

A Review on Nutraceuticals for Management of Type 2 Diabetes Mellitus

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Abstract

Diabetes mellitus is a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both. Chronic hyperglycemia is associated with long-term damage, dysfunction, and failure of various organs, especially the eyes, kidneys, nerves, heart, and blood vessels. Diabetes is the most prominent disease for which alternative medicine is necessary for treatment. Traditionally, many herbs have been recommended for diabetes and their hypoglycemic effects have been reported by many researchers. This review was performed to analyze and search for the best nutraceuticals which can contribute as a complementary therapy in type 2 diabetes mellitus.

Key words: Hyperlipidemia; Nutraceuticals; Total Cholesterol; Lipoproteins

Introduction

Diabetes Mellitus is a complex, chronic illness associated with a state of high blood glucose level/hyperglycemia, occurring from a deficiency in insulin secretion, insulin action or both [1]. The prevalence of diabetes is predicted to double globally from 171 million in 2000 to 366 million in 2030 with a maximum increase in India [2]. It is predicted that by 2030 diabetes mellitus may afflict up to 79.4 million individuals in India. There are three types of diabetes: Type I, Type II and Gestational diabetes. Type I is caused by the immune system which destroys the cells in the pancreas that make insulin. This leads to diabetes by leaving the body without enough insulin to function normally. This is called an autoimmune reaction. Causes of Type II diabetes are obesity, sedentary lifestyle, increasing age, bad diet. Gestational diabetes is caused by family history, obesity/overweight or Polycystic Ovarian Syndrome (PCOS). People with diabetes are more likely to have cardiovascular disease. Some of the complications are diabetic retinopathy, glaucoma, cataract, kidney failure.

Many chemical agents such as sulfonylureas, thiazolidinediones, Glucagon-Like Peptide (GLP) -1 agonists, biguanides, etc are available to control and to treat diabetes but a complete cure has not been reported up to this date. In developing countries, products are expensive and not accessible [3]. It is one of the refractory diseases identified by ICMR for which alternative medicine is necessary for treatment. Renewed attention to alternative medicines and natural therapies has stimulated a new phase of research interest in traditional practices, and the WHO expert committee has listed one of its recommendations that traditional methods of treatment of diabetes should be further investigated.

Antihyperglycemic effects of these drugs are attributed to their ability to restore the function of pancreatic cells by causing an increase in insulin output/inhibit the intestinal absorption of glucose/ to the facilitation of metabolites in insulin-dependent processes. Herbal drugs have always been an important source for finding new medications for human health problems. Traditionally, many herbs have been recommended for diabetes and their hypoglycemic effects have been reported by many researchers. Almost all these case reports are confirmed by animal models and in-vitro studies [4].

Diabetes mellitus: role of inflammation and oxidative stress

Systemic inflammation and oxidative stress may have an important role in the pathogenesis of diabetes mellitus as well as in their vascular complications. Failure of pancreatic β -cell is the common characteristic of type 1 and type 2 diabetes mellitus. Oxidative stress resulting from the increased generation of Reactive Oxygen Species (ROS) is involved in the dysfunctioning of pancreatic β -cell and insulin resistance. Hyperglycemia causes the autooxidation of glucose, activation of poly-o-1 metabolism and glycation of proteins. All these changes lead to the generation of ROS and results in oxidative chemical modification of lipids, DNA and proteins in various tissues. The development of diabetes complications such as lens cataracts, nephropathy, neuropathy is caused due to the role of oxidative stress. The current review focuses on the herbal drugs, the blood glucose-lowering actions of which have been supported by different clinical studies on diabetic patients [5].

Research methodology

The literature was done in databases of Google Scholar, Medline, and Science Direct, using the key terms diabetes, plants, herbs, glucose, nutraceuticals and patients. Only those nutraceuticals with hypoglycaemic actions shown by at least two clinical studies were incorporated in the manuscript. The detailed results of these studies are not included in this paper.

