.03), disability (-7.8, p=0.006), and increased quality of life (mental component: +6.1, p=0.016; bodily function: +7.8, p=0.0001; social function: +6.0, p=0.027; emotional role: +7.9, p=0.005) compared to the exercise group. They also had increase flexion (+27.1, p=0.036) and extension (+8.3, p=0.025) range of motion, and increased pain thresholds (p<0.001).

A randomized controlled trial conducted in Germany investigated Hatha yoga (asanas plus breathing control) for individuals with ulcerative colitis (n=77), compared to written, evidence-based self-care advice [63]. The Hatha yoga group attended 90-minute classes weekly for 12 weeks and were also encouraged to undertake daily practice, although the latter was optional. Both groups were followed up for 24 weeks. Compared to the self-care group, participants in the yoga group reported increased quality of life at Week 12 (Inflammatory Bowel Disease Questionnaire [IBD-Q]: +14.7, p=0.02) and Week 24 (IBD-Q: +16.4, p=0.02) as well as reduced disease activity at Week 24 (Rachmilewitz clinical activity index: -1.2, p=0.03).

A randomized controlled trial was conducted in India involving individuals with migraines (n=60) [27]. The study compared usual care to a yoga intervention combined with usual care. The yoga intervention involved 1-hour sessions incorporating relaxation and *pranayama* breathing exercises as well as *asanas*, 5 days per week for 6 weeks. Compared to the control group, the study found that the yoga group reported significantly reduced headache impact (p<0.001), headache frequency (p<0.001), and headache intensity (p<0.001) along with a higher proportion of participants indicated self-perceived

benefit from the intervention.

Yoga Breathing

Seven studies examined yogic breathing or *pranayama* as a standalone intervention [66-72] in healthy populations (n=6) [66-70, 72] and in one study involving individuals with pulmonary tuberculosis [71]. A crossover randomized controlled trial was conducted in India with healthy males using 40 min sessions of specific nostril-manipulating yoga breathing practices [66]. Participants were either allocated to practice (1) right nostril yoga breathing and left nostril yoga breathing, (2) alternate nostril yoga breathing, or (3) breath awareness breathing and normal breathing control. Participants demonstrated significant changes in heart rate (30 sec: +4.73, $p<0.01$; 5 minutes post-intervention: +4.73, $p<0.05$) after practicing alternating nostril yoga breathing but no other breathing interventions. Blood pressure was reduced for participants following left nostril yoga breathing (systolic: -4.19, $p<0.01$), alternating yoga breathing (systolic: -1.14, $p<0.05$; diastolic: -0.67, $p<0.05$) and normal breathing control (diastolic: -0.67; $p<0.05$).

A randomized controlled trial was conducted in India involving individuals with pulmonary tuberculosis receiving usual care (n=73) investigated the clinical effect of *pranayama* breathing compared to breath awareness practices [71]. Participants in the *pranayama* group practiced simple breathing, *pranayama* breathing and supine relaxation 60 minutes per day, 6 days per week for 60 days. The study found participants in the *pranayama* group had significantly reduced symptom scores compared to the breath awareness group (*pranayama*: -10.4 vs breath: -2.02, $p<0.05$). It also found, compared to the breath awareness group, a greater proportion of *pranayama* participants had improved sputum microscopy throughout the intervention period (Day 30: *pranayama* 19/25, breath 10/23, p=0.045; Day 45: *pranayama* 24/25, breath 4/19, p=0.002; Day 60: *pranayama* 10/13, breath 4/19, p=0.005), and improved postero-anterior chest x-ray at the end of the study (*pranayama* 19/25, breath 3/22, p=0.001). 30 studies integrated *pranayama.*

Yoga Meditation

In addition to the studies conducted by naturopathic researchers that examine mind-body medicine practices as presented in *Chapter 34: Mind-Body Medicine Counselling*, five studies explored meditation or other mindfulness practices as a sole therapy, measuring its effects both physically and psychologically [42, 65, 73-75]. In a randomized crossover trial conducted in India, healthy individuals (n=30) demonstrated that *dharana* and *dhyana* meditative practices significantly improved individual stress response as measured through breath and heart rate factors [65].

An uncontrolled trial conducted in India involving 18- to 25-year-old female college students (n=72) investigated the effects of a yoga-based meditation technique on emotional regulation [73]. The technique was described as 'Mastering Emotions Technique' and was practiced for 45 minutes per day for 2 weeks. The participants emotional regulation was measured using the Emotional Regulation Questionnaire and found an increase from baseline in cognitive reappraisal (+1.62, $p<0.001$) and a reduction in expressive suppression (-1.25, $p<0.001$). Participants also showed increased positive affect (+1.23, $p<0.001$) and reduced negative affect (-1.25, $p<0.001$), as measured by the Positive and Negative Affect Schedule. Furthermore, participants demonstrated increased self-compassion (Self Compassion Scale: +0.09, $p<0.01$) and mindfulness (Mindfulness Attention Awareness Scale: +0.53, $p<0.001$).

A crossover randomized controlled trial was conducted in India involving healthy male yoga students (n=50) examined the effects of cyclic meditation on oxygen consumption [74]. The study group compared to a control group practicing *shavasana* (supine rest) for 30 minutes whereas the cyclic meditation group practiced meditation for 20 minutes with 5 minutes supine rest before and after. Participants practicing cyclic meditation group showed increased oxygen consumption during the intervention ($p<0.001$) and reduced after the intervention ($p<0.001$). In comparison, the participants demonstrated reduced oxygen consumption during and after the intervention when practicing *shavasana* ($p<0.001$).

Table 38.1 Clinical research investigating yoga interventions conducted by naturopathic researchers

Author (year) [Country, World region]	Design	Study Population	Intervention(s)	Concomitant Therapies	Control or Comparison	Participants (Intervention/ Control)	Measure of Outcome	Outcome
Allende, et al. (2018) [Germany, EURO] [56]	Randomized controlled trial	Chronic non-specific neck pain	Iyengar yoga (90 min classes, weekly for 9 weeks, with 10 min daily home practice)	Nil	Self-directed exercise	47 (23/24)	Visual Analogue Scale, neck pain intensity (weekly average of daily diary) [BL to Wk 10]	**Reduced pain** Trend in reduction of neck pain intensity, with substantial variation between participants
Ameya and Nair (2017) [India, SEARO] [18]	Case report	Acne vulgaris	Yoga: *asanas, pranayama* breathing, cleansing *kriyas* (45 min, daily on non-fasting days)	Dietary plan, therapeutic fasting and naturopathy	Nil	1	Acne lesions and inflammation [BL to Dy 30, 60]	**Reduced lesions** Dy 30: noticeable reduction in lesions, with no noticeable inflammation or swelling. Dy 60: No relapse of symptoms reported.
Banerjee, et al. (2007) [India, SEARO] [19]	Randomized controlled trial	Breast cancer (undergoing radiotherapy or adjuvant chemotherapy)	Guided meditation, *asanas, pranayama* breathing, *nidra* chanting and home practice (90 min progression sessions for 6 wks)	Nil	Supportive counselling	68 (35/33)	Hospital Anxiety and Depression Scale [BL to Wk 6, pre- and post-radiation]	**Reduced anxiety** Yoga (-4.4, p<0.001) Control (+2.3, p<0.001) **Reduced depression** Yoga (-4.6, p<0.001) Control (+1.9, p<0.001)
							Perceived Stress Scale [BL to Wk 6, pre and post radiation]	**Reduced Stress** Yoga (-5.5, p<0.001) Control (+1.4, p<0.001)
							Radiation-induced DNA damage – Alkaline Single-Cell Gel Electrophoresis (Comet) Assay [BL to Wk 6, pre and post radiation]	**Increased radiation-induced DNA damage** Yoga (+21.7, p<0.001) Control (+26, p<0.001) Between groups difference 14.5% (p<0.001)
Cramer, et al. (2013) [Germany, EURO] [57]	Randomized controlled trial	Chronic neck pain	Iyengar yoga (90 min classes, weekly for 9 wks, with 10 min daily home practice)	Nil	Exercise, self-directed using evidence-based manual (10 min daily)	51 (25/26)	Visual Analogue Scale, pain intensity (100mm) [BL to Wk 9]	**Reduced pain intensity** Yoga -28.6; exercise -3.1 Between group 13.9 (p=0.030) Pain at motion NS
							Functional disability – Neck Disability Index [BL to Wk 9]	**Reduced disability** Yoga: -10.0; Exercise: -0.4 Between group: -7.8 (p=0.006)

Author (year) [Country, World region]	Design	Study Population	Intervention(s)	Concomitant Therapies	Control or Comparison	Participants (Intervention/ Control)	Measure of Outcome	Outcome
							Health related quality of Life Short form-36 [BL to Wk 9]	**Improved quality of life** Between groups: Bodily pain (7.8, p=0.001) Social functioning (6.0, p=0.027) Emotional role functioning (7.9, p=0.005) Mental quality of life (6.1, p=0.016)
							Range of Motion [BL to Wk 9]	**Increased ROM** Yoga 32.5; exercise -1.0 Between group 27.1 (p=0.036)
							Joint position errors [BL to Wk 9]	**Reduced errors** Yoga: -2.0; Exercise: -0.9 Between group: -1.8 (p=0.006)
							Pressure pain threshold (PPT) – Site of maximal pain [BL to Wk 9]	**Increased threshold** Yoga: +66.9; Exercise: -21.1 Between group: +99.5 (p<0.001)
							PPT – Levator scapulae muscle, right side [BL to Wk 9]	**Increased threshold** Yoga: +47.2; Exercise: +2.7 Between group: +56.4 (p<0.001)
							PPT – Levator scapulae muscle, left side [BL to Wk 9]	**Increased threshold** Yoga: + 24.3; Exercise: -23.1 Between group: 47.5 (p=0.028)
							PPT – Trapezius muscle, right side [BL to Wk 9]	**Increased threshold** Yoga: +55.6; Exercise: +2.7 Between group: +0.83 (p=0.026)
							PPT – Trapezius muscle, left side [BL to Wk 9]	**Increased threshold** Yoga: +57.5; Exercise: +14.3 Between group: +54.1 (p=0.044)

Author (year) [Country, World region]	Design	Study Population	Intervention(s)	Concomitant Therapies	Control or Comparison	Participants (Intervention/ Control)	Measure of Outcome	Outcome
Cramer, et al. (2013) [Germany, EURO] [58]	12 month follow-up					36 (22/14)	PPT – Semispinalis capitis, right side [BL to Wk 9]	**Increased threshold** Yoga: +33.9; Exercise: -7.6 Between group +50.0 ($p<0.001$)
							PPT – Semispinalis capitis, left side [BL to Wk 9]	**Increased threshold** Yoga: +52.2; Exercise: -11.4 Between group: +63.8 ($p<0.001$)
							Visual Analog Scale, pain intensity [BL to Mth 12]	**Reduced pain** Mth 12: -16.5 ($p<0.001$)
							Neck Disability Index [BL to Mth 12]	**Reduced disability** Mth 12: -5.77 ($p=0.001$)
							Generic disability (days non-functioning) [BL to Mth 12]	NS
							Short Form-36 (SF-36) health survey [BL to Mth 12]	**Increased bodily function** Pain-related bodily function: +9.98 ($p=0.005$) Physical functioning: NS Physical role: NS General health: NS Vitality: NS Social functioning: NS Emotional role: NS Mental health: NS: Total physical component: NS Total mental component: NS
Cramer, et al. (2013) [Germany, EURO] [59]	Secondary sub-analysis					18	Participant drawings and semi-structured interview – Physical dimension [Wk 9]	**Improved physical dimension** Renewed awareness of and approach to bodily functions. More balanced and natural perception of body.

Author (year) [Country, World region]	Design	Study Population	Intervention(s)	Concomitant Therapies	Control or Comparison	Participants (Intervention/ Control)	Measure of Outcome	Outcome
							Participant drawings and semi-structured interview – Cognitive dimension [Wk 9]	**Improved cognitive dimension** Greater perceived control over body, health and general wellbeing in daily life. Feeling less controlled by pain.
							Participant drawings and semi-structured interview – Emotional dimension [Wk 9]	**Improved emotional dimension** Deep relaxation, less irritability and different perceptions of emotions. Improved coping and pain acceptance.
							Participant drawings and semi-structured interview – Behavioural dimension [Wk 9]	**Improved behavioral dimension** Use of yoga as self-help/ coping strategy to relieve or prevent stress and pain. Reduced reliance on pain medication.
							Participant drawings and semi structured interview – Social dimension [Wk 9]	**Improved social dimension** Re-engagement with preferred social activities, greater self-determination. Enriched work and social lives.
Cramer, et al. (2015) [Germany, EURO] [60]	Randomized controlled trial (open label)	Menopausal symptoms (breast cancer survivors)	Hatha yoga and meditation (Tibetan Buddhism) (90 min, weekly, 12 wks)	Nil	Control (usual care)	40 (19/21)	Menopausal Rating Scale (MRS) – Total score [BL to Wk 12, 24]	**Reduced symptoms** Wk 12: -5.6 (p=0.004) Wk 24: -4.5 (p=0.023)
							MRS – Somatovegetative symptoms [BL to Wk 12, 24]	**Reduced symptoms** Wk 12: -1.8 (p=0.035) Wk 24: -1.9 (p=0.028)
							MRS – Psychological symptoms [BL to Wk 12, 24]	**Reduced symptoms** Wk 12: -2.4 (p=0.012) Wk 24: NS
							MRS – Urogenital symptoms [BL to Wk 12, 24]	**Reduced symptoms** Wk 12: -1.5 (p=0.025) Wk 24: -1.3 (p=0.025)

Author (year) [Country, World region]	Design	Study Population	Intervention(s)	Concomitant Therapies	Control or Comparison	Participants (Intervention/ Control)	Measure of Outcome	Outcome
							Functional Assessment of Cancer Therapy – Breast (FACT-B) – Total score [BL to Wk 12, 24]	**Increased function** Wk 12: +12.5 (p=0.002) Wk 24: +12.6 (p=0.004)
							FACT-B – Physical function [BL to Wk 12, 24]	**Increased function** Wk 12: NS Wk 24: +3.6 (p=0.01)
							FACT-B – Social function [BL to Wk 12, 24]	**Increased function** Wk 12: +2.4 (p=0.24) Wk 24: +2.6 (p=0.16)
							FACT-B – Emotional function [BL to Wk 12, 24]	**Increased function** Wk 12: +2.8 (p=0.005) Wk 24: +1.6 (p=0.036)
							FACT-B – Functional [BL to Wk 12, 24]	**Increased function** Wk 12: +3.3 (p=0.024) Wk 24: NS
							FACT-B – Breast cancer-specific [BL to Wk 12, 24]	NS
							Functional Assessment of Chronic Illness Therapy – Fatigue [BL to Wk 12, 24]	**Increased energy** Wk 12: +6.0 (p=0.10) Wk 24: (7.3, p=0.012)
							Hospital Anxiety and Depression Scale [BL to Wk 12, 24]	Anxiety: NS Depression: NS
Cramer, et al. (2016) [Germany, EURO] [61]	Randomized controlled trial (open label)	Colorectal cancer (stage I-III)	Hatha yoga, *pranayama* breathing, meditation, *yoga nidra* (90 min, weekly, 10 wks)	Nil	Waitlist control	54 (27/27)	Functional Assessment of Cancer Therapy – Colorectal [BL to Wk 10, 22]	**Increased emotional wellbeing** Wk 10: NS Wk 22: Emotional: +1.59 (p=0.019) Physical: NS Social: NS Functional: NS Colorectal cancer-specific: NS Total: NS

