Nutraceuticals in the management of diabetes mellitus

Abstract

Recent years witnessed an upsurge in the use of nutraceuticals, nutritionals and naturals in therapeutics at global level. Conventional treatment options available as synthetic drugs does not meet properly the therapeutic needs for treating diabetes and the herbal drugs provide a better therapeutic hope with lesser side effects. Nutraceuticals are non-specific biological therapies including botanicals, vitamins, antioxidants, minerals, amino acids and fatty acids, which are used to promote wellness, prevent malignant processes and control symptoms. Nutraceutical agents have multidimensional therapeutic benefits and have been claimed to have effective disease preventing, curative and health promotive virtues. Several nutraceuticals used in clinical practice have been shown to target the pathogenesis of diabetes mellitus, metabolic syndrome and their complications and to favourably modulate a number of biochemical and clinical endpoints. Hypoglycaemic drugs are widely used in several traditional systems of medicine to prevent diabetes mellitus. This review attempts to display and remark some of the most popular nutraceuticals being use as anti-diabetic.

Keywords: Nutraceuticals, Diabetes Mellitus, Herbal drugs, Macronutrient, Micronutrient, Oxidative stress, Vitamin

Introduction

Diabetes Mellitus is a complex metabolic disorder associated with developing insulin resistance, impaired insulin signalling and β-cell dysfunction, abnormal glucose and lipid metabolism, sub-clinical inflammation and increased oxidative stress; It was estimated to affect 2.8% of the worldwide population in the year 2000, and it is expected to affect 4.4% in 2030 due to the population aging and a constant increase in obesity; these metabolic disorders lead to long-term pathogenic conditions including micro-vascular and macro-vascular complications, neuropathy, retinopathy, nephropathy, and a consequent decrease in quality of life and an increase in the rate of mortality. Among the multiple risk factors underling the incidence and progression of type 2 diabetes mellitus, diet is the main modifiable factor. An increasing number of epidemiological investigations show that diet rich in foods with high content of phytochemicals, high total antioxidant capacity and polyphenolic compounds may be related to lower risk of diabetes and predisposing factors. Based on the current understanding of pathophysiology of insulin resistance and type 2 diabetes mellitus, multiple pharmacological and non-pharmacological interventions have been developed with the aim of improving glycaemic control and prevention of diabetes complications; in this area, recently the use of functional foods and their bioactive components have been considered as a new approach in the prevention and management of diabetes and its complications. A nutraceutical is a food with a medical-health benefit, including the prevention and treatment of disease. Nutraceuticals also refer to natural functional/medical foods or bioactive phytochemicals that have health promoting, disease preventing or medicinal properties.
These nutraceuticals normally contain the required amount of vitamins, lipids, proteins, carbohydrates, minerals, or other necessary nutrients, depending on their emphases. Traditional medicinal plants are used throughout the world for a range of diabetic presentations. Herbal drugs are prescribed widely because of their effectiveness, less side effects and relatively low cost. Therefore, investigation on such agents from traditional medicinal plants has become more important. The present review, deals with some selective Herbal medicinal plants having pharmacologically established hypoglycaemic potential.

**Categories of nutraceuticals and their role in diabetes**

Nutraceuticals are non-specific biological therapies used to promote wellness, prevent malignant processes and control symptoms. These can be grouped into the following three broad categories.

Nutrients: Substances with established nutritional functions, such as vitamins, minerals, amino acids and fatty acids.

Herbals: Herbs or botanical products as concentrates and extracts.

Dietary supplements: Reagents derived from other sources (e.g. pyruvate, chondroitin sulphate, steroid hormone precursors) serving specific functions, such as sports nutrition, weight-loss supplements and meal replacements (Figure 1).

**Antioxidant of vitamins**

Animal studies have shown that an adequate supply of dietary antioxidants may prevent or delay diabetes complications including renal and neural dysfunction by providing protection against oxidative stress. However, clear evidence in humans is lacking. Vitamin C (ascorbic acid) is a chain-breaking antioxidant, scavenging ROS directly, and preventing the propagation of chain reactions that would otherwise lead to a reduction in protein glycation. In animals, vitamin C also reduces diabetes-induced sorbitol accumulation and lipid peroxides in erythrocytes. Vitamin C (800 mg/day) partially replenishes vitamin C levels in patients with type 2 DM and low vitamin C levels but does not improve endothelial dysfunction or insulin resistance.

