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Review Article

Phytomedicine for Diabetes mellitus: An overview

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Diabetes mellitus is a complex metabolic disorder resulting from either insulin insufficiency or insulin dysfunction. Diabetes mellitus affect most of the people of both developed and developing countries. The treatment of diabetes with synthetic drugs is costly and chances of side effects are high. Phytomedicine has been used since ancient time in many parts of the world where access to modern medicine is limited. Low-fat vegan diet has improved glycemic control in type II diabetic patients. Photochemical identified from medicinal plants presents an exciting opportunity for the development of new types of therapeutics for diabetes mellitus. Most prevalent of photochemical groups are the alkaloids, terpenes, and phenolics. Several formulations like herbal teas, extracts, decoctions, infusions, tinctures, etc are prepared from medicinal plants. Despite considerable progress in the development of synthetic drugs, the search for the invention of phytomedicine as alternative therapy is progressing.

Keywords: Diabetes mellitus, phytomedicine, vegan diet, synthetic drugs.

India is the largest producer of medicinal herbs and is called as botanical garden of the world. Ayurveda, Unani, Siddha and Folk (also called tribal) medicines are the major systems of Indian medicines. Among these systems, Ayurveda is most developed and widely practiced in India. A number of plants have been described in Ayurveda and other traditional medicine for the treatment of diabetes. Isolation of the main compounds from the active extract is a crucial step in all research activities for developing a novel phytomedicine for diabetes mellitus.

Diabetes mellitus

Diabetes mellitus is a complex metabolic disorder resulting from either insulin insufficiency or insulin dysfunction. Type I diabetes (insulin dependent) is caused due to insulin insufficiency. Type II diabetes (insulin independent) is due to immunological destruction of pancreatic β cells leading to insulin deficiency. Type II diabetes is characterized with insulin resistance. It is the more common form of diabetes constituting 90% of the diabetic population. Symptoms for both diabetic conditions may include: (i) high levels of sugar in the blood; (ii) unusual thirst; (iii)

frequent urination; (iv) extreme hunger; (v) loss of weight; (vi) nausea and vomiting; (vii) blurred vision; (viii) Excessive tiredness, irritability etc.

Glycemic control

Glycemic control is a medical term referring to the typical levels of blood sugar (glucose) in a person with diabetes mellitus. "Perfect glycemic control" would mean that glucose levels were always normal (70–130 mg/dl, or 3.9-7.2 mmol/L) and indistinguishable from a person without diabetes. Control and outcomes of both types I and II diabetes may be improved by patients. Home glucose meters can be used to regularly measure their glucose levels (Gray et al., 2000). The American Diabetes Association in 1994 recommended that 60-70% of caloric intake should be in the form of carbohydrates. But some researchers claim that 40% is better, (Garg et al., 1994) while others claim benefits for a high-fiber, 75% carbohydrate diet (Kiehm et al., 1976).

Importance of phytomedicine

Traditional herbal medicine has been used since ancient time in many parts of the world. The many side effects of insulin therapy and other oral hypoglycemic agents necessitate the use of more effective and safer antidiabetic drugs. For example, long-term use of Metformin (Bolen et al., 2007) causes diarrhea, nausea, gas, weakness, indigestion, abdominal discomfort and headache. Plant based drug are considered to be less toxic and free from side effects than synthetic one. Hence, they play an important role as alternative medicine. Phytomedicines are mainly whole, fragmented or cut, plants parts of plants, algae, fungi, lichen in an unprocessed state, usually in a dried form, but sometimes fresh. Herbal drugs are defined by their botanical (scientific) binomial. The active principles present in medicinal plants have been reported to possess pancreatic beta cells regenerating, insulin releasing and fighting the problem of insulin resistance (Welihinda et al., 1982). Anti diabetic plants also possess strong antioxidant/free-radical scavenging properties.

Phytochemicals

Plants have evolved secondary biochemical pathways allowing them to synthesize a raft of chemicals, often in response to specific environmental stimuli, such as herbivore-induced damage, pathogen attacks, or nutrient depravation (Raymond et al., 2000; Hermsmeier et al., 2001). These secondary metabolites increase their overall ability to survive and overcome local challenges by allowing them to interact with their environment. These chemicals also help humans to protect themselves against diseases and are called Photochemical. Thus there is a need to know about the health benefits and possible risks to ensure the efficacy and safety of dietary supplements.