Author (year) [Country, World region]	Design	Study Population	Intervention(s)	Concomitant Therapies	Control or Comparison	Participants (Intervention/ Control)	Measure of Outcome	Outcome
							Functional Assessment of Chronic Illness Therapy [BL to Wk 10, 22]	Fatigue: NS Spiritual wellbeing: NS
							Sleep disturbance – Pittsburgh Sleep Quality Inventory [BL to Wk 10, 22]	**Reduced sleep disturbance** Wk 10: NS Wk 12: -1.08 (p=0.043)
							Hospital Anxiety and Depression Scale [BL to Wk 10, 22]	**Reduced** Wk 10: Anxiety: -1.14 (p=0.034) Depression: -1.34 (p=0.038) Wk 22: NS
							Bodily awareness and dissociation – Scale of Body Connection [BL to Wk 10, 22]	NS
							Treatment expectancy – Body-Efficacy Expectation Scale [BL to Wk 10, 22]	NS
Cramer, et al. (2016) [Germany, EURO] [62]	Randomized controlled trial	Abdominal obesity (females, abdominal obesity)	Traditional Hatha yoga (full day workshop followed by 2 x weekly 90 min classes)	Nil	Waitlist control	60 (40/20)	Impact on Quality of Life, Short form-23 [BL to Wk 12]	**Reduced impact on quality of life** Yoga: -3.7; Wait list: +0.01 Between group: -3.8 (p=0.001)
							Impact on Self-Esteem, Rosenberg Self Esteem Scale [BL to Wk 12]	**Reduced impact on self-esteem** Yoga: -0.02; Wait list: -0.0 Between group: -0.02 (p=0.03)
							Perceived Stress Scale [BL to Wk 12]	**Reduced stress** Yoga: -3.1; Wait list: -1.7 Between group: -3.1 (p=0.016)
							Body Awareness Questionnaire [BL to Wk 12]	**Increased body awareness** Yoga: +6.1; Wait list: -1.0 Between group: +9.3 (p=0.001)

Author (year) [Country, World region]	Design	Study Population	Intervention(s)	Concomitant Therapies	Control or Comparison	Participants (Intervention/ Control)	Measure of Outcome	Outcome
							Body Responsiveness Scale [BL to Wk 12]	**Increased body responsiveness** Trust in bodily sensations Yoga: +3.5; Wait list: -0.5 Between group: +4.4 (p<0.001)
							Waist circumference (cm) [BL to Wk 12]	**Reduced waist circumference** Yoga: -3.7; Wait list: +.01 Between group: -3.8 (p=0.001)
							Waist-hip ratio [BL to Wk 12]	**Reduced waist-hip ratio** Yoga: -0.02; Wait list: -0.0 Between group: -0.02 (p=0.03)
							Body weight (kg) [BL to Wk 12]	**Reduced body weight** Yoga: -1.5; Wait list: +0.7 Between group: -2.4 (p=0.003)
							Body mass index (BMI) [BL to Wk 12]	**Reduced BMI** Yoga: -0.5; Wait list: +0.3 Between group: -0.8 (p=0.008)
							Percentage of body fat (%) [BL to Wk 12]	**Reduced body fat** Yoga: -1.4; Wait list: -0.1 Between group: -1.7 (p=0.01)
							Percentage of body muscle mass (%) [BL to Wk 12]	**Increased body muscle fat** Yoga: +0.6; Wait list: -0.0 Between group: +0.8 (p=0.01)
							Blood pressure (mmHg) [BL to Wk 12]	NS

Author (year) [Country, World region]	Design	Study Population	Intervention(s)	Concomitant Therapies	Control or Comparison	Participants (Intervention/ Control)	Measure of Outcome	Outcome
Cramer, et al. (2017) [Germany, EURO] [63]	Randomized controlled trial	Ulcerative colitis	Hatha yoga (90 min classes, weekly for 12 wks, with optional daily practice)	Nil	Written self-care advice (evidence-based informative books)	77 (39/38)	Inflammatory Bowel Disease Questionnaire [BL to Wk 12, 24]	**Increased quality of life** Wk 12: Yoga: +16.3; Self-care: +0.8 Between group: +14.7 (p=0.02) Wk 24: Yoga: +21.5; Self-care: +9.6 Between group: +16.4 (p=0.02)
							Disease activity – Rachmilewitz clinical activity index [BL to Wk 12, 24]	**Reduced disease activity** Wk 12 : NS Wk 24: Yoga: -1.8; Self-care: +0.8 Between group: -1.2 (p=0.03)
Das, et al. (2016) [India, SEARO] [20]	Controlled trial (matched)	Psychomotor performance and self-efficacy (healthy volunteers – school children)	Yoga: *asana* postures, *pranayama* breathing, meditation (*Dhyana*), relaxation techniques, cleansing (*Kriyas*), and reciting hymns from traditional yoga texts, music, yoga games, and happy assembly (10 hrs per day for 10 days)	Nil	Age-matched control without any experience of yoga	420 (210/210)	Psychomotor tests – Trail Making Task A (numeric drawing task) [BL to Dy 10]	**Reduced wrong attempts** Yoga: -0.56 (p<0.001); Control: -0.68 (p<0.001) **Increased right attempts** Yoga: +0.56 (p<0.001); Control: +0.67 (p<0.001) **Increased total attempts** Yoga: +0.12 (p=0.026); Control: NS **Reduced time (s)** Yoga: -9.44 (p<0.001); Control: NS
							Psychomotor tests – Trail Making Task B (alpha-numeric drawing task) [BL to Dy 10]	**Reduced wrong attempts** Yoga: -1.13 (p<0.001); Control: NS **Increased right attempts** Yoga: +1.12 (p<0.001); Control: NS **Increased total attempts** Yoga: +0.25 (p<0.001); Control: NS

Author (year) [Country, World region]	Design	Study Population	Intervention(s)	Concomitant Therapies	Control or Comparison	Participants (Intervention/ Control)	Measure of Outcome	Outcome
								Reduced time (s) Yoga: -23.05 (p<0.001); Control: -1.51 (p=0.002)
							Self-efficacy questionnaire for children (SEQ-C) – Total score [BL to Dy 10]	**Increased self-efficacy** Yoga: +14.7 (p<0.001); Control: +1.55 (p<0.001)
							SEQ-C – Academic domain [BL to Dy 10]	**Increased academic self-efficacy** Yoga: +4.2 (p<0.001); Control: NS
							SEQ-C – Social domain [BL to Dy 10]	**Increased social self-efficacy** Yoga: +4.86 (p<0.001); Control: +0.46 (p=0.004)
							SEQ-C – Emotional domain [BL to Dy 10]	**Increased emotional self-efficacy** Yoga: +5.72 (p<0.001); Control: +0.63 (p=0.001)
Gangadhar, et al. (2013) [India, SEARO] [21]	Controlled trial (comparative, open label)	Major depressive disorder (non-suicidal hospital out-patients)	Yoga therapy module developed for patients with depression: *asana* postures, stretching, *pranayama* breathing, chanting, yogic counselling (60 min, daily for 10 days, then weekly for 2 wks, booster class at Wk 12, and home practice)	Nil	Comparison: Yoga with anti-depressant medication OR Anti-depressant medication alone.	58 (15/27/16) (yoga alone, yoga with medication, medication alone)	Hamilton Depression Rating Scale [BL to Mth 1, Mth 3]	**Reduced depression** Mth 1: Yoga only, -12.5; Yoga + medication, -10.00; Medication only, -7.1 Between group: p=0.029 Mth 3: Yoga only, -14.9; Yoga + medication, -12.7; Medication only, -9.0 Between group: p=0.001
							Clinical Global Impression Scale (CGI) – Depression Severity [BL to Mth 1, Mth 3]	**Reduced depression severity** Mth 1: Yoga only, -2.2; Yoga + medication, -1.7; Medication only: -0.9 Between group: p=0.001 Mth 3: Yoga only, -2.9; Yoga + medication, -2.5; Medication only, -1.6 Between group: p=0.001

Author (year) [Country, World region]	Design	Study Population	Intervention(s)	Concomitant Therapies	Control or Comparison	Participants (Intervention/ Control)	Measure of Outcome	Outcome
							CGI – Depression Improvement (lower score represents greater improvement) [Mth 1 to Mth 3]	**Increased symptom improvement** Mth 3: Yoga only, -0.6; Yoga + medication, -0.7; Medication only: -0.6 Between group: p=0.001
							Responders/Remitters (no. of participants) [BL to Mth 1, Mth 3]	**Increased response to treatment** Mth 1: Yoga only, +11; Yoga + medication, +11; Medication only, +2 Between group: p=0.003 Mth 3: Yoga only, +14; Yoga + medication, +22; Medication only, +5 Between group: p=0.001
Naveen, et al. (2013) [India, SEARO] [22]	Secondary analysis					62 (19/22/21) (yoga alone, yoga with medication, medication alone)	Hamilton Depression Rating Scale [BL to Wk 12]	**Reduced depression** Yoga only: -14.0; Yoga and medication: -13.5; Medication only: -8.3 Between group: p=0.005
							Clinical Global Impression (of depression severity) [BL to Wk 12]	**Reduced depression** Yoga only: -2.8; Yoga and medication: -2.7; Medication only: -1.9 Between group: p=0.001
							Brain-derived neurotrophic factor – serum (ng/mL) [BL to Wk 12]	**Increased levels** Yoga only: +1.1; Yoga and medication: +1.9; Medication only: +2.1 Between group: p=0.02
Thirthalli, et al (2013) [India, SEARO] [23]	Secondary analysis				Plus control (healthy hospital staff volunteers)	54 (19/19/16) (Plus 18 healthy volunteers)	Serum cortisol [BL to Mth 3]	**Reduced cortisol** Yoga groups: p=0.006 Medication alone group: NS Control group: NS

Author (year) [Country, World region]	Design	Study Population	Intervention(s)	Concomitant Therapies	Control or Comparison	Participants (Intervention/ Control)	Measure of Outcome	Outcome
Naveen, et al. (2016) [India, SEARO] [24]	Secondary analysis				Comparison: Yoga with anti-depressant medication, Anti-depressant medication alone.	54 (19/19/16) (yoga alone, yoga with medication, medication alone)	Hamilton Depression Rating Scale [BL to Mth 3]	**Direct correlation between reduction in depression and reduction in cortisol** Treatment groups total: p=0.001 Yoga alone: p=0.008 Yoga and medication: NS Medication alone: NS Control group: NS
							Cortisol, serum (reduction vs. increase [BL to Wk 12]	**Reduced cortisol** Yoga only: 68.4%; Yoga and medication: 68.4%; Medication only: 31.3% Between group: p=0.042
							Brain-derived neurotrophic factor (BDNF), serum (ng/mL) [BL to Wk 12]	**Increased with cortisol reduction** Negative correlation between change in BDNF and change in cortisol. Yoga only: p=0.008; Yoga and medication: NS; Medication only: NS
Geethanjali, et al. (2016) [India, SEARO] [25]	Randomized controlled trial	Migraine without aura	Yogi *kriyas – jaleneti* nasal flush, *vamanakriya* water-induced self-emesis, *kaplabhathi* postures *cancer* and breathing (30 days – *jaleneti*: 5 days per wk, *vamanakriya:* 2 days per wk followed by *kaplabhathi*)	Nil	Waitlist control	60 (30/30)	Migraine Disability Assessment Score [BL to Dy 30]	**Reduced disability** Yoga: -13.0; Waitlist: -8.0 Between group: p<0.0001
							Pain Visual Analogue Score [BL to Dy 30]	**Reduced pain** Yoga: -3.15; Waitlist: -1.52 Between group: p=0.008
							Headache Impact Test [BL to Dy 30]	**Reduced headache impact** Yoga: -16.8; Waitlist: -12.06 Between group: p<0.0001
							Physical Health – WHO Quality of Life-BREF (WHO QoL-BREF) [BL to Dy 30]	**Increased physical health quality of life** Yoga: +35.9; Waitlist: +27.0 Between group: p<0.07

Author (year) [Country, World region]	Design	Study Population	Intervention(s)	Concomitant Therapies	Control or Comparison	Participants (Intervention/ Control)	Measure of Outcome	Outcome
							Psychological Health – WHO QoL-BREF [BL to Dy 30]	NS
							Social relationships – WHO QoL-BREF [BL to Dy 30]	**Increased social relationships quality of life** Yoga: +9.9; Waitlist: +6.6 Between group: p<0.0001
							Environment – WHO QoL-BREF [BL to Dy 30]	**Increased environment quality of life** Yoga: +4.8; Waitlist: +2.8 Between group: p<0.0001
Govindaraj, et al. (2018) [India, SEARO] [26]	Uncontrolled trial (pilot study)	Schizophrenia (stabilized patients on antipsychotic medications)	Yoga: *asana* postures, *pranayama* breathing, and AUM chanting (1 hr sessions, 20 sessions over 6 wks)	Nil	Nil	15 (15/0)	Scale for Assessment of Negative Symptoms (of schizophrenia) [BL to 1 Mth]	**Reduced symptoms** Mth 1: -30.36 (p<0.001)
							Scale for Assessment of Positive Symptoms (of schizophrenia) [BL to 1 Mth]	**Reduced symptoms** Mth 1: -21.34 (p<0.001)
							Socio-occupational dysfunction – Groningen Social Disability Scale [BL to 1 Mth]	**Reduced dysfunction** Mth 1: -25.01 (p<0.001)
							Social cognition – Social Cognition Rating Tool for Indian Setting [BL to 1 Mth]	**Increased social cognition** Mth 1: +18.97 (p<0.001)
Kisan, et al. (2014) [India, SEARO] [27]	Randomized controlled trial	Migraine (frequent, with or without aura)	Yoga: loosening and breathing exercises, *asanas* posture (1 hr sessions, 5 days per wk, for 6 wks)	Conventional care	Conventional care alone	60 (30/30)	Headache impact test (HIT-6) [BL to Wk 6]	**Reduced headache impact** Yoga: -27.7 (p<0.001); Usual care: -6.8 (p<0.001) Between group: p<0.001
							Headache frequency (per Mth) [BL to Wk 6]	**Reduced headache frequency** Yoga: -9.5 (p<0.001); Usual care: -5.3 (p<0.001) Between group: p<0.001