**Calcium/vitamin D**

One of the first large prospective studies to examine the role of habitual diet on diabetes risk identified high calcium intake as protective; women in the top quintile of calcium intake, as contrasted to those in the bottom quintile, were 30% less likely to develop diabetes over a 6 year follow up, after correction for various potential confounders. Surprisingly, it appears that no subsequent studies have followed this lead. No prospective studies have examined the implications of habitual vitamin D intake (or sunlight exposure) for diabetes risk. Yet there are theoretical grounds for suspecting that, by suppressing secretion of parathyroid hormone (PTH), good calcium/vitamin D status may help to preserve insulin sensitivity and thus help prevent diabetes mellitus.

**Vitamin E**

Vitamin E is an essential fat soluble vitamin and functions primarily as an antioxidant. Low levels of vitamin E have been associated with increased incidence of diabetes and some research suggests people with diabetes have decreased levels of antioxidants. Additional evidence indicates that people with diabetes may also have greater anti-oxidant requirements, due to increased free radical production secondary to hyperglycaemia. Doses of vitamin E up to 400 IU are generally believed to be safe. Doses over 800 IU may alter blood clotting although supplement trials that have monitored Prothrombin times in subjects have noted no increases.

**Carbohydrates**

Carbohydrates are the energetic substrate related to the greatest impact on glycaemia levels. The total amount of carbohydrates is the main factor responsible for the post-prandial response, but there are other variables, such as type of carbohydrate, richness in fibre, the way of cooking, degree of maturity, etc., that can play a role. Moreover, there are other factors that can also influence post-prandial glycaemia such as pre-prandial glycaemia, macronutrient distribution of the whole meal (fats and proteins) and the hypoglycaemic treatment administered: oral tablets or insulin. Most scientific societies recommend the individualization of carbohydrate contribution, agreeing with the fact that the diet should provide carbohydrates in the form of fruits, cereals, pasta, legumes, vegetables and tubers. Although there are no long-term studies, it seems that eating starches of legumes has a positive effect on glycaemia, because of the persistent effect on post-prandial glycaemia, with no sudden increases; it may prevent both post-prandial hyperglycaemia and late hypoglycaemia.

**Fats**

Numerous studies indicate high-fat diets can impair glucose tolerance and promote obesity, dyslipidemia and atherosclerotic heart disease. Research also shows these same metabolic abnormalities are reversed or improved by reducing saturated fat intake. Current recommendations on fat intake for the general population apply equally to people with diabetes: reduce saturated fats to 10% or less of total energy intake and cholesterol intake to 300 mg/d. Scientific debate continues over which alternative is preferable to saturated fat polyunsaturated fat, monounsaturated fat or carbohydrate calories. Research suggests monounsaturated fat such as canola, olive and peanut oils may have beneficial effects on triglycerides and glycaemic control in some individuals with diabetes, but care must
be taken to avoid weight gain.\textsuperscript{24,25} Omega-3 fatty acids, found in fish such as salmon and mackerel may reduce serum triglycerides without impairing glycaemic control.\textsuperscript{26}

**Fibre**

Foods rich in fibre, such as fruits and vegetables, are still recommended; special mention is made of whole cereals.\textsuperscript{27} Although the protective effect of fibres against some chronic diseases is well established the effectiveness of fibres in lipid and glycaemic metabolism remains uncertain. For the general population, an intake of 26 g/day and 38 g/day is recommended, for women and men, respectively. There is no reason to increase the fibre dose in diabetic patients.\textsuperscript{28}

**Chromium**

Chromium is a trace element that may be deficient in persons with diabetes.\textsuperscript{30} It has been suggested that chromium supplements may increase insulin sensitivity and improve glucose tolerance in patients with type 2 diabetes mellitus. A meta-analysis of randomized controlled trials investigating the effects of chromium supplementation on glucose and insulin response in healthy individuals and those with diabetes showed a modest but significant improvement in glycaemic control in the latter, but not in the former.\textsuperscript{31} The American Diabetes Association’s official position is that there is inconclusive evidence for the benefit of chromium supplementation in diabetes.\textsuperscript{32}

