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Natural Products for the Treatment of Type 2 Diabetes Mellitus

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Abstract

In the past decade, there has been an increase in the use of natural products in type 2 diabetes mellitus (T2DM). Several agents, such as guar gum, magnesium, oat bran, blond psyllium, and soy, have shown efficacy for treatment of T2DM. Objective: To review the scientific literature to identify effects of natural products (*i.e.*, dietary supplements) for the treatment of T2DM. Methods: A search of Natural Medicines Comprehensive Database was performed to identify natural products advocated for the treatment of T2DM. Natural products categorized as both "possibly effective" and "likely safe" (guar gum, magnesium, oat bran, blond psyllium, and soy) were selected for review. A MEDLINE (1950-March 2013) literature review was performed. Articles published within the last ten years (January 2003-March 2013) and pertinent articles published prior to 2003 were included in this review. Diabetes prevention studies were not selected for this review. Conclusions: Based on the published information, there is little evidence to support the use of herbal products for the treatment of T2DM. Some agents may be useful as adjunctive therapy; however, patients should be encouraged to speak with their health care practitioner before starting or stopping any herbal products.

Keywords

Dietary, Supplements, Natural, Products, Diabetes

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1. Introduction

Diabetes mellitus is a group of metabolic disorders described by elevated blood glucose. The criteria for diagnosing diabetes include a glycated hemoglobin (A1C) > 6.5%, fasting plasma glucose (FPG) > 126 mg/dL, or a 2-hour plasma glucose test > 200 mg/dL [1]. Currently, 25.8 million children and adults in the United States (8.3% of the population) have diabetes. Considering the 7.0 million undiagnosed individuals along with noncompliance in those with diabetes, the economic burden for the United States is vastly increasing every year, with a current estimate of $176 billion from medical expenses [2].

Several approaches can be taken to reduce the economic burden and improve patients' quality of life. Lowering a patient's A1C to less than 7% can help prevent macrovascular and microvascular complications of diabetes [3]. Treatment of diabetes involves not only pharmacotherapy but also an emphasis on diet and exercise. Adults with diabetes are advised to perform at least 150 minutes per week of moderate-intensity aerobic physical activity, spreading over three days per week with no more than two consecutive days without exercise [3]. Despite pharmacologic treatments and healthy lifestyle choices, optimum diabetes control is not always maintained. Therefore, patients may seek other alternatives, such as natural products to help control their diabetes.

The use of natural products has increased in the past decade. A natural product is defined as a "vitamin, a mineral, an herb or other botanical, an amino acid, a dietary substance for use by man to supplement the diet by increasing the total daily intake, or a concentrate, metabolite, constituent, extract, or combination of these ingredients [4]". According to a 2007 government survey, Americans spend $33.9 billion on herbal products or herbal-related physician visits [5]. Furthermore, a national survey from 1997-1998 reports 57% of patients with diabetes used some form of complementary or alternative medicine. Of these patients, 16% utilized herbal remedies, commercial diets, or folk remedies specifically intended for diabetes [6]. Even though patients may be using these herbal products for type 2 diabetes mellitus (T2DM), very few products have evidence showing their benefits for the treatment of T2DM. The purpose of this article is to evaluate the efficacy of guar gum, magnesium, oat bran, blond psyllium, and soy in patients with diabetes. This article focuses on these natural products and their effects on blood glucose and/or A1C levels in T2DM. The goal is to provide healthcare practitioners with information that can be incorporated into their clinical assessment and management of patients with diabetes.

2. Data Sources

Figure 1 displays the literature search and selection process used to identify clinical trials for this review. Natural Medicines Comprehensive Database was initially searched to identify natural products advocated for the treatment of T2DM. Natural products categorized as both "possibly effective" and "likely safe" were chosen, which included guar gum, magnesium, oat bran, blond psyllium, and soy. A literature review was performed in MEDLINE (1950-March 2013) using the keywords diabetes mellitus type 2, guar gum, magnesium, oat bran, psyllium, and soy. Additional references related to the topic were identified through primary literature, review articles, and textbooks. The references identified from the literature review were evaluated for the treatment of T2DM. All MEDLINE searches published within the last ten years (January 2003-March 2013) and pertinent articles published prior to 2003 were included in this review. Trials were required to contain measurable doses, be written in English, involve human subjects, and evaluate the natural medicine's effect on blood glucose and/or A1C. Diabetes prevention studies were not selected for this review.

3. Herbal Product Review

3.1. Guar Gum

Guar is a galactomannan soluble fiber derived from the seeds of the Indian Cluster bean, *Cyamopis tetragonoloba* [7]. When ingested, it expands in the presence of water to normalize bowel function. Guar's effect on carbohydrate metabolism is explained by its marked gel-forming ability resulting in delayed stomach emptying and slowed nutrient absorption. This action of slowing carbohydrate absorption makes guar gum an attractive choice for treating diabetes. However, there is concern that long-term guar use can lead to nutritional risks based on this mechanism of action [8] [9]. Several side effects including diarrhea, flatulence, and loose stools should be taken into consideration when using guar gum [10]. These side effects can be minimized by titrating guar up to the

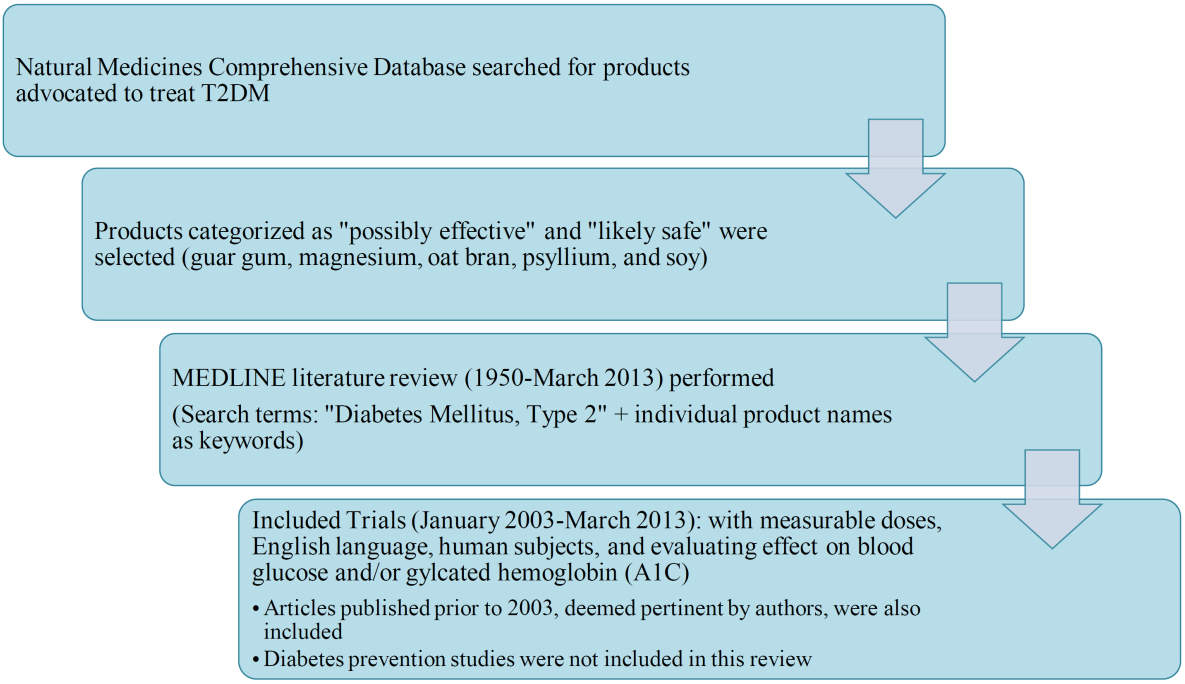

Figure 1. Literature search and product selection.

intended maintenance dose. Guar gum can decrease absorption of other medications that are taken orally; therefore it would be important to counsel patients to take their medication either one hour before or four hours after taking guar gum. It is also beneficial to educate patients on taking guar gum with eight ounces of water to prevent obstruction [11].

