REVIEW ARTICLE

# Nutraceuticals as therapeutic agents for holistic treatment of diabetes

**Ashish Baldi, Naveen Choudhary[1], Sumit Kumar**
Department of Quality Assurance, Indo Soviet Friendship College of Pharmacy, Moga, Punjab, [1]Department of Pharmacognosy, Mandsaur Institute of Pharmacy, Mandsaur, Madhya Pradesh, India

Nutraceuticals is one of the promising approaches for prevention and treatment of a large number of ailments. Nutrients, herbals and dietary supplements are major constituents of nutraceuticals, which make it instrumental in maintaining health, acting against various diseased conditions and thus to promote the quality of life. Diabetes mellitus is one of them. It is a multi-factorial metabolic disorder reflected by high blood sugar/glucose level. In spite of significant development in drug discovery to treat this disease, extensive efforts are on for finding a holistic approach by combining compounds from natural and synthetic drugs. Botanicals, vitamins, anti-oxidants, minerals, amino acids and fatty acids, collectively referred as 'nutraceuticals', are important sources of new therapies for type 2 diabetes and insulin resistance. This review summarises nutraceuticals with proven anti-diabetic potential in pre-clinical and clinical studies and explores the possibility of a new approach, 'polypathy' for synergistic management of diabetes.

**Key words:** Anti-diabetic drugs, diabetes mellitus, herbal, natural products, nutraceuticals, nutrients, polyherbals, polypathy

## INTRODUCTION

Diabetes mellitus is a metabolic disorder characterised by hyperglycaemia or high blood sugar.[1] The characteristic symptoms of diabetes are polyuria (excessive urine production), polydipsia (thirst and increased fluid intake) and blurred vision; these symptoms may be absent; if the blood sugar is only mildly elevated.[2,3] The World Health Organisation (WHO) recognises three main forms of diabetes mellitus: Type 1, Type 2 and gestational diabetes (occurring during pregnancy), which have similar signs, symptoms and consequences, but different causes and population distributions. Ultimately, all forms are due to the beta cells of the pancreas being unable to produce sufficient insulin to prevent hyperglycaemia. Type 1 is usually due to autoimmune destruction of the pancreatic beta cells, which produce insulin. Type 2 is characterised by tissue-wide insulin resistance, but impairment of beta cell function is necessary for its development. Gestational diabetes is similar to Type 2 diabetes (T2D), in that it involves insulin resistance due to predisposal of pregnancy hormones.[3,4]

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Types 1 and 2 were incurable chronic conditions, but have been treatable since insulin became medically available in 1921, and today are usually managed with a combination of dietary treatment, tablets (in T2D), insulin supplementation. Gestational diabetes typically resolves with delivery.[2,4]

Diabetes can cause many complications. Acute complications include hypoglycaemia, ketoacidosis or non-ketonic hyperosmolar coma, if the disease is not adequately controlled.[5] Serious long-term complications include cardiovascular disease, chronic renal failure or diabetic nephropathy, retinal damage, which may lead to blindness, nerve damage of several kinds, microvascular damage, followed by erectile dysfunction and poor healing.[6] Poor healing of wounds may lead to gangrene, which can require amputation. Adequate treatment of diabetes, along with emphasis on balanced diet and lifestyle factors may improve the risk profile of most aforementioned complications.

As per WHO, 171 million persons were suffering from diabetes worldwide in 2006, it is estimated that, this number will be doubled till 2030.[7] Diabetes mellitus occurs throughout the world, but most cases are found in the more developed countries. The greatest increase in prevalence is, however, expected to occur in Asia and Africa, where most patients will likely be found by 2030. The increased incidence of diabetes in developing countries follows the trend of urbanisation and lifestyle changes, perhaps most importantly a 'Western-style' diet.[7,8]

**Address for correspondence:** Dr. Ashish Baldi, Department of Quality Assurance, Indo Soviet Friendship College of Pharmacy, Moga - 142 001, Punjab, India. E-mail: baldiashish@gmail.com
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Diabetes is considered in the top five of the most significant diseases in the developed world. Although extensive armamentarium has been developed to combat this ancient disease but now-a–days, focus has been shifted to identify effective agents that can be used along with developed drug to treat this disease synergistically.[9]

## NUTRACEUTICALS: NEW WEAPON FOR HOLISTIC TREATMENT

Food and drugs from nature are playing a quite significant role in public healthcare system throughout the world. Human inquisitiveness and search for specific constituents of plants, animals, minerals and microbial origin, which are beneficial to our overall health, has coined terms like 'functional food' or 'nutraceuticals'. Dr. Stephen L. Defelice defined nutraceuticals as any substance that may be considered as food or part of food, which in addition to its normal nutritive value; provide health benefits including prevention of disease. The term 'nutraceuticals' came from a combination of 'nutrition' and 'pharmaceuticals' and can be defined as a food or part of a food that provides medical or health benefit including the prevention and treatment of a disease.[10]

Perhaps no other disease is as closely linked to nutrition as diabetes. Although nutrition plays a significant role in its development; it is also one of the most powerful tools in treatment of diabetes. The use of nutritional supplements in the treatment of the diabetes like vitamins, such as vitamin C and B, minerals such as chromium, as well as herbs like *Gymnema sylvestre*, is well documented as safe and effective way to lower blood sugars as well as for prevention of diabetic complications. More importantly, combined of scientifically validated diabetic formula to work synergistically for effective management of diabetes and related complications.[11] Various classes of nutraceuticals are given in Figure 1.

