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DIABETES

LITERATURE REVIEW

The Safety and Efficacy of Common Herbal and Dietary Supplements in Patients with Type 2 Diabetes Mellitus: Part 3

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One of the reasons to discuss complementary and alternative medicine (CAM) supplements used by patients with diabetes is that this subpopulation is 1.6 times more likely than those without diabetes to consume CAM supplements. Thus, patients with diabetes might be more prone to problems relating to CAM.[1]

While part 1 of this literature review series discussed *Aloe vera* and alpha-lipoic acid, part 2 of this series presented information on chromium, cinnamon, fenugreek, garlic, and *Gymnema sylvestre*. This last part provides study findings relating to ginseng, magnesium, nopal, and psyllium. Table 1 summarizes the common dosages, adverse effects, and drug interactions of the herbal supplements discussed in this review, and Table 2 summarizes the studies and their findings examined in this review.

GINSENG RESULTS

American ginseng has shown to be superior to Chinese ginseng in reduction of blood glucose levels in numerous study findings.[2-4] One study with 10 nondiabetic participants indicated that administration resulted in a change of 19% ± 22% and 22% ± 17% for subjects with type 2 diabetes mellitus.[5] A second study with 10

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Summary Points

- The evidence on ginseng, magnesium, nopal, and psyllium relating to type 2 diabetes management is inconsistent, thus more studies are warranted to shed some light on their effectiveness regarding glycemic management.
- Although most of the studies included in this literature review series were randomized clinical trials and meta-analyses of randomized clinical trials, there was high heterogeneity across the studies and data were considered to have limited quality because of various preparations of supplements, dosages of supplements, and duration of treatment, as well as different subject cohorts.

participants with type 2 diabetes produced similar results when comparing administration with placebo, 3 g, 6 g, or 9 g of ginseng. Administration resulted in a significantly ($P < 0.05$) incremental glycemic reduction at 30 minutes (16.3%, 18.4%, and 18.4%, respectively), 45 minutes (12.5%, 14.3%, and 14.3%, respectively), and 120 minutes (59.1%, 40.9%, and 45.5%, respectively).[6] Taking American ginseng 100 mg to 200 mg daily for eight weeks also reduced fasting blood glucose levels in patients with type 2 diabetes.[7]

Although the number of experimental trials and participants was small, these studies suggest American ginseng is superior to Chinese ginseng for glycemic management.

GINSENG DISCUSSION

Ginseng is one of the 700 plant species, including carrots, parsnips, and celery, belonging to the *Araliaceae* family. This herb has existed for thousands of years, first being discovered in Manchuria, China. Today, ginseng continues to be a relevant topic of holistic alternatives in the treatment of cancer, diabetes, and cardiovascular disease.

MAGNESIUM RESULTS

Magnesium is an electrolyte that plays many physiological roles in the human body, ranging from supporting a healthy immune system to maintaining normal nerve and muscle function. This electrolyte also aids in regulating blood glucose levels and serves as a cofactor in the production of energy and protein.[8]

Two studies indicated that magnesium supplementation may reduce the risk of developing type 2 diabetes, resulting in higher fasting insulin levels in people without diabetes.[9,10] Three individual studies and one meta-analysis indicated that supplementation of various forms and dosages of magnesium in patients with type 2 diabetes resulted in a reduction of fructosamine, fasting blood glucose, two-hour postprandial blood glucose, and hemoglobin A1c (HbA1c) levels at the end of each trial.[11-14] In contrast, two individual randomized controlled trials yielded no significant difference between treatment and placebo groups at the end of the studies.[15,16]

MAGNESIUM DISCUSSION

Hypomagnesemia is a condition that occurs in 25% to 38% of patients who have type 2 diabetes, and it is especially common in patients with poorly managed diabetes.[17] Lower serum magnesium levels also are associated with a rapid decline in renal function.[9] The information available for magnesium as a supplement in managing type 2 diabetes has had mixed results, mostly owing to the different variations of dosing and formulations. When magnesium is given orally, it generally is well-tolerated, but it may cause symptoms, such as nausea, vomiting, and diarrhea. Due to variations in dosing and formulations, it is difficult to assess magnesium's efficacy on reducing blood glucose in patients with a history of diabetes.