Six studies evaluated the effects of guar gum on fasting blood glucose or A1C in patients with T2DM [8] [12]-[16]. **Table 1** summarizes the trials related to guar gum. All studies were conducted over periods of ten to fifty-two weeks [12] [14] [16]. Various preparations of guar gum including mini tablets, high carbohydrate high fiber (HCF) bars, bread, granules, and powder were analyzed. The majority of studies used the typical dose of guar gum, which is 15 grams per day [8] [12]-[16] while one studied 5 grams per day [13]. A few studies found improvement in glycemic control ($p < 0.02$) [13]-[15]. The other trials demonstrated that use of guar gum did not significantly decrease fasting blood glucose, postprandial glycemia, or A1C [8] [12] [16]. Wilson *et al.* [15] compared use of a sulfonylurea alone to a sulfonylurea with guar gum. The authors found no differences in fasting plasma glucose or A1C in the guar gum group, however they did find benefit with the addition of metformin [16].

3.2. Magnesium

Magnesium is the second most abundant intracellular cation and the fourth most abundant cation in the body [17]. Hypomagnesemia is more common in people with poorly controlled diabetes [18] [19] and has been associated with decreased glucose uptake and insulin sensitivity. In addition, intracellular calcium may increase due to a decrease in intracellular magnesium, resulting in additional insulin resistance. Lower serum magnesium levels are associated with a more rapid decline in renal function in patients with T2DM [18] [19]. The most common side effects associated with magnesium supplements include gastrointestinal irritation, nausea, vomiting, and diarrhea [20]. While rare, larger amounts might cause magnesium toxicity with symptoms including thirst, hypotension, drowsiness, confusion, loss of tendon reflexes, muscle weakness, respiratory depression, cardiac arrhythmias, coma, cardiac arrest, and death [21].

Seven trials evaluating the use of magnesium supplementation in the treatment of T2DM met the search criteria with study populations ranging from nine to 128 patients [18] [22]-[27]. **Table 2** discusses the various trials evaluating magnesium supplementation. Three studies evaluated the use of magnesium for either 12 [23] or 16 weeks in duration [22] [26] while the remaining studies included treatment periods of four to six weeks [18]

Table 1. Guar gum trials.

Authors (Year)	Study Design	Subjects	Methods	Results
Groop (1993)	Single Blind Placebo Controlled	15 T2DM (8M; 7F)	Placebo Period 1: 8 weeks (placebo) Study Phase: 48 weeks (15 g guar gum/day) Placebo Period 2: 8 weeks (placebo)	Placebo 1 / Guar Gum / Placebo 2 A1C (%): 9.0 ± 0.3 / 8.5 ± 0.3 / 8.5 ± 0.3 Mean Plasma Glucose (mmol/L): 9.5 ± 0.5 / 9.2 ± 0.5 / 10.3 ± 0.5
Kirsten (1992)	Randomized Open-labeled Controlled	41 (29M; 11F)	Study Phase: 3 months Group A: 3 × 4 g daily of new guar preparation (GU-052, Steigerwald, Darmstadt, Germany) Group B: 3 × 5 g daily of Glucotard (Beohringer, Mannheim, Germany)	Time / A1C (%): Group A / Group B Initial: 12.6 ± 2.6 / 12.0 ± 2.6 30 days: 12.2 ± 2.3 / 11.7 ± 2.4 90 days: 10.5 ± 1.5 / 10.9 ± 1.8
Uusitupa (1989)	Control Phase: Double Blind Parallel Group Treatment Phase: Open-labeled	39 T2DM (12M; 26F)	Control Phase: 3 months (Group A: 5 g guar gum granules TID or Group B: placebo) Treatment Phase: 10 months (Group A & B: 5 g guar gum granules TID)	Time (months) / FPG (mmol/L): Group A (n = 20) / Group B (n = 19) / A1C (%): Group A (n = 20) / Group B (n = 19) Control Phase 0: 12.23 ± 2.37 / 12.80 ± 2.60 / 8.88 ± 1.35 / 9.41 ± 1.50 Control Phase 3: 2.00 ± 2.32 / 13.87 ± 3.54 / 8.38 ± 1.24 / 9.35 ± 1.86 Treatment Phase 5: 11.56 ± 2.59 / 12.53 ± 4.06 / 9.58 ± 1.94 / 9.93 ± 2.25 Treatment Phase 7: 11.79 ± 2.49 / 12.41 ± 3.25 / 9.39 ± 1.69 / 10.01 ± 2.13 Treatment Phase 9: 11.88 ± 2.50 / 12.13 ± 2.70 / 8.94 ± 2.04 / 9.21 ± 3.18 Treatment Phase 11: 12.69 ± 2.55 / 12.97 ± 3.21 / 9.36 ± 1.75 / 9.51 ± 1.79 Treatment Phase 13: 12.83 ± 2.59 / 13.01 ± 3.14 / 9.26 ± 2.19 / 9.57 ± 1.89 Two-way ANOVA: p < 0.001 / NS / p < 0.05 / NS
Wilson (1989)	Cross over	15 T2DM (12M; 3F)	Washout Phase 1: 6 weeks Study Phase 1: 8 weeks (Guar 5 g TID before main meals or metformin 0.5 g TID) Washout Phase 2: 6 weeks Study Phase 2: 8 weeks (Guar 5 g TID before main meals or metformin 0.5 g TID)	FPG (mmol) / A1C (%) Sulfonylurea alone: 12.9 ± 0.9 / 12.1 ± 0.5 Addition of guar: 13.7 ± 1.3 / 13.0 ± 0.6 Addition of metformin: 11.6 ± 1.2 / 12.4 ± 0.8 Significance: guar vs metformin: p < 0.01 / NS Significance: guar vs sulfonylurea alone: NS / NS Significance: metformin vs sulfonylurea alone: p < 0.01 / NS
Beattie (1988)	Randomized	27 T2DM (9M; 18F)	Study Phase: 20 weeks Group A: low fat, high carb (80 g), low energy diet with 15 g of fiber Group B: low fiber diet for 4 weeks, then changed; for 8 weeks as group A with 10 - 15 g of additional cereal fiber; for remaining time or 4 weeks; returned to low fiber diet with 15 g guar gum Group C: low fiber diet; guar gum diet for 8 weeks; high cereal fiber diet for 8 weeks	Weeks / Type of Diet / A1C[a] / FPG (mmol/l) Group A 0 / - / 66 (58 to 74) / 11.2 (8.4 to 14.0) 4 / Low fiber / 58 (52 to 64)[b] / 7.8 (5.5 to 10.1)[b] 12 / Low fiber / 50 (40 to 60)[b] / 8.0 (4.7 to 11.3)[b] 20 / Low fiber / 50 (38 to 61)[bc] / 7.8 (4.4 to 11.0)[b] Group B 0 / - / 64 (57 to 70) / 9.6 (7.1 to 11.9) 4 / Low fiber / 60 (53 to 67) / 8.2 (6.9 to 9.7) 12 / High fiber / 51 (46 to 55)[bc] / 7.4 (6.0 to 8.8)[c] 20 / Guar gum / 49 (43 to 54)[bc] / 6.8 (5.0 to 8.7) Group C 0 / - / 62 (50 to 74) / 9.6 (6.7 to 12.5) 4 / Low fiber / 53 (45 to 61)[b] / 7.8 (4.9 to 10.7)[b] 12 / Guar gum / 44 (38 to 50)[bc] / 6.5 (4.2 to 8.8)[bc] 20 / High fiber / 45 (40 to 50)[bc] / 6.5(4.9 to 8.1)[b] [a]Units = mmolhydrox-yl-methylfurfural/mmolHb [b]Significant reduction compared with beginning of trial (p < 0.05) [c]Significant reduction compared with week 4 (p < 0.05)