Botanicals, vitamins, anti-oxidants, minerals, amino acids and fatty acids (natural products collectively referred to here as 'nutraceuticals' and dietary supplements) are important sources of new therapies for T2D and insulin resistance. These agents are marketed in the US under the Dietary Supplement Health and Education Act (DSHEA), passed by Congress in 1994. DSHEA defined a new category of food for regulatory purposes, termed dietary supplements, one that also includes concentrates, metabolites, constituents, extracts and combinations and has resulted in major changes in the marketing and use of nutraceuticals in the US.[12] Numerous nutraceuticals had also shown promise in diabetes management. A study, published in 2002, reported that diabetics were 1.6 times more likely to use complementary and alternative medicine (CAM) than individuals without diabetes. Another study found that 57% of individuals with diabetes used CAM.[13] Representative nutraceuticals from herbal source are given in Figure 2. Few of the nutraceuticals with significant efficacy in treatment of diabetes and reported pharmacological evidences are given below:

### *Aloe Vera* (Aloe)

*Aloe vera* extract is useful for skin infections, wound and burn healing due to the presence of compounds

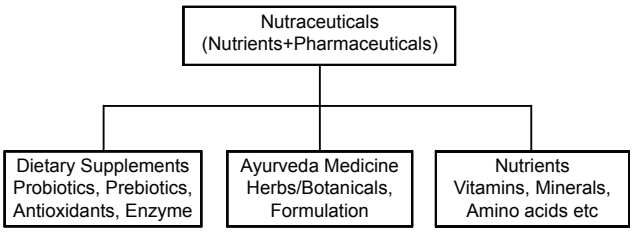


**Figure 1:** Classes of nutraceuticals

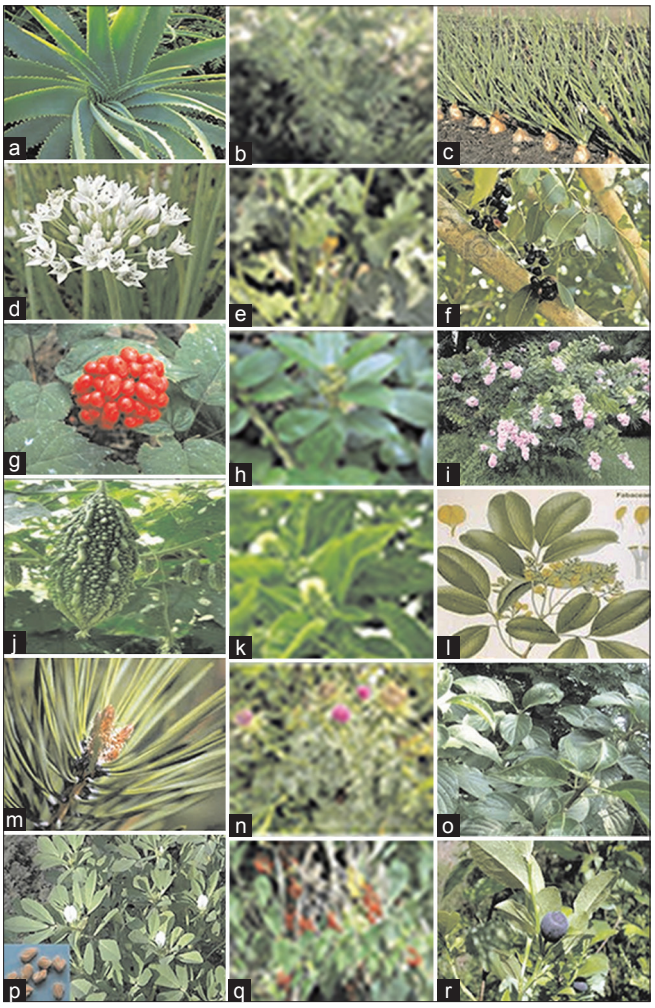


**Figure 2:** Nutraceuticals from herbal origin having potential to treat diabetes (a) *Aloe vera* (b) *Acacia arabica* (c) *Allium cepa* (d) *Allium sativum* (e) *Curcubita maxima* (f) *Eugenia jambolana* (g) *Panax ginseng* (h) *Gymnema sylvestre* (i) *Lagerstroemia speciosa (j) Momordica charantia* (k) *Ocimum sativum* (l) *Pterocarpus marsupium* (m) Pycnogenol (n) *Silybum marianum* (o) *Salacia reticulate* (p) *Trigonella foenum graecum* (q) *Tinospora cordifolia* (r) *Vaccinium myrtillus*

as polysaccharides, anthraquinones and lectins, which have also been reported for anti-diabetic activity.[14] A placebo-controlled, single-blind human clinical trial found that diabetics receiving 15 ml of aloe gel twice a day for 42 days experienced 43% and 44% reductions in blood sugar and blood triglycerides, respectively, while controls experienced no change. Aloe may also provide an alternative for patients unresponsive to glibenclamide, an anti-diabetic drug. It has been found that people whose fasting levels of blood glucose and triglycerides had been unchanged by glibenclamide experienced a 48% drop in blood sugar and a 52% drop in triglycerides after treatment with *Aloe vera* juice.[15,16]