**Magnesium**

Prospective epidemiology links magnesium-rich diets to decreased risk for diabetes, with an inverse correlation between magnesium intake and fasting insulin levels, suggesting an improvement in insulin sensitivity. This view is supported by limited clinical data, as well as by animal studies demonstrating that magnesium helps preserving adipocyte insulin sensitivity.\textsuperscript{33} The retina is particularly vulnerable to oxidative damage because of its abundance of polyunsaturated fatty acids, predominantly found in photoreceptor outer membranes, which are readily oxidized.\textsuperscript{34} Nutritional supplementation for age-related macular degeneration (AMD) has been investigated in the Age-Related Eye Disease Study that reported a 25% reduction in the risk of progression to advanced AMD in people who had later stages of AMD and were supplemented with a high-dose zinc plus antioxidants formulation.

**α- Lipoic Acid**

α- Lipoic acid is a naturally occurring antioxidant with potent Reactive oxygen species ROS-scavenging activity. It has the unusual property of being a Reactive oxygen species ROS scavenger in its oxidized state, quenching several radicals. α- Lipoic acid and dihydrolipoic acid work in a redox couple (an electron donating molecule and its oxidized form), and together have other antioxidant properties including chelation of transition metals and the regeneration of other antioxidants such as glutathione, Vitamin C and Vitamin E.\textsuperscript{35} α- Lipoic acid has been shown to protect the retina against ischemia-reperfusion injuries \textit{in vivo} and \textit{in vitro}. Ischemic injury to the retina is considered to be one of the major causes of visual loss and occurs in diabetic retinopathy. α- Lipoic acid increases insulin sensitivity by approximately 18–20% in patients with type 2 diabetes mellitus. A review of the clinical trials of α- Lipoic acid in the treatment of diabetic neuropathy reported beneficial effects on acute symptoms and disease progression.\textsuperscript{36}

**Vanadium**

Research indicates that this mineral acts similarly to insulin in transporting glucose into the cells, and is therefore valuable for both type 1 and Type 2 diabetes mellitus. Vanadium supplementation also decreased fasting blood glucose levels, Haemoglobin A1c levels and cholesterol levels 50.\textsuperscript{40,41} Dosages ranging from 45-150 mg/day can be useful for improving fasting glucose levels (how much sugar is in the blood when one wakes up in the morning). Toxicity studies show these dosage levels to be safe and well tolerated by most people. Some individuals experience mild gastrointestinal distress, either during the first week of use or at higher dosage levels (up to 400 mg/day).\textsuperscript{42}

**Protein**

Current evidence indicates people with diabetes have similar protein requirements to those of the general population-about 0.86 g/kg per day.\textsuperscript{43} Although protein plays a role in stimulating insulin secretion excessive intakes should be avoided as it may contribute to the pathogenesis of diabetic nephropathy.\textsuperscript{44} Some evidence suggests eating vegetable protein rather than animal protein is better for reducing serum cholesterol and managing nephropathy.\textsuperscript{45} There are a number of different types of protein supplements include liquid protein supplements, protein powders and liquid protein shots. There are a number of sources for protein supplements. Some of these sources include: Whey, Casein, Soy, Rice, and Egg.\textsuperscript{46}

**Coenzyme Q10**

The importance of this nutrient cannot be overstated, primarily because many of the drugs that are needed for management of diabetes and or its complications deplete Coenzyme Q10. Coenzyme Q10 is a promising nutritional intervention for insulin resistance, at least among subjects with hypertension. Singh et al conducted an eight week randomized, double-blind trial comparing the use of a water soluble form of CoQ10 (60 mg twice daily) to a vitamin B complex in 59 hypertensive patients. Their results indicated CoQ10 at this dose lowered glucose and fasting insulin levels, suggesting possible improved insulin resistance.\textsuperscript{47}