Continued

Fuessl (1987)	Double Blind Crossover	18 T2DM (12M; 6F)	Study Phase 1: 4 weeks [5 g of guar gum (guarem, Rybar Laboratories, Amersham, Bucks) or the same weight of granulated wheat bran (TP2)] Washout Phase: 2 weeks Study Phase 2:4 weeks [5 g of guar gum (guarem, Rybar Laboratories, Amersham, Bucks) or the same weight of granulated wheat bran (TP2)]		Guar period		Placebo period	
					Initial	End	Initial	End
				FPG (mmol/L)	9.31 ± 0.53	8.29 ± 0.47	8.74 ± 0.49	8.78 ± 0.53
					$p < 0.05$		NS	
				A1C (%)	9.67 ± 0.40	8.70 ± 0.39	9.27 ± 0.41	9.09 ± 0.39
					$p < 0.02$		NS	

A1C = hemoglobin A1C; F = Female; FPG = Fasting Plasma Glucose; M = Male; NS = Not Significant; T2DM = Type 2 Diabetes Mellitus Patients; TID = Three Times Daily.

[24] [25] [27]. Magnesium chloride (384 mg sustained release $MgCl_2$ per day and 2.5 g $MgCl_2$ per day) [25] [26] and magnesium oxide (600 mg Mg oxide per day and 20.7 or 41.4 mmol Mg per day) [18] [23] were the most common dosage forms utilized by investigators. The remaining studies used magnesium pidolate (15.8 mmol Mg per day) [23], lactate-citrate (15 mmol Mg per day) [22], or an unidentified magnesium salt form [27].

Only one trial, which involved non-pharmacologic (diet and exercise) and pharmacologic (5 mg glibenclamide three times a day and 2.5 g $MgCl_2$ once a day) interventions, demonstrated significant decreases ($p < 0.05$) in FPG and A1C in both the placebo (FPG = −27.5%; A1C = −14.4%) and magnesium (FPG = −37.5%; A1C = −30.4%) groups, with superior reductions ($p < 0.05$) in the magnesium group compared to placebo [26]. The remaining studies did not show any significant changes in FPG or A1C levels [18] [22]-[25] [27].

3.3. Oat Bran

Oat bran contains beta-glucan, a viscous dietary fiber that has frequently been associated with decreasing blood glucose levels. Beta-glucan increases the viscosity of food in the small intestine and delays absorption, thereby reducing both peak postprandial plasma glucose and insulin levels in people with diabetes [28]. Typically, oat bran is well tolerated. Adverse effects include flatulence, bloating, abdominal distention, and unpleasant taste. Doses should be titrated to minimize adverse effects. As with guar gum, oat bran can decrease absorption of drugs that are taken orally. Patients should take medication either one hour before or four hours after taking oat bran. Oat bran should also be taken with eight ounces of water [29].

Various studies have investigated the effects of oat bran containing beta-glucan on patients with T2DM. **Table 3** discusses the clinical trials included in the search criteria. The studies investigating the blood glucose-lowering effect of beta-glucan contained fewer than 12 subjects. Both studies evaluated the effects of beta-glucan enriched oat bran flour, bread, buns, muffins, or crisp on glucose response. One study was conducted over a period of six months [30], while the other failed to mention how long the trial lasted [31]. Tapola *et al.*, demonstrated that oat bran high in beta-glucan could decrease postprandial glycemic response after an oral glucose load ($p < 0.01$).

3.4. Blond Psyllium

Blond psyllium (ispaghula husk from the seeds of *Plantago ovata*), made up of a mixture of polysaccharides, is a gel-forming, water-soluble fiber that is commonly used in the treatment of constipation [32] as a bulk-forming laxative [33]. Soluble fibers, such as psyllium, can have beneficial effects in T2DM patients [34]. It is speculated that this effect may be due to the slowing of food transit and absorption of carbohydrates in the gastrointestinal tract [35]. Typical adverse effects associated with blond psyllium are flatulence or abdomenal pain [36]. Titrating doses can minimize the gastrointestinal adverse effects. Occasionally, headaches, backache, rhinitis, increased cough, and sinusitis have been reported [34]. Psyllium can decrease absorption of drugs that are taken

Table 2. Magnesium trials.