### *Acacia Arabica* (Babul)

*Acacia arabica* is generally known as babul or prickly acacia. It belongs to the genus Acacia and family Fabaceae. *A. Arabica,* also known as *A. nilotica*, has been used to treat high cholesterol, diabetes, cancer, gingivitis, stomatitis (mouth sores) and pharyngitis. The powdered seeds of *A. arabica* and roots of *Caralluma edulis* were administered in doses of 2, 3 and 4 g/kg body-weight to normal rabbits induced hypoglycaemic effect by initiating release of insulin of pancreatic β cells.[17,18]

### *Allium Cepa* (Onion)

Onions have been known to have several putative health benefits since ancient times. Onions are rich in flavonoids such as quercetin as well as sulphur compounds. The health benefits of onions have been linked to everything from the common cold due to diabetes and osteoporosis. In a comparative study, 100 g of Allium cepa (red onion) resulted in a 89 mg/dl reduction in fasting blood glucose levels (4 hours later), fasting blood glucose was lowered by 145 mg/dl in response to administration of insulin (4 hours later).[19,20]

### *Allium Sativum* (Garlic)

Garlic is best known for its cardiovascular and lipid lowering and hypoglycaemic effects. Some initial studies suggested that members of the Allium family have mild hypoglycaemic activity. The active constituents are believed to be volatile sulphur-containing compounds (more than 20 have been isolated from garlic) including alliin (diallyl disulfide oxide), allyl propyl disulfide, S-allyl cysteine and S-allyl mercaptocysteine. It is hypothesised that sulphur-containing compounds in garlic decrease the rate at which insulin is degraded, effectively increasing circulating insulin levels.[21]

### *Cucurbita Maxima* (Pumpkin)

In a recent report, the low molecular weight fraction in pumpkin juice at the dose of 300 mg/kg produced significant reductions in plasma glucose at the end of treatment.[22] Pumpkin extract could also reduce or eliminate the need for insulin injections in Type 1 diabetics by increasing insulin production and regenerate damaged pancreatic cells.

### *Eugenia Jambolana* (Jamun)

Eugenia jambolana, Family: Myrtaceae), commonly known as black plum or Jamun is a plant native to India. Jamun is a plant with known ethnomedicinal uses. Before the discovery of insulin, Jamun was useful in the treatment of diabetes and is an integral part in the various alternative systems of medicine. *Eugenia jambolana* does have very well reported hypoglycaemic, or blood-sugar lowering action.[23]

### *Ginseng*

Both *Panax ginseng* and American ginseng have been used to manage diabetes. *Panax ginseng* has been found to remarkably reduce blood sugar levels in normal and hyperglycaemic mice. Two 8-week trials following patients with T2D found American ginseng significantly decreased fasting blood glucose, haemoglobin and post-prandial blood glucose levels.[24]

### *Gymnema Sylvestre* (Gurmarbooti, Gurmar)

*Gymnema sylvestre* is an herb widely used in Ayurveda. Few non-randomised controlled clinical trials confirmed improved glycaemic control in patient after receiving extract of *Gymnema* over those who received conventional treatment alone. Patients using insulin were able to decrease their insulin requirements.[25]

### *Lagerstroemia Speciosa* (Banaba)

The leaves of the *Banaba* plant contain corosolic acid, which exhibit anti-diabetic properties. Two placebo-controlled crossover trials demonstrated that Gluco Trim a product containing, corosolic acid 1% lowers blood glucose levels.[26,27]

### *Momordica Charantia* (Bitter melon)

Bitter melon, also known as *Momordica charantia,* has been further studied in mice, rats and rabbits to reduce blood glucose levels. Results in humans are also encouraging. Two controlled short-term trials found that the herb had acute effects on blood glucose and haemoglobin in those with T2D. Additionally, two small, uncontrolled trials reported that the herb had positive effects on blood sugar control when used for 7-11 weeks.[28]

### *Ocimum Sanctum* (Tulsi)

Tulsi is used in Ayurveda for over 2000 years. It has been tested for treatment of diabetes and has indicated a decrease in blood glucose during treatment of T2D.[29]

### *Pterocarpus Marsupium* (Vijayasar)

*Pterocarpus marsupium* (Leguminosae) is a traditional anti-diabetic plant used in Ayurvedic medicine. Concentrated

extracts of the bark and the heartwood of the plant have been tested under uncontrolled conditions in subjects with T2D. In subjects with less advanced diabetes, 2-4 g/day of dried *Pterocarpus* extract decreased fasting blood glucose levels (~30 mg/dl), post-prandial blood glucose (~45 mg/dl) and haemoglobin (0.4%). Studies in animals had suggested that *Pterocarpus* may also affect lipid levels, gastrointestinal glucose absorption, improve beta-cell function and has insulin-like actions. The bioactive constituents are believed to include (-) epicatechin (a flavonoid), marsupsin (a benzofuranone), pterosupin (a dihydrochalcone) and liquiritigenin (a stilbene).[30,31]

