



Contents lists available at ScienceDirect

Canadian Journal of Diabetes

journal homepage:

www.canadianjournalofdiabetes.com

**DIABETES
CANADA****2018 Clinical Practice Guidelines****Complementary and Alternative Medicine for Diabetes**

Diabetes Canada Clinical Practice Guidelines Expert Committee

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Anita R. Shack BFA, DC, FATA**KEY MESSAGES**

- Anywhere from 25% to 57% of people with diabetes report using complementary or alternative medicine.
- Some natural health products have shown a lowering of A1C by $\geq 0.5\%$ in trials lasting at least 3 months in adults with type 2 diabetes, but most are single, small trials that require further large-scale evaluations before they can be recommended for widespread use in diabetes.
- A few more commonly used natural health products for diabetes have been studied in larger randomized controlled trials and/or meta-analyses refuting the popular belief of benefit of these compounds.
- Health-care providers should always ask about the use of complementary and alternative medicine as some may result in unexpected side effects and/or interactions with traditional pharmacotherapies.

KEY MESSAGES FOR PEOPLE WITH DIABETES

- Many people with diabetes use complementary medicine (along with) or alternative medicine (instead of) with conventional medications for diabetes.
- Although some of these therapies may have the potential to be effective, they have not been sufficiently studied and others can be ineffective or even harmful.
- It is important to let your health-care providers know if you are using complementary and/or alternative medicine for your diabetes.

Introduction

Despite advances in the management of type 1 and type 2 diabetes, therapeutic targets are often not met. People dissatisfied with conventional medicine often turn to nontraditional alternatives. Complementary and alternative medicine (CAM) can be loosely defined as health-care approaches developed outside of mainstream Western, or conventional medicine, with “complementary” meaning used together with, and “alternative” meaning used in place of conventional medicine (1). According to a report from the Fraser Institute, 50% to 79% of Canadians had used at least 1 CAM sometime in their lives, based on surveys from 1997, 2006 and 2016 (2). The most common types used in 2016 were massage (44%), chiropractic care (42%), yoga (27%), relaxation techniques (25%) and acupuncture (22%). According to the United States 2012 National Health Interview Survey (NHIS), 17.7% of American adults

used a dietary supplement other than vitamins and minerals (3). A few surveys have sought to characterize the use of CAM in persons with diabetes. In a Canadian study of 502 people with diabetes, 44% were taking over-the-counter supplements with 31% taking alternative medications (4). A United States national survey reported 57% of those with diabetes using CAM in the previous year (5). The Medical Expenditure Panel Surveys (MEPS) showed that those with diabetes were 1.6 times more likely to use CAM than those without diabetes, with older age (≥ 65 years) and higher educational attainment (high school education or higher) independently associated with CAM use (6). An Australian study reported 25% of people with diabetes stated they had used CAM within the previous 5 years (7).

This chapter will review CAM, including natural health products (NHP) and others, such as yoga, acupuncture, tai chi and reflexology, that have been studied for the prevention and treatment of diabetes and its complications.

NHP for the Prevention and Treatment of Diabetes and Its Complications

In Canada, NHP are defined as vitamins and minerals, herbal remedies, homeopathic medicines, traditional medicines, such as traditional Chinese medicines, probiotics, and other products like amino acids and essential fatty acids (8). They are regulated under the Natural Health Products Regulations, which came into effect in 2004. In general, the current level of evidence for the efficacy and safety of NHP in people with diabetes is lower than that for pharmaceutical agents. Trials tend to be of shorter duration and involve smaller sample sizes. Concerns remain about standardization and purity of available compounds, including their contamination with regular medications and, in some cases, toxic substances (9–11). Various NHP have been studied to evaluate their impact on the development of both type 1 and type 2 diabetes, glycemic control in people with diabetes, and on the various complications of diabetes.

NHP for the Prevention and Treatment of Diabetes

A number of immune modulators have been studied in an attempt to prevent or arrest beta cell decline in type 1 diabetes, most with limited success. A few NHP have also been studied in this

Conflict of interest statements can be found on page S157.