<table>
<tr><th>Authors (Year)</th><th>Study Design</th><th>Subjects</th><th>Methods</th><th>Results</th></tr>
<tr><td>Yokota (2004)</td><td>Open-labeled</td><td>9 T2DM (6M; 3F)</td><td>Study Phase: 30 days
Study Group: 300 mg of magnesium via 300 mL of diluted MAG21 solution (100 mg magnesium/100 mL)</td><td>
<table>
<tr><th></th><th>Before</th><th>After</th><th>p-value</th></tr>
<tr><td>FPG (mg/dL)</td><td>149.4 ± 13.8</td><td>147.4 ± 12.0</td><td>NS</td></tr>
<tr><td>A1C (%)</td><td colspan="2">Data not given</td><td>NS</td></tr>
</table>
</td></tr>
<tr><td>Rodriguez-Moran (2003)</td><td>Randomized Double Blind Placebo Controlled</td><td>63 T2DM</td><td>Washout Phase: 3 months (diet of >50% calories from carbs, 20% mono and polyunsaturated fat, ~1 g protein/kg IBW per day and 30 mins physical activity ≥ 3x’s/week)
Study Phase: 16 weeks
Mg Group: glibenclamide 5 mg TID + 2.5 g $MgCl_2$
Placebo Group: glibenclamide 5mg TID + placebo</td><td>
<table>
<tr><th></th><th colspan="2">Mg (n = 32)</th><th colspan="2">Placebo (n = 31)</th></tr>
<tr><th></th><th>Baseline</th><th>16 Weeks</th><th>Baseline</th><th>16 Weeks</th></tr>
<tr><td>FPG[a] (mmol/L)</td><td>12.8 ± 5.6</td><td>8.0 ± 2.4</td><td>14.2 ± 3.9</td><td>10.3 ± 2.1</td></tr>
<tr><td>Change (p)</td><td colspan="2">−37.5% (p < 0.05)</td><td colspan="2">−27.5% (p < 0.05)</td></tr>
<tr><td>A1C[a] (%)</td><td>11.5 ± 4.1</td><td>8.0 ± 2.4</td><td>11.8 ± 4.4</td><td>10.1 ± 3.3</td></tr>
<tr><td>Change (p)</td><td colspan="2">−30.4% (p < 0.05)</td><td colspan="2">−14.4% (p < 0.05)</td></tr>
</table>
[a]p < 0.05 comparing change associated with magnesium versus placebo group at the end of the study.
</td></tr>
<tr><td>Lal (2003)</td><td>Open-labeled</td><td>40 T2DM (19M; 21F)
54 Non-diabetics (25M; 29F)</td><td>Study Phase: 12 weeks
Mg Group: diabetics on oral hypoglycemic agents (sulfonylureas) + 600 mg magnesium oxide/day
Placebo Group: Non-diabetic relatives or hospital employees</td><td>
<table>
<tr><th></th><th colspan="2">Mg (n = 40)</th><th colspan="3">Placebo (n = 54)</th></tr>
<tr><th></th><th>Baseline</th><th>After 12 weeks</th><th>Baseline</th><th>After 12 weeks</th><th>p-value</th></tr>
<tr><td>FPG (mg/dL)</td><td>142.7 ± 52.64</td><td>154.2 ± 29.24</td><td>89.63 ± 12.05</td><td>Not given</td><td>p > 0.05</td></tr>
<tr><td>PPBGL (mg/dL)</td><td>202.3 ± 80.95</td><td>212.7 ± 55.44</td><td>114.20 ± 10.36</td><td>Not given</td><td>p > 0.05</td></tr>
</table>
</td></tr>
<tr><td>de Lordes Lima (1998)</td><td>Randomized Double Blind Placebo Controlled</td><td>128 T2DM (32M; 96F)
57 blood donors</td><td>Study Phase: 30 days
Group A: 20.7 mmol MgO/day in 3 doses
Group B: 41.4 mmol MgO/day in 3 doses
Group C: Placebo</td><td>
<table>
<tr><th></th><th colspan="2">Group A (n = 35)</th><th colspan="2">Group B (n = 39)</th><th colspan="2">Group C (n = 54)</th></tr>
<tr><th></th><th>Baseline</th><th>30 Days</th><th>Baseline</th><th>30 Days</th><th>Baseline</th><th>30 Days</th></tr>
<tr><td>FPG (mmol/L)</td><td>10.3 ± 3.3</td><td>11.5 ± 4.4</td><td>12.6 ± 4.2</td><td>12.7 ± 4.2</td><td>12.9 ± 4.3</td><td>12.2 ± 73</td></tr>
<tr><td>A1C (%)</td><td>10.2 ± 2.8</td><td>9.7 ± 2.3</td><td>9.0 ± 2.4</td><td>9.2 ± 3.0</td><td>9.3 ± 2.6</td><td>9.5 ± 2.2</td></tr>
</table>
No significant difference from baseline to 30 days regarding FPG and A1C readings for all groups.
</td></tr>
<tr><td>Paolisso (1994)</td><td>Randomized Double Blind Crossover</td><td>9 T2DM (5M; 4F)</td><td>Pre-study Phase: 3 weeks (weight maintaining diet only with ~300 mg magnesium/day and ≥250 g carbohydrates/day)
Study Phase 1: 4 weeks (placebo or 4.5 g (15.8 mmol)) magnesium pidolate/day group)
Crossover Washout Phase: 4 weeks
Study Phase 2: 4 weeks (placebo or 4.5 g (15.8 mmol)) magnesium pidolate/day group)</td><td>
<table>
<tr><th></th><th colspan="2">Mg (n = 4)</th><th colspan="2">Placebo (n = 5)</th></tr>
<tr><th></th><th>Baseline</th><th>4 weeks</th><th>Baseline</th><th>4 weeks</th></tr>
<tr><td>FPG (mmol/L)</td><td>Not given</td><td>7.8 ± 0.1</td><td>Not given</td><td>8.0 ± 0.1</td></tr>
<tr><td>p-value</td><td colspan="2">NS</td><td colspan="2">NS</td></tr>
</table>
</td></tr>
</table>

Continued

Gullestad (1994)	Randomized Double Blind Placebo Controlled	54 T2DM	Pre-study Run-in Period: 2 weeks (placebo) Study Period: 4 months Mg Group: 15 mmol magnesium-lactate-citrate/day Placebo Group: Placebo		Mg (n = 25)		Placebo (n = 29)	
					Baseline	After 4 months	Baseline	After 4 months
				FBG (mmol/L)	8.8 ± 2.3	9.6 ± 3.2	8.5 ± 2.7	8.9 ± 3.0
				A1C (%)	7.3 ± 1.5	7.8 ± 1.5	7.4 ± 1.6	7.4 ± 1.5
				No significant difference from baseline to 4 months regarding FPG and A1C readings for either group.				
Purvis (1994)	Randomized Placebo Controlled Crossover	28 T2DM (4M; 24F)	Run-in Placebo Phase: 2 weeks Study Phase 1: 6 weeks (placebo or 384 mg sustained release magnesium chloride (Slo-Mag)/day) Crossover Placebo Washout Phase: 2 weeks Study Phase 2: 6 weeks (placebo or 384 mg sustained release magnesium chloride (Slo-Mag)/day)		Mg (n = 14)	Placebo (n = 14)	Difference	
				FPG (mg/dL)	208.8 ± 11.5	213.9 ± 11.5	−5.1 ± 10.1; NS	

A1C = hemoglobin A1C; F = Female; FPG = Fasting Plasma Glucose; M = Male; NS = Not Significant; PPBGL = Post-prandial Blood Glucose Level; T2DM = Type 2 Diabetes Mellitus Patients; TID = Three Times Daily.

orally so medication should be taken one hour before or four hours after psyllium. FDA labeling requires psyllumto be administered with eight ounces of water [37].

There were six trials identified evaluating the effects of psyllium fiber (*Plantago ovata*) on glycemic control in T2DM patients [32]-[35] [38] [39]. The trials included in this review are described with detail in **Table 4**. Psyllium products included Metamucil®, Agiofibe™, Plantaben®, and Diamed®. Subjects managed their diabetes with one of the following 1) controlled diet alone; 2) a controlled diet with a sulfonylurea; 3) a controlled diet with metformin; 4) or they continued their usual medications. Treatment durations lasted from one day to twelve weeks with doses ranging from 5.1 - 15 g per day of psyllium fiber. These studies evaluated several metabolic values such as glucose levels (fasting and post-prandial) and A1C. Four trials demonstrated a decrease in fasting glucose levels and A1C [32]-[35]. Three of the four studies found improvements in post-prandial glucose levels ($p < 0.08$) [32] [34] [38] and one showed a decrease in mean plasma glucose levels [39]. All studies demonstrated significant improvements in glycemic control with the addition of psyllium fiber.

3.5. Soy

Soy products have been shown to exhibit beneficial effects on lipids, however their effects on T2DM are not as well understood [40]. *In vitro* data have suggested that isoflavones present in soy protein have antidiabetic properties. Soy-based diets have led to improved insulin resistance and reduced insulin levels [41] [42]. Soy may also improve glycemic control by inhibiting tyrosine kinase activity, increasing tissue sensitivity to insulin, and improving insulin receptor affinity and glucose transport [43]. When taken orally, soy is very well tolerated, but it can cause some mild side effects such as constipation, bloating, and nausea. Allergic reactions involving rash and itching have also been reported in some people. One study in postmenopausal women showed an increased occurrence of endometrial hyperplasia when consuming soy isoflavone tablets 150 mg per day for five years [44], therefore it may be beneficial to avoid high, long termdoses.

There were 11 trials found that evaluated the effects of soy supplementation on patients with T2DM. **Table 5** includes more information related to the eleven trials. Many included patients with complications such as obesity, hypertension, proteinuria, and nephropathy. In all of the studies identified, patients continued their usual diabetes therapy, which included monotherapy with insulin, diet, oral glucose-lowering agents (sulfonylureas, metformin), or combinations of the above. The soy treatments used included: Sobhan textured soy protein, Essential Nutrition, Abalon®, Sojaprotein, soy-based beverages, meat analogues, black soy peptides, isolated soy

protein, soy polysaccharide, or soybean pinitol. Doses in eight of the trials ranged from 4.5 - 50 g soy protein a day over a duration of six weeks to four years [40]-[42], [45]-[49]. The remaining trials administered 10 g of soy polysaccharide, [50] or 0.6 to 1.2 g of soybean pinitol [51] in a single test meal. Although many of the trials focused on cardiovascular endpoints, glucose-related endpoints such as A1C and FPG were evaluated.