### Pycnogenol (French Maritime Pine Bark)

Pycnogenol® is an extract of French maritime pine bark with powerful anti-oxidant properties. A double-blind, placebo-controlled, randomised, multi-centre study found Pycnogenol, used in conjunction with standard anti-diabetic treatment, significantly lowered blood glucose compared with placebo. The ingredient has also gained notoriety for its ability to halt or slow the progression of diabetic retinopathy, the leading cause of blindness in people under the age of 60. Five clinical studies in Europe consisting of more than 1000 patients have shown that Pycnogenol seals the leaky capillaries of the retina, preventing vision loss.[32,33]

### *Silybum Marianum* (Milk Thistle)

It is a member of the aster family Asteraceae. It is believed to have hepatoprotective effects and has been used to treat and prevent hepatotoxic reactions in alcoholic cirrhosis, viral hepatitis, mushroom and medication poisonings. It may also alter insulin resistance in patients with hepatic damage. During a clinical trial examining the effects of 600 mg/d silymarin (one of the known active ingredients in milk thistle) in subjects with cirrhosis and T2D, insulin requirements, fasting blood glucose and haemoglobin declined significantly with supplementation.[34]

### *Salacia Reticulate* (Salacia, Kotalahimbatu)

Salacia species belong to Celastraceae family. In a study, aqueous extract from stem of *Salacia reticulate* in rats and humans resulted in suppression of increased serum glucose levels when fed with sucrose, maltose and starch in a dose dependent manner.[35]

### *Trigonella Foenum-graecum* (Fenugreek)

Fenugreek or *Trigonella foenum* is used both as herb and spices. It is a member of Fabaceae family. A number of studies have confirmed that fenugreek has a hypoglycaemic effect. The herb's high fibre content forms a gel in the stomach, which slows gastric emptying and delays glucose absorption. One double-blind, placebo-controlled study compared diabetics practicing dietary control and exercise with those receiving 1 g/day hydro alcoholic extract of fenugreek seeds. At the end of 2 months it has been concluded that adjunct use of fenugreek seeds improves glycaemic control and decreases insulin resistance in mild type T2D patients. Acatris produces an odourless extract of fenugreek glucomannan (gum) called FenuLife® and has started a clinical research program for the product. Another company involved with fenugreek is Technical Sourcing International, Missoula, MT, which manufactures Promilin™, a proprietary bioactive complex of amino acids including 4-hydroxyisoleucine (4-OH-Ile) extracted from fenugreek. Following administration of glucose, 4-OH-Ile improves glucose tolerance in normal and insulin-resistant rats and dogs by increasing insulin release and reducing the spike in blood sugar.[36,37]

### *Tinospora Cardifolia* (Guduchi)

The anti-diabetic effects of guduchi plant have been well documented in traditional medicines. Recent researched revealed that water extract of guduchi enhance insulin secretion and improve glucose metabolism, thereby lowering blood glucose levels.[38]

### *Vaccinium Mytillus* (Bilberry)

*Vaccinium mytillus*, also referred to as bilberry or European blueberry, is a close relative of North American blueberry and huckleberry. The leaves have been used in traditional tea for diabetes and in animal studies; extract from bilberry leaves decreased blood glucose and blood triglyceride levels. The berry of the plant has been used to improve visual activity and night vision and has been studied in animals as a treatment for diabetic retinopathy. Bilberry fruit is a rich source of anthocyanosides, a class of bioflavonoids that are believed to be responsible for the berry's therapeutic properties. Bilberry extracts typically contain 25% anthocyanosides (at least 15 different types), tannins and other flavonoids. Anthocyanosides are reported to increase vascular permeability, improve microvascular circulation, decrease platelet aggregation and improve retinal regeneration. The anthocyanosides, myritillin, has also been proposed as a hypoglycaemic agent. The leaf of the bilberry plant has also been used as a component of 'diabetic' tea and is a rich source of chromium. Although care should be taken as high dose of bilberry leaves (greater than 480 mg/day) may lead to toxicity.[39]

### Polyherbal Formulations

Several polyherbal formulations have been tested from years for their anti-diabetic potential. In one of the representative study, hypoglycaemic effect of polyherbal formulation, consisting of *Tribulus terrestris, Piper nigrum and Ricinus communis*, was established in alloxan-induced diabetic rats. Four weeks treatment with polyherbal formulation (100, 200 and 300 mg/kg) and glibenclamide lowered elevated blood glucose level, which was reported high in diabetic control

animals.[40] Maximum reduction in the blood glucose level noted with polyherbal formulation 300 mg/kg, which was comparable to standard drug used, that is glibenclamide.[40] A comprehensive list of nutraceuticals from plant origin is given in Table 1.[41]