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<https://doi.org/10.1016/j.jcjd.2017.10.023>

regard. A randomized controlled trial of people with new-onset type 1 diabetes assessed the effect of vitamin D supplementation on regulatory T (Treg) cells (12). After 12 months, Treg suppressive capacity was improved, although there was no significant reduction in C-peptide decline. Observational studies have suggested an inverse relationship between vitamin D levels and the development of type 2 diabetes (13), although randomized controlled trials are lacking (14). In the large, prospective cohort study, The Environmental Determinants of Diabetes in the Young (TEDDY), early probiotic supplementation may reduce the risk of islet autoimmunity in children at the highest genetic risk of type 1 diabetes (15).

A number of NHP have been evaluated to assess their effect on the progression from impaired glucose tolerance (IGT) to diabetes. Tianqi is a traditional Chinese medicine consisting of 10 different herbs. In a double-blind, placebo-controlled trial of 12 months duration, Tianqi was shown to reduce the progression from IGT to type 2 diabetes by 32% (16). A systematic review and meta-analysis of observational studies of omega-3 fatty acids or fish intake showed that an increased intake of alpha linoleic acid (ALA) and fatty fish reduced the risk of type 2 diabetes significantly with ALA, only in Asians (17). In a randomized controlled trial, the traditional Chinese medicine Shenzhu Tiaopi granule (SZTP) significantly reduced the conversion from IGT to type 2 diabetes to 8.52% from 15.28% with placebo, with a significantly higher number of people with IGT reverting to normal blood glucose levels as well (42.15% vs. 32.87% for placebo) (18).

In adults with type 2 diabetes, the following NHP have been shown to lower glycated hemoglobin (A1C) by at least 0.5% in randomized controlled trials lasting at least 3 months:

- Ayurveda polyherbal formulation (19)
- *Citrullus colocynthis* (20)
- *Coccinia cordifolia* (21)
- Eicosapentaenoic acid (22)
- *Ganoderma lucidum* (23)
- Ginger (*Zingiber officinale*) (24)
- *Gynostemma pentaphyllum* (25)
- *Hintonia latiflora* (26)
- Lichen genus *Cladonia* BAFS “Yagel-Detox” (27)
- Marine collagen peptides (28)
- Nettle (*Urtica dioica*) (29)
- Oral aloe vera (10)
- *Pterocarpus marsupium* (vijayasar) (30)
- *Salacia reticulata* (31)
- *Scoparia dulcis* porridge (32)
- Silymarin (33,34)
- Soybean-derived pinitol extract (35)
- Touchi soybean extract (36)
- Traditional Chinese medicine herbs:
 - Berberine (37)
 - Fructus Mume (38)
 - Gegen Qinlian Decoction (GQD) (39)
 - Jianyutangkang (JYTK) with metformin (40)
 - Jinlida with metformin (41)
 - Sancaijiangtang (42)
 - Shen-Qi-Formula (SQF) with insulin (43)
 - Tang-Min-Ling-Wan (TM81) (44)
 - Xiaoke (contains glyburide) (11)
 - Zishentongluo (ZSTL) (45)
 - *Trigonella foenum-graecum* (fenugreek) (46,47)

These products are promising and merit consideration and further research, but, as they are mostly single, small trials or meta-analyses of such, it is premature to recommend their widespread use.