The majority of trials showed improvement in A1C, FPG, and postprandial plasma glucose [41] [42] [46]-[48] [50] [51]. One study demonstrated significant improvements in glycemic control with the addition of soy ($p < 0.03$) [46]. Two of the studies used soy isoflavones and did not find any benefit when used to supplement the patients' diets [40] [49]. Also, Anderson JW [45] and colleagues studied the effects of administering 1 g/kg of soy protein over 8 weeks and found no benefit in A1C.

4. Summary

Of the clinical trials reviewed, the most promising natural products are the fiber products such as psyllium and oat bran. Although there is no strong evidence from large, randomized, controlled clinical trials to support its use, fiber can safely be recommended in doses of 25 to 30 grams each day. High fiber foods include oats, barley, whole grain cereals, brown rice, beans, peas, lentils, nuts, fruits, and vegetables. Most patients do not get adequate fiber in their diet from such foods; therefore recommending them provides additional benefits including lowering blood glucose levels [52].

Psyllium has been shown to have the most promising preliminary evidence. All studies found significant

Table 3. Oat bran trials.

<table>
<tr><th>Authors (Year)</th><th>Study Design</th><th>Subjects</th><th>Methods</th><th>Results</th></tr>
<tr><td>Tapola (2005)</td><td>Randomized Controlled Repeated Measures Design with Two Test Series</td><td>12 T2DM (7M; 5F)</td><td>Phase 1: Experiments were carried out with 12.5 g glycemic carbohydrate. Cold water was mixed properly into oat bran flour (61.6 g) with a fork and cold water (250 g) was poured onto oat bran crisp (29.1 g) just before eating.
Phase 2: Oat bran flour (30 g, providing 6.1 g glycemic carbohydrate) and glucose solution were mixed in a shaker just before eating.</td><td>
<table>
<tr><th></th><th colspan="5">Incremental glucose change from baseline (mmol/L)</th></tr>
<tr><th></th><th>Oat bran flour</th><th>Oat bran crisp</th><th>12.5 g glucose load</th><th>p-value[a]</th><th>p-value[b]</th></tr>
<tr><td>15 min</td><td>0.2 (0.4)</td><td>0.5 (0.7)</td><td>1.4 (0.7)</td><td><0.006</td><td>NS</td></tr>
<tr><td>30 min</td><td>0.3 (0.4)</td><td>1.1 (0.6)</td><td>2.7 (0.7)</td><td><0.006</td><td>NS</td></tr>
<tr><td>45 min</td><td>0.4 (0.6)</td><td>1.2 (0.5)</td><td>2.2 (0.6)</td><td><0.006</td><td>NS</td></tr>
<tr><td>60 min</td><td>0.5 (0.8)</td><td>1.1 (0.5)</td><td>1.1 (0.7)</td><td>NS</td><td>NS</td></tr>
<tr><td>90 min</td><td>0.3 (0.7)</td><td>0.8 (0.7)</td><td>−0.3 (0.5)</td><td>NS</td><td>NS</td></tr>
<tr><td>120 min</td><td>0.1 (0.6)</td><td>0.2 (0.6)</td><td>−0.6 (0.4)</td><td>0.012</td><td>NS</td></tr>
</table>
[a]The overall significance of the difference between the oat bran flour and glucose load analyzed with the GLM repeated measures and paired samples t-test adjusted with the Bonferroni correction (incremental change) or with the paired samples t-test adjusted with the Bonferroni correction (areas under curve).
[b]The overall significance of the difference between the oat bran crisp and glucose load analyzed with the GLM repeated measures adjusted with the Bonferroni correction (incremental change) or with the paired samples t-test adjusted with the Bonferroni correction (areas under curve).
</td></tr>
<tr><td>Pick (1996)</td><td>Randomized Crossover Experimental Design</td><td>8 T2DM (8M)</td><td>Study Phase: 6 months
Phase 1: Oat bran (total dietary fiber = 45% by weight; beta-glucan = 22.8% by weight) or white bread for 12 weeks.
Phase 2: Alternate treatment of oat bran (total dietary fiber = 45% by weight; beta-glucan = 22.8% by weight) or white bread for 12 weeks.</td><td>
<table>
<tr><th>Variable</th><th>White bread period</th><th>Oat bran concentrate</th></tr>
<tr><td>Breakfast response</td><td colspan="2">Glucose (mmol/L)</td></tr>
<tr><td>Maximum</td><td>15.4 ± 0.8</td><td>13.4 ± 0.8</td></tr>
<tr><td>Excursion</td><td>6.6 ± 0.5</td><td>5.6 ± 0.5</td></tr>
<tr><td>Lunch response</td><td colspan="2">Glucose (mmol/L)</td></tr>
<tr><td>Maximum</td><td>13.1 ± 1.0</td><td>11.1 ± 1.0</td></tr>
<tr><td>Excursion</td><td>4.4 ± 0.6</td><td>3.3 ± 0.6</td></tr>
</table>
</td></tr>
</table>

F = Female; M = Male; NS = Not Significant; T2DM = Type 2 Diabetes Mellitus Patients.

Table 4. Blond psyllium trials.

Authors (Year)	Study Design	Subjects	Methods	Results
Sartore (2009)	Randomized Controlled	40 T2DM	Study Phase: not specified Psyllium Group: 3.5 g psyllium treatment (one dose of sugar-free Agiofibre, Plantagoovata) TID before breakfast, lunch, and dinner for 2 months. Mixed into 250 mL water, 50 mL to rinse Placebo Group: dietary measures alone	See table below
Ziai (2005)	Randomized Double Blind Parallel	49 T2DM	Study Phase: 8 weeks Psyllium Group: 5.1 g psyllium husk fiber (PlantagoovataForsk., Diamed®) BID Placebo Group: Placebo	See table below
Sierra (2002)	Experimental Crossover	20 T2DM (12M; 8F)	Study Phase 1: 1 week of diet and sulfonylurea Study Phase 2: 6 weeks, addition of 3.5 g psyllium QID (14 g/day) Washout Phase: 2 weeks Study Phase 3: 4 weeks of diet and sulfonylurea	See table below

	Psyllium (n = 20)		Placebo (n = 20)	
	Baseline	End	Baseline	End
A1C (%)	6.78 ± 0.44	6.58 ± 0.50	7.03 ± 0.58	6.60 ± 0.45
	$p < 0.05$		$p < 0.001$	
FPG (mg/dL)	140.39 ± 23.80	135.56 ± 19.92	154.25 ± 23.79	135.85 ± 26.38
	$p < 0.05$		$p < 0.001$	

	Week 0		Week 4		Week 8	
	Psyllium	Placebo	Psyllium	Placebo	Psyllium	Placebo
FPG (mg/dL)	208.2 ± 12.7	179.1 ± 10.8	169.3 ± 11.0	193.6 ± 10.9	155.6 ± 9.5[a]	216.2 ± 25.3
A1C (%)	10.5 ± 0.73	9.1 ± 0.51	Not given	Not given	8.9 ± 0.23[a]	10.5 ± 0.59

[a]$p < 0.05$
Glucose changes from baseline:
1) Psyllium: −52.77 (52.33)
2) Placebo: 31.36 (85.74)

Time (min)	Mean Serum Glucose After Meal (mmol/L)		
	Phase 1	Phase 2	Phase 3
0	8.66 ± 2.22	7.73 ± 1.98	8.21 ± 2.32
10[a]	9.43 ± 2.29	7.98 ± 1.96	8.85 ± 2.45
20[a]	10.81 ± 2.45	9.05 ± 2.01	10.29 ± 2.61
30[a]	12.02 ± 2.82	10.46 ± 2.15	11.93 ± 2.59
45[a]	13.52 ± 2.92	12.06 ± 2.21	13.29 ± 2.49
60[a]	14.00 ± 2.67	12.83 ± 2.58	14.27 ± 2.93
75[a]	14.19 ± 3.02	12.51 ± 2.81	14.04 ± 3.23
90[a]	13.63 ± 3.12	11.93 ± 3.12	13.52 ± 3.63
120[a]	12.54 ± 3.53	10.76 ± 3.43	11.91 ± 3.63

[a]Significant differences among phases for glucose ($p < 0.05$)
Significant differences found between phase 2 and other phases for glucose values.

