

Therapeutic potential of Indian medicinal plants in diabetic condition

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Abstract

Diabetes mellitus is the fourth leading cause of death worldwide. In the year 2000, there were approximately 150 million individuals with diabetes which is likely to get doubled by 2025. Insulin resistance and impaired glucose homeostasis underlie the development of the chronic complications in diabetes, which are responsible for higher mortality and decreased life expectancy. Oxidative stress has been implicated as a causative factor in the development of diabetic complications. Plants and their products, used in traditional medicine, have represent a valuable alternative for the management of diabetic alterations. In the present article, we have updated the current status of diabetes mellitus worldwide and possible role of some Indian medicinal plants in ameliorating the impairments during type 2 diabetes mellitus.

Key words: Diabetes, Free radicals, Oxidative stress, Antidiabetic plants

Introduction

Diabetes is a group of metabolic disorder, characterized by hyperglycemia resulting from defects in insulin secretion and/or insulin action (American Diabetic Association, 2012). Chronic hyperglycemia leads to macrovascular complications such as coronary artery and peripheral arterial diseases and stroke as well as microvascular complications such as microalbuminuria and renal failure (Choe *et al.*, 2013). Abnormal heart rate, vascular imbalance and retinopathy are other secondary complications of hyperglycemia (Fowler, 2008; Cade, 2008; Heydari *et al.*, 2010; Choe *et al.*, 2013).

Prevalence of diabetes mellitus is increasing worldwide. There are numerous reasons behind the increase in number of diabetics. Aging population, urbanisation, rising cases obesity, physical inactivity and other life style changes are

the major culprits, responsible for prevalence of hyperglycaemia, followed by diabetes (Grundy, 2012). Unlike in the West, where older persons are most affected, diabetes in Asian countries is disproportionately high in young to middle-aged adults (Ramachandran *et al.*, 2010). In 2010, around 6.4% of adults (285 million) were affected by this disease. This figure is expected to reach 7.7%, affecting 439 million adults by 2030. Between 2010 and 2030, there will be a 69% increase in numbers of adults with diabetes in developing countries and a 20% increase in developed countries (Shaw *et al.*, 2010).

The International Diabetes Federation (IDF) estimates the total number of people in India with diabetes to be around 50.8 million in 2010, rising to 87.0 million by 2030 (Shaw *et al.*, 2010). The prevalence of diabetes in India is likely to be due to a significant change in the life style, caused by unprecedented rates of urbanization, which results in environmental and change of physical activities (Ramachandran and Snehalatha, 2009).

Currently available therapies for diabetes include oral antidiabetic agents such as sulfonylureas, biguanides, metformin, glinides and insulin, many of them have serious

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adverse side effects (Patel *et al.*, 2012). Ayurveda and other traditional medicinal system for the treatment of diabetes describe a number of plants, used as an herbal drugs. Hence, they play an important role as alternative medicine, due to less side effects and low cost. The active principles present in medicinal plants have been reported to possess pancreatic beta cells, regenerating and insulin releasing properties (Saxena *et al.*, 2006). Although more than 800 traditional plant treatments for diabetes mellitus have been described but not all of them have received scientific and medical evaluation to assess their efficacy (Sathishsekar and Subramanian, 2005). In the present article, we have described the cellular consequences of diabetes mellitus and the role of some of traditional plants in diabetic interventions.

Oxidative stress and diabetes

The condition of imbalance between regeneration of free radicals and defence mechanism in the body is called as oxidative stress. Role of oxidative stress in development and progression of diabetes, has been reported in many studies (Uttara *et al.*, 2009; Rahimi *et al.*, 2005). Hyperglycaemia itself has been documented as reason of prevalence of oxidative stress (Dungan *et al.*, 2009). Oxidative stress is deleterious in many aspects to the cellular molecules. It oxidizes nucleic acids, lipids, proteins and, thus, alters their status and functions. Lipids and proteins are the major structural biomolecules in the body. Damage to them impairs several biophysical properties of the cell including malfunctioned fluidity of membranes due to disturbed deformity (Haliwell and Gutteridge, 2007; Pandey *et al.*, 2010). Peroxidation of lipids produces highly reactive byproducts, including malondialdehyde (MDA), acrolein, 4-hydroxynonenal (HNE), 4-oxononenal (ONE), and isolevuglandins 'IsoLGs' (Guoa *et al.*, 2012). Significant changes in lipid metabolism and structure have been reported in diabetes, particularly in patients with vascular complications (Fowler, 2008). Increased lipid peroxidation in diabetics has been reported in most of the studies (Saddala *et al.*, 2013).