The following NHP either failed to lower A1C by 0.5% in trials lasting at least 3 months in adults with type 2 diabetes, or

were studied in trials of shorter duration, nonrandomized or uncontrolled:

- *Agaricus blazei* (48)
- American ginseng (*Panax quinquefolius* L.) (49)
- Antioxidants: (fruit/vegetable extract) (50), (pomegranate extract) (51)
- *Camellia sinensis* (52)
- Flaxseed oil (53)
- French maritime pine bark (54)
- Ginseng (55,56)
- *Juglans regia* extract (57)
- Liuwei Dihuang Pills (LDP) (58)
- *Momordica charantia* (bitter melon or bitter gourd) (59,60)
- *Rosa canina* L. (rose hip) (61)
- *Salvia officinalis* (62)
- Soy phytoestrogens (63)
- *Tinospora cordifolia* (64)
- *Tinospora crispa* (65)
- Vitamin C (66–68)
- Vitamin E (69–73)

The following NHP have demonstrated conflicting effects on A1C in trials lasting at least 3 months in adults with type 2 diabetes:

- Cinnamon (74–79)
- Coenzyme Q10 (80–83,85,86)
- *Ipomoea batatas* (caipao) (87,88)
- L-carnitine (89–92)
- Magnesium (93–99)
- Omega 3 fatty acids (100,101)
- Probiotics (102,103)
- Zinc (104,105)

A few products, such as chromium, vitamin D and vanadium, have been the subjects of special interest in diabetes.

Chromium is an essential trace element involved in glucose and lipid metabolism. Early studies revealed that chromium deficiency could lead to IGT, which was reversible with chromium repletion. This led to a hypothesis that chromium supplementation, in those with both adequate and deficient chromium stores, could lead to improved glucose control in people with diabetes (106,107). Indeed, an analysis of the large NHANES database showed that, in those in the general population who reported consuming a chromium supplement, the odds of developing diabetes was 19% to 27% lower than those not taking a chromium supplement (108). However, randomized controlled studies of chromium supplementation have had conflicting results, with most showing no benefit on improving A1C (109–121), although some showed an improved fasting glucose level (120,121). Most were small studies, of short duration, and some not double-blinded. More recent meta-analyses have also reported conflicting results, with some concluding no benefit of chromium on reducing A1C, lipids or body weight in people with diabetes (122), and others reporting some benefit depending upon the dose and formulation consumed (84). The later meta-analysis reported marked heterogeneity and publication bias in the included studies.

Vitamin D has received much interest recently with purported benefits on cardiovascular disease (CVD), cancer and diabetes. Randomized controlled trials have not demonstrated a benefit of vitamin D supplementation on glycemic control in diabetes (123–138), further confirmed by meta-analyses (139,140).

Vanadium, a trace element that is commonly used to treat type 2 diabetes, has not been studied in randomized controlled trials evaluating glycemic control by A1C over a period of 3 months or longer.

NHP for the Treatment of the Co-Morbidities and Complications of Diabetes

A number of NHP have been evaluated for the various co-morbidities and complications of diabetes, including lipids and blood pressure (BP) in diabetes, as well as CVD, nephropathy, retinopathy and peripheral neuropathy. As with the studies of glycemic control, most had small sample sizes and meta-analyses had marked heterogeneity of included studies, making strong conclusions difficult.

Randomized controlled trials demonstrating a benefit on lipid parameters in diabetes include: Ayurvedic polyherbal formulation (19), *Hintonia latiflora* (26) and magnesium (99). In postmenopausal women with type 2 diabetes, vitamin D supplementation for 6 months reduced serum triglycerides (TG) without effect on other lipid parameters (141), while a meta-analysis with high heterogeneity showed benefit on lowering total cholesterol and TG (142). Other studies have failed to show significant benefit of vitamin D supplementation on lipids in people with diabetes (130,137,143). A meta-analysis of Berberine showed it to reduce TG and increase high-density lipoprotein cholesterol (HDL-C) more than traditional lipid-lowering drugs, with no difference on total or low-density lipoprotein cholesterol (LDL-C) (37). Berberine was also shown to reduce total and LDL-C and increase HDL-C combined with traditional lipid-lowering drugs compared with those drugs alone.

Randomized controlled trials demonstrating a benefit on systolic and/or diastolic BP include: magnesium (99), American ginseng (*Panax quinquefolius* L.) (49) and Purslane extract (*Portulaca oleracea* L.) (144). Berberine when combined with traditional BP medications can lower systolic BP by an additional 4.9 mmHg and diastolic BP by 2 mmHg, but not when compared with traditional antihypertensive medications alone (37). In 1 meta-analysis, vitamin D was shown to reduce BP by a statistically significant, but not clinically meaningful amount (145).

