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Review Paper

Role of oxidative stress and herbal medicines in diabetes mellitus

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Abstract

Diabetes mellitus is a chronic disease caused by inherited deficiency in production of insulin by the pancreas and results increased concentration of glucose in the blood. There are different chemical agents available in medicinal plants and treatment for diabetic patients. There are several medicinal plants have investigated for their potential source of hypoglycemic drugs use in treatment of diabetes. Herbal formulation are preferred due to less side effects and low cost. Present investigation focuses mainly plants used as antidiabetics in various medicines and some antidiabetic product available in the market.

Keywords: Diabetes, Oxidative stress, Herbal medicine, Antidiabetics.

Introduction

Diabetes mellitus is a serious health problem affecting millions of individuals worldwide. By the year 2025, the World Health Organization (WHO) predicts that over 300 million people worldwide will have diabetes mellitus [1]. Diabetes is a chronic disease, which occurs when the pancreas does not produce enough insulin, or when the body cannot effectively use the insulin it produces. Diabetes mellitus is a group of metabolic diseases characterized by high blood glucose level that result from defects in insulin secretion, or action, or both.

The reported prevalence of diabetes in adults between the ages of 20 and 80 is as follows: India 8.31%, Bangladesh 9.85%, Nepal 3.03%, Sri Lanka 7.77%, and Pakistan 6.72% [2]. Preliminary results from a large community study conducted by the Indian Council of Medical research (ICMR) revealed that a lower proportion of the population is affected in states of Northern India (Chandigarh 0.12 million, Jharkhand 0.96 million) as compared to Maharashtra (9.2 million) and Tamil Nadu (4.8 million) [3]. The National Urban Survey conducted across the metropolitan cities of India reported similar trend: 11.7 per cent in Kolkata (Eastern India), 6.1 per cent in Kashmir Valley (Northern India), [4], 11.6 per cent in New Delhi (Northern India), and 9.3 per cent in West India (Mumbai) compared with (13.5 per cent in Chennai (South India), 16.6 per cent in Hyderabad (south India), and 12.4 per cent Bangalore (South India) [5].

Hyperglycemia generates reactive oxygen species (ROS), which in turn cause damage to the lipid, protein and carbohydrate cells in many ways. Damage to the cells ultimately results in primary complications in diabetes mellitus [6,7]. In the present paper, we have discussed of the oxidative stress in diabetes mellitus.

Herbal medicine, also called ayurvedic medicine refers to the use of any plant's seeds, roots, leaves, bark and flowers for medicinal purposes. Long duration practiced outside of conventional medicine, herbalism is becoming more main stream as up to date analysis and research show their value in the treatment and prevention of this disease [8]. Indian ayurvedic traditionally approximately 1400 herbal

plants are used for over 1000 years, analysis of many herbal drugs and herbal preparations of Indian traditional health care systems. These medicinal drugs work against alloxan induced diabetes mellitus.

Role of oxidative stress metabolism

Under normal physiological conditions, approximately 0.2%– 5% of oxygen that enters the electron transport chain is reduced to superoxide, a ROS and the rest are used in metabolic processes. ROS can also be generated from other sources other than the mitochondrial electron transport chain including cytochrome P450, the NAD (P) H oxidase(s) and nitric oxide synthases [9].

Elevated oxidative stress plays an important role in the pathogenesis of diabetic complications [10]. Increased oxidative stress in diabetes is postulated to promote the development of neuropathy [11], nephropathy, myocardial injury and retinopathy[12,13,14]. The possible sources of oxidative stress in diabetes might include autoxidation of glucose, shifts in redox balances, decreased tissue concentrations of low molecular weight antioxidants such as reduced glutathione (GSH) and vitamin E, and impaired activities of antioxidant defense enzymes such as superoxide dismutase (SOD) and catalase [10,16,17]. ROS generated by high glucose are considered as a causal link between elevated glucose and the other metabolic abnormalities important in the development of diabetic complications [18].

Diabetes is a metabolic disease characterized by pancreatic beta cell dysfunction and insulin resistance in the liver and peripheral tissues [19]. It is a multi factorial disease [20]. The free radicals have been incriminated in the pathogenesis of membrane damage in diabetes as well as malaria. Therefore, this membrane damage has been linked to the generation the cascade process resulting in cellular death of tissues [21]. In diabetes there is increase in production of free radicals which affects the antioxidants reactions catalyzed by scavenging enzyme [22]. This equally happens in malaria infected patients. In the same vein, the free radicals attack proteins, enzymes and DNA and hence causing some pathological derangement [23]. The occurrence of free radical induced lipid peroxidation caused considerable changes in the cell membrane [24]. Free radicals are highly reactive molecules generated by biochemical reactions that occur as part of the normal cell metabolism [25]. The level of lipid peroxidation is expressed as malondialdehyde (MDA) which is the breakdown product of major chain reactions causing oxidation of polyunsaturated fatty acids and hence serves as a marker of lipid peroxidation [26, 27].