Author (year) [Country, World region]	Design	Study Population	Intervention(s)	Concomitant Therapies	Control or Comparison	Participants (Intervention/ Control)	Measure of Outcome	Outcome
							Headache intensity (Visual analogue scale) [BL to Wk 6]	**Reduced headache intensity** Yoga: -6.67 ($p<0.001$); Usual care: -1.57 ($p<0.001$) Between group: $p<0.001$
							Self-perceived benefit scale [BL to Wk 6]	**'Greatly improved my clinical condition'** Yoga: 96.7%; Usual care: 30.0% **'More helpful than harmful'** Yoga: 100.0%; Usual care: 73.3%
							Heart rate [BL to Wk 6]	NS
							Heart rate variability (HRV) [BL to Wk 6]	NS
Manjunath, et al. (2001) [India, SEARO] [28]	Randomized controlled trial	Executive functioning (healthy volunteers – adolescent girls)	Yoga: *asana* postures, *pranayama* breathing, internal cleansing *kriyas*, meditation, *bhajans* singing, relaxation techniques (75 min per day, for 1 mth)	Nil	Physical training: standing and sitting exercises, jogging and lifting dumbbells (1 hr 15 min per day, for 1 mth)	20 (10/10)	Tower of London (ToL) test of executive function – Time for planning (secs) [Dy 1 to Dy 30]	**Reduced time** 2 Moves test: Yoga, -13.0 ($p<0.02$); Physical training, NS 4 Moves test: Yoga, -28.00 ($p<0.01$); Physical training, NS 5 Moves test: NS
							ToL test – Time for execution (secs) [Dy 1 to Dy 30]	**Reduced time** 2 Moves test: NS 4 Moves test: Yoga, -42.4 ($p<0.02$); Physical training, NS 5 Moves test: Yoga, -56.7 ($p<0.001$); Physical training, NS
							ToL test – Number of moves (to complete task) [Dy 1 to Dy 30]	**Reduced moves** 2 Moves test: NS 4 Moves test: Yoga, -3.6 ($p<0.01$); Physical training, NS 5 Moves test: NS

Author (year) [Country, World region]	Design	Study Population	Intervention(s)	Concomitant Therapies	Control or Comparison	Participants (Intervention/ Control)	Measure of Outcome	Outcome
Manjunath, et al. (2004) [India, SEARO] [29]	Controlled trial (comparative)	Spatial and verbal memory (healthy volunteers – adolescent girls)	Yoga camp: *asana* postures, *pranayama* breathing, *kriyas* cleansing techniques, meditation, guided relaxation, games, story-telling (8 hrs per day for 10 days)	Nil	Fine arts camp: creative activities, games, presentations (8 hrs per day for 10 days). No intervention control: routine vacation activities.	90 (30/30/30)	Spatial memory tests (recall of visual materials through drawing) [BL to Dy 10]	**Increased spatial memory** Yoga: +1.7 (p=0.002) Fine arts: NS Control: NS
							Verbal memory tests (written recall of visual materials) [BL to Dy 10]	NS
Manjunath, et al. (2005) [India, SEARO] [30]	Randomized controlled trial	Sleep (aged care residents)	Yoga training: breathing exercises, loosening exercises, *asana* postures, guided relaxation, devotional songs, lectures on theory and philosophy of yoga, meditation (60 min, 6 days per wk)	Nil	Ayurveda: herbal tonic and milk (dosed morning and evening). Waitlist control.	69 (23, 23, 23)	Time taken to fall asleep (min) [BL to Mth 3, Mth 6]	**Reduced time** Mth 3: Yoga, -7.3 (p<0.05); Ayurveda, NS Control, NS Mth 6: Yoga, -10.47 (p<0.01); Ayurveda, NS Control: NS
							Duration of sleep (hrs per night) [BL to Mth 3, Mth 6]	**Increased sleep** Mth 3: NS Mth 6: Yoga, +1.1 (p<0.05); Ayurveda, NS Control: NS
							Feeling of being rested rating scale [BL to Mth 3, Mth 6]	**Increased** Mth 3: NS Mth 6: Yoga, +0.4 (p<0.05); Ayurveda, NS Control: NS
							Sleep in the afternoon (min) [BL to Mth 3, Mth 6]	NS
							Number of awakenings at night [BL to Mth 3, Mth 6]	NS

Author (year) [Country, World region]	Design	Study Population	Intervention(s)	Concomitant Therapies	Control or Comparison	Participants (Intervention/ Control)	Measure of Outcome	Outcome
McDermott, et al. (2014) [India, SEARO] [31]	Randomized controlled trial (pilot)	Type II diabetes mellitus risk (elevated blood glucose) (adults)	Yoga (*pranayama* breathing, loosening exercises, *asana* postures, guided relaxation, chanting) (75 mins, 3-6 classes per Wk, for 8 Wks)	Counseling session on healthy lifestyle changes covering diet, physical activity and smoking (8 Hrs)	Counseling session on healthy lifestyle changes and walking (30 mins, 3 – 6 days per Wk, for 8 Wks)	41 (21/20)	Fasting blood glucose (mmol/L) [BL to Wk 8]	NS
							Postprandial blood glucose (mmol/L) [BL to Wk 8]	NS
							Body mass index (BMI) (kg/m^2) [BL to Wk 8]	**Reduced BMI** Yoga: -0.2 (NS); Control: +0.6 (NS) Between group: p=0.05
							Weight (kg) [BL to Wk 8]	**Reduced body weight** Yoga: -0.8 (NS); Control: +1.4 (NS) Between group: p=0.02
							Waist circumference (cm) [BL to Wk 8]	**Reduced waist circumference** Yoga: -4.2 ($p<0.05$); Control: +0.7 (NS) Between group: $p<0.01$
							Blood pressure – systolic (mmHg) [BL to Wk 8]	NS
							Blood pressure – diastolic (mmHg) [BL to Wk 8]	NS
							Insulin (fasting) (pmol/L) [BL to Wk 8]	NS
							Insulin resistance [BL to Wk 8]	NS
							Low-density lipoprotein (mmol/L) [BL to Wk 8]	NS
							Total cholesterol (mmol/L) [BL to Wk 8]	NS
							Triglycerides (mmol/L) [BL to Wk 8]	NS
							Hospital Anxiety and Depression Scale (HADS) [BL to Wk 8]	NS

Author (year) [Country, World region]	Design	Study Population	Intervention(s)	Concomitant Therapies	Control or Comparison	Participants (Intervention/ Control)	Measure of Outcome	Outcome
							Positive affect – Positive and Negative Affect Schedule (PANAS) [BL to Wk 8]	NS
							Negative affect – PANAS [BL to Wk 8]	NS
							Stress – Perceived Stress Scale [BL to Wk 8]	NS
Mooventhan, et al. (2014) [India, SEARO] [72]	Randomized controlled trial	Pulmonary function (healthy volunteers – young adults)	Bhramari pranayama and OM chanting, under supervision (10 min, 6 mornings per wk, for 2 wks)	Nil	Control	79 (40/39)	Weight (kg) [BL to Wk 2]	**Reduced body weight** Yoga: -0.56 ($p<0.001$); Control: NS Between group: $p=0.038$
							Body mass index (BMI) (kg/m^2) [BL to Wk 2]	**Reduced BMI** Yoga: -0.53 ($p<0.001$); Control: NS Between group: NS
							Pulmonary function (PF) – Slow vital capacity (SVC) [BL to Wk 2]	**Increased pulmonary function** Yoga: +0.09 ($p=0.004$); Control: NS Between group: NS
							PF – Forced vital capacity (FVC) and [BL to Wk 2]	NS
							PF – FEV_1 (first sec forced expiratory volume) [BL to Wk 2]	**Increased FEV_1** Yoga: +0.1 ($p=0.006$); Control: NS Between group: NS
							PF – FEV_1/SVC (%) [BL to Wk 2]	NS
							PF – Peak expiratory flow (PEF) (L/sec) [BL to Wk 2]	**Increased PEF** Yoga: +0.29 ($p=0.011$); Control: NS Between group: $p=0.015$

Author (year) [Country, World region]	Design	Study Population	Intervention(s)	Concomitant Therapies	Control or Comparison	Participants (Intervention/ Control)	Measure of Outcome	Outcome
							PF – Forced expiratory flow (FEF) (25%, 50%, 75%) [BL to Wk 2]	**Increased (yoga), Reduced (control)** $FEF_{25\%}$: Yoga, +0.25 (p=0.028); Control, NS Between group: p=0.019 $FEF_{50\%}$: NS $FEF_{75\%}$: Yoga, NS; Control, -0.18 (p=0.038) Between group: NS
							Maximal voluntary ventilation (MVV) (L/min) [BL to Wk 2]	**Increased MVV** Yoga: 5.53 (p=0.008); Control: NS Between group: p=0.048
Nagasukeerthi, et al. (2017) [India, SEARO] [32]	Randomized controlled trial	Type II Diabetes Mellitus (Adults)	Integrated approach of yoga therapy (IAYT) residential program: *asana* postures, *pranayama* breathing, meditation, devotional songs, lectures on yoga, counselling, vegetarian diet (4 days, 05:30 to 21:00)	Bell pepper juice (*capsicum annuum var grossum* – 100mL morning and evening, for 4 days)	Comparison of IAYT with or without bell pepper juice	50 (25/25)	Fasting blood glucose [BL to Day 4]	NS
							Postprandial blood glucose (mg/dL) [BL to Day 4]	**Reduced postprandial blood glucose** IAYT+Juice: -68.3 (NS); IAYT only: -42.7 (NS) Between group: p<0.001
							Weight [BL to Day 4]	NS
							BMI [BL to Day 4]	NS
							Systolic blood pressure (mmHg) [BL to Day 4]	**Reduced systolic blood pressure** IAYT+Juice: -14.5 (p<0.05); IAYT only: -6.8 (p<0.05) Between group: p=0.002
							Diastolic blood pressure (mmHg) [BL to Day 4]	NS
							Pulse rate [BL to Day 4]	NS
							Mean arterial pressure [BL to Day 4]	NS
							Pulse pressure (mmHg) [BL to Day 4]	**Reduced pulse pressure** IAYT+Juice: -9.7 (p<0.05); IAYT only: +0.48 (NS) Between group: p=0.003

Author (year) [Country, World region]	Design	Study Population	Intervention(s)	Concomitant Therapies	Control or Comparison	Participants (Intervention/ Control)	Measure of Outcome	Outcome
							Rate pressure product [BL to Day 4]	**Reduced rate pressure product** IAYT+Juice: -19.7 ($p<0.05$); IAYT only: -8.7 ($p<0.05$) Between group: p=0.001
							Double product [BL to Day 4]	**Reduced double product** IAYT+Juice: -12.6 ($p<0.05$); IAYT only: -7.9 ($p<0.05$) Between group: p=0.03
Nalgirkar, et al. (2018) [India, SEARO] [33]	Randomized controlled trial (pilot study)	Dysfunctional uterine bleeding	Integrated approach of yoga therapy: loosening exercises, *asana* postures, *pranayama* breathing, meditation, deep relaxation technique (60 min, 3 days per wk, for 3 mths)	Nil	Waitlist control receiving standard gynecological care (3 Mths)	28 (14/14)	Hemoglobin (g/dl) [BL to Wk 12]	**Increased hemoglobin in control** Yoga: no change; Control: +0.43 ($p<0.01$)
							PBAC (Pictorial blood loss assessment) [BL to Wk 12]	NS
							Endometrial thickness (mm) [BL to Wk 12]	NS
							Perceived Stress Scale [BL to Wk 12]	**Reduced stress** Yoga: -4.69 ($p<0.05$); Control: NS
							Strait-Trait Anxiety Inventory [BL to Wk 12]	**Reduced anxiety** Yoga: -12.79 ($p<0.05$); Control: NS
							Pittsburg Sleep Quality Index (PSQI) – Global score [BL to Wk 12]	**Reduced difficulties with sleep** Yoga: -2.41 ($p<0.001$); Control: NS
							PSQI – Subjective Sleep Quality [BL to Wk 12]	NS
							PSQI – Sleep latency (time to fall asleep) [BL to Wk 12]	NS
							PSQI – Sleep duration [BL to Wk 12]	NS
							PSQI – Habitual sleep efficiency [BL to Wk 12]	NS

Author (year) [Country, World region]	Design	Study Population	Intervention(s)	Concomitant Therapies	Control or Comparison	Participants (Intervention/ Control)	Measure of Outcome	Outcome
							PSQI – Sleep disturbances [BL to Wk 12]	**Reduced disturbances** Yoga: -3.75 ($p<0.001$); Control: -1.92 ($p<0.05$)
							PSQI – Use of sleeping medication [BL to Wk 12]	**Reduced medication use** Yoga: 0.58 ($p<0.01$); Control: NS
							PSQI – Daytime dysfunction [BL to Wk 12]	NS
Nandini, et al. (2018) [India, SEARO] [34]	Randomized controlled trial	Neck pain (non-specific or common)	Yoga: stretching, *asana* postures, *pranayama* breathing, relaxation techniques, meditation, lecture on yoga philosophy (5 day program)	Hot sand fomentation (15 min per day), diet, sesame oil application	Yoga, diet, sesame oil application without hot sand fomentation	60 (30/30)	Pain, Visual Analog Scale [BL to Dy 5]	**Reduced pain** Hot Sand: -5.18; Control: -1.54 Between group: $p<0.001$
							Neck Disability Index [BL to Dy 5]	**Reduced neck disability** Hot Sand: -23.27; Control: -11.07 Between group: $p<0.001$
							Pittsburg Sleep Quality Index [BL to Dy 5]	NS
							Short Form-36 health survey, version 2 [BL to Dy 5]	**Increased quality of life** Social Functioning Hot Sand: +26.5; Control: +15.25 Between group: $p=0.035$ Pain Hot Sand: +28.25; Control: +10.09 Between group: $p<0.001$ Physical functioning: NS Physical health: NS Emotional problem: NS Energy: NS Emotional wellbeing: NS General Health: NS
Ostermann, et al. (2019) [Germany, EURO] [64]	Case report	Anorexia (38 years old, female)	Hatha yoga: *asana* postures, *pranayama* breathing, meditation (initially as part of inpatient care, then as home practice)	Intermittent rehabilitative inpatient care	Nil	1 (1/0)	Weight (kgs) [BL to post-intervention]	**Increased body weight** Post-intervention: +12.2
							Body mass index (BMI) (kg/m^2) [BL to post-intervention]	**Increased BMI** Post-intervention: +4.45