Antidiabetic herbs

Gymnema sylvestre: *G.sylvestre* is an indigenous herb, belonging to the class dicotyledonous of the family Asclepiadaceae. It is used as a sugar destroyer. Secondary metabolites of this herb are *oleanane saponins* and *dammarane saponins* [6]. *Oleanane saponins* are of two types: gymnemic acids (0.96–1.54 g/100 g) and *gymnemasaponins* (0.7-1.02 g/100 g). They act as GLP-1 agonists by GPCR to activate cAMP pathway which is responsible for insulin secretion [7].

Multiple animal studies have reported hypoglycemic effects associated with the ingestion of *Gymnema* leaves. *Gymnema* reduced hyperglycemia in experimentally and spontaneously diabetic rats and rabbits. *Gymnema* has also been reported to restore levels of glycoproteins in diabetic rats to normal, thereby potentially preventing diabetic microangiopathy and other pathological organ changes [8].

By accumulating all the evidence, it is found that the leaves of *Gymnema sylvestre* (Gurmar, Mesharshingi) can improve glycemic control in diabetes. Shanmugasundaram et al. evaluated the potential of *G. sylvestre* leaf extract in improving the glycemic control of 27 T2D patients under insulin therapy. The dose of 400 mg/day for 18 months significantly decreased FBG, HbA1c and serum lipids of the patients when compared with the similar group of the patients who received insulin. Also, administering this extract (400 mg/day for 18-20 months) in addition to oral hypoglycemic drugs reduced FBG and HbA1c of T2D patients. Thus, this can help to decrease the dosage of the conventional drug [9]. In a study by Joffe and Freed, the patients were given a product containing *G. sylvestre* leaf extract (400 mg) twice a day. FBG and PPBG levels were decreased by 11% and 13% respectively after 3 months. HbA1c level was also decreased by 0.6%-0.8% [10]. In another study, treatment of T2D patients with a product containing *Gymnema sylvestre* 1 g/day for 2 months led to a significant decrease in FBG and PPBG levels which were accompanied by an increase in circulating insulin and c-peptide. A mild decrease was observed in FBG (1%) and PPBG (1%) levels in 20 T2D patients treated with 6g/day of *G.sylvestre* leaf powder.

***Nigella sativa* (Kalonji)**

N. sativa is an annual flowering plant. Traditionally, it is used in the treatment of several diseases like infertility, fever, cough, bronchitis, asthma and many more. The chemical constituents are nigellicine, nigellidine, thymol, linoleic, oleic, etc [11]. The bioactive constituent for diabetes is thymoquinone (1.8% - 48%). The seeds of *N.sativa*, also called black seeds are been used for centuries as a natural remedy for various diseases. *Nigella sativa* has some positive effects such as antihyperglycaemic, antioxidants such as anti-hypertensive, antihyperlipidemic, and anti- microbial.

Mechanism of hypoglycemic effects: According to the evidence and studies conducted on the experimental animals it is reported that the plant helps in insulin secretion by restoring the activity of enzymes involved in glucose metabolism such as glucose-6-phosphatase and fructose-1,6- phosphatase and fructose-1,6- bisphosphatase of gluconeogenesis. It also acts like SGLT-2 inhibitors and thiazolidinediones [12].

Clinical trials: All these effects are reported by (Mehta et al., Shafiee-Nick et al.). Along with clinical studies, its therapeutic action in metabolic syndrome and diabetes has been marked in recent years [13]. Patients with metabolic

syndrome consuming 2.5 ml of N. Sativa oil twice a day for 6 weeks showed significant decreases in FBG and LDL and HDL levels (Najmi, et al.) [14]. Administration of N. sativa oil for 40 days to 41 T2D patients showed a significant decrease in FBG and increase in insulin. In a clinical study, N. sativa seeds 1 g, 2 g, 3 g/day were added to anti-diabetic drugs of 94 T2D patients. After 3 months of treatment, a significant reduction was observed in FBG, PPBG and HbA1c levels (Bamosa et al.) [15]. Qidwai et al. also reported a favorable impact of N.sativa on blood glucose, serum lipids and blood pressure [16]. Hosseini et al. observed a significant reduction in FBG, PPG, HbA1c levels by administering 5 ml of N. sativa oil daily with oral hypoglycemic agents to 35 patients for 3 months. Mild adverse reactions such as nausea, mild gastric irritation, rashes were reported by a few patients [17].