**L-carnitine**

L-carnitine (β-hydroxy-γ-trimethylaminobutyrate), a natural vitamin like compound, is an ubiquitous constituent of mammalian plasma and tissues, mainly distributed among skeletal and cardiac muscles. L-carnitine is supplied through dietary sources (e.g., meat, dairy products), and by biosynthesis from lysine and methionine.\textsuperscript{48} Supplementation studies have shown that L-carnitine promotes insulin sensitivity and has lipid-lowering actions. L-carnitine performs a number of essential intracellular and metabolic functions, such as fatty acid transport across the inner mitochondrial membrane into the matrix for β-oxidation, detoxification of potentially toxic metabolites, regulation of the mitochondrial acyl-Co A/CoA ratio, and stabilization of cell membranes.\textsuperscript{49} L-carnitine facilitates the elimination of short- and medium-chain fatty acids accumulating in mitochondria as a result of normal or abnormal metabolism. L-carnitine also has effects on oxidative metabolism of glucose in tissues. L-carnitine could improve insulin action in the fructose- fed rat model of insulin resistance. Skeletal muscle is an insulin-sensitive tissue, which is also a site of insulin resistance in the fructose-fed rat and it is vulnerable to oxidative damage. Considering this, these authors evaluated the role of L-carnitine in mitigating oxidative stress and lipid accumulation in...
the insulin sensitive skeletal muscle in a well-characterized model of insulin resistance. The effects of L-carnitine in this model suggest that its supplementation may have some benefits in patients suffering from insulin resistance.51

**Anti-diabetic claims of herbs**

Diabetes mellitus is a worldwide menace and exponentially growing metabolic disease in India,52 affecting the lipid and carbohydrate metabolism and affecting the person physically as well as mentally.53,54 The knowledge on the heterogeneity of this order is advanced, the need for more appropriate therapy increases. Traditional herbal medicines are used as a safe alternative for conventional hypoglycaemic agents, because synthetic drugs in Non-insulin dependent diabetes mellitus (NIDDM) or insulin in Insulin dependent diabetes mellitus (IDDM) have a limited role to play, and have high risk of drug tolerance, thereby causing a raise in dosage or a change of drug.55 By virtue of richness in essential phytoneutrients, ayurvedic herbs may help as “Potentiators” for these drugs and play a supportive role to maintain the quality of the diabetic life.56,57 There is vast potential of selected medicinal plants from Ayurveda and Indian folk role medicine. Several works have been attempted by CSIR, ICMR, DBT, and academia on role of herbal nutraceuticals, nutraceuticals and naturals in metabolic disorders like diabetes (Table 1).