**Table 1: Herbal nutraceuticals with anti-diabetic potential**

| Plant | Family | Plant part |
|---|---|---|
| *Artocarpus integrifolia* Linn | Moraceae | Root barks |
| *Abelmoschus esculentus* Linn | Malvaceae | Fruits |
| *Acacia arabica* | Leguminosae | Seeds |
| *Acacia modesta* Wall | Fabaceae | Leaves |
| *Adhatoda zeylanica* Nees | Acanthaceae | Leaves and fruits |
| *Aegle marmelos* | Rutaceae | Root bark, fruits and leaves |
| *Allium cepa* | Liliaceae | Bulbs |
| *Aloe vera* Linn | Lilliaceae | Leaves |
| *Alpinia calcarata* Rosc | Zingiberaceae | Rhizomes |
| *Alpinia galanga* Willd | Zingiberaceae | Rhizomes |
| *Alternanthera sessilis* Linn | Amarantaceae | Whole plant |
| *Amaranthus esculents* | Amaranthaceae | Whole plant, oil |
| *Ampelodesma mauritanica* Durand | Poaceae | Roots |
| *Andrographis paniculata* Nees | Acanthaceae | Roots |
| *Annona squamosa* | Annonaceae | Leaves |
| *Artemisia pallens* | Compositeae | Aerial parts |
| *Biophytum sensitivum* Linn | Oxalidaceae | Leaves |
| *Boerhaavia diffusa* Linn | Nyctagenaceae | Aerial parts |
| *Bridelia Retusa Spreng* | Euphorbiaceae | Stem barks |
| *Caesalpinia bonducella* Roxb | Caesalpiniaceae | Seeds |
| *Camellia sinensis* | Theaceae | Leaves |
| *Casearia esculenta* | Flacourtiaceae | Roots |
| *Cassia auriculata* Linn | Leguminosae | Flowers |
| *Catharanthus roseus* | Apocyanacee | Aerial parts |
| *Chamaemelum nobile* | Asteraceae | Leaves |
| *Chrysanthellum indicum* Linn | Compositae | Aerial parts |
| *Citrullus colocynthis* Linn | Cucurbitaceae | Fruits |
| *Cinnamomum zylanicum* Nees | Lauraceae | Stem barks |
| *Coccinia indica* | Cucurbitaceae | Leaves |
| *Coscinium fenestratum* | Menispermaceae | Stem barks |
| *Cucurbita maxima* Duch | Cucurbitaceae | Aerial parts |
| *Dioscorea bulbifera* Linn | Dioscoreaceae | Bulbs |
| *Diospyros cordifolia* Roxb | Ebenaceae | Stems |
| *Dodonae viscose* Linn | Sapindaceae | Leaves |
| *Egyptian morus* | Moraceae | Root barks |
| *Elaeodendron glaucum* Pers | Celastraceae | Stem barks |
| *Enicostemma littorale* | Gentiaceae | Whole plant |
| *Eugenia jumbolana* Lam | Myrtaceae | Seeds |
| *Ficus bengalensis* | Moraceae | Barks |
| *Ficus glomerata* | Moraceae | Leaves |
| *Ficus racemose* Linn | Moraceae | Fruits |
| *Foeniculum Vulgare* Mill | Apiaceae | Volatile oil |
| *Glycrrhiza glabra* Linn | Leguminosae | Roots |
| *Gnidia glauca* Linn | Thymelaeaceae | Whole plant |
| *Helicteres isora* | Sterculiaceae | Roots |
| *Hibiscus rosa* | Malvaceae | Whole plant |

*Contd...*

## Micronutrients

Micronutrients are vitamins, minerals and other compounds that our body needs in small amounts in order to accomplish certain functions and they can help to regulate metabolism, to convert sugars and other carbohydrates in your diet into energy. Micronutrients are a subset of the larger group of known dietary essential nutrients for man. Table 1 show the list of various herbal nutraceuticals with anti-diabetic potential.[41] The Recommended Dietary Allowances (RDA) or an Estimated Safe and Adequate Daily Dietary Intake (ESADDI) for an individual micronutrient is less than 100 mg. This category encompasses all of the vitamins and many of the minerals, including those sometimes referred to as 'trace' minerals.[42] Figure 3 shows various nutraceuticals used in treatment of diabetes.