	Phase 1	Phase 2	Phase 3
FPG-breakfast (mmol/L)	7.72 ± 1.90	7.34 ± 1.88	7.46 ± 1.88
PPG-breakfast (mmol/L)	11.58 ± 3.31[a]	9.98 ± 2.81[a]	10.39 ± 3.13
FPG-lunch (mmol/L)	7.27 ± 2.64	6.69 ± 2.49	6.68 ± 2.33
PPG-lunch (mmol/L)	9.67 ± 4.14	8.92 ± 2.76	9.56 ± 3.11
FPG-dinner (mmol/L)	6.73 ± 2.79	6.47 ± 2.56	6.43 ± 2.27
PPG-dinner (mmol/L)	10.02 ± 3.28	9.20 ± 2.60	9.63 ± 2.83
A1C (%)	6.8 ± 1.0	6.5 ± 0.9	6.9 ± 1.2

[a]Significant ($p < 0.05$).

Continued

Anderson (1999)	Double Blind Placebo Controlled Parallel	34 T2DM	Study Phase: 8 weeks Placebo Group: Placebo Psyllium Group: 5.1 g Psyllium (Orange-flavored, sugar-free Metamucil)	Outpatient: Placebo (n = 14) / Psyllium (n = 15) BGL (mmol/L): 10.74 ± 0.56 / 2.8 ± 4.6 / 10.02 ± 0.41 / −6.1 ± 4.5 A1C: 0.075 ± 0.002 / −0.8 ± 4.3 / 0.073 ± 0.003 / −6.3 ± 3.1 Metabolic ward: PPG (mmol/L) Breakfast: 13.54 ± 0.95 / 3.8 ± 4.7 / 13.44 ± 0.82 / −3.0 ±4.6 Lunch: 10.43 ± 0.83 / 12.7 ± 5.6 / 10.75 ± 0.69 / −6.5 ± 4.2 Dinner: 10.89 ± 0.61 / 2.2 ± 3.9 / 11.80 ± 0.75 / −5.7 ± 4.5 All day: 11.53 ± 0.76 / 6.8 ± 3.9 / 11.90 ± 0.70 / −4.2 ± 3.3
Rodrígue z-Morán (1998)	Double Blind Placebo Controlled	123 T2DM (55M; 68F)	Washout Phase: 6 week of diet counseling and diet adherence Study Phase: 6 weeks Placebo Group: Placebo Psyllium Group: Plantago Psyllium (Metamucil) 15 g/day	BGL (mg/dL): Placebo / Psyllium 6 weeks (Baseline): 181 / 175 8 weeks: 188 / 150 10 weeks: 186 / 138 12 weeks: 187 / 137
Pastors (1991)	Placebo Controlled Crossover	18 (6M; 12F)	Study Phase: not specified Psyllium Group: 2 Psyllium (Orange flavored Metamucil) doses Each dose = 6.8 g Psyllium Placebo Group: Placebo	Peak Glucose Level (mmol/L): Psyllium / Placebo / p-value Breakfast: 6.03 ± 0.65 / 7.02 ± 0.62 / 0.08 Dinner: 2.98 ± 0.42 / 3.76 ± 0.42 / 0.06

A1C = hemoglobin A1C; BGL= blood glucose level, not specified as pre-prandial or post-prandial; F = Female; FPG = Fasting Plasma Glucose; M = Male; PPG= Post-prandial Plasma Glucose; T2DM = Type 2 Diabetes Mellitus Patients.

improvements in glycemic control. However the majority of trials included a sample size of less than 50, which makes it difficult to assess whether the results could be extrapolated to the T2DM population. Typically with herbal products, it is difficult to evaluate which dosage form to recommend based on the variety of products used in studies. For psyllium, glycemic control was achieved even with various forms. None of the trials evaluated the efficacy of psyllium compared to conventional therapies, therefore more head-to-head trials would need to be conducted before treatment of psyllium in T2DM can be recommended.

Oat bran evaluation included two clinical trials which resulted in lower blood glucose levels [30] [31]. The trials had several limitations such as small study samples (n < 12) and durations (<6 months). A longer duration is necessary to evaluate the treatment of T2DM. Although the trials did not justify the use of oat bran in patients with T2DM, increasing oat bran can be safely recommended to patients with T2DM. Oat bran does appear to be useful in other co-morbid conditions such as hypercholesterolemia. Current FDA regulations and guidelines allow food products containing whole oat to be labeled with a health claim stating that the products may reduce the risk of heart disease if they contain at least 0.75 g of soluble fiber per serving [37]. Even though the clinical data does not support the use of oat bran in T2DM, incorporation of oat in the daily diet may be beneficial for other conditions.

Soy demonstrated significant improvements in glycemic control with the clinical trials included; therefore it may be beneficial to include soy as part of the diet for T2DM patients. Soy-based products are readily available and can be incorporated into the diet, however adherence to soy-based diets have previously been reported to be poor [46]. The trials reviewed here reported good adherence, which could potentially account for the improvement in fasting and postprandial glucose levels. Many of the trials provided education to the subjects at enroll

Table 5. Soy trials.

Authors (Year)	Study Design	Subjects	Methods	Results
Kwak (2010)	Randomized Double Blind Placebo Controlled	42 pre-diabetes and T2DM	Study Phase: 12-weeks Black Soy Peptide Group: 3 pouches of black soy peptides (4.5 g supplement/day) Placebo Group: placebo	See nested tables below
Azadbakht (2008)	Randomized Open Label Controlled Longitudinal	41 T2DM (18M; 23F)	Study Phase: 4 years All patients consumed a diet containing 0.8 g protein/kg body weight Soy Protein Group: 35% animal protein, 35% soy protein (Sobhan textured soy protein), 30% vegetable protein Control Group: 70% animal protein, 30% vegetable protein	See nested tables below
Gonzalez (2007)	Randomized Double Blind Placebo Controlled Crossover	26 Post-menopausal T2DM (26F)	Study Phase 1: 12 weeks (132 mg soy isoflavones (Essential Nutrition) or placebo) Crossover Washout Phase: 4 weeks Study Phase 2: 12 weeks (132 mg soy isoflavones (Essential Nutrition) or placebo)	See nested tables below

	Soy (n = 21)		Placebo (n = 21)	
	Baseline	Week 12	Baseline	Week 12
FPG (mg/dL)	121.62 ± 2.96[a]	117.95 ± 4.06[a]	115.38 ± 3.03	114.38 ± 3.61
A1C (%)[b]	6.70 ± 0.14	6.65 ± 0.14	6.42 ± 0.13	6.45 ± 0.14

Data are mean ± standard error of the mean; [a]Difference between baseline and end of treatment: two-tailed p = 0.166, one-tailed p = 0.083; [b]Analyzed after log transformation.

Subjects with Baseline FPG ≥ 110 mg/dL.