Photochemical are chemical compounds that occur naturally in plants that have protective or disease preventive properties. Each type of fruit or vegetable may contain hundreds of photochemical. Selenium, for example, is involved with major metabolic pathways, including thyroid hormone metabolism and immune function (Brown and Arthur, 2001). These photochemical show multiple beneficial effects in combating diabetes and diabetes-related complications.

The herbal drug preparation (phytomedicine) is obtained subjecting herbal drugs to treatments such as extraction, distillation, fractionation, purification, concentration and fermentation. These include cut or powered herbal drugs, tinctures, extracts, essential oils, fatty oils, expressed juices and processed exudates.

Getting enough phytochemicals

Food provides not only essential nutrients needed for life but also other biologically active compounds for health promotion and disease prevention. The easiest way to get more photochemical is to eat more fruit (blueberries, cherries, apple…) and vegetables (cauliflower, cabbage, carrots...). Fruits and vegetables contain many beneficial nutrients and photochemical that is thought to protect against cardiovascular disease (Liu and Manson, 2001; Bazzano et al., 2003) and diabetes (Colditz et al., 1992; Feskens et al., 1995). Fruit and vegetable consumption was inversely related to incident type II diabetes (Ford and Mokdad, 2001). More than 5000 photochemical have been identified, but a large percentage still remains unknown. Largest and most prevalent of photochemical groups are the alkaloids, terpenes, and phenolics.

Table I: Medicinal plants used for the treatment of Diabetes mellitus

Medicinal Plant	Family	Common Names	Distribution	Part Used	Active Ingredient	Reference
Aloe vera	Asphodelaceae	Goddess, Kumari, Guarpatha	North Africa, Canary Islands, Spain, India	Leaf, gel extract	Polysaccharides, Mannans, Lophenol, Lectins	Eshun and He, 2004
Azadirachta indica	Meliaceae	Neem, Nimtree	Myanmar, India, Sri Lanka, Pakistan	fruit, leaf, flower, seed	Nimbin, Nimbidin, Nimbinin, Azadirachtin	Pillai and Santhakumari, 1981
Momordica charantia	Cucurbitaceae	Karela, Bittermelon, Bittergourd.	United States, India	Fruit, seed	Charantin	Lolitkar and Rajarama Rao, 1962
Gymnema sylvestre	Asclepiadaceae	Gudmar, Periploca of the woods	Tropical regions of Africa, Asia	Leaf callus, stem	Gymnemic acids, Gymnema saponin	Sugihara et al., 2000
Holostemma ada-kodien	Asclepiadaceae	Holostemma creeper, Charivel	Sri Lanka, India, Myanmar, China	Root	Flavonoids, Tannins, Terpenoids	Iwu, 1980

Alkaloids

The name "alkaloids" was introduced in 1819 by the German chemist Carl F.W. Meissner. Alkaloids are a structurally diverse group of over 12,000 cyclic nitrogen-containing compounds that are found in over 20% of plant species (Zulak et al., 2006). Alkaloids are most common in flowering plants, especially in Fabaceae, Ranunculaceae and Solanaceae (Filho et al., 2006). If several alkaloids are extracted from one plant then their names often contain suffixes "idine", "anine", "aline", "inine", etc. There are also at least 86 alkaloids containing the root "vin" (extracted from the Vinca plant).

Most plants contain several alkaloids. Their mixture is extracted first and then individual alkaloids are separated. Biological precursors of most alkaloids areamino acids, such as ornithine, lysine, phenylalanine, tyrosine, tryptophan, histidine, aspartic acid and anthranilic acid. Alkaloids such as

aconitine, anisodamine, charantine, leurosine show antidiabetic effects (Li et al., 2004).

Berberine a quaternary ammonium salt from the protoberberine group of isoquinoline alkaloids is used successfully in experimental (Wang et al., 2010) and human diabetes mellitus (Gu et al., 2010). It is found in such plants as *Berberis* e.g. *Berberis aquifolium* (Oregon grape), *Berberis vulgaris* (Barberry). Berberine has been shown to lower elevated blood glucose as effectively as metformin (Yin et al., 2008). The mechanisms of action include inhibition of aldose reductase, inducing glycolysis, preventing insulin resistance through increasing insulin receptor expression.