| Table 1 Plants and their action of mechanism |
|---------------------------------------------|
| **Name of the plant** | **Reported mechanism of action** |
| Acacia arabica (Lam.) Muhl. | Acts through release of insulin from pancreatic beta cells, which accounts for the hypoglycaemic activity (Singh, 1975; Wadood, 1989) |
| Aegle marmelos (L.) Correa | Increases utilization of glucose; either by direct stimulation of glucose uptake or via the mediation of enhanced insulin secretion and also decreases the elevated glucose and glycosylated haemoglobin levels (Kamalakankan, 2003) |
| Allium cepa L. | Lowers blood glucose level and has potent antioxidant activity, which may account for the hypoglycaemic potential (Augusti, 1973) |
| Allium sativum L. | Has strong antioxidant activity and rapid reactivity with thiol containing proteins responsible for the hypoglycaemic property (Rabinov, 1998) |
| Aloe vera (L.) Burn.f. | Maintains glucose homeostasis by controlling the carbohydrate metabolizing enzymes and stimulates insulin release from pancreatic beta cells (Ajabnoor, 1990) |
| Annona squamosa L. | Lowers blood glucose level (Shirwaikar, 2004) |
| Azadirachta indica A.Juss. | Inhibits glucose re-absorption or increase in peripheral glucose utilization (Subramaniam, 1996) |
| Artemisia pallens Wolf. Ex DC. | Inhibits action of epinephrine on glucose metabolism, resulting in increased utilization of peripheral glucose and exhibits hypoglycaemic activity without altering the serum cortisol concentration (Chattopadhyay, 1999; Gholap and Kar, 2004) |
| Andrographis paniculata Nees | Prevents glucose absorption from gut. Has hypotriglycaeridemic effect and antioxidant activity which may be responsible for beneficial effect in the diabetic state (Zhang, 2000 a,b) |
| Biophytum sensitivum (L.) DC | Stimulates pancreatic beta cells to release insulin (Puri, 1998) |
| Beta vulgaris L. | Lowers blood glucose level (Yoshikawa, 1996) |
| Brassica juncea (L.) Czern. | Increases the concentration of hepatic glycogen and glycogenesis and suppressed the activity of glycogen phosphorylase and gluconeogenic enzymes, lead to reduction in glycogenolysis and gluconeogenesis (Khan, 1995) |
| Cassia auriculata L. | Suppresses enhanced gluconeogenesis during diabetes and enhance utilization of glucose through increased glycolysis in addition to pronounced alpha-glucosidase inhibitory actions resulting in a significant and potent lowering of blood glycaemic response (Latha 2003; Abesundara, 2004) |
| Plant Name                      | Common Name                  | Family               | Effects                                                                 |
|--------------------------------|------------------------------|----------------------|-------------------------------------------------------------------------|
| Boerhavia diffusa L.           | Common name: Tar vine        | [Family: Nyctaginaceae] | Increases plasma insulin levels and improves glucose tolerance, produces significant antioxidant activity (Pari, 2004; Satheesh, 2004) |
| Caesalpinia bonducella (L.) Roxb. | Common name: Chinese Cinnamon | [Family: Caesalpiniaceae] | Increases the release of insulin from pancreatic cells (Sharma, 1997)   |
| Citrullus colocynthis (L.) Schrad. | Common name: Bitter apple    | [Family: Cucurbitaceae] | Exerts an insulinotropic effect (Abdel-Hassan, 2000)                   |
| Cajanus cajan (L.) Milsp.       | Common name: Pigeon pea       | [Family: Fabaceae]    | Lowers plasma glucose level (Amalraj, 1998)                              |
| Coccinia indicaWight & Arn.    | Common name: Ivy gourd       | [Family: Cucurbitaceae] | Suppresses glucose synthesis, through depression of the key gluconeogenic enzymes glucose-6-phosphatase and fructose-1, 6-bisphosphatase and enhances glucose oxidation by shunt pathway through activation of its principal enzyme glucose-6-phosphate. Also has an insulin secretagogue effect and acts like insulin by correcting elevated enzymes in glycolytic pathway (Kamble, 1998) |