**Table 1:Contd...**

| Plant | Family | Plant part |
|---|---|---|
| *Lycium shawii Roem* | Solonaceae | Aerial parts |
| *Madhuka longifolia* | Sapotaceae | Barks |
| *Mangifera indica* Linn | Anacardiaceae | Leaves |
| *Melia azadirachta* Linn | Meliaceae | Leaves |
| *Michelia champaca* Linn | Magnoliaceae | Leaves |
| *Mirabilis jalapa* Linn | Nyctagineceae | Roots |
| *Momordica charantia* | Cucurbitaceae | Fruits |
| *Momordica cymbalaria* | Cucurbitaceae | Fruits |
| *Morinda tinctoria* Roxb | Rubiaceae | Fruits |
| *Morus alba* | Moraceae | Leaves |
| *Morus indica* | Moraceae | Leaves |
| *Mucuna pruriens* | Leguminosae | Whole plant |
| *Murraya koenigii* | Rutaceae | Leaves |
| *Noolamarckia cadamba* Roxb | Rubiaceae | Leaves |
| *Ocimum sanctum* Linn | Labiateae | Leaves |
| *Orthosiphon stamineus* Benth | Lamiaceae | Leaves |
| *Ougeinia oojeinensis* Roxb | Fabaceae | Barks |
| *Piper betle* | Piperaceae | Leaves |
| *Psidium guajava* | Myrtaceae | Whole plant |
| *Pterocarpus marsupium* Roxb | Fabaceae | Wood and barks |
| *Punica granatum* | Puniaceae | Whole plants |
| *Rubus ellipticus* Smith | Rosaceae | Fruits |
| *Salacia reticulate* | Celastaceae | Leaves |
| *Sesbania sesban* Linn | Fabaceae | Leaves |
| *Shorea tumbuggaia* Roxb | Dipterocarpaceae | Leaves |
| *Sida acuta* Burm | Malvaceae | Leaves |
| *Sida cordifolia* | Malvaceae | Roots |
| *Sorbus decora* | Rosacea | Inner barks |
| *Strychnos potatorum* Linn | Loganiaceae | Ripened fruits |
| *Swertia chirayita* | Gentiaceae | Barks |
| *Tabernaemontana divaricata* Linn | Apocynaceae | Flowers |
| *Terminalia chebula* | Combretaceae | Seeds |
| *Tinospora cordifolia* | Menispermaceae | Roots |
| *Trigonella foenum-graecum* | Leguminosae | Seeds |
| *Triumfetta rhomboidea* | Liliaceae | Whole plant |
| *Viscum album* | Llorenthaceae | Whole plant |
| *Withania somnifera* | Solanaceae | Roots |

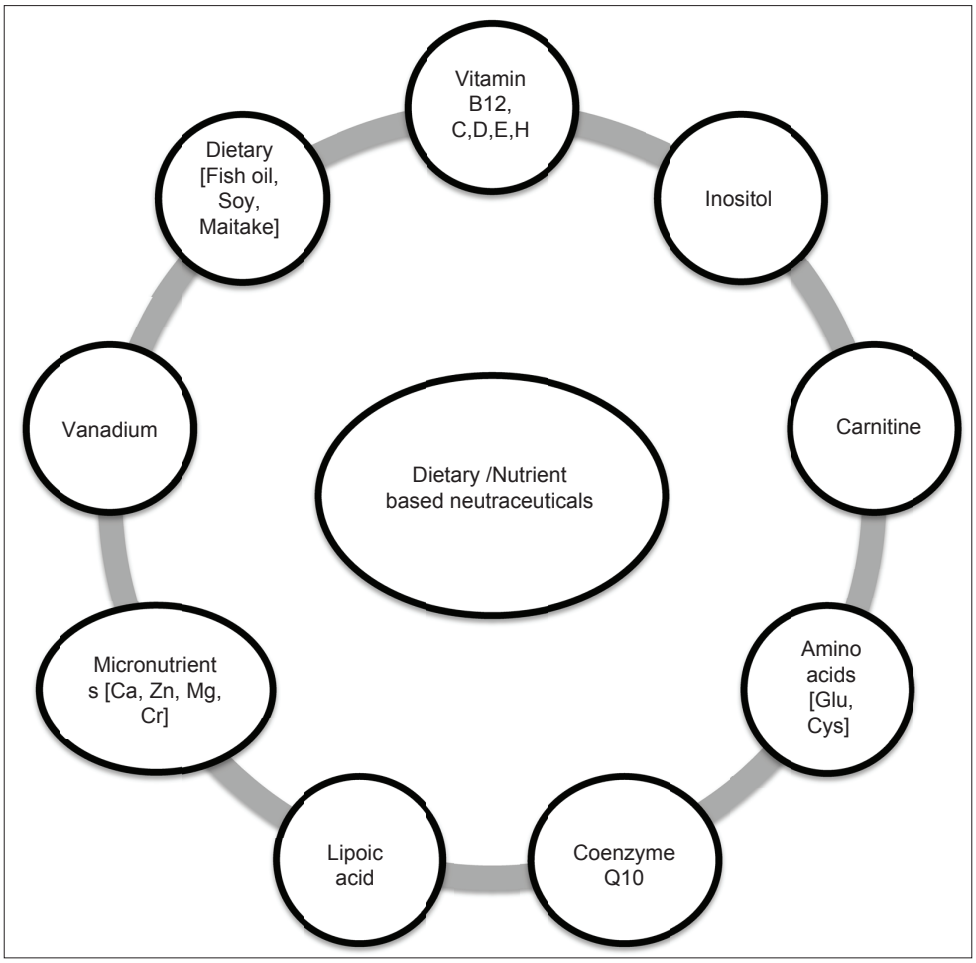


**Figure 3:** Various vitamins and micronutrients used as nutraceuticals in treatment of diabetes

### *Alpha Lipoic Acid*

One of the most promising natural treatments for diabetes is alpha lipoic acid (ALA). There are more than 15 clinical trials that had been performed with ALA to date. The researchers concluded that 3-week treatment using 600 mg/day of the ingredient reduced the chief symptoms of diabetic neuropathy – a complication of diabetes that affects the nerves and also confer long-term improvement in motor and sensory nerve conduction in the lower limbs.[43] ALA is potent anti-oxidants and has been shown to significantly reduce the symptoms of neuropathy. It has also been shown to improve insulin sensitivity by recruiting glucose transporter-4 to plasma membranes causing uptake of glucose. New studies have also suggested that ALA stimulates glucose disposal in patients with T2D. In experimental and clinical studies, ALA markedly reduced diabetic pathologies including: Cataract formation, vascular damage and polyneuropathy.[44]