NOPAL RESULTS

Nopal, also known as prickly pear, is commonly used for food in Mexico and the southwestern United States. The specific species *Opuntia streptacantha* has been researched for its potential for glycemic management. A meta-analysis in 2019 of the *Opuntia spp*. concluded that, specifically, the cladode, or leaf, of the cactus had significant antihyperglycemic effects in healthy people and patients with type 2 diabetes.[18]

However, a majority of the studies for cladode consumption were performed by the

Table 1. Common Dosages and Adverse Effects of Herbs and Dietary Supplements

Supplement	Typical Dosages	Adverse Effects	Drug Interactions
Ginseng	• American ginseng capsules 1,000 mg to 3,000 mg daily prior to meals	Insomnia, restlessness, increased blood pressure or heart rate, headache, mastalgia, mood changes, nervousness	• Warfarin • Diuretics • Antihypertensives • Immunosuppressive • Monoamine oxidase inhibitors • Cytochrome P450 2D6 interactions
Magnesium	• Magnesium oxide 41.4 mmol/day • Magnesium chloride 2.5 g/day • Magnesium sulfate 300 mg capsules three times daily with meals	Gastrointestinal irritation, nausea, vomiting, diarrhea, hypermagnesemia when given to renally impaired patient	• Antacids • Bisphosphonates • Calcium channel blockers • Digoxin
Nopal	• Steamed cactus 300 g with meal • Broiled stems 500 g as single dose	Diarrhea, nausea, abdominal fullness, headache	• Antidiabetic drugs
Psyllium	• Black psyllium 15 g/day	Flatulence, bloating	• Carbamazepine • Digoxin • Lithium

Source: Jellin JM, Gregory P, Batz F, et al. *Natural Medicines Comprehensive Database*. 3rd ed. Therapeutic Research Faculty; 2000.

Frati et al group, and glucose levels were measured after a single consumption of *Opuntia spp*. cladode.[18] The most recent studies by Linares et al, Bacardia-Gascon et al, and Guevare-Cruz et al spanned a period of three to six weeks, but two out of the three studies reported no significant difference to placebo after glucose tolerance testing.[19-21] The variation in duration and conflicting results from each trial have created doubt on nopal's long-term effects on blood glucose management.

NOPAL DISCUSSION

O. streptacantha contains high-soluble fiber that may contribute to its antiglycemic effect by slowing down carbohydrate absorption.[22] Nopal also may have synergistic effects with insulin, but an experiment with pancreatectomized animals suggests its antiglycemic effects do not completely depend on the presence of insulin.[23]

PSYLLIUM RESULTS

A meta-analysis consisting of 35 randomized controlled trials reported significant improvement in both fasting blood glucose concentration and HbA1c, indicating that psyllium dosed before meals would be an effective addition to a lifestyle intervention program.[24]

In patients who were being treated for type 2 diabetes, long-term psyllium use showed a significant mean reduction in fasting blood glucose by -37 mg/dL ($P < 0.001$) and mean HbA1c reduction of -0.97% ($P = 0.048$).[24] A more recent randomized controlled study published in 2016 reported significant reduction in body mass index when compared to the control group in patients with type 2 diabetes (31.8 kg/m^2 to 30.9 kg/m^2 vs. 31.5 kg/m^2 to 31.8 kg/m^2; $P < 0.001$).[25] It also reported improvements in fasting blood glucose levels (163 mg/dL to 119 mg/dL) and HbA1c levels (8.5% to 7.5%).[25]

PSYLLIUM DISCUSSION

Psyllium is commonly known as a dietary fiber used as a bulk-forming laxative to treat chronic constipation and for softening stools in a wide range of conditions. Psyllium is classified as a soluble fiber that can dissolve in water and form a gel-like material. The forming of a viscous material reduces digestion and absorption of carbohydrates, thus delaying glucose absorption into the circulation.[24] Although the current data show that psyllium would be an effective intervention in patients with diabetes, the variability of subject cohorts, protocols, and quality of trials may obscure information. Additional studies are needed to determine the best way to incorporate psyllium into clinical practice.