	Soy		Placebo	
	Baseline	Week 12	Baseline	Week 12
FPG (mg/dL)	126.6 ± 2.92[a]	121.7 ± 4.68[a]	124.7 ± 3.15	124.5 ± 3.85
A1C (%)[b]	6.83 ± 0.17	6.78 ± 0.16	6.77 ± 0.11	6.78 ± 0.14

Data are mean ± standard error of the mean; [*]Difference between baseline and end of treatment: −4.88 ± 2.79 (two-tailed p = 0.098, one-tailed p = 0.049); [b]Analyzed after log transformation.

	Soy Protein Group (n = 20)				
	Baseline	Year 1	Year 2	Year 3	Year 4
FPG[a] (mg/dL)	141 ± 55	130 ± 32	132 ± 43	129 ± 36	121 ± 42
Mean change in FPG			−18 ± 3		
	Control Group (n = 21)				
	Baseline	Year 1	Year 2	Year 3	Year 4
FPG[a] (mg/dL)	137 ± 54	142 ± 49	145 ± 51	146 ± 61	147 ± 57
Mean change in FPG			11 ± 2		
	Soy vs Control				
p-value			0.03		

Data are mean ± standard error of the mean
[a]$p_{time} = 0.03$, $p_{group} = 0.01$, $p_{time \cdot group} = 0.02$
Soy protein intake was ~16 g/day; mean A1C was 6.2%.

	Placebo Group		
	Baseline	3 months	% change
A1C (%)	6.7 ± 0.6	6.8 ± 0.7	1.00 (−0.20 − 2.2)
FPG (mmol/l)	7.0 ± 1.4	6.9 ± 1.3	−0.34 (−3.6 − 2.9)
	Soy Group		
	Baseline	3 months	% change
A1C (%)	6.8 ± 0.6	6.8 ± 0.6	1.56 (−0.43 − 3.5)
FPG (mmol/l)	6.9 ± 1.3	6.8 ± 1.2	−1.6 (−4.3 − 1.13)
	p-value		
% change in A1C	0.58		
% change in FPG	0.59		

Data are mean ± standard error of the mean or mean (95% confidence interval).

Continued

Kang (2006)	Randomized Open Label Controlled Crossover	15 T2DM (7M; 8F)	The tests were administered in a random order to each subject on 10 separate occasions, spaced at least 2 weeks apart Control Group: 64.2 g white rice (50 g available carbohydrate) Pinitol Group 1 : 1.2 g soy pinitol 0 minutes prior to 64.2 g white rice (50 g available carbohydrate) Pinitol Group 2 : 1.2 g soy pinitol 60 minutes prior to 64.2 g white rice (50 g available carbohydrate) Pinitol Group 3 : 1.2 g soy pinitol 120 minutes prior to 64.2 g white rice (50 g available carbohydrate) Pinitol Group 4: 1.2 g soy pinitol 180 minutes prior to 64.2 g white rice (50 g available carbohydrate) Pinitol Group 5: 0.6 g soy pinitol 60 minutes prior to 64.2 g white rice (50 g available carbohydrate)	Postprandial glucose (mg/dL). Treatment Groups / Time Intervals (minutes): 30 / 60 / 90 / 120 / 180 / 240 Control Group: 65.5 ± 5.6 / 119.3 ± 6.7 / 122.5 ± 8.0 / 108.7 ± 8.0 / 65.7 ± 9.7 / 22.5 ± 9.4 Pinitol Group 1: 51.5 ± 5.3 / 116.0 ± 6.5 / 120.4 ±7.9 / 96.4 ± 6.4 / 53.0 ± 10.3 / 18.2 ± 10.4 Pinitol Group 2: 55.5 ± 6.2 / 92.3 ± 6.3 / 92.9 ± 6.9[a] / 73.6 ± 5.0[a] / 32.8 ± 10.4 / −5.0 ± 10.6 Pinitol Group 3: 61.8 ± 6.0 / 107.4 ± 7.0 / 117.7 ± 6.6 / 105.4 ± 8.3 / 63.6 ± 9.1 / 28.9 ± 11.0 Pinitol Group 4: 56.7 ± 7.1 / 112.2 ± 7.0 / 122.8 ± 7.6 / 110.6 ± 8.0 / 65.0 ± 10.0 / 26.2 ± 11.3 Pinitol Group 5: 58.4 ± 7.1 / 119.6 ± 8.6 / 125.4 ± 8.0 / 100.5 ± 6.8 / 65.0 ± 10.0 / 18.3 ± 7.9 Data are mean ± standard error of the mean. [a]$p < 0.05$.
Ristić Medić (2006)	Experimental	47 T2DM (23M; 24F)	Study Phase: 12 weeks (34.8% soy protein (Soja protein))	FPG (mmol/L): Baseline / After treatment / Change (%) All patients (n = 47): 9.49 ± 2.56 / 8.67 ± 2.75[a] / −9.00 Patients (n = 14) with glucose (≤7.8 mmol/L): 7.15 ± 0.45 / 6.62 ± 1.07[a] / −7.00 Patients (n = 33) with glucose (>7.8 mmol/L): 10.37 ± 2.47 / 9.44 ± 2.81[a] / −9.00 Data are mean ± standard deviation. [a]$p \leq 0.05$.
Teixeira (2004)	Randomized Open-label Controlled Crossover	14 T2DM (14M)	Lead-in: 4 weeks (a basal diet with 1 g/(kg.d) of protein from non-soy sources, 30% of energy as fat, 10% as saturated fat, and 300mg/d of cholesterol) Study Phase 1: 8 weeks (replaced 0.5 g (kg.d) of total dietary protein intake with either isolated soy protein with 2.0 mg isoflavones aglycone units/g protein or casein) Crossover Washout Phase 1: 4 weeks (a basal diet with 1 g/(kg.d) of protein from non-soy sources, 30% of energy as fat, 10% as saturated fat, and 300 mg/d of cholesterol) Study Phase 2: 8 weeks (replaced 0.5 g (kg.d) of total dietary protein intake with either isolated soy protein with 2.0 mg isoflavones aglycone units/g protein or casein) Crossover Washout Phase 2: 4 weeks (a basal diet with 1 g/(kg.d) of protein from non-soy sources, 30% of energy as fat, 10% as saturated fat, and 300 mg/d of cholesterol)	Soy protein intervention: Before / After / Change[a] / Washout after soy A1C (%): 7.3 ± 0.3 / 7.3 ± 0.4 / 0.06 ± 0.1 / 7.3 ± 0.4 Casein intervention: Before / After / Change[a] / Washout after casein A1C (%): 7.5 ± 0.4 / 7.1 ± 0.4 / −0.4 ± 0.1 / 7.1 ± 0.4 Data are mean ± standard error of the mean. [a]Obtained by multiple linear regression and adjusted for baseline concentrations.