Ethylene diamine tetra-acetic (EDTA) acid chelation therapy has been postulated to have a number of cardiovascular (CV) benefits. A large randomized controlled trial (Trial to Assess Chelation Therapy—TACT) showed a modest benefit of an 18% risk reduction for a composite of CV complications in people with a recent myocardial infarct (146). A pre-specified subanalysis of people with diabetes showed a more robust 39% to 41% risk reduction in the primary endpoint out to 5-years follow up (147).

The traditional Chinese medicine product, The Compound Danshen Dripping Pill (CDDP), consisting of 3 herbal preparations, was evaluated in a randomized controlled trial of 24 weeks duration, for its effect on the progression of diabetic retinopathy (148). Using a nonstandardized method of grading fluorescence fundal angiography, higher doses of CDDP were found to delay the progression of diabetic retinopathy.

A number of NHP have been reported to improve diabetic nephropathy. However, there is variation in the definition of diabetic nephropathy in the various studies, with many assessing urinary albumin excretion (UAE) and/or 24-hour urine protein excretion without a confirmatory diagnosis. Many are of short duration, some without reporting an assessment of renal function or its progression, or with conflicting results on the various measures. Some products showing a reduction in UAE in people with diabetes include: the traditional Chinese medicines Yiqi Huayu, Yiqi Yangyin (149), Qidan Dihuang Grain (150), and Jiangzhuo (SKC-YJ) (151), Huangshukuihua (*Flos Abelmoschi Manihot*) (152,153), *Pueraria lobata* (gegen, puerarin) (154), Tangshen Formula (155), Zishentongluo (ZSTL) (45), vitamin D (156), and vitamin D analogue paricalcitol in type 1 diabetes (157).

A number of NHP have been reported to improve diabetic peripheral neuropathy, as assessed by pain scores and/or nerve conduction studies (NCS). Topical *Citrullus colocynthis* (bitter apple) extract

oil was studied in a small randomized controlled trial in people with painful diabetic polyneuropathy (158). After 3 months, there was a significantly greater decrease in mean pain score and improvement in nerve conduction velocities compared with placebo. A meta-analysis of puerarin in diabetic peripheral neuropathy reported benefits in pain scores and NCS (159). In a small randomized controlled trial, the traditional Chinese medicine MHGWT showed reduced pain scores compared with placebo after 12 weeks of treatment (160).

A number of the above and other NHP have been evaluated for their effects on various pre-clinical parameters, biomarkers and surrogate clinical markers involved in the pathogenesis of diabetes and its complications. A discussion of these papers is beyond the scope of this chapter.

Adverse Effects

It is important to consider potential harm from the use of NHP. A number of studies of NHP report adverse events, such as gastrointestinal (Fenugreek, Berberine, TM81, bitter melon, oral aloe vera) and dizziness (JYTK). In 1 trial of *Tinospora crispa*, hepatotoxicity was seen in 2 participants (65). Large doses of *Citrullus colocynthis* can induce diarrhea, but no side effects were reported in the lower doses used in 1 trial (20). *Momordica charantia*, an NHP commonly used for glycemic control, is an abortifacient (161). Most clinical trials have evaluated small sample sizes over relatively short periods of time and, thus, may not identify all potential side effects or risks.

Some NHP contain pharmaceutical ingredients and/or properties. The Xiaoake Pill contains glibenclamide (glyburide) (11). Nettle has insulin secretagogue, peroxisome proliferator-activated receptor (PPAR) and alpha-glucosidase activities. Only NHPs that are properly labelled with a valid natural product number (NPN) should be used to avoid adulteration with unlabelled pharmaceuticals or other contaminants.