> In particular, the available data suggest that [*Aloe vera*, psyllium, *Gymnema sylvestre*, and fenugreek] may reduce HbA1c levels in patients with diabetes, and, thus, may have long-term effects.

OVERALL ANALYSES

The efficacy of each supplement on lowering blood glucose levels varied greatly across the available evidence. The more promising supplements that seem to have a favorable outcome in patients with diabetes are *A. vera*, psyllium, *G. sylvestre*, and fenugreek. In particular, the available data suggest that these four supplements may reduce HbA1c levels in patients with diabetes, and, thus,

Table 2. Summary of Notable Studies for Dietary and Herbal Supplements

Supplement	Notable Studies	Type of Study	Participants	Measurements	Findings
Ginseng	Kim et al (2011)[3]	Meta-analysis of four RCTs	n = 76 (type 2 diabetes)	Fasting glucose and HbA1c	• No significant decrease in FPG (weighted mean difference: -0.43 mmol/L; 95% CI, -1.16 to 0.30; *P* = 0.25) and HbA1c (weighted mean difference: 0.14%; 95% CI, -0.14 to 0.42; *P* = 0.32) for 12 weeks of treatment
		See Table 2A at https://bit.ly/3smpU3N.			
Magnesium	Song et al (2006)[13]	Meta-analysis of nine RCTs	n = 370 (type 2 diabetes)	Fasting glucose and HbA1c	• No significant decrease in HbA1c -0.31%; 95% CI, -0.81 to 0.19 • Significant decrease in FBG (weighted mean differences: -0.56 mmol/L; 95% CI, -1.10, -0.01; *P* = 0.03)
		See Table 2B at https://bit.ly/3smpU3N.			
Nopal	Gouws et al (2019)[18]	Systematic review of 12 RCTs with cladode leaf and four RCTs with a mix of cladode leaf/ fruit	Healthy people and patients with type 2 diabetes	Blood glucose levels	• A mix of cladode leaf/fruit and cladode leaf alone may exhibit reduction in serum glucose.
		See Table 2C at https://bit.ly/3smpU3N.			
Psyllium	Gibb et al (2015)[24]	Meta-analysis of 35 RCTs with 10 studies on participants with type 2 diabetes	1,267 healthy and at-risk subjects) and 245 participants with type 2 diabetes	HbA1c, fasting glucose, and postprandial glucose	• Individuals with type 2 diabetes: significant improvement observed in fasting glucose -37.0 mg/dL; *P* < 0.001 and in HbA1c, -0.97% (-10.6 mmol/mol); *P* = 0.048
		See Table 2D at https://bit.ly/3smpU3N.			

RCT: randomized controlled trial; HbA1c: hemoglobin A1c; FPG: fasting plasma glucose; CI: confidence interval; FBG: fasting blood glucose

may have long-term effects. In addition to these four supplements, studies suggest that magnesium, cinnamon, and garlic also may have an effect on fasting blood glucose levels.

However, magnesium, cinnamon, nopal, and garlic do not seem to have any long-term glycemic effects (e.g., HbA1c). Ginseng did not have strong supportive evidence for glycemic control because of the low number of studies and participants, but findings suggest that American ginseng may have postprandial glucose reduction. Most, if not all, of the studies varied greatly in terms of their study methods, dosages, and types of preparations of the supplements. These factors were accounted for when analyzing the data, making it difficult to make any definitive conclusions on the effectiveness of these supplements.

Magnesium, garlic, cinnamon, chromium, and alpha-lipoic acid all had conflicting research findings. Some studies reported reductions in glycemic levels while others reported no effect at all. This observation may suggest that there has not been a consistent benefit when taking these supplements and may vary in its effectiveness from individual to individual.

Because of inconsistent data from these supplements to support their effectiveness in glucose management, no conclusions could be made at this point. Interestingly, alpha-lipoic acid seems to have beneficial effects on peripheral neuropathy in patients with diabetes, which was not reported for any of the other supplements.