Protein acts as the functional molecule of the cells. Oxidation of proteins adversely influences the biochemical pathways, physiology and signalling. Protein carbonyls and advanced oxidation protein products (AOPPs) are the oxidation product of proteins and are considered as the potent marker of oxidative stress (Pandey and Rizvi, 2010; Niki, 2009). Oxidative stress in diabetics leads to increased oxidation of proteins which leads to development of severe diabetic complications (Pandey *et al.*, 2010; Piwowar *et al.*, 2007). Depleted levels of inherent defensive molecules against oxidative stress have also been characterised during type 2 diabetes mellitus. Glutathione (GSH), an efficient antioxidant present in almost all living cells, is known as a biomarker of redox imbalance at cellular level (Pandey and Rizvi, 2011). Under oxidative conditions, GSH is reversibly oxidized to glutathione disulfide

'GSSG' (Zhu *et al.*, 2006). Reduced glutathione level in tissue has often been considered to be indicative of increased oxidative stress in diabetes and may be one of the factors in the oxidative DNA damage in type 2 diabetics (McLennan *et al.*, 1991; Maknia *et al.*, 2011).

Malfunctioned enzymatic antioxidant defence machinery is a key feature in diabetics. An array of experimental evidence suggests that there is impairment in the enzymes associated in antioxidative defence during diabetic mellitus (Rashid *et al.*, 2013). Catalase (CAT), one of the main enzyme in antioxidative defence, enzymatically converts deleterious hydrogen peroxide (H_2O_2) into oxygen and water. Increased frequency of diabetes has been documented in patients with CAT deficiency which leads in the β -cell to an increase in oxidative stress and ultimately to its failure. β -cells are rich in mitochondria and that this organelle might be a source of ROS (Goth and Eaton, 2000). Superoxide dismutases (SOD) catalyse the dismutation of superoxide anion (O_2^-) into H_2O_2 and molecular oxygen (Faraci and Didion, 2004). Impaired activity of SOD in diabetes indicates the pivotal role of oxidative stress in type 2 diabetes which is responsible for the onset of many late complications of diabetes such as kidney and neuronal problems.

Indian medicinal plants as antidiabetic agents

The plant kingdom has become a target for the search for new drugs and biologically active compounds. Plants are the rich source of antioxidants and have a great potential to act as defence to free radical attack. Plants contain bioactive compounds, known as phytochemicals that work along with essential nutrients and dietary fibres to protect against diseases. Originally, plants produce these compounds for self protection whereas recent studies establish the defensive role of these phytochemicals against human diseases as well. These compounds are prevalent in almost all parts of plant and have the potential to reduce the diabetic complications through their multidimensional properties (Atale *et al.*, 2011). In addition, plants have inorganic macroelements and microelements such as vanadium, zinc, chromium, copper, iron, potassium, sodium and nickel which play an important role in the maintenance of normoglycemia by activating the β -cells of the pancreas (Narendhirakannan *et al.*, 2005). Here we will discuss the antidiabetic property of some of the Indian medicinal plants, easily available in Indian continent.

Ocimum sanctum

Ocimum sanctum L. (Labiata), commonly known as holy basil, is an herbaceous plant, found throughout the south Asian region, is used medicinally in catarrhal, bronchitis, bronchial asthma, dysentery, dyspepsia, skin diseases, chronic fever, haemorrhage, helminthiasis and topically for ringworms (Hannan *et al.*, 2006). The leaf is claimed to possess hypoglycemic and antihyperglycaemic effects in experimental

animals (Khan *et al.*, 2010). Eugenol (1-hydroxy-2-methoxy-4-allylbenzene) is an active constituent, found in *O. sanctum* as antidiabetic, cardioprotective, hypolipidemic and hepatoprotective agent. Eugenol and the essential oils have been found to reduce raised blood sugar, triglyceride and cholesterol levels and activities of LDH, GPT, GOT and alkaline phosphatase in blood serum (Prakash and Gupta, 2005). *O. sanctum* leaf powder significantly reduced the fasting blood sugar, uronic acid, total amino acids, total cholesterol, triglyceride, phospholipids and total lipids; also found decreasing level of lipid and cholesterol in liver, kidney and heart (Rai *et al.*, 1997; Sethi *et al.*, 2004).

