Complementary and alternative medicine for the treatment of type 2 diabetes

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Abstract

OBJECTIVE To review clinical evidence supporting complementary and alternative medicine interventions for improving glycemic control in type 2 diabetes mellitus.

QUALITY OF EVIDENCE MEDLINE and EMBASE were searched from January 1966 to August 2008 using the term *type 2 diabetes* in combination with each of the following terms for specific therapies selected by the authors: *cinnamon*, *fenugreek*, *gymnema*, *green tea*, *fibre*, *momordica*, *chromium*, and *vanadium*. Only human clinical trials were selected for review.

MAIN MESSAGE Chromium reduced glycosylated hemoglobin (HbA_{1c}) and fasting blood glucose (FBG) levels in a large meta-analysis. *Gymnema sylvestre* reduced HbA_{1c} levels in 2 small open-label trials. Cinnamon improved FBG but its effects on HbA_{1c} are unknown. Bitter melon had no effect in 2 small trials. Fibre had no consistent effect on HbA_{1c} or FBG in 12 small trials. Green tea reduced FBG levels in 1 of 3 small trials. Fenugreek reduced FBG in 1 of 3 small trials. Vanadium reduced FBG in small, uncontrolled trials. There were no trials evaluating microvascular or macrovascular complications or other clinical end points.

CONCLUSION Chromium, and possibly gymnema, appears to improve glycemic control. Fibre, green tea, and fenugreek have other benefits but there is little evidence that they substantially improve glycemic control. Further research on bitter melon and cinnamon is warranted. There is no complementary and alternative medicine research addressing microvascular or macrovascular clinical outcomes.

Résumé

OBJECTIF Faire le point sur les données cliniques en faveur d'interventions de médecine complémentaire et alternative pour améliorer le contrôle de la glycémie dans le diabète de type 2.

QUALITÉ DES PREUVES On a consulté MEDLINE et EMBASE entre janvier 1966 et août 2008 à l'aide du terme *type 2 diabetes* en combinaison avec chacun des termes suivants pour des traitements spécifiques, choisis par les auteurs : *cinnamon*, *fenugreek*, *gymnema*, *green tea*, *fibre*, *momordica*, *chromium* et *vanadium*. Seuls les essais cliniques humains ont été retenus pour cette étude.

PRINCIPAL MESSAGE Le chrome a réduit l'hémoglobine glycosylée (HbA_{1c}) et la glycémie à jeun (GÀJ) dans une grande méta-analyse. Le gymnema sylvestre a réduit les niveaux d' HbA_{1c} dans 2 petits essais sans insu. La cannelle a amélioré la GÀJ, mais on ignore ses effets sur l' HbA_{1c}. La margose n'a eu aucun effet dans 2 petits essais. Les fibres ont eu des effets variables sur le HbA_{1c} ou sur la GÀJ dans 12 petits essais. Le thé vert a abaissé la GÀJ dans 1 essai sur 3. Le fenugrec a diminué la GÀJ dans un essai sur 3. Le vanadium a réduit la GÀJ dans des petits essais non contrôlés. Aucun essai n'a évalué les complications micro ou macro-vasculaires, ou d'autres issues cliniques.

CONCLUSION Le chrome et possiblement le gymnema sylvestre semblent améliorer le contrôle de la glycémie. Les fibres, le thé vert et le fenugrec ont d'autres effets bénéfiques, mais il y a peu de données indiquant qu'ils améliorent le contrôle de la glycémie. La margose et la cannelle mériteraient d'autres études. Il n'existe aucune recherche en médecine complémentaire et alternative sur les issues cliniques micro ou macro-vasculaires.