Momordica charantia (Karela)

Momordica charantia (Karela, bitter gourd, bitter melon) has received a reputation for the management of diabetes. The chemical constituents present in *M. charantia* are vicine, polypeptide-p and charantin.

Mechanism of hypoglycemic effect: The fruit juice significantly increased the no. of beta cells. It lowers the blood glucose level by depressing the key enzymes glucose-6-phosphatase and fructose-1,6-phosphatase and on the other way by enhancing glucose oxidation by the shunt pathway through activation of its principle enzyme G6PDH [18]. There are many preclinical studies and the clinical studies can be dated back many years ago.

The preclinical intervention group includes animals that exhibited the efficacy or safety of the treatment with *M.charantia* preparations (whole extract or fraction of any part of the *M.charantia*) in any doses and frequency. The isolated pure compounds and concurrent treatment with standard oral hypoglycaemic drugs, insulin or any other drug were excluded because the effective size may not be due to *M.charantia* alone but partly due to other agents [19]. Eg. Rao et al. observed that in non-diabetic animals at 100, 200 and 500 mg/kg body weight, the karela did not have a hypoglycemic effect.

Clinical trials: Intake of *M. charantia* seeds to six T1D and 14 T2D patients significantly decreased PPBG level in both the groups [20]. Drinking suspension of the vegetable pulp resulted in a significant reduction of FBG and PPBG levels in 86 out of 100 patients with moderate T2D [21]. Also, Fruit Juice of *M. charantia* was found to significantly improve glucose tolerance in 73% of 18 maturity-onset diabetic patients [22]. In a case study, aqueous extract was given to diabetic patients (7 cases) or dried powder of *M. charantia* fruit (5 cases), as a single dose or thrice a day respectively. After 3 weeks, the extract and powder caused a 54% and a 25% reduction in blood glucose respectively (Srivastava et al.) [23]. A significant reduction was observed in HbA1c level from 8.37% to 6.1% by the extract. Leatherdale et al. found a decrease in HbA1c in T2DM patients who consumed fried *M. charantia* fruits 0.23 kg/day for 8-11 weeks. Also, there was an improvement in glucose tolerance in patients who consumed 50 ml of karela juice [24]. Consumption of dried powder of *M.charantia* fruit showed a reduction of FBG in 10 T2D patients with a history of taking oral hypoglycemic drugs. The same effect was observed with aqueous and alcoholic extracts of *M. charantia* fruit. Recently, Rahman et al compared the effects of *M. charantia* and Rosiglitazone, a thiazolidinedione derivative among 25 patients treated with *M.charantia* juice 55 ml/day for 5 months [25]. A study showed the better effects of *M.charantia*, as compared to rosiglitazone in the management of diabetes and its further complications (retinopathy and myocardial infarction). Similarly, Fuangchan et al reported the antihyperglycemic effect of *M.charantia* was less than metformin. Besides, in their multicenter randomized double-blind study, the fructosamine level was decreased significantly in T2D patients who consumed *M.charantia* for 4 weeks. Dans et al reported no significant reduction in FBG and total cholesterol of T2D patients treated with 2 capsules thrice a day daily of *M.charantia* given for 3 months. 0.24% of the decline in HbA1c was noted after the treatment [26,27]. In an attempt to the test active compound underlying the antidiabetic effect of *M.charantia*, a clinical trial was performed on 9 diabetic patients using an insulin-like agent from this nutraceutical. Subcutaneous injection of the agent led to a remarkable decrease in the blood glucose level after 30-60 min (Baldwa et al) [28]. Polypeptide-p was isolated from fruits, seeds, and tissues of the plant which exhibited hypoglycaemic effect when administered subcutaneously to the patients (Khanna et al.) [29]. Karela, when taken with oral hypoglycaemic effect, may lead to severe hypoglycemic shock.