| Cœusaria esculenta Roxb.       | Common name: Carilla Fruit   | [Family: Flacourtiaceae] | Exhibits significant reduction in blood glucose level, a decrease in the activities of glucose-6-phosphatase and fructose-1,6-bisphosphatase and an increase in the activity of liver hexokinase, resulting in potent hypoglycaemic activity (Prakash, 2002) |
| Catharanthus roseus (L.) G. Don | Common name: Madagascarperiwinkle | [Family: Apocynaceae] | Increases metabolism of glucose and enhances secretion of insulin either from the beta cells of Langerhans or through extra pancreatic mechanism (Nammi, 2003) |
| Camellia sinensis Kuntze.      | Common name: Green tea       | [Family: Theaceae]    | Epigallocatechin gallate, present in tea increases insulin activity and prevents oxidative damages, responsible for the hypoglycaemic activity (Anderson, 2002) |
| Enicostemma littorale Blume    | Common name: Nahi            | [Family: Gentioceae]  | Enhances glucose-induced insulin release from isolated rat pancreatic islets, mediated through K (+)-ATP channel-dependent pathway (Maroo, 2002) |
| Eugenia jambolana Lam. (syn. Syzygium cumini L.) | Common name: Indian black berry | [Family: Myrtaceae] | It enhances serum insulin activity and exhibits norm glycaemia and better glucose tolerance (Ravi, 2004) |
| Helicteres isora L.             | Common name: Screw tree      | [Family: Sterculiaceae] | Acts through insulin-sensitizing activity (Chakraborti, 2002)           |
| Ipomoea batatas (L.) Lam.      | Common name: Sweet potato    | [Family: Convolulaceae] | Reduces insulin resistance and possibly acts by maltase inhibition (Matsui, 2002) |
| Morus alba L.                  | Common name: White mulberry  | [Family: Moraceae]    | Acts by increasing glucose uptake (Chen, 1995).                         |
| Scopoaria dulcis L.            | Common name: Sweet Broomweed | [Family: Scrophulariaceae] | Suppresses glucose influx into the polyol pathway leading to increased activities of antioxidant enzymes and plasma insulin and decreases activity of sorbitol dehydrogenase. Also potentiates insulin release from pancreatic islets (Latha, 2004) |
| Murraya koenigii (L.) Spreng.  | Common name: curry-leaf tree | [Family: Rutaceae]    | Increases glycogenesis and decreases glycolgenolysis and gluconeogenesis (Khan, 1995) |
| Ocimum sanctum L.              | Common name: Holy Basil      | [Family: Lamiaceae]   | Acts by cortisol inhibiting potency (Gholap, 2004)                      |
| Punica granatum L.             | Common name: Pomegranate     | [Family: Punicaceae]  | Inhibits intestinal alpha-glucosidase activity, leading to anti-hyperglycaemic property (Li, 2005) |
Conclusion
Among many disease or disorders of carbohydrate, fat and protein metabolism, diabetes is a serious disorder affecting large population of the world. It is associated with decreased insulin production or resistance towards its action. Plants have been traditionally used to treat diabetes patients, both insulin dependent & non-insulin dependent diabetes. Nutraceuticals are food supplements and have nutritional value. All the nutrients discussed in this review have exhibited significant clinical & pharmacological activity. The potency of herbal drugs is significant & they have negligible side effects than the synthetic anti-diabetic drugs. There is increasing demand by patients to use the natural products with anti-diabetic activity. The efficacy of hypoglycaemic herbs is achieved by increasing insulin secretion, enhancing glucose uptake by adipose and muscle tissues, inhibiting glucose absorption from intestine and inhibiting glucose production from hepatocytes. A place for nutraceuticals in clinical practice is emerging, but important pharmaceutical and clinical issues need to be addressed by further research.