Type 2 diabetes mellitus (DM) is one of the most prevalent and fastest growing diseases in Canada, responsible for expenditures of 9 billion dollars per year.[1] Family physicians play a central role in the management of diabetes. Although many drugs improve glycemic control, they do not necessarily provide real-world benefits. In the recent ACCORD (Action to Control Cardiovascular Risk in Diabetes)[2] and ADVANCE (Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation)[3] trials, intensive glycemic control had minimal effect on clinical cardiovascular outcomes. In fact, in a recent meta-analysis, combination therapy with metformin and glyburide increased the risk of a composite end point of cardiovascular events and mortality (relative risk 1.43, 95% confidence interval [CI] 1.10 to 1.85).[4] The use of thiazolidinediones has recently been called into question because they increase cardiovascular risk and fracture risk.[5]

More than one-third of Canadians are using complementary and alternative medicine (CAM) therapies,[6] often without consulting or even informing their FPs. It is important for FPs to ask patients about their CAM use and provide evidence-based information about the safety and efficacy of commonly used CAM therapies.

Here we provide a brief review of the evidence supporting the use of several CAM therapies commonly used to treat type 2 DM.

Quality of evidence

MEDLINE and EMBASE were searched from January 1966 to August 2008. The search key words were *type 2 diabetes* in combination with each of *cinnamon, fenugreek, gymnema, green tea, fibre, momordica, chromium,* and *vanadium.* These interventions were selected by the authors based on

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literature reviews and clinical experience. Results were screened by one author to include clinical trials, systematic reviews, and meta-analyses. Only human clinical trials were selected for review.

Main findings

Relevant findings for each search term are briefly summarized in **Table 1** and are detailed as follows:

Cinnamon. True cinnamon (*Cinnamomum verum*) is a small evergreen tree, the bark of which is a common culinary spice. Most cinnamon sold in the United States and Canada is actually derived from *C aromaticum* or *C cassia,* sometimes called "Chinese cinnamon" to distinguish it from *C verum.* Cinnamon has been used for thousands of years to treat diabetes and other conditions. The aqueous extract appears to activate the insulin receptor by multiple mechanisms, and also increases glycogen synthase activity.[7-10]

A recent meta-analysis identified 5 trials (N = 282) that evaluated *C cassia* at 1 to 6 g daily for 40 days to 4 months.[11] One trial was not randomized, while another trial investigated adolescents with type 1 diabetes. The other 3 randomized controlled trials (RCTs) involved 196 patients. In one, 60 patients with poorly controlled diabetes were given 1, 3, or 6 g of *C cassia* for 40 days. Fasting blood glucose (FBG) levels decreased by 18% to 29%, but chromium-reduced glycosylated hemoglobin (HbA_{1c}) levels were not investigated.[12] In a second trial, 79 well-controlled diabetes patients received 3 g of *C cassia* daily for 4 months. More moderate reductions in FBG levels (average 10.3% vs 3.4% in placebo group, $P = .046$) were noted, but HbA_{1c} levels were unchanged.[13] In the third trial, 43 patients with diabetes with an average HbA_{1c} measurement of 7.1% were treated with 1 g daily for 3 months. No change was reported in FBG or HbA_{1c} levels.[14]

No significant adverse effects were reported in the reviewed trials. The only reported risk of cinnamon use is contact dermatitis from volatile oils. Safety in pregnancy has not been studied.

Overall, there is moderate evidence that cinnamon lowers blood glucose levels. Its effect on HbA_{1c} appears negligible, but long-term studies are required to properly evaluate this outcome.

Chromium. Chromium is an essential trace element with many sites of action, including carbohydrate and lipid metabolism. Trivalent chromium is a constituent of a complex known as the "glucose tolerance factor,"[15] and chromium deficiency causes reversible insulin resistance and diabetes.[16-18]

A meta-analysis identified 41 trials (N = 1198) that evaluated the effects of various chromium formulations at doses of 200 to 1000 µg daily for 2 to 26 weeks. Of these, 14 trials (n = 431) evaluated patients with type 2 DM and baseline HbA_{1c} levels of 7.0% to 10.2%. Chromium picolinate and brewer's yeast at doses of 200 to 1000 µg for 6 to 26 weeks reduced HbA_{1c} levels by an average of 0.6% (95% CI -0.9% to -0.2%) and FBG levels by an average of 1 mmol/L (95% CI -1.4 to -0.5).[19] These findings are limited by the fact that more than half the studies included were of poor quality and used different formulations and doses of chromium in populations that might have had very different amounts of chromium in their diet. No significant adverse effects were reported in any of the reviewed trials.