Terpenes

Terpenes are a large and varied class of organic compounds, produced primarily by a wide variety of plants, particularly conifers. Vitamin A is an example of a terpene. When terpenes are modified chemically, such as by oxidation or rearrangement of the carbon skeleton, the resulting compounds are generally referred to as terpenoids. Terpenes are derived biosynthetically from units of isoprene, which has the molecular formula C_5H_8. The basic molecular formulae of terpenes are multiples of $(C_5H_8)_n$ where n is the number of linked isoprene units. This is called the isoprene rule or the C5 rule. Terpenes may be classified by the number of terpene units in the molecule; a prefix in the name indicates the number of terpene units needed to assemble the molecule. It is classified into Hemiterpenes, Monoterpenes, Sesquiterpenes, Diterpenes, Sesterterpenes and Polyterpenes. These are extracted from green vegetables, soy products and grains, and represent one of the largest classes of phytochemicals. They are synthesized through two potential pathways, the mevalonate and, more recently identified, deoxy-d-xylulose pathways (Rohmer, 1999). Terpenes can be used for the prevention and/or treatment of diabetes type II, obesity and neuropathy.

Phenolics

In organic chemistry, phenols, sometimes called phenolics, are a class of chemical compounds consisting of a hydroxyl group (-OH) bonded directly to an aromatic hydrocarbon group. The simplest of the class is phenol also called as carbolic acid C_6H_5OH. They have higher acidities due to the aromatic ring's tight coupling with the oxygen and a relatively loose bond between the oxygen and hydrogen. Phenols are found in the natural world, especially in the plant kingdom. Whole grain cereals are a good source of phenolics.

Gallic acid is a trihydroxybenzoic acid, a type of phenolic acid, a type of organic acid, also known as 3,4,5-trihydroxybenzoic acid, found in gallnuts, sumac, witch hazel, tea leaves, oak bark, and other plants (Reynolds and Wilson, 1991). It is used to treat albuminuria and diabetes.

Is Phythochemicals Dangerous

Many plants that humans consume become toxic when attacked by pathogens. The plants produce very dangerous phytochemicals, phytoalexins, in response to being attacked by bacterial or fungal pathogens. Certain phytochemicals have been found to contribute to cancer cell growth. Beta-carotene, (it can be beneficial when taken naturally), has been found to increase the risk of lung cancer in male smokers when taken in high-doses. Some flavonoids can cause serious gastrointestinal or allergic problems.

Vegan vs. Diabetes mellitus

The incidence of diabetes has found to be lower in vegetarians. Vegan diets also lower advanced glycation end products (McCarty, 2005). Several studies have shown

that a vegan diet may be effective in managing type II diabetes (Barnard et al., 2006). Clinical trials using low fat vegan diets have shown improvements in glycemic control and cardiovascular health (Jenkins et al, 2003; Fraser, 2003). Plant-based diet diets are low in fat and high in fiber, they typically cause associated reductions in dietary energy density and energy intake, which are not fully compensated for by increased food intake (Kendall et al., 1991; Howarth et al., 2001). Whole-grain consumption also reduces the risk of type II diabetes. The vegetarian diet forms of benefit for both the carbohydrate and lipid abnormalities in diabetes. Vegan diets have been associated with very low LDL cholesterol levels (Sacks et al., 1985). The weight loss may be one of the advantages of vegetarian diets. Diet and lifestyle changes can prevent the development of diabetes in susceptible individuals (Knowler et al., 2002).

Animal studies

Proper animal model have to be used for testing the anti diabetic activity (Versphol, 2002). The only model with supporting data for type II diabetes is the streptozotocin diabetic rat (Islas-Andrade et al., 2000). But according to Versphol, the only way to get type II diabetic animals by chemical induction is by the proper use of streptozotocin in neonatal rats (n-STZ), or use genetically models like fa/fa zucker diabetic fatty rat. Anti diabetic plants have been observed to possess potent antioxidant activity, which may contribute to anti-diabetic property in streptozotocin/alloxan, induced animal model (Grover et al., 2002).