Author (year) [Country, World region]	Design	Study Population	Intervention(s)	Concomitant Therapies	Control or Comparison	Participants (Intervention/ Control)	Measure of Outcome	Outcome
							Qualitative interview findings [post-intervention]	Personal developments allowing reconnection with self and body (reduced dissociation), sense of inner peace and security. Improved progress with psychotherapy attributed by the patient to influence of yoga. Patient better able to respect and respond to physical needs such as hunger.
Patel, et al. (2018) [India, SEARO] [73]	Uncontrolled trial	Emotional regulation (healthy volunteers – young adult females)	Yoga-based meditation technique: Mastering Emotions Technique (45 mins, daily, for 2 wks)	Nil	Nil	72 (72/0)	Emotional Regulation Questionnaire – cognitive reappraisal and expressive suppression [BL to Wk 2]	**Increased cognitive reappraisal** Wk 2: +1.62 ($p<0.001$) **Reduced expressive suppression** Wk 2: -1.25 ($p<0.001$)
							The Positive and Negative Affect Schedule [BL to Wk 2]	**Increased positive affect** Wk 2: +1.23 ($p<0.001$) **Reduced negative affect** Wk 2: -1.25 ($p<0.001$)
							Self-Compassion Scale [BL to Wk 2]	**Increased self-compassion** Wk 2: +0.09 ($p<0.01$)
							Mindful Attention Awareness Scale [BL to Wk 2]	**Increased mindfulness** Wk 2: +0.53 ($p<0.001$)
Raghavendra, et al. (2007) [India, SEARO] [35]	Randomized controlled trial	Breast cancer (stage II and III operable) with chemotherapy-induced nausea and emesis	Yoga: *asana* postures, *pranayama* breathing, meditation and yogic relaxation techniques with imagery (60 min, 6 days per wk, during chemotherapy – taught by instructor, then practiced from home, plus a supervised session once in 10 days)	Conventional therapy, including 4-6 cycles of chemotherapy and standard anti-emetic medications.	Control (psychodynamic supportive – expressive therapy with coping preparation)	62 (28/34)	Nausea frequency and intensity – Morrow Assessment of Nausea and Emesis (MANE) [after 4th cycle of chemotherapy (CT)]	**Reduced nausea** Post-CT frequency: Between group: Yoga -0.9 ($p=0.01$) Post-CT intensity: Between group: Yoga -1.1 ($p<0.001$) Anticipatory frequency: Between group: Yoga -0.6 ($p=0.06$) Anticipatory intensity: Between group: Yoga -1.1 ($p=0.003$)

Author (year) [Country, World region]	Design	Study Population	Intervention(s)	Concomitant Therapies	Control or Comparison	Participants (Intervention/ Control)	Measure of Outcome	Outcome
							Emesis frequency and intensity – MANE [after 4th cycle of CT]	**Reduced emesis** Post-CT frequency: Between group: Yoga -0.6 (p=0.06) Post-CT intensity: Between group: Yoga -0.6 (p=0.05) Anticipatory frequency: NS Anticipatory intensity: Between group: Yoga -0.57 (p=0.04)
							State Trait Anxiety Inventory (STAI) [after 4th cycle of CT]	**Reduced anxiety** Between group: Yoga -8.3 (p<0.001)
							Beck Depression Inventory [after 4th cycle of CT]	NS
							Distressful treatment-related symptoms (number of) [after 4th cycle of CT]	**Reduced no. symptoms** Between group: Yoga -3.3 (p=0.002)
							Severity of treatment-related symptoms [after 4th cycle of CT]	**Reduced severity** Between group: Yoga -9.7 (p<0.001)
							Symptom distress experienced [after 4th cycle of CT]	**Reduced distress** Between group: Yoga -13.3 (p<0.001)
							Functional Living Index for Cancer – Overall quality of life [after 4th cycle of CT]	**Increased quality of life** Between group: Yoga +30.4 (p<0.001)
							Total chemotherapy toxicity score [after 4th cycle of CT]	**Reduced toxicity** Between group: Yoga -3.8 (p<0.001)

Author (year) [Country, World region]	Design	Study Population	Intervention(s)	Concomitant Therapies	Control or Comparison	Participants (Intervention/ Control)	Measure of Outcome	Outcome
Raghuraj and Telles (2008) [India, SEARO] [66]	Randomized controlled trial (crossover)	Healthy volunteers (adult males)	Specific nostril manipulating *yoga* breathing practices (right (RNYB), left (LNYB), and alternate (ANYB) nostril yoga breathing) (40 min per session)	Nil	Breath awareness (BAW) breathing, Normal breathing control (CTL)	21 (five conditions per participant)	Heart rate (bpm) [BL to 22.5 sec, 30 sec, 5 min post]	**Increased** 22.5 sec: NS 30 sec: RNYB/LNYB, NS; ANYB, +4.73 ($p<0.01$); BAW/CTL, NS 5 min post: RNYB/LNYB, NS; ANYB, +4.73 ($p<0.05$); BAW/CTL, NS
							Skin conductance level (μS) [BL to 22.5 sec, 30 sec, 5 min post]	**Increased** 22.5 sec: NS 30 sec: NS 5 min post: RNYB, +1.16 ($p<0.05$); LNYB, NS; ANYB, +1.26 ($p<0.05$); BAW/CTL, NS
							Finger plethysmogram amplitude (cm) [BL to 22.5 sec, 30 sec, 5 min post]	**Reduced** 22.5 sec: RNYB, -0.18 ($p<0.05$); LNYB/ ANYB, NS; BAW, NS; CTL, -0.16 ($p<0.05$) 30 sec: RNYB, -0.21 ($p<0.01$); LNYB, NS; ANYB, -0.15 ($p<0.05$); BAW, -0.2 ($p<0.05$); CTL, -0.24 ($p<0.01$) 5 min post: RNYB, -0.26 ($p<0.001$); LNYB/ ANYB: NS; BAW, -0.3 ($p<0.001$); CTL, -0.24 ($p<0.05$)
							Breath rate (cpm) [BL to 22.5 sec, 30 sec, 5 min post]	**Reduced** 22.5 sec: RNYB, -5.05 ($p<0.001$); LNYB, -5.31 ($p<0.01$); ANYB, -7.74 ($p<0.001$); BAW/CTL: NS 30 sec: RNYB, -5.21 ($p<0.001$); LNYB, -5.17 ($p<0.01$); ANYB, -7.7 ($p<0.05$); BAW/CTL: NS 5 min post: RNYB/ LNYB: NS; ANYB, -3.21 ($p<0.05$); BAW/ CTL: NS

Author (year) [Country, World region]	Design	Study Population	Intervention(s)	Concomitant Therapies	Control or Comparison	Participants (Intervention/ Control)	Measure of Outcome	Outcome
							Heart rate variability – Low frequency (LF) power (n.u.) [BL to 22.5 sec, 30 sec, 5 min post]	**Increased** 22.5 sec: NS 30 sec: RNYB/ LNYB: NS; ANYB, +7.16 ($p<0.05$); BAW/ CTL: NS 5 min post: NS
							Heart rate variability – High frequency (HF) power (n.u.) [BL to 22.5 sec, 30 sec, 5 min post]	**Reduced** 22.5 sec: NS 30 sec: RNYB/ LNYB, NS; ANYB, -7.92 ($p<0.05$); BAW, CTL, NS 5 min post: NS
							Heart rate variability – LF/HF ratio [BL to 22.5 sec, 30 sec, 5 min post]	**Increased** 22.5 sec: NS 30 sec: RNYB/LNYB, NS; ANYB, +0.43 ($p<0.05$); BAW/ CTL, NS 5 min post: NS
							Blood pressure (BP) – Systolic (mmHg) [BL to 5 min post]	**Increased** RNYB, +6.1 ($p<0.001$) **Reduced** LNYB, -4.19 ($p<0.01$); ANYB, -1.14 ($p<0.05$); BAW, CTL, NS
							BP – Diastolic (mmHg) [BL to 5 min post]	**Increased** RNYB: +3.33 ($p<0.001$) **Reduced:** ANYB, -0.67 ($p<0.05$); RBYN, NS; CTL, -0.67 ($p<0.05$); BAW, NS
							Blood pressure – Mean pressure (mmHg) [BL to 5 min post]	**Increased** RNYB: +4.12 ($p<0.01$) **Reduced** LNYB, -2.16 ($p<0.01$); ANYB, NS; CTL, -0.67 ($p<0.05$); BAW, NS

Author (year) [Country, World region]	Design	Study Population	Intervention(s)	Concomitant Therapies	Control or Comparison	Participants (Intervention/ Control)	Measure of Outcome	Outcome
Rao, et al. (2008) [India, SEARO] [36]	Randomized controlled trial	Breast cancer (stage II and III, states, quality of life and immune outcomes following surgery)	Integrated yoga program: *pranayama* breathing and yogic relaxation techniques (home practice, 30 min daily for 3 wks)	Surgery and related usual care	Control (supportive counselling sessions and postoperative exercise rehabilitation) (30 min, daily, at home, for 3 wks)	69 (33/36)	State Trait Anxiety Inventory [BL to Wk 3 post surgery]	**Reduced anxiety state** Yoga: -10.2 ($p<0.01$); Control: NS Between group: $p=0.04$ **Reduced anxiety trait** Yoga: -9.4 ($p<0.01$); Control: NS Between group: $p=0.002$
							Beck Depression Inventory [BL to Wk 3 post surgery]	**Reduced depression** Yoga: NS; Control: NS Between group: $p=0.008$
							Functional Living Index of Cancer [BL to Wk 3 post surgery]	**Increased quality of life** Yoga: NS; Control: NS Between group: $p=0.01$
							Distressful treatment-related symptoms (number of) [BL to Wk 4 post-surgery]	NS
							Severity of treatment-related symptoms [BL to Wk 4 post surgery]	**Reduced severity of symptoms** Yoga: NS; Control: NS Between group: $p<0.01$
							Symptom distress experienced [BL to Wk 4 post-surgery]	**Reduced symptom distress** Yoga: -2.9 ($p=0.05$); Control: NS Between group: $p<0.01$
							Immune assays – immunoglobulins (serum IgA, IgG, IgM in g/L) [BL to Wk 4 post surgery]	**Increased IgA in control** IgA: Yoga, NS; Control, +0.64 ($p=0.005$) Between group: $p=0.001$ IgM: NS IgG: NS

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Rao, et al. (2008) [India, SEARO] [37]							Immune assays – lymphocytes (CD4+, CD8+, CD56+ counts in %) [BL to Wk 4 post-surgery]	**Reduced lymphocytes in control** CD4+:Yoga, NS; Control, -3.5 (p=0.002) Between group: NS CD8+: Yoga, NS; Control, -3.7 (p=0.001) Between group: NS CD56+: Yoga, NS; Control, -4.3 (p=0.001) Between group: p=0.019
							Drain retention following surgery (days) [BL to wk 4]	**Reduced drain retention** Yoga -1.74 (p=0.001)
							Duration of hospital stay (days) [BL to wk 4]	**Reduced duration of hospital stay** Yoga: -1.3 (p=0.003)
							Postoperative duration (days) [BL to wk 4]	NS
							Interval for suture removal (days) [BL to wk 4]	**Reduced interval for suture removal** Yoga: -2.4 (p=0.031)
							Postoperative complications (% yes/no) [BL to wk 4]	NS
							Plasma cytokines (TNF-alpha) [BL to wk 4]	**Reduced plasma cytokines** Yoga: -6.8 (p<0.001)
Rao, et al. (2009) [India, SEARO] [38]	Randomized controlled trial	Anxiety related to breast cancer (Stage II and III) and associated treatment	Integrated yoga program: *pranayama* breathing, meditation and yogic relaxation techniques (60 min, 4 sessions pre- and post-operatively, 3 sessions per wk during 6-wk radiotherapy, during each chemotherapy session)	Usual care (surgery, radiotherapy, chemotherapy)	Control (supportive therapy as part of routine care)	38 (18/20)	State Trait Anxiety Inventory [Between group – BL to post-surgery; BL to during radiotherapy (RT), post-RT; BL to during chemotherapy (CT), post-CT]	**Reduced anxiety state** Post-surgery: p<0.05 During and post-RT: p<0.05 During and post-CT: p<0.001 Reduced anxiety trait Post-surgery: p<0.001 Post-RT: p<0.01 Post-CT: p<0.001

Author (year) [Country, World region]	Design	Study Population	Intervention(s)	Concomitant Therapies	Control or Comparison	Participants (Intervention/ Control)	Measure of Outcome	Outcome
							Symptom distress [Between group – BL to post-surgery, BL to during RT, post-RT, BL to during CT, post-CT]	**Reduced distress** Post-surgery: p<0.001 During and Post-RT: p<0.001 During CT: p<0.001 Post-CT: p<0.05
Rao, et al. (2015) [India, SEARO] [39]	Randomized controlled trial	Depression related to breast cancer (Stage II and III) and associated treatment	Integrated yoga program: *pranayama* breathing, meditation and yogic relaxation techniques (60 min, during hospital visits and stays, with at home practice at least three days per wk)	Usual care (surgery, radiotherapy, chemotherapy)	Control (supportive therapy as part of routine care) (60 min initial session, 15 min session during subsequent hospital visits, additional as required)	69 (33/36)	Beck Depression Inventory [Between group – BL to post-surgery; BL to during radiotherapy (RT), post-RT; BL to during chemotherapy (CT), post-CT]	**Reduced depression** Post-surgery: p<0.01 During and Post-RT: p<0.001 During CT: p<0.001 Post-CT: p<0.01 Positive correlation between depression scores with symptom severity and distress post-surgery, mid RT and mid CT (p<0.001)
Rao, et al. (2017) [India, SEARO] [40]	Secondary analysis	Mood states, quality of life and toxicity related to breast cancer (stage II and III) and associated treatment					State Trait Anxiety Inventory [Between group – BL to post-surgery; BL to during radiotherapy (RT), post-RT; BL to during chemotherapy (CT), post-CT]	**Reduced anxiety state** Post-surgery: p=0.04 Pre-RT: p=0.005 During RT: p=0.009 Post-RT: p<0.001 During CT: p<0.001 Post-CT: p<0.05
							Beck Depression Inventory [Between group – BL to post-surgery; BL to during radiotherapy (RT), post-RT; BL to during chemotherapy (CT), post-CT]	**Reduced depression** Post-surgery: p=0.01 Pre-RT: p=0.007 During RT: p=0.001 Post-RT: p<0.001 Pre-CT: p=0.02 During CT: p<0.001 Post CT p<0.002
							Subjective symptoms – no. of symptoms, severity, total distress [Between group – BL to post-surgery; BL to during radiotherapy (RT), post-RT; BL to	**Reduced no. symptoms** During RT: p=0.009 During and Post-CT: p=0.003 **Reduced severity** Post-surgery: p<0.001