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Conflict of interest
None.

References
1. Santaguida PL, Balion C, Hunt D, et al. Diagnosis, prognosis, and treatment of impaired glucose tolerance and impaired fasting glucose. Evid Rep Technol Assess. 2005;128:1–11.
2. Evans JL, Goldfine ID, Maddux BA, et al. Oxidative stress and stress-activated signaling pathways: a unifying hypothesis of type 2 diabetes. Endocr Rev. 2002;23(5):599–622.
3. Spranger J, Kroke A, Möhlig M, et al. Inflammatory cytokines and the risk to develop type 2 diabetes: results of the prospective population-based European Prospective Investigation into Cancer and Nutrition (EPIC)-Potsdam Study. Diabetes. 2003;52(3):812–817.
4. Montonen J, Knelt P, Järvinen R, et al. Dietary antioxidant intake and risk of type 2 diabetes. Diabetes Care. 2004;27(2):362–366.
5. Pandey KB, Rizvi SI. Plant polyphenols as dietary antioxidants in human health and disease. Oxid Med Cell Longev. 2009;2(5):270–278.
6. Bahadoran Z, Golzarand M, Mirmiran P, et al. The association of dietary phytochemical index and cardio-metabolic risk factors in adults: Tehran lipid and glucose study. J Hum Nutr Diet. 2013;26(Suppl 1):145–153.
7. Bahadoran Z, Golzarand M, Mirmiran P, et al. Dietary total antioxidant capacity and the occurrence of metabolic syndrome and its components after a 3-year follow up in adults: Tehran lipid and glucose study. Nutr Metab. 2012;9(1):70.
8. Mirmiran P, Bahadoran Z, Golzarand M, et al. Association between dietary phytochemical index and 3-year changes in weight, waist circumference and body adiposity index in adults: Tehran lipid and glucose study. Nutr Metab. 2012;9(1):108.
9. Mirmiran P, Noori N, Zavareh MB, et al. Fruit and vegetable consumption and risk factors for cardiovascular disease. Metabolism. 2009;58(4):460–468.
10. Perera PK, Li Y. Functional herbal food ingredients used in type 2 diabetes mellitus. Pharmacogn Rev. 2012;6(11):37–45.
11. Zeisel SH. Regulation of Nutraceuticals. Science. 1999;285(5435):1853–1855.
12. Whitman M. Understanding the perceived need for complementary and alternative nutraceuticals: lifestyle issues. Clin J Oncol Nurs. 2001;5(5):190–194.
13. Venkateswaran S, Pari L. Effect of Coccinia indica leaves on antioxidant status in streptozotocin-induced diabetic rats. J Ethnopharmacol. 2003;84(2-3):163–168.
14. Suhb V, Murugesan T, Arunachalam G, et al. Anti-diabetic potential of Barleria lupulina extract in rats. Fitoterapia. 2004;75(1):1–4.
15. Hartcock J. Dietary supplement: How they are used and regulated. J Nutr. 2001;13(3s):1145S–1175S.
16. Bartlett HE, Eperjesi F. Nutritional supplementation for type 2 diabetes: A systematic review. Ophthalmic Physiol Opt. 2008;28(6):503–523.
17. Franzini L, Ardigo D, Zavaroni I. Dietary antioxidants and glucose metabolism. Curr Opin Clin Nutr Metab Care. 2008;11(4):471–476.
18. Riccioni G, Bucciarelli T, Mancini B, et al. Antioxidant vitamin supplementation in cardiovascular diseases. Ann Clin Lab Sci. 2007;37(1):89–95.
19. Chen H, Karne RJ, Hall G, et al. High-dose oral vitamin C partially replenishes vitamin C levels in patients with type 2 diabetes and low vitamin C levels but does not improve endothelial dysfunction or insulin resistance. Am J Physiol Heart Circ Physiol. 2006;290(1):H137–H145.
20. Colditz GA, Manson JE, Stampfer MJ, et al. Diet and risk of clinical diabetes in women. Am J Clin Nutr. 1992;55(5):1018–1023.
21. Ni Z, Smogorzewski M, Massory SG. Effects of parathyroid hormone on cytosolic calcium of rat adipocytes. Endocrinology. 1994;135(5):1837–1844.
22. Saratin A. The Health Professional's Guide to Popular Dietary Supplements. Chicago, IL: The American Dietetic Association; 2000. 692p.
23. Bantle JP, Wylie-Rosett J, Albright AL, et al. Nutrition recommendations and interventions for diabetes: a position statement of the American Diabetes Association. Diabetes Care. 2008;31(Suppl 1):S61–S78.
24. Paula DD, Kathryn A, Gougeon R, et al. Canadian Diabetes Association 2008 clinical Practice Guidelines for the Prevention and Management of Diabetes in Canada: Nutrition Therapy. Can J Diabetes. 2013;37(Suppl 1):S45–S55.
25. Mann JI, De Leeuw I, Hermansen K, et al. Evidence-based nutritional approaches to the treatment and prevention of diabetes mellitus. Nutr Metab Cardiovasc Dis. 2004;14(6):373–394.
26. Anderson JW, Blake JE, Turner J, et al. Effects of soy protein on renal function and proteinuria in patients with type 2 diabetes. Am J Clin Nutr. 1998;68(Suppl 6):1347S–1353S.
27. Summary of the second report of the National Cholesterol Education Program expert panel on detection, evaluation and treatment of high blood cholesterol in adults (Adult Treatment Panel II). JAMA. 1993;269(23):3015–3023.
28. Prunell JG, Brunzell JD. The central role of dietary fat, not carbohydrate, in the insulin resistance syndrome. Curr Opin Lipidol. 1997;9(1):17–22.
29. Reaven GM. Do high carbohydrate diets prevent the development or attenuate the manifestations (or both) of syndrome X? A viewpoint strongly against. Curr Opin Lipidol. 1997;8(1):23–27.
30. Garg A. High-monounsaturated-fat diets for patients with diabetes mellitus, a meta-analysis. Am J Clin Nutr. 1998;67(Suppl 3):577S–582S.
31. Yamada Y, Hosoya S, Nishimura S, et al. Effect of bread containing resistant starch on postprandial blood glucose levels in humans. *Biosci Biotechnol Biochem*. 2005;69(3):559–566.

32. Higgins JA. Resistant starch: metabolic effects and potential health benefits. *J AOAC Int*. 2004;87(3):761–768.

33. Lau FC, Bagchi M, Sen CK, et al. Nutrigenomic basis of beneficial effects of chromium(III) on obesity and diabetes. *Mol Cell Biochem*. 2008;317(1-2):1–10.

34. Althuis MD, Jordan NE, Ludington EA, et al. Glucose and insulin responses to dietary chromium supplements: A meta-analysis. *Am J Clin Nutr*. 2002;76(1):148–155.

35. American Diabetes Association. Nutrition recommendations and interventions for diabetes (Position Statement). *Diabetes Care*. 2007;30(Suppl 1):S48–S65.

36. Bo S, Pisu E. Role of dietary magnesium in cardiovascular disease prevention, insulin sensitivity and diabetes. *Curr Opin Lipidol*. 2008;19(1):50–56.