Anti-diabetic activity and Phytomedicine

A number of plants have been described in Ayurveda and other traditional medicine for the treatment of diabetes. In Ayurveda, diabetes is described as 'Madhumeha'. In developing countries 80% of populations are using traditional medicine in primary medical problems (Grover and Yadav, 2004). Drug Metformin (a biguanide) is a derivate of an active natural product, galegine a guanidine isolated from the plant *Galega officinalis* L., which was used to relieve the intense urination in diabetic people (Witters, 2001). Even the root juice of *Helicteres isora* Linn. (Family – Sterculiaceae) is claimed to be useful in diabetes, empyema, and a favorite cure for snakebite (Singh et al., 1984).

Despite considerable progress in the management of diabetes by conventional drugs, the search for natural antidiabetic plant products as alternative therapy is progressing.

Many medicinal plants have shown experimental or clinical antidiabetic activity and that have been used in traditional systems of medicine. Plants such as *M. charantia, Eugenia jambolana, Mucuna pruriens, Murraya koeingii* and *Brassica juncea* have found to have anti diabetic property (Grover et al 2002). All plants have shown varying degree of hypoglycemic and anti-hyperglycemic activity. In the recent years more than 500 herbal medicines have been reported to possess antidiabetic property (Handa et al., 1989; Jia et al., 2003). An ethno botanical survey of semi-structured questionnaire of medicinal plants in five districts of Lagos State of Nigeria reputed for the treatment of diabetes have been reported (Gbolade, 2009). The principal antidiabetic plants included *Vernonia amygdalina, Bidens pilosa, Carica papaya, Citrus aurantiifolia, Ocimum gratissimum, Momordica charantia* and *Morinda lucida.*

The database maintaining the record of medicinal plants having anti-hyperglycemic or anti-diabetic activity has been reported on 2009 (Singh et al., 2009). The herbal drugs with antidiabetic activity are yet to be commercially formulated as modern medicines, even though they have been

acclaimed for their therapeutic properties in the traditional systems of medicine.

The market for herbal medicines is booming (Brevoort, 1998) and evidence for effectiveness is revealed to all at a faster rate. Some of the most promising plants for diabetes mellitus were *Aloe vera, Azadirachta indica, Momordica charantia, Gymnema sylvestre, Holostemma ada-kodien.,* etc. Table I depicts the characteristics of these anti diabetic plants.

Aloe vera

Aloe vera is a stemless/short-stemmed succulent plant growing to 60–100 cm tall, spreading by offsets. *Aloe vera* has been widely grown as an ornamental plant. *Aloe vera* gel is better known as a home remedy for minor burns and other skin conditions. *Aloe vera* extracts may be useful in the treatment of wound and burn healing, minor skin infections, diabetes, and elevated blood lipids in humans. These positive effects are thought to be due to the presence of compounds such as polysaccharides, mannans, anthra - quinones, and lectins (Eshun and He, 2004). Intake of *Aloe vera* has been reported to improve blood glucose levels in diabetics (Yongchaiyudha et al., 1996) and lowered blood lipids in hyperlipidaemic patients (Nassiff et al., 1993).

Azadirachta indica

Azadirachta indica is commonly known as neem, margosa or Indian lilac. *Azadirachta indica* is a tree in the mahogany family Meliaceae. It was introduced to Africa by Indian immigrants and has since been naturalized in many African countries and cultivated in several others. The seeds contain a complex secondary metabolite azadirachtin. Three bitter compounds were extracted from neem oil, which were named nimbin, nimbinin, and nimbidin (Pillai and Santhakumari, 1981). The efficacy of neem as a broad spectrum pesticide, non-toxic to humans has important implications for its application to parasitic diseases. The neem tree offers an opportunity to reduce insulin requirements with a safe and proven herb. Many scientists have done clinical trial supporting the hypothesis that leaf extracts, seed oil and nimbidin exert hypo-glycaemic/anti-hyperglycaemic effects.

Momordica charantia

Momordica charantia, called bitter melon or bitter gourd in English, is a tropical and subtropical vine of the family Cucurbitaceae, widely grown in Asia and Africa. There are many varieties that differ substantially in the shape and bitterness of the fruit. Bitter melon has been used in various Asian and African traditional medicine systems for a long time (Beloin et al., 2005).