Author (year) [Country, World region]	Design	Study Population	Intervention(s)	Concomitant Therapies	Control or Comparison	Participants (Intervention/ Control)	Measure of Outcome	Outcome
							during chemotherapy (CT), post-CT]	During RT: p<0.001 During CT: p<0.001 Post-CT: p=0.002 **Reduced distress** Post-surgery: p<0.001 During RT: p<0.001 During CT and Post-CT: p<0.001
							Functional Living Index of Cancer [BL to post-surgery; BL to during radiotherapy (RT), post-RT; BL to during chemotherapy (CT), post-CT]	**Increased quality of life** Between group: Post-surgery: p=0.01 During RT: p<0.001 During CT: p<0.001
							Chemotherapy-related toxicity – WHO toxicity criteria [during CT]	**Reduced overall toxicity** Between group: p=0.01
Rao, et al. (2017) [India, SEARO] [41]	Randomized controlled trial	Sleep quality related to breast cancer (stage IV)	Integrated yoga-based stress-reduction program: didactic lectures, *pranayama* breathing, meditation and yogic relaxation techniques (60 min, at least twice per wk, for 12 wks)	Informal individual counselling sessions	Control (education and supportive therapy sessions)	91 (45/46)	Pittsburgh Insomnia Rating Scale [Between group – BL to Wk 12]	**Reduced insomnia** Symptom distress: p<0.001 Insomnia parameters: p=0.02 Impact on quality of life: p=0.001 Total score: p=0.001
							Diurnal salivary cortisol [mean of 3 consecutive days at 0600h, 0900h, 2100h, overall mean [BL to Wk 12]	**Reduced at 0600h** Yoga: p=0.31 Control: NS
							Natural killer cells (NK) [BL to Wk 12]	**Increased NK cells** Between group: p=0.03
							Absolute lymphocyte count [BL to Wk 12]	NS

Author (year) [Country, World region]	Design	Study Population	Intervention(s)	Concomitant Therapies	Control or Comparison	Participants (Intervention/ Control)	Measure of Outcome	Outcome
Revadi, et al (2018) [India, SEARO] [42]	Case report	Hepatic cirrhosis & ascites	Integrated yoga: cyclic meditation, breathing exercises (2 hrs, daily for 2 wks)	Integrated with naturopathy (acupuncture, massage, hydrotherapy, mud therapy, diet therapy), Ayurveda tonic, conventional medications (4 wk protocol, beginning 2 wks before yoga)		1	Blood pressure (BP) (mmHg) [BL to Wk 4]	**Reduced BP** Systolic: -10; Diastolic: -12
							Weight (kg) [BL to Wk 4]	**Reduced body weight** Wk 4: -17
							Body mass index (kg/m^2) [BL to Wk 4]	**Reduced BMI** Wk 4: -6.3
							Abdominal girth (in) [BL to Wk 4]	**Reduced abdominal girth** Wk 4: -12
							Breath holding time (seconds) [BL to Wk 4]	**Increased breath holding time** Wk 4: +6
							Bilirubin, total (mg/dL) [BL to Wk 4]	**Reduced total bilirubin** Wk 4: -0.6
							Bilirubin, direct (mg/DL) [BL to Wk 4]	**Reduced direct bilirubin** Wk 4: -0.2
							Serum albumin (g/dL) [BL to Wk 4]	**Increased serum albumin** Wk 4: +1.3
							Aspartate aminotransferase (AST) (U/L) [BL to Wk 4]	**Reduced AST** Wk 4: -6
							Alanine transaminase (ALT) (U/L) [BL to Wk 4]	**Reduced ALT** Wk 4: -14
							Urea (mg/dL) [BL to Wk 4]	**Reduced urea** Wk 4: -8
							Creatinine (mg/dL) [BL to Wk 4]	**Reduced creatinine** Wk 4: -0.4
Saoji, et al. (2017) [India, SEARO] [75]	Randomized controlled trial (crossover)	Cognitive performance (healthy volunteers – adult medical students)	Yogic advanced deep relaxation meditation: Mind sound resonance technique (MSRT) (10 day orientation, 30 min test session)	Nil	Supine rest (SR) (30 min test session)	42	Six-Letter Cancellation Task (total attempted minus no. incorrect) [BL to post-test]	**Increased cognitive performance** MSRT: +2.32 ($p<0.001$) SR: +2.7 ($p<0.01$)
							Digit Letter Subsitution Task (total attempted minus no. incorrect) [BL to post-test]	**Increased cognitive performance** MSRT: +2.97 ($p<0.001$) SR: +1.65 ($p<0.01$)

Author (year) [Country, World region]	Design	Study Population	Intervention(s)	Concomitant Therapies	Control or Comparison	Participants (Intervention/ Control)	Measure of Outcome	Outcome
Saoji, et al. (2018) [India, SEARO] [67]	Randomized controlled trial	Pyschologcal functions (healthy volunteers – experienced yoga practitioners)	Yoga-based breathing intervention based on classic yogic text (8 Wks training in 20 min intervention)	Routine daily yoga practice (60 min)	Control: Routine daily yoga practice only (60 min)	116 (60/56)	State mindfulness attention awareness scale [BL to Wk 8]	**Increased mindfulness** Yogic breathing: +0.21 ($p<0.01$) Control: NS
							Mind Wandering Questionnaire [BL to Wk 8]	**Reduced mind wandering** Yogic breathing: -4.84 ($p<0.001$) Control: -1.03 ($p<0.05$)
							State Trait Anxiety Inventory [BL to Wk 8]	**Reduced anxiety** Yogic breathing: -0.5 ($p<0.001$) Control: -0.15 ($p<0.01$)
Saoji, et al. (2018) [India, SEARO] [68]	Randomized controlled trial (crossover)	Autonomic and cardiovascular variables (healthy volunteers-yoga students)	Yoga-based intermittent breath holding based on classic yogic text (8 Wks training, 6 days per week, in 20 min)	Nil	Control: breath awareness (20 min)	39	Heart rate (beats/min) [pre- and post-test]	**Reduced** Yogic breathing: -3.62 ($p<0.001$) Control: -2.73 ($p<0.01$)
							Heart rate variability (HRV) – Standard deviation of NN intervals [pre- and post-test]	**Increased** Yogic breathing: +10.29 ($p<0.01$) Control: NS
							HRV – Root mean of sum of squares (RMSSD) [pre- and post-test]	**Increased** Yogic breathing: +6.41 ($p<0.001$) Control: +5.58 ($p<0.05$)
							HRV – Proportion (pNN50) (%) [pre- and post-test]	**Increased** Yogic breathing: +3.73 ($p<0.01$) Control: +5.47 ($p<0.01$)
							HRV – Low frequency (LF) band (0.04-0.15 Hz) power [pre- and post-test]	**Increased** Yogic breathing: +5.79 ($p<0.05$) Control: NS
							HRV – High frequency (HF) band (0.15-0.5Hz) power [pre- and post-test]	**Reduced** Yogic breathing: -5.88 ($p<0.05$) Control: NS
							HRV – LF:HF ration [pre- and post-test]	NS

Author (year) [Country, World region]	Design	Study Population	Intervention(s)	Concomitant Therapies	Control or Comparison	Participants (Intervention/ Control)	Measure of Outcome	Outcome
							Respiratory rate (cycles/ min) [pre- and post-test]	NS
							Blood pressure – Systolic and diastolic (mmHg) [pre- and post-test]	**Increased in BP control** Systolic: Yogic breathing, NS; Control, +2.39 ($p<0.001$) Diastolic: NS
							Mean arterial pressure (mmHg) [pre- and post-test]	**Reduced mean arterial pressure** Yogic breathing: -1.53 ($p<0.05$) Control: NS
							Stroke volumn (ml) [pre- and post-test]	**Reduced in intervention** Yogic breathing: -2.15 ($p<0.05$) **Increased in control** Control increase: +1.86 ($p<0.001$)
							Cardiac output (l/min) [pre- and post- test]	**Reduced cardiac output** Yogic breathing: -0.39 ($p<0.001$) Control: -0.06 (<0.01)
							Total peripheral resistance [pre- and post-test]	**Increased total peripheral resistance** Yogic breathing: +0.05 ($p<0.001$) Control: NS
							Baroflex sensitivity (ms/mmHg) [pre- and post- test]	**Increased baroflex sensitivity** Yogic breathing: +1.25 ($p<0.01$) Control: NS
Saoji, et al. (2018) [India, SEARO] [69]	Randomized controlled trial (within-subject)	Cognitive response inhibition (healthy volunteers – young adult yoga students)	Yogic breathing with intermittent breath holding (YBH) (8 wk training)	Nil	Yogic breath awareness (YBA) (8 wk training) as comparison, Baseline as control	36	Stop-signal task – Reaction time [BL to post-test]	**Reduced reaction time** YBH: -13.65 ($p<0.05$) YBA: -18.83 ($p<0.05$)

Author (year) [Country, World region]	Design	Study Population	Intervention(s)	Concomitant Therapies	Control or Comparison	Participants (Intervention/ Control)	Measure of Outcome	Outcome
Sarang and Telles (2006) [India, SEARO] [74]	Randomized controlled trial (crossover)	Oxygen consumption (healthy volunteers – male yoga students)	Cyclic meditation (20 min with 5 min supine rest before and after)	Nil	Shavasana (SH) supine rest (30 min)	50	Oxygen consumption (ml/min) [BL to Min 5, Min 10, Min 15, Min 20, post-test]	**Increased during CM** Min 5, Min 10, Min 15: $p<0.001$ Min 20: NS **Reduced post-CM** Post test: $p<0.001$ **Reduced during and** post-SH Min 5, Min 10, Min 15, Min 20 and post-test: $p<0.001$
							Breath rate (cycles/min) [BL to Min 10, Min 15, Min 20, Min 30, post-test]	**Increased during CM** Min 10, Min 15: $p<0.001$ Min 5, Min 20: NS **Increased post-CM** Post-test: $p<0.001$ During and post-SH: NS
							Tidal volume (L) [BL to Min 10, Min 15, Min 20, Min 30, post-test]	**Increased during CM** Min 5, Min 15: $p<0.001$ Min 10: $p<0.05$ Min 20: NS **Reduced post-CM** Post-test: $p<0.001$ During and post-SH: NS
							Minute ventilation (L/min) [BL to Min 10, Min 15, Min 20, Min 30, post-test]	**Increased during CM** Min 5, Min 10, Min 15: $p<0.001$ Min 20: NS **Reduced post-CM** Post-test: $p<0.001$ During and post-SH: NS
Satish, et al. (2018) [India, SEARO] [43]	Randomized controlled trial	Cardio-respiratory fitness (healthy volunteers – adolescent school children)	Yoga training: *asana* postures, *pranayama* breathing, meditation and relaxation (60 min, 6 days per wk, for 2 mths)	Nil	Physical activity training (60 min, 6 days per wk, for 2 mths)	748 (377/371)	Aerobic power – Maximum multistage 20m shuttle run (beep test) [Level/speed, Rounds and Velocity, pre- and post-test]	**Increased level** Yoga: +0.52 ($p<0.001$); Physical activity: +0.39 ($p<0.001$) Between group: NS **Increased rounds** Yoga: Increased (NS); Physical activity: Reduced (NS) Between group: $p<0.05$ **Increased velocity** Yoga: +1.77 ($p<0.001$); Physical activity: +1.32 ($p<0.001$) Between group: NS

Author (year) [Country, World region]	Design	Study Population	Intervention(s)	Concomitant Therapies	Control or Comparison	Participants (Intervention/ Control)	Measure of Outcome	Outcome
Sharma, et al. (2018) [India, SEARO] [44]	Controlled trial (prospective)	Migraine headache (adults)	Yoga: *asana* postures, *pranayama* breathing, relaxation techniques, chanting (40 min, daily for 1 wk, then 5 days per wk home practice until day 90)	Ayurveda: herbal medicine, oil application, steam bath, dietary protocol (90 days)	Control: usual care	60 (30/30)	Comprehensive Headache-related Quality of Life Questionnaire [BL to Dy 90]	**Increased quality of life** Yoga: +32.09; Usual care: -1.61 Between group: p<0.001
							Visual Analog Scale, pain [BL to Dy 90]	**Reduced pain** Yoga: -5.1; Usual care: +0.24 Between group: p<0.05
Shetty, et al. (2018) [India, SEARO] [45]	Randomized controlled trial	Flexibility and psychomotor skills (healthy volunteers – yoga naïve young adults)	Yoga: *asana* postures, *pranayama* breathing, deep relaxation, meditation (60 min, 6 days per wk, for 3 mths)	Nil	Control	100 (50/50)	Flexibility – Sit and Reach (SAR) test [BL to post-test]	**Increased flexibility** Yoga: +5.44 (p<0.05); Control: NS Between group: p<0.05
							Psychomotor performance – Digit Letter Substitution Test (DLST) [BL to post-test]	**Increased psychomotor performance** Yoga: +3.4 (p<0.05); Control: NS Between group: p<0.05
Telles, et al. (2004) [India, SEARO] [46]	Controlled trial	Voluntary heart rate reduction (healthy volunteers-yoga novices)	Yoga: *asana* postures, *pranayama* breathing, *kriya* cleansing practices, meditation, devotional sessions, guided relaxation, lectures (6.5 hrs per day for 30 days)	Nil	Control	24 (12/12)	Heart rate (HR) (lowest achieved in 6 min attempt to voluntarily reduce) [pre- to post- test]	**Reduced lowest HR achieved** Yoga: -9 (p<0.05); Control: NS **Reduced baseline HR** Yoga: -10.6 (p<0.05)
Telles, at el. (2006) [India, SEARO] [47]	Randomized controlled trial	Visual discomfort (healthy volunteers – professional computer users)	Yoga: *asana* postures, *pranayama* breathing, joint exercises, visual cleansing eye exercises, relaxation (60 min, 5 days per wk, for 60 days)	Nil	Waitlist control (usual routine)	117 (62/55)	Visual discomfort questionnaire (self-rated, mean of 12 items) [BL to Dy 60]	**Reduced visual discomfort** Yoga: -0.33 (p<0.001); Control: +0.45 (p<0.001) Between group: p<0.001
Telles, at al. (2007) [India, SEARO] [70]	Controlled trial (crossover)	Cognitive performance (healthy volunteers – adult males)	Specific nostril manipulating *yoga* breathing practices (right, left, and alternate nostril yoga breathing, and breath awareness) (30 min per session)	Nil	Nil	20	Performance in Letter Cancellation task (letters left out, letters wrongly cancelled, total errors) [BL to post-test]	**Reduced letters left out** Right nostril: -1.8 (p<0.02) Left nostril: NS Alternate nostril: -1.55 (p<0.02) Breath awareness: NS Letters wrongly cancelled: NS

Author (year) [Country, World region]	Design	Study Population	Intervention(s)	Concomitant Therapies	Control or Comparison	Participants (Intervention/ Control)	Measure of Outcome	Outcome
								Reduced total errors: Right nostril: NS Left nostril: NS Alternate nostril: -1.65 ($p<0.01$) Breath awareness: NS
Telles, et al (2013) [India, SEARO] [65]	Randomized crossover trial	Autonomic and respiratory function (healthy volunteers – adult males)	Meditative states from traditional yoga texts: *Dharana* meditative focusing and *Dhyana* effortless meditation (20 min sessions, 3 mth orientation program)	Nil	Non-meditation controls: *Cancalata* random thinking and *Ekagrata* non-meditative focus (20 min sessions)	30	Breath rate (cycles per min) [BL, during, post-test]	**Reduced in meditation** Dharana during: NS; Dharana post-test: $p<0.05$; Dhyana during: $p<0.001$; Dhyana post-test: $p<0.001$ Increased in control Cancalata control during: $p<0.05$; Cancalata control post-test: NS; Ekagrata control: NS Between group: $p=0.01$
							Heart rate (beats per min) [BL, during, post-test]	**Reduced heart rate** Dharana: NS; Dhyana during: $p<0.001$; Dhyana post-test: $p<0.05$; Control groups: NS Between group: $p=0.001$
							Photo-plethysmogram amplitude (μ/V) [BL, during, post-test]	**Increased levels** Dharana: NS; Dhyana during: $p<0.05$; Dhyana post-test: NS; Control groups: NS Between group: $p=0.05$
							Skin resistance [BL, during, post-test]	**Increased skin resistance** Dharana during: $p<0.05$; Dharana post-test: NS Dhyana during: $p<0.001$ Dhyana post-test: $p<0.001$ Cancalata control during: $p<0.05$ Cancalata post-test: NS