Allium sativum (Garlic)

Allium sativum has been a traditional herb recommended for treating heart disease, arthritis, toothache, constipation and various infections [30]. The bioactive constituent of garlic is Allicin (0.2-0.53%).

Mechanism of hypoglycemic effect: Allicin helps as an anti-diabetic compound by activating PI3K/AKT pathway which helps in insulin secretion from pancreatic beta cells and reduces the production of advanced glycation end products [31].

Garlic has been shown to reduce blood glucose levels in Streptozotocin-induced and alloxan- induced diabetes models

(rats and mice). Many experimental studies showed that garlic and its different forms can help to reduce hyperglycemia in diabetic mice, rats and rabbits. Garlic oil was found to be effective in seven different types 1 diabetic animal studies where garlic homogenate, garlic powder and garlic extract containing allicin have been shown to reduce diabetes and related complications [32].

Clinical trials: Administration of 300 mg, 600 mg, 900 mg, 1200 mg, in T2D patients for 24 weeks per day of garlic with oral hypoglycaemic drugs showed a significant reduction in FBG and HbA1c levels. (Rizwan et al.) [33]. Rahat et al. reported a significant reduction in FBG and PPBG by administering 500 mg/day of garlic along with metformin in T2D patients for 12 weeks [34]. A clinical study, where 30 T2D patients were consuming 300 mg of allicin twice a day with oral hypoglycaemic drugs for 4 weeks. A drastic change was observed in FBG and fructosamine levels. Thus, it indicates that garlic has good tolerability and is safe for use.

Cinnamomum cassia (Cinnamon)

Cinnamon is a prevalent spice used in toothpaste, perfumes, candy, etc. The oil is used as an antiseptic, carminative and astringent [35]. The active constituents are cinnamaldehyde (0%-77.21%), eugenol (0%-20%) and methyl hydroxyl chalcone polymer (MHCP) which are responsible for anti-diabetic activity.

Mechanism of hypoglycemic effects: Cinnamaldehyde activates PPAR gamma to upregulate insulin and thereby exhibit a glucose-lowering effect. It also activates AMPK pathway to inhibit gluconeogenesis. By these two mechanisms, it is clear that cinnamaldehyde acts similarly to thiazolidinediones and alpha-glucosidase inhibitors [36].

Kim et al studied the anti-diabetic activity of *Cinnamomum cassia* extract in type 2 diabetic animal models. It was found that blood glucose level was significantly decreased in the treatment group as compared to the control group. Further, serum insulin levels and intestinal glycosidase activity was significantly lowered after 6 weeks. Similarly, many other studies were reported which helped in diabetes were conducted on animal models.

Clinical trials: Akilen et al. evaluated the potential of cinnamon bark powder in improving the glycemic control of 30 T2D patients under oral hypoglycemic drugs. The dose of 1 g twice a day for 90 days significantly reduced the HbA1c levels of the patients when compared to the similar of patients receiving oral hypoglycaemic drugs. Similarly, the dose of 500 mg twice a day for 90 days also reduced HbA1c levels in 55 T2D patients [37]. Administration of 3g of cinnamon powder to 33 T2D patients for 4 months decreased the levels of FBG and HbA1c levels [38,39]. A study investigated a significant reduction in FBG, PPBG and HbA1c levels with the dose of 500 mg twice a day for 3 months, which was used as a supplement with oral hypoglycaemic drugs in 140 T2D patients [40,41]. Anderson et al observed that the dose 250 mg twice a day for 2 months in 70 T2D patients showed a reduction in FBG and PPBG and increased the level of insulin production [42]. A pilot study reported that 500 mg 4 times a day for 40 days used as a supplement with oral hypoglycaemic drugs in 15 patients significantly reduced FBG and PPBG levels [43]. Ting Lu et al evaluated the reduction in FBG and HbA1c levels by administering 120 mg/day and 360 mg/day dose with gli-clazide for 3 months in 44 T2D patients. The results were significant in the 360 mg/day group of patients as compared to the other group of patients.