37. Evans JR, Henshaw K. Antioxidant vitamin and mineral supplements for preventing age-related macular degeneration. *Cochrane Database Syst Rev*. 2008;1:CD000253.

38. Singh U, Jialal I. Alpha-lipoic acid supplementation and diabetes. *Nutr Rev*. 2008;66(11):646–657.

39. Ziegler D, Reljanovic M, Mehnert H, et al. Alpha-lipoic acid in the treatment of diabetic polyneuropathy in Germany: Current evidence from clinical trials. *Exp Clin Endocrinol Diabetes*. 1999;107(7):421–430.

40. Halberstam M, Cohen N, Shlimovich P, et al. Oral vanadyl sulfate improves insulin sensitivity in NIDDM but not obese nondiabetic subjects. *Diabetes*. 1996;45(5):659–666.

41. Cohen N, Halberstam M, Schilovich P, et al. Oral vanadyl sulfate improves hepatic and peripheral insulin sensitivity in patients with non-insulin dependent diabetes mellitus. *J Clin Invest*. 1995;95(6):2501–2509.

42. Boden G, Chen X, Ruiz J, et al. Effects of vanadyl sulfate on carbohydrate and lipid metabolism in patients with non-insulin dependent diabetes mellitus. *Metabolism*. 1996;45(9):1130–1135.

43. Wyn Snow, Managing Editor. With Diabetes Surging Some Look For Alternative Treatment. 20 October 2006.

44. Canadian Minister of National Health and Welfare. *Nutrition Recommendations*. The report of the scientific review committee. Ottawa: Canadian Government Publishing Centre; 1990.

45. Nuttall FQ, Gannon MC. Plasma glucose and insulin response to macronutrients in nondiabetic and NIDDM subjects. *Diabetes Care*. 1991;14(9):824–838.

46. Kontessis P, Jones S, Dodds R, et al. Renal, metabolic and hormonal responses to ingestion of animal and vegetable proteins. *Kidney Int*. 1990;38(1):136-144.

47. Jim Duffy. *Diabetics and High Protein Diets*. Ezine articles;2010.

48. Singh RB, Niaz MA, Rastogi SS, et al. Effect of hydro soluble coenzyme Q10 on blood pressures and insulin resistance in hypertensive patients with coronary artery disease. *J Hum Hypertens*. 1999;13(3):203–208.

49. Rajasekar P, Anuradha CV. Effect of L-carnitine on skeletal muscle lipids and oxidative stress in rats fed highfructose diet. *Exp Diabetes Res*. 2007;2007:72741.

50. Calo LA, Pagnin E, Davis PA, et al. Antioxidant effect of L-carnitine and its short chain esters: relevance for the protection from oxidative stress related cardiovascular damage. *Int J Cardiol*. 2006;107(1):54–60.

51. Dayanandan A, Kumar P, Panneerselvam C. Protective role of L-carnitine on liver and heart lipid peroxidation in atherosclerotic rats. *J Nutr Biochem*. 2001;12(5):254–257.

52. Sharma R, Prajapati PK. Rising risk of type 2 diabetes among inhabitants of Jamnagar, Gujarat: A cross-sectional survey. *Ann. 2015;36(1):10–17.*

53. Sharma R, Amin H, Prajapati PK. Comparative lipid profile of type 2 obese diabetics and obese non-diabetics: A hospital based study from hilly terrains of Mandi, Himachal Pradesh. *Int J Health Allied Sci*. 2016;5(1):63–64.

54. Sharma R, Amin H, Prajapati PK. Comparative lipid profiles in non-diabetic obese and type2 diabetic obese. *Astrocyte*. 2015;2(2):99–100.

55. Sharma R, Amin H, Prajapati PK. Influence of psychiatric comorbidity on the treatment process of type 2 diabetic patient. *Indian J Soc Psychiatry*. 2016;32(2):177–178.

56. Raut A, Bichile L, Chopra A, et al. Comparative study of amruthballataka and glucosamine sulphate in osteoarthritis: Six months open label randomized controlled clinical trial. *J Ayurveda Integr Med*. 2013;4(4):229–236.

57. Chopra A, Saluja M, Tillu G, et al. A randomized controlled exploratory evaluation of standardized ayurvedic formulations in symptomatic osteoarthritis knees: A Government of India NMITLI Project. *Evid Based Complement Alternat Med*. 2011;2011:724291.