Author (year) [Country, World region]	Design	Study Population	Intervention(s)	Concomitant Therapies	Control or Comparison	Participants (Intervention/ Control)	Measure of Outcome	Outcome
								Ekagrata control during: $p<0.05$ Ekagrata control post-test: $p<0.01$ Between group: $p=0.001$
							Low frequency [BL, during, post-test] (LF) power (Hz) [BL, during, post-test]	**Reduced in meditation** Dharana: NS Dhyana during: $p<0.001$ Dhyana post-test: $p<0.05$ Increased in control Cancalata control during: $p<0.001$ Cancalata control post-test: $p<0.05$ Ekagrata control during: $p<0.05$ Ekagrata control post-test: $p<0.05$ Between group: $p=0.05$
							High frequency (HF) power (Hz) [BL, during, post-test]	**Increased in meditation** Dharana: NS Dhyana during: $p<0.001$ Dhyana post-test: $p<0.05$ **Reduced in control** Cancalata: NS Ekagrata during and post-test: $p<0.05$ Between group: NS
							LF/HF ratio [BL, during, post-test]	**Increased in control** Dharana: NS Dhyana: NS Cancalata control: NS Ekagrata control during and post-test: $p<0.05$ Between group: NS

Author (year) [Country, World region]	Design	Study Population	Intervention(s)	Concomitant Therapies	Control or Comparison	Participants (Intervention/ Control)	Measure of Outcome	Outcome
							Heart rate variability (RR) (mean, ms) [BL, during, post-test]	**Increased heart rate variability** Dharana: NS Dhyana during: $p<0.05$ Dhyana post-test: NS Cancalata control: NS Ekagrata control during: $p<0.01$ Ekagrata control post-test: NS Between group: $p=0.05$
							HRV – Root mean of sum of squares (RMSSD) (ms) [BL, during, post-test]	Within group: NS Between group: $p=0.05$
							HRV – NN50 count [BL, during, post-test]	**Increased levels** Dharana: NS; Dhyana during: $p<0.001$; Dhyana post-test: NS; Controls: NS Between group: $p=0.01$
							HRV – Proportion (pNN50) (%) [BL, during, post-test]	**Increased levels** Dharana: NS; Dhyana during: $p<0.001$; Dhyana post-test: NS; Controls: NS Between group: $p=0.01$
Vadiraja, et al. (2009) [India, SEARO] [48]	Randomized controlled trial	Breast cancer symptom management (Stage II & III, receiving radiotherapy)	Integrated yoga program: *asana* postures, *pranayama* breathing, meditation, yogic relaxation (60 min, at least 3 time per wk, with home practice encouraged, for 6 wks)	Nil	Control: brief supportive therapy with education (15 min, 3-4 sessions over 6 wks)	88 (44/44)	Rotterdam Symptom Check list – psychological, physical, activity level [pre- and post-radiotherapy]	**Reduced psychological distress** Yoga: -2.5 ($p<0.001$); Control: NS Between group: $p<0.001$ **Reduced physical distress** Yoga: -3.23 ($p<0.01$); Control: NS Between group: NS Activity level: NS

Author (year) [Country, World region]	Design	Study Population	Intervention(s)	Concomitant Therapies	Control or Comparison	Participants (Intervention/ Control)	Measure of Outcome	Outcome
Vadiraja, et al. (2009) [India, SEARO] [49]		Cortisol rhythm and mood states in breast cancer (Stage II-III) (adjuvant radiotherapy)					European Organization for the Research and Treatment of Cancer – Quality of Life (EORTC QoL C30 questionnaire V1) [pre- and post-radiotherapy]	**Reduced fatigue** Yoga: -12.22 ($p<0.001$); Control: NS Between group: $p=0.001$ **Reduced pain** Yoga: -9.63 ($p<0.01$); Control: NS Between group: $p<0.01$ **Reduced insomnia:** Yoga: -23.71 ($p<0.001$); Control: NS Between group: $p=0.04$ **Reduced appetite loss** Yoga: NS; Control: +9.89 ($p=0.005$) Between group: $p=0.002$ Dyspnoea: NS Nausea and vomiting: NS Diarrhea: NS Constipation: NS
							Hospital Anxiety and Depression Scale [BL to wk 6]	**Reduced anxiety** Yoga: -3.17 ($p<0.001$); Control: -1.23 ($p<0.05$) Between group -3.34 ($p<0.001$) **Reduced depression** Yoga: -3.43 ($p<0.01$); Control: -1.47 ($p<0.01$) Between group: -2.39 ($p<0.01$)
							Perceived Stress Scale [BL to wk 6]	**Reduced stress** Yoga: -5.61 ($p<0.001$); Control: NS Between groups -4.96 ($p<0.001$)
							Diurnal salivary cortisol [collected 6am, 9am, 9pm for 3 consecutive days, BL to Wk 6]	**Reduced in yoga group** Between group: 6am, $p=0.009$; 9am, NS; 9pm, NS Pooled mean: $p=0.03$

Author (year) [Country, World region]	Design	Study Population	Intervention(s)	Concomitant Therapies	Control or Comparison	Participants (Intervention/ Control)	Measure of Outcome	Outcome
Vadiraja, et al. (2009) [India, SEARO] [50]		Breast cancer (Stage II and III, undergoing adjuvant radiotherapy) associated quality of life				88 (44/44) [final number of patients contributing 75 (42/33)]	Positive and Negative Affect Schedule (PANAS) [BL to Wk 6]	**Increased positive affect** Yoga: +3.8 (p<0.001); Control: NS Between group: p=0.007 **Reduced negative affect** Yoga: -9.24 (p<0.001); Control: -3.37 (p=0.02) Between group: p<0.001
							European Organization for the Research and Treatment of Cancer – Quality of Life [BL to Wk 6]	**Increased physical function** Yoga: NS; Control: +6.24 (p=0.03) Between group: NS **Increased emotional function** Yoga: +18.67 (p<0.001); Control: +7.65 (p=0.009) Between group: p=0.001 **Increased cognitive function** Yoga: +5.28 (p=0.05); Control: NS Between group: p=0.03 Role function: NS Social function: NS
Vadiraja, et al. (2017) [India, SEARO] [51]	Randomized controlled trial	Fatigue in breast cancer	Integrated yoga program: *asana* postures, *pranayama* breathing, meditation, yogic relaxation, chanting, self-appraisal and counselling (at least 2 individual sessions per week over 3 mths)	Nil	Control: supportive counselling sessions	65 (42/33)	Perceived Stress Scale [BL to Wk 12]	**Reduced stress** Yoga: -32.6% (p=0.01); Control: NS Between group: p<0.001
							Fatigue Symptom Inventory – severity, frequency, interference, diurnal variation [BL to Wk 12]	**Reduced severity** Yoga: -61.15% (p<0.001); Control: NS Between group: p<0.001 **Reduced frequency** Yoga: -52.64% (p<0.001); Control: NS Between group: p<0.001 **Reduced interference** Yoga: -72.6% (p<0.001); Control: NS Between group: p<0.001

Author (year) [Country, World region]	Design	Study Population	Intervention(s)	Concomitant Therapies	Control or Comparison	Participants (Intervention/ Control)	Measure of Outcome	Outcome
								Reduced diurnal variation Yoga: -52.33% ($p<0.001$); Control: NS Between group: $p<0.001$
Venugopal, et al. (2017) [India, SEARO] [53]	Uncontrolled trial	Type II diabetes mellitus (Adults)	Yoga-based Lifestyle intervention (Stop Diabetes Movement): loosening exercises, *asana* postures, *pranayama* breathing, theorectical lecture (90 min daily, for 10 days)	Nil	Nil	1292 (primary outcome data on 896)	Fasting blood glucose [BL to Dy 10]	**Reduced fasting blood glucose** Dy 10: -11.2 ($p<0.001$)
Vijayakumar, et al (2018) [India, SEARO] [52]	Uncontrolled trial	Type II diabetes mellitus (Adults)	Yoga evening vs. morning: loosening exercises, *asana* postures, *pranayama* breathing, theoretical lecture (90 min daily, for 10 days)	Nil	Healthy control	310 (189/121)	Fasting blood glucose [BL to Dy 10]	**Reduced in evening practice** T2DM between group (morning vs. evening): -20.4 ($p<0.001$) Control, female evening practice -23.06 ($p=0.001$) Control, male evening practice: NS
Vinchurkar and Arankelle (2015) [India, SEARO] [54]	Case report	Urinary incontinence	Yoga: *asana* postures, *pranayama* breathing, neuromuscular locks and *mudras*, meditation (twice daily, 3 hrs total, for 21 days)	Vegetarian diet, fluid management, counselling, walking exercise.	Nil	1	Resting heart rate (beats/min) [BL to Dy 21]	**Reduced resting heart rate** Dy 21: -2
							Blood pressure (BP) (mmHg) [BL to Dy 21]	**Reduced systolic BP** Systolic: -6; Diastolic: -0.0
							Weight (kg) [BL to Dy 21]	**Reduced body weight** Dy 21: -1.9
							Body mass index (BMI) (kg/m^2)	**Reduced BMI** Dy 21: -0.7
							Frequency volume chart score	**Reduced frequency volume** Dy 21: -2
							International Consultation on Incontinence Modular Questionnaire – Urinary Incontinence Short Form	**Reduced incontinence** Dy 21: -7

Author (year) [Country, World region]	Design	Study Population	Intervention(s)	Concomitant Therapies	Control or Comparison	Participants (Intervention/ Control)	Measure of Outcome	Outcome
Vinutha, et al. (2015) [India, SEARO] [55]	Uncontrolled trial	Type 2 diabetes mellitus (Adults)	Integrated Approach of Yoga Therapy: *asana* postures, *pranayama* breathing, cleansing techniques *(kriyas)*, meditation, devotional songs and lectures on yoga (1 wk residential program, 5.30am-9pm)	Nil	Nil	15	Fasting plasma glucose (mg/dL) [BL to Wk 1]	**Reduced fasting plasma glucose** -24.4 ($p<0.05$)
							Heart rate variability [BL to Wk 1]	NS
							Heart rate response to deep breathing [BL to Wk 1]	NS
							Blood pressure response to sustained handgrip (mmHg) [BL to Wk 1]	**Increased BP response to handgrip** +3.2 ($p<0.01$)
							Post prandial plasma glcuose [BL to day 7]	NS
Visweswaraiah and Telles (2004) [India, SEARO] [71]	Randomized controlled trial	Pulmonary tuberculosis	Yoga: simple breathing, *pranayama* breathing, supine relaxation (60 min, 6 days per wk, for 60 days)	Anti-tuberculosis treatment (usual care)	Breath awareness	73 (36/37)	Symptom scores [BL to day 60]	**Reduced symptoms** Dy 60: Yoga -10.4 ($p<0.001$); Breath -2.02 ($p<0.05$)
							Body weight (kg) [BL to day 60]	**Increased body weight** Dy 60: Yoga + 4.5 ($p<0.001$); Breath +0.8 ($p=<0.01$)
							FVC (litres) [BL to day 60]	**Increased FVC** Dy 60: Yoga +0.6 ($p<0.001$); Breath NS
							FEV (litres) [BL to day 60]	**Increased FEV** Dy 60: Yoga +0.5 ($p<0.001$); Breath +0.2 ($p<0.05$)
							FEV/FVC (%) [BL to day 60]	NS
							Improved sputum microscopy [BL to Dy 30, Dy 45, Dy 60]	**Reduced microscopy** Dy 30: Yoga, 19/25; Breath, 10/23 Between group, p=0.045 Dy 45: Yoga, 24/25; Breath, 12/23 Between group, p=0.002 Dy 60: Yoga, 10/13; Breath, 4/19 Between group, p=0.005
							Improved posteroanterior chest x-ray [BL to Dy 60]	**Increased chest x-ray** Yoga: 19/25; Breath: 3/22 Between group: p=0.001

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39 Optimizing Pharmaceutical-based Interventions

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HIGHLIGHTS

- Most patients that seek naturopathic care are taking one or more prescription medication.
- Comparing naturopathic interventions and conventional treatments warrants further investigation.
- The side-effects of pharmaceutical medications may be minimized with the inclusion of adjunctive therapies.
- Naturopaths/NDs have unparalleled expertise in drug-herb and drug-nutraceutical interactions.
- Clinical research by the naturopathic community has examined the applications of pharmaceuticals and adjunctive treatments for disease or symptom management and for pharmaceutical side-effect management, as well as comparing pharmaceuticals with non-pharmacological treatments.
- In line with the role of primary care, naturopathic researchers have examined the clinical effects of pharmaceutical drug treatments in the context of naturopathic practice in individuals with depression and cancer.

Pharmaceutical drugs play an integral role in the prevention and treatment of disease and are relied on by health care practitioners throughout the world in the care of their patients. Pharmaceuticals are chemically defined molecules with defined pharmacological mechanisms of action and therapeutic targets [1]. They are scheduled substances and are generally prescribed by medical doctors and/or dispensed by licensed pharmacists.

In some countries within jurisdictions, particularly the USA and Canada, naturopathic doctors are licensed to prescribe a limited schedule of pharmaceutical drugs as part of their naturopathic scope of practice (e.g. bioidentical hormones, high-dose nutrients, nutrients for Intravenous Therapies, etc.) [2]. The prevalent use of both non-prescription and prescription pharmaceutical drugs by people in the general population means most people seeking the care of naturopaths/naturopathic doctors will have used or be using at least one pharmaceutical medication [3-5]. Although naturopathic treatment primarily focuses on non-pharmacological therapies, the naturopathic therapeutic order identifies that in some circumstances therapies such as pharmaceutical medications are required [6].

Within the global context, the naturopathic workforce with prescribing rights as part of their scope of naturopathic practice are a minority [2, 7]. However, it is common for naturopaths and naturopathic doctors to provide care to patients who: want an alternative to pharmaceutical drugs; would like to limit the number of pharmaceutical drugs they are taking; are seeking to manage unwanted medication side effects; are looking for advice about supportive treatments that improve medication treatment outcomes and/or; would like to reduce potential drug-herb/nutrient interactions [3]. This is especially relevant for people with chronic complex conditions of whom many seek the care of naturopaths/naturopathic doctors [3]. The focus of this chapter is to synthesize the available literature reporting clinical studies conducted by naturopathic researchers that have involved naturopathic interventions as adjunctive treatments to improve pharmaceutical drug effects, studies focused on reducing pharmaceutical drug side effects, and those that are a direct comparison to pharmaceutical drug effects.