### *Calcium and Vitamin D*

Good calcium/vitamin D status may help to preserve insulin sensitivity and thus help prevent diabetes by suppressing secretion of parathyroid hormone (PTH) because PTH can compromise the insulin sensitivity of adipocytes (and possibly other tissues) by increasing intra-cellular free calcium.[45,46]

### *Carnitine (L-Carnitine, Acetyl L-Carnitine)*

Carnitine is required by the body in order to correctly use body fat in the production of energy. It is naturally occurring and derives from hydrophilic amino acids. Diabetics who try carnitine generally respond well and high levels of fat in the bloodstream (cholesterol and triglycerides) may fall fast. Carnitine helps to break down fatty acids in the body and binds acyl residues. For these reasons, it may be useful to prevent diabetic ketoacidosis.[47,48]

### *Coenzyme Q10*

Coenzyme Q10 is a compound that occurs naturally in the body, and may be able to help with carbohydrate metabolism. It is has been proven that animals suffering from diabetes are coenzyme Q10 deficient. Clinical trials using coenzyme Q10 suggested that supplementation may significantly lower blood sugar levels. Coenzyme Q10 also oxygenates the blood, and therefore may be able to help in some cases of diabetic retinopathy.[49]

### *Chromium*

Perhaps the most known of anti-diabetic ingredients, chromium, a trace mineral, which potentiates the actions of insulin, is also widely researched. The benefit of added chromium for diabetes has been studied and debated for several years. Several studies have been reported that chromium supplementation may improve diabetes control. Chromium is needed to make glucose tolerance factor, which helps insulin to improve its action. Because of insufficient information on the use of chromium to treat diabetes, no recommendations for supplementation yet exist. Nine out of fifteen randomised controlled trials on chromium's ability to enhance insulin sensitivity and improve blood sugar control in diabetics showed significant benefit.[50,51]

### *Fish Oils*

Omega 3 fatty acids contained within fish may help to prevent and treat diabetes. In one trial of overweight individuals with insulin resistance, 50% of participants showed a clinically significant change in insulin-related function after taking docosahexaenoic acid (DHA). Another study found that diabetic women who regularly ate fish had reduced risk of heart disease by as much as 64%. Enzymotec manufactures carDiabet®, a proprietary combination of enzymatically derived lipids including DHA and eicosa pentaenoic acid (EPA). The 'carDiabet' does what current diabetes treatments do not; it supplies a specific solution for the major risk of death in diabetes patients–cardiovascular disease.[52,53]

### *Grifola Frondosa* (Maitake)

Several animal studies have shown that Maitake fractions have glucose-lowering potential. Two human trials have also been undertaken. The first showed that patients with T2D taking oral medication showed 30-63% declines in blood sugar levels after taking Maitake powder containing SX-fraction for 2-4 weeks. According to Maitake Products, Inc., Ridgefield Park, NJ, an unpublished 2-month Japanese trial involving 14 diabetic patients found that fasting blood glucose and haemoglobin Alc significantly decreased after a month of supplementation with the mushroom fraction, as did body weight, cholesterol and triglycerides.[54]

### *Inositol*

Inositol is an important part of several key bodily processes including the health of cell membranes and blood cholesterol levels. Furthermore, inositol may have a role to play in reversing the effects of diabetic neuropathy (nervous damage) caused by diabetes.[55,56]

### *Magnesium*

Although the relationship between magnesium and diabetes has been studied for decades, it is not yet fully understood. Studies suggest that a deficiency in magnesium may worsen the blood sugar control in T2D. Scientists believe that a deficiency of magnesium interrupts insulin secretion in the pancreas and increases insulin resistance in the body's tissues. Evidence suggests that a deficiency of magnesium may contribute to certain diabetes complications.[57,58]

### *N Acetyl Cysteine*

It can significantly decrease the progression of vascular damage that occurs with diabetics. It also helps to protect the integrity of erythrocytes and reduces structural changes in T2D. It may also reduce the glycation processes that lead to cataract formation.[59]

### *Soy*

Soy protein has been observed in animal and human studies to have anti-diabetic activity. Maintaining a low GI score, it is well known for its heart-protective properties. Solbar, Israel, produces soy protein (Solcon S) and soy isoflavones (Solgen 40), both of which have been clinically studied. One study found that diet supplemented with these two ingredients improved insulin resistance and blood sugar and cholesterol levels in post-menopausal diabetic women. In fact, soy was as effective at lowering blood sugar as some prescription diabetes drugs.[60,61]

### *Vitamin H (Biotin)*

Vitamin H, more commonly known as biotin, is part of the B complex group of vitamins. All B vitamins help the body to convert food (carbohydrates) into fuel (glucose), which is used to produce energy. These B vitamins, often referred to as B complex vitamins, also help the body metabolise fats and protein. Biotin levels influence blood sugar levels and tend to be lower in people with T2D. A combination supplement that contains chromium picolinate and biotin may reduce healthcare costs by improving blood sugar management. Biotin supplementation has been shown to enhance the performance of insulin, the hormone that plays a critical role in helping your body incorporate blood sugar. The supplements can also increase the activity of an enzyme, glucokinase, which the liver uses early in the process of utilising blood sugar.[62]