Azadirachta indica

Azadirachta indica A. Juss is a member of the Meliaceae family that is predominantly found in the Asian subregion but is also grown in Nigeria and other parts of Africa, where it is functionally used as an antidiabetic medicinal plant. *A. indica* is commonly known as neem in India. Extract from *A. indica*, is also used to treat gastrointestinal upset, diarrhoea and intestinal infections, skin ulcers, infections and malaria (Anyaehe, 2009). The blood glucose lowering effect of *A. indica* leaf extract, which was found to be either through significant blockage of the inhibitory effect of serotonin on insulin secretion, mediated by glucose or peripheral utilization of glucose and glycogenolic effect due to epinephrine action blockage, was observed higher than others (Gholap and Kar, 2004). The petroleum ether extract of neem seed kernel (NSK) and neem seed husk (NSH) showed significant protection against diabetes which is associated with oxidative damage induced by streptozotocin in heart and erythrocytes of rats (Gupta *et al.*, 2004). *A. indica* could be of benefit in diabetes mellitus in controlling the blood sugar or may also be helpful in preventing or delaying the onset of the disease (Khosla *et al.*, 2000).

Murraya koenigii

Murraya koenigii L. Spreng, a member of the family Rutaceae, is used as a spice in India for its characteristic flavour and aroma and commonly known as "curry". Curry leaves can be used as antioxidants in high fat diets as they contain the antioxidants tocopherol, β -carotene and lutein (Ningappa *et al.*, 2008). Since sufficient dose of antioxidants may prevent or delay β -cell dysfunction in diabetes by providing protection against glucose toxicity, the observed antioxidant potential of *M. koenigii* may partially responsible for its antidiabetogenic properties (Arulselvan and Subramanian, 2007). *M. koenigii* possesses potent antioxidant properties which may be due to the presence of biological active ingredient such as carbazole alkaloids, glycoside, triterpenoids and phenolic compounds. It has been postulated that the antidiabetic activity of *M. koenigii* leaves is probably due to

the presence of its antioxidant property (Tembhurne and Sakarkar, 2010; Kesari *et al.*, 2005). Yadav *et al.* (2002) suggested that the aqueous extract and dry powder of these leaves may be prescribed as adjunct to dietary therapy and drug treatment for controlling diabetes mellitus. *M. koenigii* leaves can serve as a good adjuvant in the present armamentarium of antidiabetic drugs (Arulselvan *et al.*, 2006).

Aegle marmelos

Aegle marmelos L. Corr. (Rutaceae), commonly known as the bel fruit tree, is a highly reputed medicinal plant in the Ayurvedic system of medicine. It has found application in folklore medicine as an astringent, antidiarrheal, antidysenteric, demulcent, antipyretic, antiscourbutic, haemostatic, aphrodisiac and antidote against snake venom (Gandhi *et al.*, 2012).

A. marmelos extract effectively reduced the oxidative stress induced by alloxan and produced a reduction in blood sugar (Sabu and Kuttan, 2004). Scopoletin (7-hydroxy-6-methoxy coumarin) was isolated from the leaves of *A. marmelos* and evaluated for its potential to regulate hyperthyroidism, lipid peroxidation and hyperglycemia in levo-thyroxine-induced hyperthyroid rats (Panda and Kar, 2006). Leaf extract of *A. marmelos* was found to be as effective as insulin in restoration of blood glucose and body weight to normal levels (Seema *et al.*, 1996). *A. marmelos* leaf extract has marked to normalize 5-HT, 5-HT_{2A} receptor, gene expression studies along with the Elevated plus test implicate a role in reducing the stress associated with diabetic rats (Abraham *et al.*, 2010).