Overview of Studies

A total of eight papers reporting original clinical research conducted by naturopathic researchers examined the effects of pharmaceutical interventions. This research includes a total of 725 participants and was conducted in Australia (n=5), India (n=2) and Canada (n=1). The study designs included randomized controlled trials (n=6), prospective cohort study (n=1), and a non-randomized controlled trial [8]. Seven studies examined outcomes from adjunctive use of pharmaceuticals and other interventions, either to improve treatment outcomes (n=4) or to

reduce pharmaceutical treatment side effects (n=3). One study compared the clinical effects of pharmaceutical drug treatment and naturopathic interventions (n=1). The studies involved patients with depression (n=6) and cancer (n=2). All studies were conducted in hospital settings, with four occurring in hospital outpatient health care clinics and another four as inpatient hospital interventions. Details of the studies are available in *Table 39.1: Clinical research investigating pharmaceutical interventions conducted by naturopathic researchers.*

Implications

To date, the research indicates that naturopaths/naturopathic doctors are involved in developing and evaluating interventions to support safer and more effective pharmaceutical medication interventions with a view to improving patient outcomes. The key focus of most of these studies were to address pharmaceutical medication side effects and improve treatment responses. All studies involved concurrent use of pharmaceutical treatments with either nutraceuticals, yoga, or acupuncture. Such an approach supports the evolving and emerging role of naturopaths/naturopathic doctors in integrated and multidisciplinary models of patient's health care and their interest in rigorously evaluating interventions that may already be incorporated in clinical practice. Importantly, studies of integrated pharmaceutical management to improve outcomes involved naturopaths/naturopathic doctors even in jurisdictions where naturopaths/naturopathic doctors did not have prescribing rights, indicating the potential value in incorporating and integrating naturopathic perspectives in all aspects of conventional treatment as part of a multi-disciplinary team. This may be particularly relevant considering naturopaths/naturopathic doctors put a greater focus on the impact of concurrent complementary and pharmaceutical management than other health professionals [9]. For naturopathic doctors with a license to prescribe pharmaceutical medications, such research may be of even more practical relevance.

One of the potential primary benefits of naturopathic prescribing is that naturopathic doctors may be particularly well-equipped to help patients reduce doses or stop medications that are not useful, no longer needed, may be causing harm, or to facilitate changing to safer therapeutic agents or non-pharmacological approaches to care. This practice – deprescribing – is an increasingly important clinical innovation being promoted to ensure medication efficacy, reduce harms and costs and to mitigate polypharmacy [10]. Further research on how naturopaths/naturopathic doctors may be able to facilitate this globally important agenda are warranted.

The patient populations to whom these interventions were applied also indicates naturopathic researchers are contributing to the body of knowledge for conditions associated with significant health burdens to both individuals and health systems i.e., cancer and mental health. While further research is needed to confirm the findings of uncontrolled studies involving yoga and acupuncture, there is sufficient evidence that these intervention approaches taken by naturopathic practitioners in every day clinical practice provides demonstrable improvements in patient health and wellbeing. Equally, for those studies involving nutraceuticals that did not find significant improvements in the primary outcomes, the results of several secondary outcomes measured warrant further research. However, this is an emerging research area for naturopathic researchers and, in addition to the examination of adjunctive treatments to reduce pharmaceutical side-effects and improve clinical symptoms, there is also a need for research that offers a better understanding about interactions between naturopathic interventions and pharmaceutical treatments. While naturopathic researchers have engaged with the contributions of the wider health research community by conducting reviews of existing evidence regarding drug-herb and drug-nutrient interactions [11-25], it is only once naturopaths'/naturopathic doctors' specialized knowledge of their treatments are used to inform the design and conduct of such research, and that this research is translated to practice, that real gains will be made.

Studies investigating specific interventions:

Pharmaceuticals and adjunctive treatments for disease or symptom management

Five of the included studies investigated the effects of pharmaceutical medication when administered in conjunction with at least one other naturopathic intervention to improve symptoms or reduce disease progression [8, 26-29]. These studies were conducted in Australia (n=3) [26, 28, 29], India (n=1) [8], and Canada (n=1) [27]. All of these studies investigated the effects of antidepressant medication – such as selective-serotonin reuptake inhibitors (SSRIs) [26, 27, 29], selective-noradrenalin reuptake inhibitors (SNRIs) [27, 29], tetracyclics [29] or 5HT2c antagonists [29] (– although in some studies the specific class of antidepressant medication was unspecified [8, 28]. The adjunctive naturopathic interventions included in these studies were clinical nutrition (n=3) [26, 28, 29], yoga (n=1) [8], and acupuncture (n=1) [27].

A randomized controlled trial from Australia investigated the clinical effects of antidepressant medication (inclusive of SSRIs, SNRIs, tetracyclics, or 5-HT2c

antagonists) on individuals with major depressive disorder (n=158) [29]. The study compared the outcomes associated with using a multinutrient formula or a placebo in conjunction with the antidepressant medication and involved participants taking two tablets per day which contained S-Adenosyl methionine (SAMe) (800 mg/day), folinic acid (500mcg/day); and Vitamin B12 (200mcg/day). In addition to their anti-depressant medication, participants were also asked to take an additional two capsules per day of a placebo, or a multinutrient formula containing omega-3 fatty acid concentrate (EPA-esters 1000 mg/day, DHA-esters 656 mg/day) 5-HTP (200 mg/day) zinc picolinate (30 mg elemental/day); vitamin B6 (100 mg/day), vitamin C (60 mg/day), and magnesium (amino acid chelate, elemental 40 mg/day) for 8 weeks. The results suggested the placebo was superior to the adjunctive treatment as measured by the primary treatment outcome, results of the validated clinical assessment tool Montgomery and Asberg Depression Rating Scale (MADRS).

In a randomized controlled trial (n=46) conducted in Australia an adjunctive treatment with a single ingredient nutraceutical containing L-theanine (450 – 900 mg) was administered to partial or non-responders who were stable users of anti-depressants for the management of generalized anxiety disorder (GAD) [28]. The intervention lasted for 8 weeks plus a one-week pre-study and two-week post-study single-blinded observational period. While the L-theanine did not outperform placebo for anxiety reduction on the Hamilton Anxiety Rating Scale (HAM-A) ($p = 0.73$) nor insomnia severity using the insomnia severity index (ISI) ($p = 0.35$), L-theanine treatment resulted in greater self-reported sleep satisfaction (ISI item 4; $p = 0.015$).

Pharmaceuticals and adjunctive treatments for pharmaceutical side-effect management

Two studies, one conducted in India [30] and one in Australia [31], evaluated the use of pharmaceuticals in combination with adjunctive treatments to reduce pharmaceutical side-effects. Both studies examined chemotherapeutic pharmaceuticals [30, 31] and one of these also included radiotherapy [30]. One investigated clinical nutrition as the adjunctive intervention [31], while the other investigated yoga [30].

The study conducted in India was a randomized controlled trial evaluating the effect of yoga therapy when combined with radiotherapy (RT) or chemotherapy (CT) to reduce mental health symptoms and symptoms of toxicity among individuals with Stage II and Stage III breast cancer (n=98) [30]. The yoga group received daily 60-minute yoga sessions for 24 weeks while the control group received supportive counselling during their hospital visits. The yoga group reported reduced anxiety and depression for participants receiving RT (anxiety: -4.72, $p<0.05$; depression: -5.74, $p<0.05$) or CT (anxiety: -7.7, $p<0.05$; depression: -7.25, $p<0.05$) compared to control. They also reported a reduced incidence (RT: -2.34, $p<0.05$; CT: -2.97, $p<0.05$) and severity (RT: -6.43, $p<0.05$; CT: -8.83; $p<0.05$) of symptoms. Participants receiving CT were also reported a more significant reduction in toxicity ($p=0.01$) compared to control, but this was not the case for participants receiving RT. Both cancer treatment groups reported an increased quality of life (RT: +23.9, $p<0.05$; CT+31.2, $p<0.05$) compared to control.

Pharmaceuticals compared to non-Pharmacological treatments

One randomized controlled trial conducted in Australia compared a pharmaceutical intervention to another naturopathic treatment [32]. This study investigated 10-20mg of escilatopram for 12 weeks with a titrated dose of SAMe or placebo to reduce the symptoms of individual with major depressive disorder (n=144). The titration of SAMe was undertaken in two stages: participants were administered 1600mg per day for the first six weeks and, if they were not responsive, received an increased dose of 3200mg per day for the remaining six weeks of the study. A greater proportion of the participants allocated to the group receiving SAMe with escitalopram had a clinical response to treatment ($\geqslant$50% reduction from baseline in Hamilton Rating Scale for Depression [HAM-D] scores) (SAMe: 45%, escitalopram: 31%; placebo: 6%), and achieved remission (HAM-D score $\leqslant$7 at study completion) (SAMe: 34%; escitalopram: 23%; placebo: 6%), compared to all other groups.

Table 39.1 Clinical research investigating pharmaceutical interventions conducted by naturopathic researchers

Author (year) [Country, World region]	Design	Study Population	Intervention	Concomitant therapies	Control or Placebo	No. Participants (Intervention/ Placebo)	Measure of Outcome	Outcome
Bambling, et al. (2015) [Australia, WPRO] [26]	Randomized controlled trial	Depression (adults, sub-optimal treatment response to SSRI)	Selective serotonin reuptake inhibitor	15 weeks: Either 800mg or 1600 mg daily of SAMe. 2 weeks: washout 8 weeks: SAME non-responders supplemented with 1600 mg of Magnesium Orotate	Nil	36 (SAMe non-responders given magnesium orotate: 8)	ICD-DSM Mini International Neuropsychiatric Interview [BL to Wk15, Wk25]	NS
							Beck Depression Inventory [BL to Wk15, Wk25]	**Reduced SAMe** (38.2 – 11.4, p<0.001) NS difference between 800mg and 1600mg dose of SAMe. Reduced Mg orotate (33.8 – 14.1, p=0.001)
							Depression, Anxiety and Stress Scale [BL to Wk15, Wk25]	NS
							Structured Interview for the DSM-IV [BL to Wk15, Wk25]	NS
							Outcome questionnaire [BL to Wk15, Wk25]	**Reduced** functional distress scores SAMe: 113.9 vs 57.0 (p <0.001) Mg orotate and SAMe: 86.6 vs 54.2 (p<0.001)
							Quality of Life scores [BL to Wk15, Wk25]	**Increased quality of life** SAMe: 53.8 vs 75.0 (p<0.001) Mg orotate: 55.2 – 76.0 (p=0.001)
Gangadhar, et al. (2013) [India, SEARO] [8]	Non-randomized controlled trial	Major depression	Antidepressant medication (unspecified)	Yoga classes led by an advanced yoga teacher. Wks 1-2: 1-hour yoga class per day; Wks 3-4: two classes one week apart; Mth 2 – 3: one session per month. Encouragement to practice yoga at home daily.	Yoga only OR Drugs only	137 (Drugs and yoga: 36/ Yoga only: 23/ Drugs only: 78)	Hamilton Rating Scale for Depression [BL to Mth 1, Mth 3]	**Decreased in all groups (improved)** Drugs only: BL, 19.4+14.2; Mth 1, -12.3+5.43 (p=0.02); Mth 3, -10.4+5.82 (p=0.002) Yoga and drugs: BL, 7.7+13.91; Mth 1, -17.7+14.9 (p=0.02); Mth 3, -5+5.2 (p=0.001) Yoga only: BL, 17+4.5; Mth 1, -4.5+2.8 (p=0.02); Mth 3, -2.1+2.5 (p=0.001)

Author (year) [Country, World region]	Design	Study Population	Intervention	Concomitant therapies	Control or Placebo	No. Participants (Intervention/ Placebo)	Measure of Outcome	Outcome
							Clinical Global Impression [BL to Mth 1, Mth 3]	**Decrease in all groups (i.e., Improved)** BL, 4.0+0.38 Drugs only: Mth 1, -3.10+0.63 (p=0.001); Mth 3, -2.4+0.81 (p=0.001) Yoga and drugs: Mth 1, -2.3+0.78 (p=0.001); Mth 3, -1.6+0.79 (p=0.001) Yoga only: Mth 1, -1.7+0.0 (p=0.001); Mth 3, -1.1+0.35 (p=0.001)
Khamba, et al. (2013) [Canada, AMRO] [27]	Prospective cohort	Sexual dysfunction secondary to SSRIs and SNRIs (men and women)	Anti-depressant medication (SSRIs and SNRIs)	Acupuncture for 12 weeks (KI 3, GV 4, BL 23, with HT 7 and PC 6.) and various aspects of sexual function based on participant's feedback	Nil	35 (Men: 18/ Women: 17)	Mini International Neuropsychiatric Interview (MINI)	Not provided
							Beck Anxiety Inventory (BAI)	**Reduced** -2.8 (p=0.01)
							Beck Depression Inventory, Second Edition (BDI-II)	NS
							The Sexual Function Visual Analogue Scale (SFVAS)	**Increased** Total: +62.28 (p=<0.01) Desire/Libido: +13.9 (p=0.030) Erection: +12.0 (p=0.012) Ejaculation delay: +19.2 (p=0.03) Orgasm delay: +17.0 (p=0.025) Frequency of sex: +12.4 (p=0.04)
							The Arizona Sexual Experience Questionnaire (ASEX)	**Reduced impact** Total: -1.59 (p=0.027) Drive: -0.6 (p=0.014) Arousal: NS Erection: -0.5 (p=0.015) Ability to reach orgasm: -0.5 (p=0.027) Satisfaction from orgasm: NS

Author (year) [Country, World region]	Design	Study Population	Intervention	Concomitant therapies	Control or Placebo	No. Participants (Intervention/ Placebo)	Measure of Outcome	Outcome
Rao, et al. (2017) [India, SEARO] [30]	Randomized controlled trial	Breast cancer (Stage II and III)	Radiotherapy or chemotherapy	60-min yoga sessions, daily (24 weeks)	Supportive counselling therapy during their hospital visits.	98 (45/53)	State-trait anxiety inventory [BL to Wk 24]	**Reduced anxiety** Radiotherapy: Wk 24, -4.72 ($p<0.05$) Chemotherapy: Wk 24, -7.7 ($p<0.05$)
							Beck Depression Inventory [BL to Wk 24]	**Reduced depression** Radiotherapy: Wk 24, -5.74 ($p<0.05$) Chemotherapy: Wk 24, -7.25 ($p<0.05$)
							Symptom checklist [BL to Wk 24]	**Reduced incidence** Radiotherapy: Wk 24, -2.34 ($p<0.05$) Chemotherapy: Wk 24, -2.97 ($p<0.05$) Reduced severity Radiotherapy: Wk 24, -6.43 ($p<0.05$) Chemotherapy: Wk 24, -8.83 ($p<0.05$)
							Common toxicity criteria [BL to Wk 24]	**Reduced toxicity** Radiotherapy: NS Chemotherapy: $p=0.01$
							Functional living index – cancer [BL to Wk 6, Wk 12, Wk 18, Wk 24]	**Increased quality of life** Radiotherapy: Wk 24, +23.9 ($p<0.05$) Chemotherapy: Wk 24, +31.2 ($p<0.05$)
Sarris, et al. (2014) [Australia, WPRO] [32]	Randomized controlled trial	Major Depressive Disorder	Escitalopram 10-20mg/ day (SSRI) (12 weeks)	Nil	S-adenosyl methionine 1600 to 3200 mg/d (titration at 6 weeks if no response) OR Placebo	144 (35/32/ 35)	Hamilton Rating Scale for Depression – Total [BL to Wk 12]	**Reduced depression** SSRI: 20.83+4.6 to 6.69+5.1 SAMe: 19.09+4.5 to 7.3+5.90 Placebo: 20.63 +4.4 to 4.00+5.6 Between group: ($p=0.039$)