This suggests that further research is warranted for alpha-lipoic acid on its potential effect in patients with diabetes and diabetic peripheral neuropathy. Chromium was the most widely investigated supplement, and different studies have reported that there is no beneficial effect for its supplementation. However, data suggest that chromium's metabolic effects may not be significant until there is a significant chromium deficiency.[26]

The available evidence reviewed for each supplement appears to have high heterogeneity across the studies. These studies that we have included primarily were randomized clinical trials and meta-analyses of randomized clinical trials. However, most reported data were deemed to have limited quality because of the different preparations of supplements, dosages of supplements, duration of treatment, and different subject cohorts. This has made the interpretation of currently available data especially difficult,

thus hindering any firm recommendations to be made on any of these supplements. Additionally, the effective doses of these supplements were unable to be identified because of the various formulations and dosages used in the studies, leading to a wide range of therapeutic responses or lack thereof.

Few studies reported on the safety of these products. The most common side effect among these supplements was gastrointestinal-related, which included nausea, vomiting, gastrointestinal irritation, and diarrhea. One specific safety study on American ginseng showed no renal, hepatic, or hematologic side effects.[27] Some subjects also experienced contact dermatitis with garlic.[28,29] The lack of adverse effect reports may be because of publication bias to record positive effects or simply that there were no notable side effect differences between the placebo group and the treatment groups.

Nonetheless, if patients were taking herbal supplements in addition to prescription medications, it would be important to evaluate possible safety concerns. Further studies are warranted to better understand the safety of these herbal and dietary supplements, which includes toxicity levels and drug interactions. Determining their safety is especially important because the manufacturers are not required to complete any safety analyses before these products reach the market. ■

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ABSTRACT & COMMENTARY

Emotional Eating and Obesity

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SYNOPSIS: This review of research regarding the link between emotional eating (eating in response to unpleasant emotions) and obesity in adults suggested several factors that contribute to emotional eating and methods for patients to reduce it.

SOURCE: Konttinen H. Emotional eating and obesity in adults: The role of depression, sleep, and genes. *Proc Nutr Soc* 2020;79:283-289.

Definition of obesity: An abnormal accumulation of body fat to the extent that it may have an effect on health and body mass index (BMI) ≥ 30 kg/m².[1] The World Health Organization (WHO) recognized obesity as a disease state in the mid-1900s. By 2000, with the number of obese patients growing worldwide, the WHO recognized obesity as disease of epidemic proportion.[2]

The prevention and control of obesity is a challenge on multiple levels, starting with an individual, then family and community systems, and, finally, to public health. Medical implications of obesity are far-reaching and include an increased risk of type 2 diabetes, higher vulnerability to specific cancers, development of metabolic syndrome and cardiovascular diseases, gallbladder disease, osteoarthritic conditions, and some pulmonary disorders.[2,3]

However, even with widespread recognition of the medical consequences of obesity, its prevalence continues to grow worldwide, with rates tripling from 1975 until 2016. WHO statistics from 2016 note a 13% rate of obesity among adults worldwide. Among children, this trend is even more alarming, with a rise from 4% obesity worldwide in 1975 to slightly more than 18% in 2016.[4]

"Malnutrition in an Obese World," the 13th European nutritional conference, took place in Dublin in late 2019. At this meeting of nutrition researchers and clinicians, Konttinen presented a review of findings and clinical implications of emotional eating and obesity in adults. Current research investigating emotions and eating have revealed a complex interaction between the experience of emotions and the intake of food. It is clear that some high-intensity emotional states (fear, for example) are linked to physiologic states that reduce eating behaviors.

On the other hand, other emotions are linked to either increased or decreased eating. The pattern of increased eating of high-caloric, high-sugar/fat foods ("energy-dense, highly palatable foods") in response to negative emotions, such as sadness, disappointment, or anger, is termed "emotional eating." In most studies, emotional eating has shown an association with weight gain, higher BMI, and higher percentage of body fat.[5]

Understanding the characteristics of individuals who are more prone to emotional eating, and looking at clinical interventions to modify this behavior, drives much of the research in this field. In this comprehensive review article, Konttinen noted that the research has centered around three general areas in relation to emotional eating: depression, shortened night-sleep duration, and vulnerability.