Syzygium cumini

Syzygium cumini L. is one of the genera of the myrtle family Myrtaceae, which is widely used medicinal plant in the treatment of various diseases including diabetes (Ayyanar and Subash-Babu, 2012; Baliga *et al.*, 2011). The flavonoid rich extract from *S. cumini* plant has both hypoglycemic and hypolipidemic effects which can help the cure and management of diabetes (Sharma *et al.*, 2008). *S. cumini* contained higher amounts of phytochemicals which may be due to the presence of proanthocyanidins, flavonoids and other bioactive compounds and it also showed the highest antioxidant activity (Loganayaki and Manian, 2010). *S. cumini* inhibits adenosine deaminase activity and reduces glucose levels in hyperglycemic patients (Bopp *et al.*, 2009). The regression of the diabetic state on *S. cumini* seed extract administration increases the utilization of glucose, thereby depressing the mobilization of fat (Prince *et al.*, 2004). *S. cumini* was able to promote the reduction of inflammation and oxidative stress parameters, and acted against biochemical changes occurring in diabetes mellitus (Bona *et al.*, 2011). Helmstadter (2008) has been reported *S. cumini* as an adjuvant therapy in type 2 diabetes.

Momordica charantia

Momordica charantia L. is a tropical and subtropical vine of the family Cucurbitaceae, widely grown in Asia, Africa by the Caribbean for its edible fruit, which is among the most bitter of all fruits, is one of the well known medicinal plants (Reyes *et al.*, 2006). *M. charantia* fruits and other parts are commonly used for the treatment of diabetes and related conditions amongst the indigenous populations of Asia, South America, India and East Africa (Khan *et al.*, 2012; Leung *et al.*, 2009). Medicinal property of *M. charantia* has been attributed to its high antioxidant properties due in part to phenols, flavonoids, isoflavones, terpenes, anthroquinones, and glucosinolates, all of which confer a bitter taste. The fruits have high amounts of vitamin C, vitamin A, vitamin E, vitamins B1, B2, B3, B9 and also rich in minerals, including potassium, calcium, zinc, magnesium, phosphorus and iron, as well as good source of dietary fiber (Bakare *et al.*, 2010; Snee *et al.*, 2011). The alcoholic extract of *M. charantia* was effective in lowering blood sugar levels and also protected the islet tissues (Singh *et al.*, 2008). Several researches have documented that different part of the *M. charantia* possess antidiabetic property in more or less amount (Srivastava *et al.*, 1993; Joseph and Jini, 2013; Fernandes *et al.*, 2007).

Gymnema sylvestre

Gymnema sylvestre L. is belongs to the family Asclepiadaceae. It is native to the tropical forests of southern and central India and Sri Lanka. Chewing the leaves, suppresses the sensation of sweet. This effect is attributed to the presence of the eponymously named gymnemic acids. *G. sylvestre* has been used in herbal medicine as a treatment for diabetes for nearly two millennia (Kanetkar *et al.*, 2007). The pharmacological properties of *G. sylvestre* are attributed to a group of triterpene saponins, known as gymnemic acid (Karthic *et al.*, 2012). Its triterpene glycosides, isolated from plant inhibited glucose utilization in muscles (Shimizu *et al.*, 1996). It has been found that *G. sylvestre* may stimulate pancreatic β -cell function, number and increases insulin release by increasing cell permeability to insulin (Khan *et al.*, 2012). The gymnemic acid of leaf and callus extracts significantly increases the regeneration of β -cells in treated rats, when compared with the standard diabetic rats. It could have potential as a pharmaceutical drug for insulin-dependent diabetes mellitus (Ahmed *et al.*, 2010). The significant lowering of cholesterol with *G. sylvestre* ingestion indicates some effect on metabolism too (Preuss *et al.*, 1998). *G. sylvestre* leaves extract exhibits antidiabetic activity, so it is recommended to use it as a complementary medicine in diabetes mellitus (El Shafey *et al.*, 2013). The novel compound dihydroxy gymnemic triacetate which was isolated from the leaves of *G. sylvestre*, represent a good candidature for alternative and/or complementary medicine in the management of diabetes mellitus (Daisy *et al.*, 2009).