Author (year) [Country, World region]	Design	Study Population	Intervention	Concomitant therapies	Control or Placebo	No. Participants (Intervention/ Placebo)	Measure of Outcome	Outcome
							Hamilton Rating Scale for Depression – Response (HAMD-17≥50% reduction) [BL to Wk 12]	**Increased clinical response** SAMe: 45% Escitalopram: 31% Placebo: 26%
							Hamilton Rating Scale for Depression – Remission (HAM-D≤7) [BL to Wk 12]	**Remission rates Increased** SAMe: 34% (p=0.003) Escitalopram: 23% Placebo: 6%
Sarris, et al. (2019) [Australia, WPRO] [28]	Randomized controlled trial	Generalised anxiety disorder (partial or non-responders to stable use of anti- depressants)	Anti-depressant medication (unspecified)	L-theanine (450 – 900 mg) for 8 weeks plus a 1-wk pre-study and 2-wk post-study single-blinded observational period	Placebo	46 (22/24)	Hamilton Rating Scale for Anxiety [BL to Wk 8]	NS
							Insomnia Severity Index [BL to Wk 8]	**Improves sleep quality** Severity: NS (ISI item 4; p = 0.015) LT treatment resulted in greater self-reported sleep satisfaction.
							STROOP [BL to Wk 8]	NS
							Montgomery and Asberg Depression Rating Scale [BL to Wk 8]	NS
							Beck Anxiety Inventory [BL to Wk 8]	NS
							Penn State Worry Questionnaire [BL to Wk 8]	NS
							World Health Organisation Quality of Life-BREF [BL to Wk 8]	NS

Author (year) [Country, World region]	Design	Study Population	Intervention	Concomitant therapies	Control or Placebo	No. Participants (Intervention/ Placebo)	Measure of Outcome	Outcome
Sarris, et al. (2019) [Australia, WPRO] [29]	Randomized controlled trial	Major depressive disorder	Anti-depressant medication (SSRI, NaRI, tetracyclic or 5-HT2c antagonist) (8 weeks)	Multinutrient combination: (a) Two tablets per day – SAMe (800mg) folinic acid (500 mcg); Vitamin B12 (200mcg). (b) Two capsules per day provided omega-3 fatty acid concentrate (EPA-esters 1000mg, DHA-esters 656mg) 5-HTP (200mg) zinc picolinate (30mg elemental); vitamin B6 (100mg), vitamin C (60mg), and magnesium (amino acid chelate, elemental 40mg)	Placebo	158 (81/77)	Montgomery and Asberg Depression Rating Scale [BL to Wk 8]	NS
							Beck Depression Inventory, 2nd edition [BL to Wk 8]	NS
							Hamilton Anxiety Rating Scale [BL to Wk 8]	NS
							SF-12 -Short Form Survey-12 [BL to Wk 8]	NS
							Leeds Sleep Evaluation Questionnaire [BL to Wk 8]	NS
							Arizona Sexual Experience Questionnaire [BL to Wk 8]	NS
							CORE Assessment of Psychomotor Change [BL to Wk 8]	NS
							Clinical Global Impression Scale and Improvement [BL to Wk 8]	NS
							The Systematic Assessment for Treatment Emergent Effects [BL to Wk 8]	NS
							The Sternbach and Hunter Serotonin Toxicity Criteria [BL to Wk 8]	NS

Author (year) [Country, World region]	Design	Study Population	Intervention	Concomitant therapies	Control or Placebo	No. Participants (Intervention/ Placebo)	Measure of Outcome	Outcome
Schloss, et al. (2017) [Australia, WPRO] [31]	Randomized controlled trial	Cancer (newly diagnosed)	Taxanes, oxaliplatin or vincristine induced neuropathy with a B vitamin complex. Each tablet contained or placebo	B complex (2x/ day): Thiamine 50 mg, riboflavin 20 mg, niacin 100 mg, pantothenic acid 163.5 mg, pyridoxine 30 mg, folate 500 µg, cyanocobalamin 500 µg, biotin 500 µg, choline 100 mg, inositol 500 µg	Placebo	71 (38/33)	Total Nueropathy Score [BL to Wk 12, Wk 24, Wk 26]	NS
							Perceived Sensory peripheral nueropathy scores [BL to Wk 12, Wk 24, Wk 26]	**Reduced peripheral neuropathy** Wk 12, (p = 0.03); Wk 24, (p = 0.005); Wk 36, (p = 0.021)
							Serum vitamin B levels [BL to Wk 12, Wk 24, Wk 26]	NS
							Quality of Life [BL to Wk 12, Wk 24, Wk 26]	NS
							Pain inventory [BL to Wk 12, Wk 24, Wk 26]	NS
							Patient Neurotoxicity Questionnaire [BL to Wk 12, Wk 24, Wk 26]	**Reduced neurotoxicity** Taxanes: Lower (p=0.03); Oxaliplatin: NS; Vincristine: NS

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40 Other Research Publications Regarding Naturopathic Therapies and Practices

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HIGHLIGHTS

- Naturopathic researchers have conducted over 1203 peer-reviewed journal articles examining the broad range of therapies commonly used in naturopathic practice.
- Observational studies on specific therapies and treatments can provide information about patient experiences and preferences towards treatments, or practitioner perspectives towards the use and usability of therapies for specific conditions or populations.
- Naturopathic researchers have published over 195 observational studies in the last 30 years.
- Reviews and meta-analyses provide a detailed insight into the breadth of clinical research pertaining to the safety, efficacy, and mechanism of action of therapies and treatments, either as a group or as single interventions.
- Naturopathic researchers have published over 297 reviews and metanalysis related to health conditions in the last 30 years.

Naturopathic researchers have conducted extensive clinical research, yet it only represents one quarter of the total published peer-reviewed journal articles produced by the naturopathic research community examining the broad range of therapies commonly used in naturopathic practice (n=1203). A substantial proportion of observational studies including research using survey, interview or focus group methods (n=195; 16.2%), and reviews and meta-analyses (n=297; 24.6%) have been published by naturopathic researchers.

While it is beyond the scope of this report to provide details for such a substantial body of knowledge, a summary of the characteristics and topics of the observational studies and the reviews and meta-analyses and further details for the two therapies receiving the most research attention to date is outlined below.

Implications

Naturopathic researchers show a strong commitment to recognizing and translating knowledge between stakeholder groups and from different systems of medicine for the benefit of the wider community. In the context of health research examining treatments and therapies widely used in naturopathic practice, this manifests through research capturing the real-world observations of treatment and therapies which may inform other health professions and policymakers about the experiences, insights, beliefs, and attitudes of those using and prescribing these therapies and treatments. It also manifests as concerted effort to consolidate the extensive and ever-growing clinical effectiveness and safety evidence related to naturopathic therapies and treatments for the benefit of naturopaths/naturopathic doctors in clinical practice, and any other health professionals, prescribing these treatments.

The degree to which herbal medicine and clinical nutrition are a focus of the reviews and meta-analyses as well as the observational research published by naturopathic researchers further reinforces the importance that it plays in contemporary naturopathic practice globally. The prominence of these therapeutic modalities is also seen in international surveys of the naturopathic curriculum [237] and practice behaviours of naturopaths/naturopathic doctors [238]. However, it is also important to note that naturopathic researchers are not only exploring the effectiveness of their treatments, but also their safety and mechanisms of action.

The naturopathic reviews and meta-analyses directly and indirectly benefit members of the community who might be self-prescribing these treatments to better understand the potential benefits and risks associated with their use. Furthermore, naturopathic researchers are paying close attention to their role in the health system and exploring the nature of their relationship with other health professionals and the characteristics and experiences of individuals who consult with naturopaths/naturopathic doctors. Overall, naturopathic researchers are generating new knowledge to share with the broader health research, policy and consumer communities while also synthesizing existing knowledge to increase its reach and impact.

Observational studies

Observational studies in health research provide real-world insights. Observational studies on specific therapies and treatments can provide information about patient experiences and preferences towards treatments, or practitioner perspectives towards the use and usability of therapies for specific conditions or populations.

The naturopathic observational studies, inclusive of survey research and those employing interview or focus group methods, were conducted in the USA (n=84), Australia (n=47), Canada (n=21), Germany (n=15), India (n=13), Saudi Arabia (n=5), United Kingdom (n=3), Sub-Saharan Africa (n=2), New Zealand (n=1), Israel (n=1), Uganda (n=1), France (n=1), and Japan (n=1). Modalities and therapies used in naturopathic practice that were most frequently researched were complex interventions (n=72), clinical nutrition (n=54), pharmaceuticals (n=43), lifestyle (n=39), and herbal medicine (n=36). While less frequent, observational studies also examined naturopathic physical medicine (n=26), yoga (n=25), applied nutrition (n=20), acupuncture (n=10), and mind-body-medicine/counselling (n=5).

The naturopathic observational studies investigating complex interventions primarily focused on aspects of naturopathic clinical practice including exploring the role naturopathy/naturopathic medicine may play in supporting underserved and vulnerable communities [1-9], the characteristics and experience of patients accessing naturopathic care or natural health products [2, 4, 5, 10-15], and the interface between naturopaths/naturopathic doctors or natural health products and other health professions [3, 8, 16-24]. A number of studies describe various aspects of naturopathic practice by describing the general clinical practice behaviours of naturopaths/naturopathic doctors [8, 20, 21, 25-32] as well as the approach taken by naturopaths/naturopathic doctors to the clinical management of health conditions such as cardiometabolic conditions [33-37], gastrointestinal disorders [38], mental health [39], women's health [40, 41], and cancer [30, 42, 43]. A number of studies also examine naturopathic approaches to public health challenges [5, 44, 45] as well as their application of knowledge and evidence within clinical practice and naturopathic education [6, 9, 18, 38, 46-52]. Naturopathic researchers also employed observational study designs to advance research priorities, capacity, and methodologies to support robust, rigorous, and relevant naturopathic research for the future [6, 9, 18, 37, 38, 43, 47, 53, 54].

Naturopathic observational studies examining clinical nutrition commonly investigated the relationship between nutrient deficiencies and the risk, progression, or outcome of disease [55-62]. Naturopathic researchers have also studied the incidence of nutritional deficiency [57, 59, 63-65] and the use of nutritional supplements [66-79] in populations with defined health conditions. Some studies focused on specific stages across the life course such as children [62, 80-82], pregnancy [80, 83] and older adults [60, 68, 75, 84]. Other naturopathic observational studies explored the potential importance of nutritional biomarkers in the disease diagnosis and management [85-88]. The research encompassed a range of nutrients including vitamins [55, 61-63, 67, 72, 73, 76, 87, 89], minerals [59, 64, 65, 73, 81], essential fatty acids [56, 58, 60, 69, 86, 87, 90] and non-essential nutraceuticals [57, 68, 85, 91].

Reviews and meta-analyses

Within the accepted hierarchy of evidence for health research, reviews and meta-analyses are acknowledged as providing the highest level of evidence. Reviews and meta-analyses consolidate a wider range of research evidence than is possible from any one single study and from more than one system of medicine. As such, reviews and meta-analyses provide a more comprehensive view of the available evidence pertaining to the research question being investigated. Reviews and meta-analyses can, for example, provide the reader with a more detailed insight into the breadth of clinical research pertaining to the safety, efficacy, and mechanism of action of therapies and treatments, either as a group or as single interventions. Reviews and meta-analyses are often used to help inform clinical intervention studies and to guide naturopathic practice decisions.

Reviews and meta-analyses have been published in peer-reviewed journals by naturopathic researchers from Australia (n=94), USA (n=84), Canada (n=78), Germany (n=31), India (n=9), and New Zealand (n=1). The therapies most frequently examined in these reviews are herbal medicine (n=121), clinical nutrition (n=93), lifestyle (n=66), yoga (n=52), pharmaceuticals (n=34), and applied nutrition (n=32). While less frequent, naturopathic researchers have also conducted reviews and meta-analyses on complex interventions (n=19),

acupuncture (n=15), mind-body-medicine/counselling (n=8), and bodywork (n=7).

Naturopathic researchers have undertaken reviews and meta-analyses to consolidate published research examining herbal medicines for several purposes. The most common purpose is to identify and evaluate research examining the effectiveness of herbal medicines in the management of health conditions. This may include focusing on herbal medicines for specific illnesses such as musculoskeletal [92-101], cancer-related [102-115], cardiometabolic [116-123], women's reproductive [124-129], and mental health [130-144] conditions. Some reviews also focused on specific populations such as children [145-150] and pregnant women [126, 129, 151-160]. The herbal medicine reviews published by naturopathic researchers also had a strong focus on safety [102, 104, 116, 124, 126, 129, 133, 151-156, 158, 159, 161-167], particularly for pregnancy and lactation [129, 151-156, 158-160] and within the context of drug-herb interactions [118, 149, 162, 164, 168-171]. Another topic focus among the published herbal medicine reviews is phyto-pharmacognosy and manufacturing or delivery methods [140, 149, 163, 164, 166, 172-174].

Naturopathic researchers have undertaken these reviews and meta-analyses to consolidate published research examining clinical nutrition from different perspectives. One such perspective is the role of clinical nutrition in the management of a range of health conditions including mental health [78, 133, 175-190], cardiometabolic disease [116, 120, 191-198] and cancer [105, 112, 113, 199-217] and populations such as pregnant women [218, 219] and children [150, 218, 220-223]. In addition to specifically examining nutrients – vitamins and minerals [99, 177, 184, 200-202, 205, 206, 211, 216, 221, 222, 224-228], essential fatty acids [176, 180, 183, 186, 191, 192, 197, 199, 220, 229], and non-essential nutraceutical compounds [105, 112, 181, 185, 187, 203, 207, 208, 213, 230-233] -, some research also investigated the concurrent use of nutrients and pharmaceutical medications to understand potential clinical benefits, risks, and interactions [24, 130, 175, 195, 206, 212, 225, 226, 234]. The physiological effects and pharmacognosy of specific nutrients were also explored in some of the reviews and meta-analyses [116, 180, 181, 189, 194, 196, 197, 206, 224, 235, 236].

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