TABLE 1. Clinical trial data of nutraceuticals in Diabetes mellitus.

| Type of study | Intervention | N | Duration | Results | Reference |
|--|--|-----|----------|---|---------------------------|
| <i>Cinnamomum cassia</i> | | | | | |
| Randomized, placebo-controlled, double-blind | 1 g twice a day containing 100% cinnamon bark powder+OHA | 58 | 90 days | HbA1c levels were decreased by 0.36% | R.Akilen et al. [39] |
| Randomized controlled | 500 mg capsule twice a day containing cinnamon with usual care | 109 | 98 days | HbA1c levels were decreased by 0.83% | Paul Crawford et al. [37] |
| Randomized controlled | 3 g of cinnamon powder per day+OHA | 79 | 4 months | HbA1c levels were decreased by 0.05%. Also FBG was reduced. | B mang et al. [38] |

| | | | | | |
|---|--|-----|-----------|--|---------------------------|
| triple-blind placebo-controlled randomized | Group 1: BMI \geq 27, Group 2: BMI<27;500 mg capsule twice a day at morning on fasting and at night before bedtime+OHA | 140 | 3 months | HbA1c levels were decreased by 0.93%. FBG and PPG were also reduced with p<0.001 | Rogaye h Zare et al. [41] |
| double blind placebo controlled | 250 mg capsule twice a day | 140 | 2 months | FBG , PPG and insulin resistance were reduced | Anders on et al. [42] |
| pilot | 500 mg capsule 4 times day + OHA | 30 | 40 days | FBG and PPG were reduced with p<0.05 | Soni et al. [43] |
| pilot | Group 2 : low dose 120 mg/d Group 3: High dose 360 mg/d | 66 | 3 months | Group 2 HbA1c level decreased by 0.67% and for Group 3 the HbA1c level was reduced by 0.92%. FBG was also reduced. | Ting Lu et al. [40] |
| <i>Nigella sativa</i> | | | | | |
| Placebo controlled Participant blinded | Ns group received 2g NS powder daily + OHA | 114 | 1 year | HbA1c and FBG levels were decreased by 6 months itself | Huda Kaatabi et al. |
| Randomized, Double-Blind, Placebo- Controlled | 2.5ml Black seed oil twice a day | 37 | 2 months | HbA1c level was decreased by 0.4% and FBG was also decreased | Mohtas hami R et al. [14] |
| pilot study | Group 1: 1g of NS capsule per day, Group 2: 2g of NS capsule per day, Group 3: 3g of NS capsule per day+OHA | 90 | 12 weeks | HbA1c level was decreased by 1.52 % . Similary FBG and PPG were also decreased | Abdullah et al. [15] |
| randomized, double-blind, placebo- controlled | 3g/d NS oil soft gel capsules+OHA | 72 | 12 weeks | FBG and HbA1c were reduced. | Javd Heshmati et al. |
| Randomized, Double-Blind, Placebo-Controlled | 5ml daily <i>N. sativa</i> oil+OHA | 70 | 3 months | HbA1c level was decreased by 0.3%. FBG and PPG were also decreased with p<0.05 | Hoessini et al. |
| <i>Gymnema sylvestre</i> | | | | | |
| open label | 400 mg/day gymnema sylvestre capsules+OHA | 47 | 12 months | The results were insignificant in 8-10 months but it showed results in 18-20 months by reducing HbA1c level by 3.43% | Baskaran et al. [9] |
| Open label | 250 mg GS capsule twice a day+OHA/INSULIN | 58 | 3 months | HbA1c was reduced by 1%. FBG and PPG was reduced with p<0.05 | Nanda et al. |
| randomized, double-blind, placebo- controlled | 300 mg powder twice a day | 46 | 12 weeks | PPG and FBG was decreased eventually. | Laura et al. |