There is evidence that β cell dysfunction results from prolonged exposure to high glucose, elevated free fatty acids level or a combination of both [28]. B cells are particularly sensitive to ROS due to inadequate expression of free radical quenching enzymes [29]. The capability of oxidative stress to damage mitochondria and ultimately decrease insulin secretion is therefore obvious [30]. It has been demonstrated that oxidative stress generated by short exposure of β cell preparations to H_2O_2 increases production of p21phox and decreases flux of insulin mRNA, cytosolic ATP and calcium into cytosol and mitochondria [31].The key role of increased glucose metabolism in the impairment of β cell function through oxidative stress has been recently confirmed. Glucose induced insulin secretion is also suppressed by H_2O_2, a chemical substitute for ROS [32]. In subjects with normal glucose tolerance, glutathione infusion failed to affect β cell response to glucose [33].

In contrast glutathione significantly potentiate glucose induced insulin secretion in patients with impaired glucose tolerance [33]. Furthermore when the latter group is studies in the condition of hyperglycemic clamp, glutathione infusion significantly potentiate the β cell response to glucose when plasma glucose levels varied between 10 and 15 mmol/l [24]. Indeed, many studies show that high glucose concentrations induce endothelial dysfunction. The role of free radical generation in production of the hyperglycemia dependent endothelial dysfunction is suggested by studies showing that both *in vitro* [34,35] and *in vivo* [36,37] the acute effects of hyperglycemia are counterbalanced by antioxidants. Recent studies have demonstrated that superoxide overproduction by the mitochondrial electron transport chain induced by hyperglycemia seems to play a key role in the activation of all other pathways involved in the pathogenesis of endothelial dysfunction.

Herbal medicinal plants

According to the World Health Organization (WHO), up to 90% of the population in developing countries uses plants and its products as traditional medicine for primary health care [38].The WHO has listed 21,000 plants, which are used for medicinal purposes around the world. Among these, 2500 species are in India [39].There are about 800 plants which have been reported to show antidiabetic potential [40]. A wide collection of plant-derived active principles representing numerous bioactive compounds has established their role for possible use in the treatment of diabetes [40].

The most common and effective antidiabetic medicinal plants of Indian origin are Babul (*Acacia arabica),* bael *(Aegle marmelose),* church steeples *(Agrimonia eupatoria),* onion *(Allium cepa),* garlic *(Allium sativum),* ghrita kumara *(Aloe vera),* neem *(Azadirachta indica),* ash gourd *(Benincasa hispida),* Beetroot *(Beta vulgaris),* fever nut *(Caesalpinia bonducella),* bitter apple *(Citrullus colocynthis),* ivy gourd *(Coccinia indica),* eucalyptus *(Eucalyptus globules),* banyan tree *(Ficus benghalenesis)*, gurmar *(Gymnema sylvestre),* gurhal *(Hibiscus rosa-sinesis)*, sweet potato*(Ipomoea batatas),* purging Nut *(Jatropha curcas)*, mango *(Mangifera indica),* karela *(Momordica charantia),* mulberry *(Morus alba),* kiwach *(Mucuna pruriens),* tulsi *(Ocimum sanctum),* bisasar *(Pterocarpus marsupium),* anar *(Punica granatum),* jamun *(Syzygium cumini),* giloy *(Tinospora cordifolia),* and methi *(Trigonella foenum-graecum).* All these plants are a rich source of phytochemicals. Scientists have studies the chemical composition of the antidiabetic medicinal herbs used in ayurveda. The article deals with work done on Indian medicinal plants with anti diabetic potential [41]. There different Indian medicinal plants are:

***Allium sativum*:** Garlic (*Allium sativum*) is a member of the Liliaceae family, is one of the most popular herbs used worldwide to reduce various risk factors associated with several diseases [42]. Actually, garlic contains a variety of effective compounds that exhibit anticoagulant (anti-thrombotic) [43,44], antioxidant [45,46], antibiotic [47], hypocholesterolaemic [48] and hypoglycaemic as well as hypotensive activities [48,49]. Most of the studies showed that garlic can reduce blood glucose levels in diabetic mice, and rats [50]. Augusti and Sheela consistently showed that S-allyl cysteine sulphoxide, (allicin), a sulphurcontaining amino acid in garlic (200 mg/kg body weight), had a potential to reduce the diabetic condition in rats almost to the same extent as did glibenclamide and insulin [44,51].

***Ocimum sanctum*:** Tulsi is an aromatic plant in the family Lamiaceae and found in india. Ethanolic extract of tulsi extract significantly decreases the blood glucose, glycosylated hemoglobin and urea with a concomitant increase in glycogen, hemoglobin and protein in streptozotocin induced diabetic rats [52]. This extracts also resulted in an increase in insulin and peptide levels and glucose tolerance. The constituents of tulsi leaf extracts have stimulatory effects [53] on physiological pathways of insulin secretion, which may underlie its reported antidiabetic action. Grovel *et al*. suggested that treatment with tulsi extract for 30 days to normal rats fed with fructose for 30 days significantly lowered serum glucose level [54] in comparison with control group.