The meta-analysis included 2 RCTs that evaluated combination therapy using 600 µg chromium picolinate and 2 mg biotin. Biotin is a B vitamin that has enhanced chromium absorption in animal studies. One 3-month trial in 447 patients with diabetes (mean baseline HbA_{1c} level 8.6%) noted an HbA_{1c} level reduction of 0.54% ($P = .03$) overall, and an impressive 1.76% reduction among patients with baseline HbA_{1c} levels above 10% ($P = .0001$).[20] In the second trial, 36 patients with diabetes were treated for 1 month; no reduction in FBG was seen.[21]

Table 1. Summary of evidence supporting complementary and alternative medicine therapies for type 2 diabetes mellitus

INTERVENTION	BODY OF EVIDENCE
Cinnamon	FBG level reduction in 2 of 3 trials
Chromium	HbA_{1c} and FBG level reduction in meta-analysis
Vanadium	FBG level reduction in uncontrolled trials
Fibre	HbA_{1c} level reduction (non-significant) in 1 of 3 trials FBG level reduction in 6 of 12 trials
Green tea	FBG level reduction in 1 of 3 trials Other benefits
Bitter melon	No benefit to HbA_{1c} or FBG levels in 2 small trials
Fenugreek	FBG level reduction in 1 of 3 trials Other benefits
Gymnema	HbA_{1c} level reduction in 2 small trials

HbA_{1c}—glycosylated hemoglobin A_{1c}, FBG—fasting blood glucose.

There is strong evidence that 200 to 1000 µg of chromium picolinate daily improves glycemic control. Based on its safety and potential cost-effectiveness, a definitive clinical trial is urgently needed. Biotin might enhance its effects, but this combination requires further study.

Vanadium. Vanadium is a poorly understood trace element that is ubiquitous in nature and believed to have many functions in human physiology. In vitro and animal studies have demonstrated its insulinomimetic effects mediated by inhibition of phosphotyrosine phosphatase enzymes that affect the insulin receptor.[22-24]

A recent meta-analysis identified 5 uncontrolled trials (N=48) in which 50 to 300 mg of vanadium was administered for 3 to 6 weeks.[25] Vanadyl sulfate was used in 4 trials and sodium metavanadate was used in 1 trial. All 5 trials reported reductions in FBG levels, but these were of short duration; none of the trials included controls. Commonly reported side effects included gastrointestinal upset, bloating, and nausea.

There is insufficient evidence to support the use of vanadium in the treatment of type 2 DM.

Fibre. Dietary fibre is recognized as an important part of a healthy diet. Soluble and insoluble fibre have positive effects on cardiovascular risk factors,[26] intestinal disorders,[27] and certain cancers.[28-30] Cohort studies suggest that consumption of cereal fibre and whole grains is inversely related to type 2 DM incidence.[31]

We identified 12 small RCTs (N=345) that evaluated the effect of fibre in diabetes patients.[32-43] Many different kinds of fibre were used, including wheat, guar, beet, soy, corn, agar, glucomannan, psyllium, and mixtures. Daily doses of 2 to 50 g were administered for 3 to 20 weeks. In 3 trials of 12 to 20 weeks' duration, only 1 found an improvement in HbA_{1c} levels: in this trial of 76 patients with well-controlled diabetes, a non-significant decrease from 6.6% to 6.1% was seen in those who consumed agar containing 4.5 g fibre daily for 12 weeks. Six of the 12 RCTs reported reductions in FBG; the other 6 RCTs reported no change in this outcome. Most of the studies also reported improvements in other risk factors, particularly those related to cholesterol levels. Some trials reported gastrointestinal side effects, including bloating, diarrhea, and abdominal pain.[44]

There is little evidence that dietary fibre improves glycemic control. Existing trials are limited by the heterogeneity of fibre formulations and the variation in doses and duration of treatment. Evidence of a short-term hypoglycemic effect in diabetes patients is conflicting. Nonetheless, fibre can be recommended based on its salutary effect on other cardiovascular risk factors.