| <i>Allium sativum</i> | | | | | |
|-----------------------------------|---|-----|----------|--|-------------------------|
| Single blind | Group A: 300mg, Group B: 600mg, Group C: 900mg, Group D: 1200mg, Group E: 1500mg per day+OHA | 210 | 24 weeks | FBG was reduced (p<0.05) | Rizwan et al. [33] |
| open label | Group 2 was given garlic, one capsule BD after meals along with metformin tablets, 500 mg BD or TDS after meals | 60 | 12 weeks | FBG and PPG was reduced p<0.03 | Rahat Kumar et al. [33] |
| double-blinded placebo-controlled | combined therapy: Allicor 300 mg twice a day+OHA, monotherapy: Allicor 300 mg twice a day | 60 | 4 weeks | The level of fructosamine was reduced. | Sobeni n et al. |

Different meta-analysis for nutraceuticals in diabetes mellitus was gathered and the results of this meta-analysis are given in TABLE 3. Vitamin E supplementation showed efficacy in patients with inadequate glycaemic control or low serum levels of vitamin E. Hyperglycemia was one of the mechanisms that caused interference in zinc reabsorption via renal cells. There is evidence of a positive effect of adequate zinc levels on glycaemic control. Zinc was found to effective in people with chronic metabolic disorders. Most of the nutraceuticals show benefit in people with diabetes and inadequate glycemic control compared to healthy people.

TABLE 2. Meta-analysis of popular nutraceuticals including vitamins and minerals.

| Sr. no. | Nutraceuticals | Number of RCTs included in the meta-analysis (Number of participants) | Results | Conclusion |
|---------|----------------|---|--|---|
| 1. | Vitamin D [44] | 22 | <ul style="list-style-type: none"> Reduction in HbA1c = -0.32% No effect on FBG Non-significant improvement in glycaemic control in vitamin D deficient patients | Substantial heterogeneity between studies and no difference in FBG |
| 2. | Vitamin E [45] | 9 (n=418) | <ul style="list-style-type: none"> Effective in baseline HbA1c ≥ 8%) and in those whose baseline serum vitamin E levels were below normal ranges. Pooled mean difference in the changes of HbA1c was -0.58% | Vitamin E supplementation in patients with inadequate glycaemic control or low serum levels of vitamin E. |
| 3. | Zinc [46] | | <ul style="list-style-type: none"> The negative correlation between the HbA1c and the plasma zinc levels. Zinc supplementation in DM2 patients has reduced % HbA1c | positive effect of adequate zinc levels on glycaemic control, |
| | Zinc [47] | 14 (n=3978) | <ul style="list-style-type: none"> Small but statistically significant reduction in fasting glucose concentrations was observed -0.19 ± 0.08 mmol/L, after zinc supplementation. HbA1c tended to decrease in zinc-supplemented individuals -0.64% Greater reduction in glucose concentration in patients with chronic metabolic conditions compared to healthy people. | zinc may contribute to the management of hyper- glycaemia in individuals with chronic metabolic disease |

| | | | | |
|----|--------------------------------|-----------------|--|---|
| 4. | Chromium [48] | 25 | <ul style="list-style-type: none"> chromium mono and combined supplementation significantly improved glycaemic control change in HbA1c=-0.55% change in FPG=-1.15 mmol/L | Glycaemic control may improve with chromium mono-supplementation of more than 200 mcg daily. HbA1c and FPG also improved in patients with inadequate glycaemic control at baseline. |
| 5. | Folate [49] | 21 (n=21081) | <ul style="list-style-type: none"> Folate decreased fasting glucose (-0.15 mmol/L,) homeostatic model assessment (HOMA)-insulin resistance (IR) (-0.83) and insulin (-1.94 μIU/mL), No clear effect on diabetes or HbA1c. | Potential benefit of folate on insulin resistance and glycaemic control, the latter requires examination in more high-quality trials. |
| 6. | Probiotics and synbiotics [50] | 14 | <ul style="list-style-type: none"> Patients with baseline FPG \geq 7 mmol/L showed a reduction in FBG of 0.68 mmol/L Multiple species of probiotics and showed a more pronounced reduction of 0.31 mmol/L compared to single species trials | Probiotic and synbiotic supplementation may be beneficial in lowering that multispecies probiotics may have more impact on FBG in adults with high baseline FBG (\geq 7 mmol/L) than single species. |
| 7. | Resveratrol [51] | 11 (n=388) | Resveratrol consumption significantly reduced fasting glucose, insulin, glycated haemoglobin, and insulin resistance (measured by using the homeostatic model assessment) levels in participants with diabetes | Resveratrol significantly improves glucose control and insulin sensitivity in persons with diabetes but does not affect glycemic measures in nondiabetic persons. |