Continued

Jayagopal (2002)	Randomized Double Blind Placebo Controlled Crossover	32 T2DM (32F)	All patients maintained an isocaloric diet Study Phase 1: 12 weeks (soy phytoestrogen supplementation (Essential Nutrition containing 30 g isolated soy protein and isoflavones 132 mg daily) or placebo) Crossover Washout Phase: 2 weeks Study Phase 2: 12 weeks (soy phytoestrogen supplementation (Essential Nutrition with soy protein 30 g, isoflavones 132 mg daily) or placebo)	Soy Group: Baseline / 12 weeks / % change FPG (mmol/l): 7.29 ± 1.49 / 7.37 ± 1.63 / +1.14 ± 10.8 A1C (%): 6.83 ± 0.64 / 6.78 ± 0.61 / −0.64 ± 3.19 Placebo Group: Baseline / 12 weeks / % change FPG (mmol/l): 7.23 ± 1.37 / 7.57 ± 1.93 / +4.31 ± 12.7 A1C (%): 6.82 ± 0.66 / 6.88 ± 0.59 / +1.08 ± 3.90 p-value % change in FPG: 0.340 % change in A1C: 0.048 Data are mean ± standard deviation.
Hermansen (2001)	Randomized Double Blind Controlled Crossover	20 T2DM (14M; 6F)	Study Phase 1: 6 weeks (Abalon (50 g soy protein with >165 mg isoflavones and 20 g cotyledon fiber daily) or control (50 g casein and 20 g cellulose daily) taken twice a day as a beverage) Crossover Washout Phase: 3 weeks Study Phase 2: 6 weeks (Abalon (50 g soy protein with >165 mg isoflavones and 20 g cotyledon fiber daily) or control (50 g casein and 20 g cellulose daily) taken twice a day as a beverage)	Abalon Group: Baseline / 6 weeks; Control Group: Baseline / 6 weeks A1C (%): 6.6 ± 1.2 / 6.6 ± 1.2 / 6.7 ± 1.3 / 6.9 ± 1.7 FPG (mmol/L): 6.9 ± 2.3 / 7.3 ± 2.8 / 7.0 ± 2.0 / 7.7 ± 2.9 Data are mean ± standard deviation.
Anderson (1998)	Randomized Open Labeled Controlled Crossover	8 T2DM (8M)	Run-in: 8 weeks (provided education, adjusted insulin therapy to achieve desirable glycemic control) Baseline: 5 days (admitted for baseline measurements) All patients on standard diabetes exchange diet (maintain body weight, 1 g protein/kg body weight, 55% energy from carbs, 30% energy from fat) throughout study Study Phase 1: 8 weeks Soy Protein Test Diet Group: 50% of the protein from beverage, meat analogue patties, or ground meat analogue or Animal Protein Diet Group: 50% of the protein from ground beef or cow milk Crossover Washout Phase: 4 weeks (standard diabetic diet) Study Phase 2: 8 weeks Soy Protein Test Diet Group: 50% of the protein from beverage, meat analogue patties, or ground meat analogue or Animal Protein Diet Group: 50% of the protein from ground beef or cow milk	Soy Protein Diet: Baseline / Treatment / Change A1C (%): 8.1 ± 0.5 / 7.3 ± 0. 3 / −0.8 ± 0.5 Animal Protein Diet: Baseline / Treatment / Change A1C (%): 7.7 ± 0.4 / 7.6 ± 0.6 / −0.1 ± 0.5 Net Change A1C (%): −0.7 Data are mean ± standard error of the mean.

Continued

Tsai (1987)	Randomized Double Blind Controlled Crossover	7 T2DM (3M; 4F)	Study Phase 1 (standard basal meal with 10 g soy polysaccharide incorporated into noodles or the standard basal meal alone) Crossover Washout Phase: 7 days Study Phase 2 (standard basal meal with 10 g soy polysaccharide incorporated into noodles or the standard basal meal alone)	Glucose levels for both test meals. Time Intervals: Baseline (FPG) / 1 hr (Peak)[a] / 2 hrs[a] Plasma Glucose (mg/dL): 162.2 ± 66 / ~220 / ~200 Data are averages [a]Changes were similar for both meals during the first 2 hrs. Reductions in plasma glucose after 2 hrs were significantly faster in the soy polysaccharide group than for the control group ($p < 0.05$). At 4hrs, plasma glucose returned to baseline for the soy polysaccharide group.

A1C = hemoglobin A1C; F = Female; FPG = Fasting Plasma Glucose; M = Male; T2DM = Type 2 Diabetes Mellitus Patients.

ment and close monitoring by dieticians and physicians throughout the treatment periods. This must be taken into consideration when extrapolating these findings to the general population since soy supplementation without proper counseling on diet adherence may not have similar results. Another concern regarding study design is the use of various soy products throughout different trials. Unless large clinical trials compare the various soy products on the market, it would be difficult to recommend a specific type of treatment. It is important to note that most studies with beneficial effects typically used soy protein products. Therefore, if a patient chooses to supplement their diet with soy for T2DM, it may be beneficial to recommend a protein-based product. Some trial limitations included small sample sizes, typically less than 50 subjects, and a primary focus on cardiovascular endpoints such as lipid levels. Since T2DM and glycemic parameters were not common primary endpoints, it may be beneficial to have further studies evaluating larger patient populations and longer durations of soy therapy with emphasis on FPG and A1C to evaluate its effects on T2DM.

Based on limited available data, there appears to be some potential benefit of magnesium supplementation for the reduction of FPG and A1C. The majority of studies demonstrated no effect on fasting plasma glucose or A1C. Many of these studies, however, were of short duration (four to six weeks) and small population size (~60 subjects or less). The short duration of magnesium use makes it difficult to assess its impact on chronic management of diabetes through parameters such as A1C. In addition, variances in dosing and product selection make it challenging to determine an optimal magnesium salt form and dose for adequate supplementation and improvement in diabetic markers. For those longer term studies of 12 to 16 weeks, only one evaluation of 63 subjects taking glibenclamide with either 2.5 g $MgCl_2$ or placebo showed improvements in FPG and A1C at 4 months when compared to baseline and placebo. Subjects in each group were poorly controlled at baseline with an average A1C of at least 11.5% and demonstrated a 30.4% and 14.4% decrease in A1C in the magnesium and placebo groups, respectively, with significant improvement in the magnesium group compared to placebo [26]. Although this study showed positive results, its distinct study population of poorly controlled patients with diabetes, small study size, limited duration of therapy, and supplementation dose may limit its use in general practice. Since patients with poorly controlled diabetes are at higher risk of hypomagnesemia, magnesium supplementation may be beneficial in those with deficiencies to correct magnesium levels. However based on current data there appears to be potential for use but not a clear benefit in improving A1C and FPG in the general population of patients with diabetes.

Guar gum use in T2DM remains controversial. A few trials show it may lower blood glucose levels, while others show no benefit. Many of the trials had appropriate treatment times (3 - 10 months) to evaluate guar gum's effect on T2DM. However all the trials had small samples sizes ($n < 41$). The type of guar varied however the doses used were similar (15 g per day). Based on the evidence at this time, guar gum should not be recommended for the treatment of T2DM.

5. Conclusions

Overall, all five herbal products have limited data to support their use over conventional therapy. Large, randomized, controlled clinical trials are necessary to determine efficacy. Many of the trials lacked adequate sample sizes, control groups, and duration. In addition, the clinical trials available lack standardization of the type of

product being investigated.

As the number of people with diabetes in the United States increases and the goals of therapy are not met, patients may seek non-conventional therapies such as natural products. Since the FDA prohibits the use of health claims for items sold as food supplements, products will not have indications. Therefore, it is especially important to educate patients and emphasize that they should discuss the use of natural medicines with their providers. Although patients may view natural products as safer routes for treatment of T2DM with fewer side effects, many natural products have similar pharmacologic effects on conventional medications, which can result in additional toxicities. For this reason, monitoring patients for hypoglycemia with concomitant use is vital. In addition, patients should be informed not to replace their conventional medications with natural products.

A few agents, such as psyllium or soy, may play adjunctive roles in achieving the therapeutic goal for a patient with T2DM and should be discussed with a healthcare provider before using them. As more supplements become available, the need for healthcare professionals to familiarize themselves on the use, efficacy, and safety of these products is essential. Until additional data are collected from well-designed trials, natural products in T2DM are not recommended over the use of conventional drug therapies.

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