The plant contains biologically active compounds, chiefly momordicin I and II, and cucurbitacin B. (Fatope et al., 1990) The plants contain also bioactive glycosides (including momordin, charantin, charantosides, and momordicosides) and other terpenoid compounds (including momordicin-28, momordicin, momordenol and momordol) (Begum et al., 1997; Kimura et al., 2005).

Use of *Momordica charantia* by diabetic patients for its hypoglycemic potential is a common practice in India (Sastri, 1962). Effect of *Momordica charantia* fruit powder on serum glucose level and body weight in Alloxan-induced diabetic rats has been studied (Jafri et al., 2009). It was found that *Momordica charantia* fruit powder is helpful in treating hyper glycemic rats in diabetes mellitus type II. Charantin has been extracted from the plant, which had hypoglycaemic effect on normal and diabetic rabbits (Lolitkar and Rajarama Rao, 1962). *Momordica charantia* has been found to increase insulin sensitivity.(Sridhar et al 2008). *Momordica charantia* also contains a substance lectin that has insulin-like activity due to its non-

protein-specific linking together to insulin receptors. This lectin lowers blood glucose concentrations by acting on peripheral tissues and act as a major contributor to the hypoglycemic effect. Tablets of bitter melon extract are also produced as a food supplement in many countries.

Gymnema sylvestre

Gymnema sylvestre is an herb native to the tropical forests of southern and central India where it has been used as a natural treatment for diabetes for nearly two millennia. The common name of the plant species is miracle fruit (Wiersema and Blanca, 1999). It is also known as gymnema, cowplant and Australan cowplant.The major bioactive constituents of *Gymnema sylvestre* are a group of oleanane type triterpenoid saponins known as gymnemic acids.

Gymneme syvestre leaves contain triterpene saponins belonging to oleanane and dammarene classes. It also contains flavones, anthraquinones, hentri-acontane, pentatriacontane, α and β- chlorophylls, phytin, resins, tartaric acid, formic acid, butyric acid, lupeol, β-amyrin related glycosides and stigmasterol.

Gymneme syvestre found to have an antidiabetic and hypolipidemic activity on both alloxan induced diabetic rats and normal rats. From extract of the leaves were isolated gymnemic acids, which exhibit anti-sweet activity (Kinghorn and Compadre, 2001). *Gymnema sylvestre* may be useful as therapeutic agents for the stimulation of insulin secretion in individuals with type II diabetes (Asare-Anane et al., 2005). It can also help prevent adrenal hormones from stimulating the liver to produce glucose, thereby reducing blood sugar levels (Gholap and Kar, 2003).

Holostemma ada-kodien

Holostemma ada-kodian, an important medicinal plant belonging to family Asclepiadaceae is used to control diabetes (Moming, 1987). Plant has various types of phytochemicals like alkaloids, flavonoids, flavanones, tannins, terpenoids, amino acids and carbohydrates. Presence of flavonoids and tannins are responsible for the observed anti diabetic activity (Iwu, 1980)

Anti diabetic activity of *Holosstemma ada-kodien* Schults in alloxan induced diabetic rats have been studied. Extracts of this plant possess a variety of actions related to the antidiabetic properties such as reducing insulin requirements by possibly enhancing endogenous insulin availability, improving vitiated blood glucose homeostasis, better controlling of hyperlipidemia associated with diabetes, and reducing amylase activity.

Conclusion

Prevention is a more effective strategy than treatment. Natural products formed by living systems, especially from plant origin, have found to be beneficial in treating human diseases such as cancer, diabetes and infectious diseases. Plant-based foods, such as fruit, vegetables, and whole grains, which contain significant amounts of bioactive photochemical, may provide desirable health benefits beyond basic nutrition to reduce the risk of chronic diseases. Analysis of the pharmacological activities of plant extracts may enable the design of less expensive therapies. Despite considerable progress in the treatment of diabetes by oral hypoglycemic agents, search for newer drugs continues because the existing synthetic drugs have several limitations. Thus phytomedicine have retained functional strength compared to other medical system because of its safe and easy accessibility.

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