Green tea. Green and black tea both originate from the leaves of the *Camellia sinensis* plant. Green tea is heated to inactivate the enzymes that would otherwise oxidize the freshly collected leaves. The numerous health benefits of tea consumption are attributed to polyphenol catechins, particularly epigallocatechin gallate.[45,46] These compounds have improved insulin sensitivity and reduced β-cell damage in animal and in vitro studies.[47-53] Although caffeine initially impairs glucose metabolism, long-term exposure stimulates lipolysis, increases basal energy expenditure, and mobilizes muscle glycogen.[54,55] Prospective and retrospective population studies suggest that green tea consumption reduces the risk of type 2 DM by up to 48%.[56,57] Surprisingly, only 1 small RCT (N=49) has evaluated green tea in the context of diabetes. In this study, patients with baseline HbA_{1c} levels of 6.5% to 9.1% were randomized to receive either an extract containing green tea catechins and black tea theaflavins or placebo for 3 months. No improvements in HbA_{1c} levels were seen and FBG values were not measured.[58] Side effects included a generalized rash in 1 patient and diaphoresis in 1 patient.

Three open-label trials (N=141) of 1 to 2 months' duration reported no changes in HbA_{1c} values.[59-61] Investigators in one trial administered 1.5 L of oolong (partly oxidized) tea to 20 patients for 4 weeks and reported a 30% decrease in FBG levels ($P<.001$).[44]

There is little evidence to support the use of green tea for glycemic control. Epidemiologic data suggest large potential benefits, but further research is warranted. Green tea consumption should still be recommended for its other potential health benefits.

Bitter melon. Bitter melon (*Momordica charantia*) is a tropical vine that produces fruit that is used to treat diabetes in many traditional cultures, including Indian Ayurvedic medicine. Several of its active ingredients, including charantin, vicine, and polypeptide-p,[62-64] are believed to stimulate insulin secretion and alter hepatic glucose metabolism.[65-67]

Two RCTs have evaluated the effects of bitter melon in patients with type 2 DM. In one RCT, 40 patients with baseline HbA_{1c} values of 7% to 9% were given either 3 g of fruit and seed extract or placebo. After 3 months, there was no change in HbA_{1c} or FBG values.[68] The other trial, in which 51 patients consumed either 6 g of fruit and seed extract or placebo for 1 month, also reported no effect on HbA_{1c} or FBG values.[69] No side effects were reported in either trial.

There is no evidence to support the use of bitter melon. It should be noted that stimulating insulin release is probably less desirable than improving insulin sensitivity. Bitter melon's widespread traditional use merits further study, particularly in patients originating from cultures with a long history of traditional use.

Fenugreek. Fenugreek (*Trigonella foenum-graecum*) has been cultivated and used medicinally and ceremonially for thousands of years in Asian and Mediterranean

cultures. Its leaves and seeds are used to treat diabetes in Ayurvedic and other traditional medical systems. The most studied active ingredient is 4-hydroxyisoleucine, which increases pancreatic insulin secretion and inhibits sucrose α-D-glucosidase and α-amylase.[70-72] Additionally, fenugreek seeds are used to lower cholesterol, as sapogenins in the seeds increase biliary secretion[73-80]; they are also a good source of fibre.

Three small short-term RCTs (N=50) have evaluated fenugreek in patients with type 2 DM. In one trial, 25 patients consumed 1 g of seed extract or placebo for 2 months with no change in FBG levels.[81] In a small crossover study, 10 patients added 25 g of defatted seed powder to 1 meal or ate the meal without the powder for 15 days. Several measures of glucose metabolism were all unchanged.[82] A third trial, which used a higher dose (100 g) of defatted seed powder in 15 patients for 10 days, did report improvements in FBG values.[83] None of the trials investigated HbA_{1c} levels. No adverse effects were reported.