### *Vanadium*

Prior to the discovery of insulin in 1922, vanadium was used for the control of blood sugar. Two studies with T2D patients had confirmed the effectiveness of vanadyl sulphate at a dose of 100 mg/day in improving insulin sensitivity.[63]

## POLYPATHY: A PROMISING APPROACH FOR HOLISTIC TREATMENT OF DIABETES

In conventional therapy, Type I diabetes is treated with exogenous insulin and Type 2 with oral hypoglycaemic

agents (sulphonylureas, biguanides, etc.). Oral hypoglycaemic agents are useful in the treatment of diabetes mellitus but their use is restricted due to their pharmacokinetic properties, secondary failure rates and side effects like causing hypoglycaemia at higher doses, liver problems, lactic acidosis, GIT disturbances, diarrhoea, hematological disorder and rise in hepatic enzymes, etc.

Apart from these therapeutic options, many herbal medicines have been recommended for the treatment of diabetes. Traditional plant medicines are used throughout the world for a range of diabetic patients. Herbal drugs are prescribed widely because of their effectiveness, less side effects and relatively low cost. Therefore, WHO Expert Committee has also enlisted its recommendations that traditional methods of treatment for diabetes should be further investigated. In Ayurvedic system of medicine, several ancient Indian books like Charak Samhita, Madhav Nidan, Astang Sanghra, etc., recommended several polyherbal formulations with anti-diabetic potential. A large number of plants/plant parts have been investigated for anti-diabetic potential till date. But the problems associated with polyherbal formulations are lack of scientific evidences with respect to their pharmacological effects and possible mode of action, difficulty to standardise and control the quality as per Food and Drug A dministration regulations.

As per FDA guidelines, not more than three herbs are permitted to formulate a polyherbal formulation. Most of the polyherbal formulations available in the market do not qualify this criterion due to large number of herbal drugs in combination.

In spite of extensive efforts, search for an effective and safe therapeutic approaches for treatment of diabetes without dyslipidaemia and other adverse effects associated with oral hypoglycaemics still remains a challenge to both ancient and modern systems of medicines. A possible solution to the problem may be 'polypathy', that is simultaneous use of synthetic and polyherbal/nutraceutical formulations with proven anti-diabetic potential for synergistic effect leading to more effectiveness, reduction of dose, less/no side effects, quicker recovery and low cost.[64]

The fundamental requirements of 'polypathy' are:

- Prior detailed information of drugs to be used either herbal, synthetic or nutraceuticals, their mechanism of therapeutic effect, related biochemistry, pharmacological interactions along with dose, single or in combination
- Each case should be studied separately. A course of treatment should be evaluated for each patient according to the severity of disease and number of drugs administered
- During treatment, the least number of medicines in minimum doses should be used
- The life force of the patient should be allowed to counter the disease force. Except in special circumstances nothing should be done to vitiate the already disturbed condition of the patient. Ideally, the patient should be encouraged to recover through the normal processes of nature.

## CONCLUSION

Clearly, many natural products have hypoglycaemic, anti-hyperglycaemic, insulin sensitising, anti-hyperlipidaemic, anti-hypertensive and anti-inflammatory activities. There are published studies reporting the anti-diabetic activity of well-over a thousand different botanicals and nutraceuticals. The number of those treatments evaluated in clinical trials is approximately 100. In majority of these trials, the botanicals and nutraceuticals were evaluated as an adjunct to diet and prescription medications. Fifty-eight of the trials were controlled and conducted in individuals with diabetes or impaired glucose tolerance. Of these, statistically significant treatment effects were reported in 88% of trials evaluating a single botanical and 67% of trials evaluating individual vitamin or mineral supplements. When reported, side effects were few and generally mild (gastrointestinal irritation and nausea) that being stated, several botanical and nutraceutical agents appear to merit consideration as complimentary approaches for the treatment of T2D. Botanical treatments with the strongest evidence of clinical efficacy include *C. indica*, *T. foenum-graecum*, American ginseng, *A. vera*, and *Opuntia* (Nopal). Nutraceutical agents with promise for improving insulin sensitivity and glycaemic control include α-lipoic acid, vitamins C and E and magnesium. If the safety profile of vanadium could be confirmed with chronic use, this agent would also be regarded as a promising treatment. In addition, there is evidence that α-lipoic acid and vitamin E improve the symptoms of individuals with microvascular complications including neuropathy and retinopathy. ω-3 PUFAs (EPA, DHA, linolenic acid), L-arginine and vitamin C merit consideration for cardiovascular complications.

In spite of extensive research, the search for the therapeutically effective treatment, of diabetes still remains elusive. Simultaneous/co-administration of synthetic, herbal and nutraceuticals, that is polypathy along with non-pharmacological approaches may be the most suitable solution for holistic treatment of diabetes. So these nutraceuticals can lead to development of new synergistic combinations for effective treatment of diabetes and may work wonders for millions of patients.

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