EMOTIONAL EATING AND DEPRESSION

A change in appetite is a prominent symptom in depression, as noted in the *Diagnostic and Statistical Manual of Mental Disorders, 5th Edition* description of symptoms of major depressive disorder: "… weight loss when not dieting or weight gain …" and a "… decrease or increase in appetite nearly every day."[6] Konttinen cites studies identifying emotional eating as one factor linking depression to weight gain. One Dutch study associated emotional eating with weight gain independent of depressive symptoms, and a large study following depressed adults for seven years in Finland indicated that the mediator of increased BMI and waist circumference was emotional eating.

A U.S. study with an 18-year follow-up indicated that the association of emotional eating and depression is likely bidirectional. That is, emotional eating is implicated as a factor on the pathway to obesity and subsequent depression as well as on the pathway to develop obesity from preexisting depression. There are some limited data that exercise, or physical activity, can reduce emotional eating in response to stressful emotions.[7] For studies looking at physical activity, emotional eating in individuals with a diagnosis of depression may be the next step in this field of research.

SHORTENED SLEEP DURATION AND EMOTIONAL EATING

Shortened night-sleep duration is loosely defined here as a "habitual sleep time of six hours or less." Three studies

Summary Points

- Three main lines of research regarding emotional eating were reviewed: emotional eating as a response to depression; emotional eating associated with shortened night-sleep duration; and genetic factors linked to emotional eating.
- Results suggest that a focus on emotional regulation, sleep improvement, and physical activity may assist with decreasing emotional eating (and subsequently decreasing obesity).
- Genetic studies suggest that there are biological factors affecting vulnerability to emotional eating.

are cited as lending evidence of an association between emotional eating and weight gain. A two-year Dutch study found that women with a combination of high emotional eating and short sleep duration had the highest BMI increase. The large seven-year Finnish study in depressed adults noted that sleep durations of more than nine hours nightly seemed protective against the higher BMI and waist circumference found in emotional eaters who slept seven hours or fewer. Finally, a six-year French-Canadian study narrowed the association of short sleep duration and emotional eating with obesity by looking at the level of inhibition. In this study, disinhibited eating refers to an inherent tendency to overeat. Results of this study indicated that the combination of short sleep with high food disinhibition led to an association with weight gain and increased waist circumference.

GENETIC FACTORS AND OBESITY

Genetic factors influencing obesity have been investigated via twin studies looking at variations in BMI. In one large study (140,000 subjects), the contribution of genes to BMI appeared to change with age but have a substantial contribution (from 60% to 80%). Current investigations have centered on genetic influences on underlying eating behaviors.

Four studies are cited — two from Finland, and one each from France and the United Kingdom — where there appears to be an association between genetic risk of obesity and emotional eating. In these studies, there seem to be at least a partial mediating effect from emotional eating on the development of obesity in individuals with genetic risk. Several North American studies suggested similar findings, but the association was not as strong. Studies that looked at behaviors other than eating habits pointed to physical activity levels and noted the increased genetic susceptibility to obesity in less physically active individuals (vs. more active individuals). It appears there may be genetic influences on obesity that involve not only eating behaviors but also other factors, including level of physical activity. The interplay between all of these factors may be the key to understanding this complex relationship.

It is important to note all of these relationships are associations, and causation cannot be assumed or extrapolated. For example, Kontitinen notes that it while it may be that obesity develops in part because of emotional eating, reverse causation also should be considered. That is, a gain in body fat may directly or indirectly cause a change in hunger sensations and lead to a deficit in control of eating.

Although many questions remain unanswered in the realm of emotional eating and obesity, it is clear that our current understanding can be transformed into meaningful clinical interventions.

1. Ask patients with depression and weight gain about emotional eating. Consider recommending therapies that address emotional regulation to address the tolerance of difficult emotions (e.g., mindfulness interventions).[8]
2. In patients with unwanted weight gain, ask about length of sleep and any connection to emotional eating. Consider interventions that target improved nighttime sleep duration.
3. Acknowledge that genetic factors will play a role in weight gain and, potentially, in emotional eating. With this knowledge, patients may want to take steps to limit the availability or easy access to high-caloric, high-sugar/high-fat foods.[9]

Notably, these specific interventions are extrapolations from the current research and have not been subject to rigorous, well-controlled investigations. However, even if weight is not affected significantly, the potential health benefits of improved emotional regulation and longer nighttime sleep are numerous, and the risks are limited, at best.