Aloe vera

Aloe vera L. burm. fil. (synonym *A. barbadensis* miller) (Liliaceae), native in North Africa, is one of the potent antidiabetic plants (Capasso *et al.*, 1998). It grows in arid climates and is widely distributed in Africa, India and other arid areas (Kavishankar *et al.*, 2011). Aloe species have been used for centuries for their various healing properties (Capasso *et al.*, 1998). *Aloe vera* contains 75 potentially active constituents: vitamins, enzymes, minerals, sugars, lignin, saponins, salicylic acids and amino acids. Plants often contain substantial amounts of antioxidants including α -tocopherol, carotenoids, vitamin C, flavonoids and tannins and it has been suggested that antioxidant action may be an important property of these plant medicine, used in diabetes (Larson, 1988; Rajasekaran *et al.*, 2005a). It also contain organic and inorganic elements like vanadium, zinc, sodium, potassium, calcium, copper, manganese, and traces of chromium in the improvement of impaired glucose tolerance play their indirect role in the management of diabetes mellitus (Rajasekaran *et al.*, 2005b). Oral administration of *Aloe vera* gel cause decline in the glucose level in diabetes mellitus and no adverse side effect symptoms were observed from the viewpoints of pathological findings (Tanaka *et al.*, 2006; Yongchaiyudha *et al.*, 1996).

Boerhaavia diffusa

Boerhaavia diffusa L., a member of Nyctaginaceae family, commonly known as 'Punarnava' in the Indian system of medicine, is a perennial creeping herb, found throughout the waste land of India. It's root has adaptogenic, immunomodulatory, antioxidant aphrodisiac and nootropic activities (Rajpoot and Mishra, 2011). The *B. diffusa* plant contains a large number of such compounds as flavonoids, alkaloids, steroids, triterpenoids, lipids, lignins, carbohydrates, proteins, glycoproteins and also contain β -sitosterol, α -2-sitosterol, palmitic acid, ester of β -sitosterol, tetracosanoic, hexacosanoic, stearic, arachidic acid, urosilic acid, hentriacontane, β -ecdysone, triacontanol *etc.* These content are responsible for antidiabetic and antioxidant as well as procuring from other complications (Murti *et al.*, 2010; Mahesh *et al.*, 2012; Apu *et al.*, 2012). The *B. diffusa* leaves are rich in compound, may be responsible for the antioxidant and antidiabetic activity which may be attributed to its protective action on lipid peroxidation and to the enhancing effect on cellular antioxidant defense, contributing to the protection against oxidative damage in diabetes (Satheesh and Pari, 2004). *B. diffusa* leaf extracts also protected lipid peroxidation and hepatotoxicity which may be mediated through augmentation of antioxidant defenses (Olaleye *et al.*, 2010). The aqueous extract of *B. diffusa* leaves was found to exhibit a significant hypoglycemic and antihyperglycemic activity in diabetic condition (Pari and Satheesh, 2004).

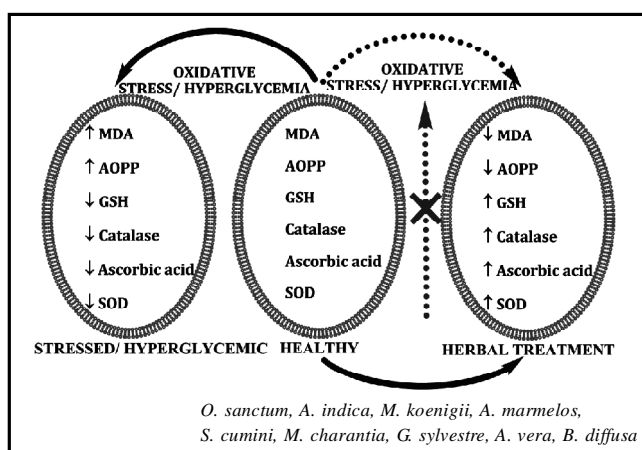


Figure 1: Schematic representation of the biochemical alterations in the cell induced by reactive oxygen species (ROS)/oxidative stress and protective effect of herbal treatment on these biomarkers of oxidative stress during diabetes mellitus. MDA: malondialdehyde, AOPP: advanced oxidation protein products, GSH: reduced glutathione, SOD: superoxide dismutase

Conclusion

The prevalence of diabetes is rapidly increasing all over the globe at an alarming rate. Conventional therapies due to their side effects, high cost and failure to provide long term protection, against hyperglycaemia are restricted. The plants discussed in this article have shown varying degree of antidiabetic activities. Future studies on isolation and characterization of bioactive compounds from these plants may generate natural drugs with potent antidiabetic properties.

Conflict of interest

The authors declare no conflict of interest.

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