Drug-herb interactions may also occur. The most well described is *Hypericum perforatum* (St. John's wort), which can affect the metabolism of many drugs, including statins, by inducing cytochrome P450 3A4 (CYP3A4). Some studies have reported poorer glycemic control in people using glucosamine sulfate for osteoarthritis, but a systematic review concluded that the evidence does not support this concern (162).

Other Complementary and Alternative Approaches for the Prevention and Treatment of Diabetes and Its Complications

A number of complementary and alternative approaches have been studied to some degree for diabetes and its complications, others have not. Included here are studies of yoga, traditional Chinese medicine and reflexology. Other modalities of CAM, such as chiropractic or osteopathic manipulation, homeopathy, shiatsu, registered massage therapy or craniosacral therapy do not have studies specific to diabetes.

Yoga

The Sanskrit definition of yoga means union or connection. Yoga is a Hindu spiritual discipline. There are many types of yoga, each with its own techniques and methods to awaken greater awareness and connection to self and life. Most practices of yoga include a series of physical postures, breathing and meditation for health, relaxation and overall well-being. Yoga or yoga therapy is often included in a holistic practitioner's (chiropractor, naturopath,

osteopath, shiatsu therapist) plan of management for stress reduction and physical strengthening.

Studies of yoga in the management of people with type 2 diabetes show some benefit on glycemic control, lipids and BP, although published studies are generally of short duration with small numbers. In a systematic review and meta-analysis, yoga was found to have positive effects on reducing A1C, as well as fasting and postprandial glucose values (163). There was high heterogeneity among the studies included in the analysis. Other systematic reviews and meta-analyses showed similar improvements in glycemic parameters, as well as improvements in the lipid profile and BP, with similar limitations in the individual studies included (164,165) (see Physical Activity and Diabetes chapter, p. S54). In a meta-analysis of smaller studies looking at comparing the effectiveness of the leisure activities yoga, walking and tai chi on glycemic control in people with type 2 diabetes, yoga with regular frequency (3 times a week) was shown to be more effective than tai chi or walking in lowering A1C levels (166).

Traditional Chinese Medicine

Traditional Chinese medicine (TCM) encompasses a holistic system that includes the combination of herbal medicines, acupuncture, tui na (rigorous massage), dietary therapy, qi gong and tai chi (mind/body techniques combining breathing, movement and mental focus). TCM works within a different paradigm than Western Medicine and, as such, can be difficult to study by Western research techniques. Treatments are complex and focused on individual imbalances detected by pulse and tongue diagnosis rather than specific diseases. Most research on the effectiveness of TCM for people with diabetes is based on specific techniques or Chinese herbal remedies as reviewed above.

Acupuncture is a branch of TCM involving the stimulation of specific points along energy meridians throughout the body to either sedate or tonify the flow of energy. There are various techniques of acupuncture, such as electro and laser acupuncture, and different systems of acupuncture, including scalp and auricular acupuncture. The system and technique most commonly referred to and most often studied refers to the technique of penetrating the skin at specific acupuncture points with thin solid metal needles that are manipulated by the hands.

Acupuncture has not been shown to improve A1C in people with diabetes, with 1 small randomized controlled trial showing it to be no different than placebo on FPG and oral glucose tolerance testing (OGTT) (167). A meta-analysis of acupuncture for diabetic gastroparesis concluded that acupuncture improved some dyspeptic symptoms, such as nausea, vomiting, loss of appetite and stomach fullness, with no improvement in solid gastric emptying (168). A systematic review of randomized controlled trials of manual acupuncture for the treatment of diabetic peripheral neuropathy reported that manual acupuncture had a better effect on global symptom improvement compared with vitamin B12 or no treatment, and that the combination of manual acupuncture and vitamin B12 had a better effect compared with vitamin B12 alone. However, the authors could not draw clinically relevant conclusions because of high risks of bias in the studies included (169).

Tai chi is an ancient mind and body practice involving gentle, slow, continuous body movements with mental focus, breathing and relaxation. Although there may be some benefit in quality of life, there is little evidence for benefit of tai chi on glycemic control in diabetes (170,171).