In a systematic review, by Bartlett H et al. 50 trials were identified as suitable for inclusion [52]. The review of trials identified positive effects of these nutrients on various outcome measures relating to insulin resistance and cardiovascular factors. Chromium was the most studied supplement, accounting for 16 of the 50 trials. A majority of the trials found a positive effect of chromium on fasting plasma glucose. Isoflavones were found to have a positive effect on insulin resistance and cardiovascular outcome measures, but only when combined with soy proteins. Vitamin E is reported to reduce oxidative stress at levels of 200 mg/day or more.

TABLE 3. Potential Future Nutraceuticals for Diabetes Mellitus.

| Sr. No. | Category/Mechanism | Nutritional Intervention | Comments |
|---------|---|--|--|
| 1 | Flavonoids | Quercetin, Kaempferol, myricetin, naringenin, hesperetin | Dose -24.2 \pm 26.7 mg/day |
| 2 | Diabetes Preventive Nutraceuticals | Soluble fibre – glucomannan, chlorogenic acid Legume derived α amylase inhibitors Conjugated linoleic acid (CLA) omega- 3 fatty acids | slow carbohydrate absorption <i>i.e.</i> they mimic action of acarbose |
| 3 | Antioxidants | Vitamin C (Ascorbic acid) | Replenishing dose: 800 mg/day |
| | | Vitamin E (α tocopherol) | Dose : 1600 – 3200 IU/day |
| 4 | Vitamin D Immunomodulatory, anti-inflammatoy, | Cholecalciferol 1332 IU | decrease insulin resistance, increase insulin secretion |
| 5 | Protective Minerals | Chromium Dose - 300 μ g/day elemental Cr(III) Magnesium Dose-Magnesium pidolate 4.5 g/day equivalent to 16.2 mmol/day | increase insulin sensitivity and improve glucose tolerance helps preserving adipocyte insulin sensitivity |

| | | | |
|---|---------------------------|--|--|
| 6 | Phytoestrogens | Soy (isoflavones) | Preclinical - reducing adipose tissue and improving glucose uptake |
| 7 | Dietary fibre supplements | Soluble fibre Insoluble fibre Cereal dietary fibre | increased insulin sensitivity |
| | | | Decreased risk of diabetes |
| | | | May reduce risk of diabetes |

Conclusion

Nutraceuticals, commonly known as food supplements obtained from natural sources have been studied for diabetes mellitus for centuries. The absence of a cure and OHA related side-effects calls for a preventive or effective anti-diabetic nutraceutical. *Gymnema sylvestre*, *Momordica charantia*, *Nigella sativa*, *Allium sativum* and *Cinnamomum cassia* have good mechanism and efficacy in diabetes mellitus supported by good quality clinical trials and previous animal studies. Anti-hyperglycemic effects of these drugs are attributed to their ability to increase insulin secretion, decrease insulin resistance and reduce the intestinal absorption of glucose. Few nutraceuticals are used as a preventive intervention in clinical studies. Combining these nutraceuticals or with an existing OHA could potentially reduce the dose and prevent adverse effects associated with long term use of OHA. Thus, physicians can rely on these nutraceuticals as complementary therapeutics, along with current hypoglycaemic drugs to improve the management of type II diabetic patients.

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