The most practical take-home message from this study for the primary care provider may be that, when working with patients with weight gain concerns, think about eating and sleep patterns, adopt a nonjudgmental stance, and ask patients opened-ended questions about emotional eating. Although some patients may be reluctant to mention this eating pattern spontaneously, appropriate queries from a trusted provider can be helpful in understanding a fuller picture and creating a meaningful wellness plan. ■

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3. Pass the online test with a score of 100%; you will be allowed to answer the questions as many times as needed to achieve a score of 100%.
4. After successfully completing the test, your browser will be directed automatically to the activity evaluation form, which you will submit online.
5. Once the completed evaluation is received, a credit letter will be emailed to you.

CME QUESTIONS

1. According to the analysis by Konttinen, which of the following is true regarding emotional eating and obesity?

a. There are clear genetic factors affecting emotional eating and sleep duration, and these same genes are implicated in the vulnerability to obesity.
b. Depression, nighttime sleep duration, and genetic factors all are areas of research linking emotional eating and obesity. Although evidence is far from conclusive, addressing these areas may help with treating obesity.
c. About 75% of individuals who engage in emotional eating also have major depressive disorder.
d. There is no evidence that links nighttime sleep duration to emotional eating, but there is an association that is mediated by depression (i.e., sleep disturbance is because of depression and emotional eating is tied to depression).

2. Based on the findings/results from the meta-analyses presented in the article about herbal and dietary supplements for people with type 2 diabetes, which of the following herbal supplements has been shown the most promising in reducing hemoglobin A1c?

a. Ginseng
b. Magnesium
c. Nopal
d. Psyllium

[IN FUTURE ISSUES]

Childhood Obesity
E-Cigarettes and Oral Health
Long COVID

Table 2A. Breakdown of Kim et al (2011) Study Analyses

	Fasting Plasma Glucose (mmol/L)		Hemoglobin A1c (%)	
	Vuksan 2008	**Kim 2008**	**Vuksan 2008**	**Kim 2008**
Sample Size (Experiment/Control)	19/19	20/18	19/19	20/18
Mean Difference	-0.60	-0.31	0.20	-0.21
95% Confidence Interval	-1.75, 0.55	-1.25, 0.63	-0.05, 0.45	-0.94, 0.52

Table 2B. Breakdown of Song et al (2006) Study Analyses

Source and Year	Magnesium Dosage
Paolisso et al (1989)	Magnesium pidolate 2 g/day (7.0 mmol/day)
Paolisso et al (1994)	Magnesium pidolate 4.5 g/day (15.8 mmol/day)
Gullestad et al (1994)	Magnesium lactate-citrate 15 mmol/day
Purvis et al (1994)	Magnesium chloride 384 g/day (1.9 mmol/day)
Eibl et al (1995)	Magnesium citrate 30 mmol/day
Eriksson et al (1995)	Magnesium 600 mg/day (24.7 mmol/day)
de Loudre Lima (1998)	Magnesium oxide 41.4 mmol/day
de Valk et al (1998)	Magnesium aspartate hydrochloride 15 mmol/day
Rodriguez-Moran et al (2003)	Magnesium chloride 2.5 g/day (12.8 mmol/day)