Manual Therapies

There is a growing number of people with diabetes who seek care for musculoskeletal complaints and overall lifestyle management

from natural and/or complementary medicine practitioners. Manual therapies, including chiropractic, physiotherapy, shiatsu, registered massage therapy and craniosacral therapy have no randomized controlled trial data in people with diabetes. A few small studies on tactile massage, a superficial gentle form of massage, have failed to demonstrate a significant beneficial effect on A1C (172–174). Reflexology is a system of massage based on the theory that reflex points on the feet, hands and head are linked to other internal parts of the body. In a small, open-label, randomized controlled trial in people with diabetic peripheral neuropathy, foot reflexology was shown to reduce A1C and FPG, and improve pain scores and nerve conduction velocity (175).

RECOMMENDATIONS

1. Health-care providers should ask about the use of complementary and alternative medicine in people with diabetes [Grade D, Consensus].
2. There is insufficient evidence to make a recommendation regarding efficacy and safety of complementary or alternative medicine for individuals with diabetes [Grade D, Consensus].

Abbreviations:

A1C, glycated hemoglobin; ALA, alpha linoleic acid; BP, blood pressure; CAM, complementary or alternative medicine; CV, cardiovascular; CVD, cardiovascular disease; FPG, fasting plasma glucose; HDL-C, high-density lipoprotein cholesterol; IGT, impaired glucose tolerance; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarct; NCS, nerve conduction studies; NHP, natural health product; NPN, natural product number; OGTT, oral glucose tolerance test; TCM, traditional Chinese medicine; TG, triglycerides, UAE, urinary albumin excretion.

Other Relevant Guidelines

Physical Activity and Diabetes, p. S54

Author Disclosures

Dr. Grossman reports grants and personal fees from Novo Nordisk, Janssen, and Eli Lilly; grants from Merck, Takeda, Sanofi, AstraZeneca, and Lexicon, outside the submitted work; and previous employee (now retired) of Eli Lilly Canada. No other authors have anything to disclose.

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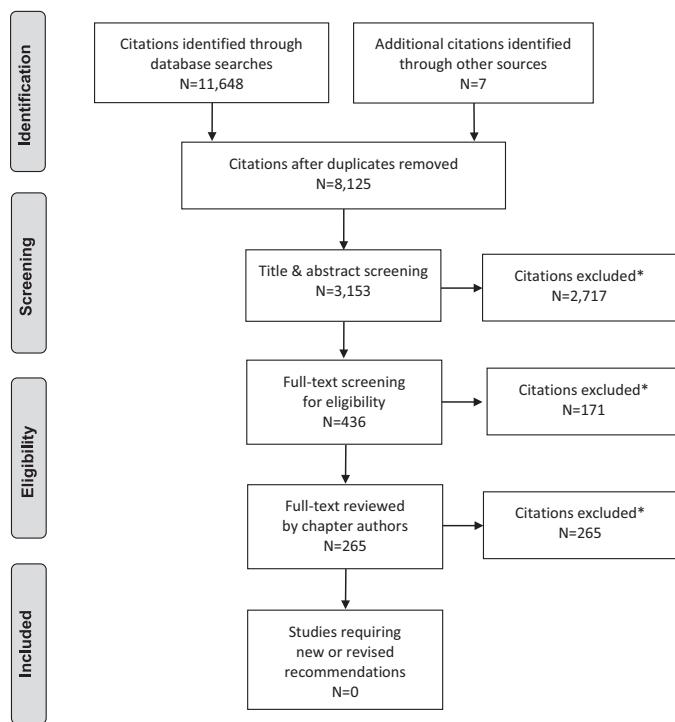
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Literature Review Flow Diagram for Chapter 22: Complementary and Alternative Medicine for Diabetes



*Excluded based on: population, intervention/exposure, comparator/control or study design.

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed.1000097 (176).

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