There is very limited evidence to support the use of fenugreek in diabetes management. High doses of seed powder might be effective but require further study and are likely impractical for most patients. Its widespread traditional use and its reported lipid-lowering benefits warrant further study.

Gymnema. *Gymnema sylvestre* is also known as *gurmar* (sugar destroyer) in Hindi. The leaves of this plant are used in Ayurvedic medicine to treat diabetes, cholesterol, and obesity.[84] Gymnemic acid, a mixture of many different saponins, is believed to be the active fraction, although a clear mechanism of action is yet to be been determined.[85]

Two small open-label trials have yielded promising results. In the first trial, 22 patients with type 2 DM were given either 200 mg of an ethanolic extract daily or their usual treatment for 18 to 20 months. Significant improvements in FBG and HbA_{1c} levels ($P<.001$ for both) were noted in the test group.[86] The other trial was uncontrolled, but reported that 3 months of treatment with 800 mg daily of a similar extract reduced FBG levels by 11% and HbA_{1c} levels by 0.6% in a mixed population of 65 patients with type 1 and type 2 diabetes.[87] No adverse effects were reported in either trial.

Preliminary evidence of any benefit is probably insufficient to support the widespread use of *G sylvestre* for diabetes management at this time. The significant improvements in HbA_{1c} levels definitely warrant further study as well as judicious use in selected patients.

Conclusion

Changes in HbA_{1c} values are most often used to evaluate hypoglycemic effects. It is important to consider that the life span of a red blood cell is 120 days. Therefore, studies investigating diabetes management should involve HbA_{1c} measurements and should be of at least 4 months' duration. Most of these trials were of insufficient duration to evaluate this outcome. None of the research examined has addressed the potential effect of CAM interventions on cardiovascular outcomes. This is important because better glycemic control might not always lead to real-world clinical benefits. It is also important because some interventions can improve other cardiovascular risk factors.

EDITOR'S KEY POINTS

- Chromium (200 to 1000 µg per day) is the only complementary and alternative medicine intervention with level 1 evidence to support its use in diabetes management, but a large-scale clinical trial is needed to confirm these findings.
- Small studies indicate that *Gymnema sylvestre* improves HbA_{1c} levels. Larger studies are required to confirm these promising findings.
- Cinnamon probably lowers blood glucose levels, but its effects on HbA_{1c} levels are unknown.
- Bitter melon has a long history of traditional use, but preliminary evidence suggests its benefits might be limited.
- Vanadium is poorly understood, has potential adverse side effects, and should probably be avoided.
- Green tea, fenugreek, and fibre can be recommended on account of their other health benefits, but evidence that they improve glycemic control is limited and conflicting.

POINTS DE REPÈRE DU RÉDACTEUR

- La seule substance en médecine complémentaire et alternative dont l'usage dans le traitement du diabète s'appuie sur des preuves de niveau 1 est le chrome (200 à 1000 µg/d), mais il faudra un essai clinique à grande échelle pour confirmer ces observations.
- Certaines petites études indiquent que le *gymnema sylvestre* améliore les niveaux de HbA_{1c}. Ces résultats prometteurs devront être confirmés par de plus larges études.
- La cannelle abaisse probablement le glucose sanguin, mais on ignore ses effets sur le HbA_{1c}.
- La margose est d'usage traditionnel depuis longtemps, mais des données préliminaires suggèrent que ses avantages pourraient être limités.
- Les effets du vanadium sont mal connus; il pourrait avoir des effets indésirables et on devrait vraisemblablement l'éviter.
- Le thé vert, le fenugrec et les fibres peuvent être recommandés à cause de leurs autres effets bénéfiques sur la santé, mais les preuves qu'ils améliorent le contrôle de la glycémie sont limitées et contradictoires.

Overall, there is a paucity of research evaluating CAM therapies that are commonly used to treat type 2 DM. This should be a high priority for CAM researchers and funding agencies.

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Contributors

Dr Nahas and **Mr Moher** contributed to the literature review, selection and review of studies, and preparation of the manuscript for publication.

Competing interests

None declared

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