Table 2C. Breakdown of Gouws et al (2019) Study Analyses

Study	Sample Size	Intervention	Results
Cladode Leaf Consumption: Acute Results with Single Consumption			
Frati et al (1983)	Healthy males (n = 5)	100 g broiled cladode stems	Glucose levels significantly reduced ($P < 0.05$)
Frati et al (1987)	Healthy adults (n = 16)	100 g of cladode, ground and mixed with 100 g of water	Various results depending on the time after consumption
Frati et al (1990)	Participants with type 2 diabetes (n = 8)	Cladode entirely broiled, blended ad broiled, blended, and blended and heated (60° C)	Glucose reduced significantly at 120 min and 190 min vs. control with $P < 0.01$
Frati et al (1991)	Group 1: type 2 diabetes (n = 8) Group 2: healthy volunteers (n = 6)	500 g broiled cladode	Glucose reduced significantly in Group 1 at two, four, and six hours ($P < 0.001$)
Frati et al (1991)	Group 1: type 2 diabetes (n = 14) Group 2: healthy volunteers (n = 14)	500 g grilled cladode	Glucose reduced significantly in participants with type 2 diabetes when compared to control ($P < 0.005$)
Frati et al (1988)	Participants with type 2 diabetes (n = 16)	500 g broiled cladode	Glucose reduced significantly when compared to baseline ($P < 0.001$)
Lopez-Romero et al (2014)	Participants with diabetes (n = 14)	150 g steamed nopal	Results varied depending on time and food item mixed with nopal
Castaneda-Andrade et al (1997)	Participants with diabetes (n = 8)	250 mg cladode capsule	Glucose reduced significantly ($P < 0.001$)
Cladode Leaf Consumption: Long-Term Results			
Frati et al (1983)	Healthy (n = 8); obese (n = 14); type 2 diabetes (n = 7) Length: 10 days	100 g broiled cladode before meals three times per day	Glucose reduced significantly compared to fasting level in participants with type 2 diabetes ($P < 0.001$)
Guevara-Cruz et al (2021)	Healthy individuals (n = 67) Length: 2 months	100 g nopal	No difference in glucose levels
Linares et al (2007)	n = 68 (placebo n = 33; treatment n = 35) Length: 6 weeks	1.5 g NeOpuntia capsule, after meals three times per day	No difference in glucose levels
Bacardi-Gascon (2007)	Participants with type 2 diabetes Length: 6 weeks	Cladode added to chilaquiles, burrito, quesadillas	Glucose reduced significantly overall with $P = 0.029$
Combined or Unidentified *Opuntia spp.* Fruit and Cladode Consumption: Acute Results with Single Consumption			
Deldicque et al (2013)	Healthy individuals (n = 11)	1,000 mg OpunDia and/or 3 g Leu	OpunDia reduced glucose levels by 7% (90 min) and 15% (120 min) when compared to placebo with $P < 0.05$
Van Proeyen et al (2012)	Healthy individuals (n = 6)	500 mg, 1,000 mg, 1,500 mg OpunDia	Pre-exercise: glucose reduction 30 mins ($P < 0.10$) and 60 mins ($P < 0.02$); post-exercise: glucose reduction 60 mins ($P < 0.04$)
Godard et al (2010)	Obese (n = 29)	200 mg OpunDia	Post OpunDia glucose levels when compared to fasting glucose level ($P < 0.05$)
Combined or Unidentified *Opuntia spp.* Fruit and Cladode Consumption: Long-Term Results			
Guevara-Arauza et al (2011)	Healthy individuals (n = 28) Length: 3 weeks	Nopal (32%) prickly pear pulp jam bar (15 g) and 100 g tortillas with nopal (48%)	Tortilla vs. control: glucose reduced significantly ($P < 0.05$); tortilla and prickly pear pulp jam bars: glucose reduced significantly ($P < 0.05$)

Table 2D. Breakdown of Gibb et al (2015) Study Analyses

Study	Number of Participants	Dose (g) per Day	Dose Form
Short-Term Duration in Populations with Type 2 Diabetes			
Sartor et al (1981)	12	6.6	Lunelax powder
Jarjis et al (1984)	14	7	Fybogel
Pastors et al (1991)	18	13.6	Metamucil
Wolever et al (1991)	6	20	Psyllium-enriched bran flakes
Franti-Munari et al (1998)	12	15	Psyllium mucilage
Dasjerdi et al (2007)	12	5	Psyllium granules
Long-Term Duration in Populations with Type 2 Diabetes			
Rodriguez-Moran et al (1998) (six-week duration)	125	15	Metamucil
Anderson et al (1999) (eight-week duration)	34	10.2	Metamucil
Ziai et al (2005) (eight-week duration)	49	10.2	Po Forsk
Feinglos et al (2013) (12-week duration)	37	13.6	Metamucil