***Aegle marmelos* (Bael):** Bael is a member of the Rutaceae family, plant part Fruit & leaves are use and found in India.

Chemistry: Tannins, active principle (marmelosin), alkaloids (aegelin & aegelinin) and coumarin (marmesin).

Pharmacological study: Das, Padayatil and Paulose [55] studied the hypoglycemic activity of leaf extract of *Aegle marmelos* in streptozocin induced diabetes. The extract significantly reversed altered parameters in tissue of the experiment rats. According to authors, the drug seems to repair the injured pancreas [55].

***Asphaltum punjabianum* (Shilajeet)**

Chemistry: Fulvic acid and hippuric acid.

Pharmacological study: Trivedi, Saxena, Mazumdar, Bhatt and Hemavathi [56] studied the effects of *Asphaltum punjabianum* on blood glucose, lipid profile and vascular preparation in alloxan induced diabetic rats. Effect of three different doses of *Asphaltum punjabianum* (50,100 and 200mg/kg, p.o.,

daily) were studied on fasting blood glucose and lipid profile at the end of the 4th week. All three doses of *Asphaltum punjabianum* not only reduced blood glucose level in dose dependent manner, but significant reduction in blood cholesterol and triglycerides was observed. *Asphaltum punjabianum* also prevented induced vascular dysfunction [56].

***Azadirachta indica* (Neem):** Neem is a member of the Meliaceae family and used whole plants.

Chemistry: Nimbidin is major source from seed oil, It is crude bitter principle. It also contains nimbin, nimbinin, nimbidinin, nimbolide, nimbilic acid. Gedunin obtained from neem's seed. It also contains mahmoodin, azadirachtin. It also contains some tannin like, gallic acid. There are also present of margolonon, polysaccharide.

Pharmacology: Anti diabetic, anti Inflammatory, anti pyretic, anti fungal, anti bacterial, anti malarial, anti arthritis, spermicidal, anti tumour, diuretic, immunomodulatory.

Pharmacological study: Researchers at India's University of Madras in the early 1990s found that high doses (40 gm of dried herb daily) of *Azadirachta indica* extracts may actually help to repair or regenerate the pancreas's beta cells, which play a crucial role in the production and secretion of insulin.

***Saraca indica* (Ashoka bark):** Ashoka is a member of the Leguminosae family, used part bark and found in india.

Chemistry: 6% condensed tannins & anthocyanin derivatives, Catechol,Sterol, Haemotoxyline, Phlobaphenes, Organic calcium compound Ktosterol, Phenolic & Nonphenolic Glycosides. –(-) Epicatechin, ProcyanidinB2, -(-)Epicatechol, antocyanin pigments, Kaempterol.

In diabetes mellitus, uterine stimulant, sedative, oxytocic activity, in menorrhagia non phenolic glycoside has Parasympathomimetic activity. In intrinsic hemorrhages Ashoka flower are used. Used in burning sensation, Dried flowers used in diabetes [57].

Herbal products available in market

Today, up to 1400 traditional plant medicines has been reported in India for diabetes. Following are few preparations available in the market for the treatment of diabetes that contains drug in powder form or as extracts. Only the names of the herbs added in the preparations are reported, along with these herbs some preparations may contain animal derived products and minerals.

Hyponidd tablets: *Momordica charantia, Swertia chirata, Melia azadiracta, Tinospora cordifolia, Gymnema sylvestre, Enicostemma litterole, Emblica officinalis, Eugenia jambolana, Cassia auriculata, Curcuma longa*.

Diagon tablets: *Eugenia jambolana, Andrograpis paniculata, Tinospora cordifolia, Curcuma longa, Berberis aristata, Vetiveria zizanoides, Strychnos potatorum, Mimosa pudica, Gymnema sylvestre*.

Glucolev capsule: Amalaki powder, Sudha shilajeet, Jasad bhasma, Methika beej, Jambu beej, Madhunasini, Ashwagandha.

Diasulin: *Casssia auriculata, Coccinia indica, Curcuma longa, Momordica charantia, Scoparia dulcis, Gymnema sylvestre, Emblica officinalis, Syzgium cumini, Tinospora cordifolia, Trigonella foenum graecum*

Glucolib: *Eugenia jambolana, Gymnema sylvestris, Aegle marmelos, Melia azadiracta, Momordica charantia, Enicostema littorale, Trigonella foenum graecum*.

Conclusion

Supplimentation of herbal druge for diabetic rats prevents the development of oxidative stress and its associated complication includes hyperglycemia. There plants have considered hypoglycemic actions

and scientists have carried out some primary investigation. Large number of plants are screening for antidiabetic effect and development as to substitute for the oral synthetic drugs.

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