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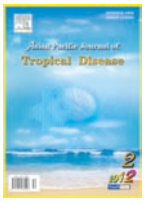

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Role of antioxidants in phytomedicine with special reference to antidiabetic herbs

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ABSTRACT

Diabetes mellitus is a severe health problem with continuously increasing rates of incidence and mortality and it may rise tremendously by 2025. This disease is characterized by elevated plasma glucose concentrations resulting from insufficient insulin and insulin resistance, or both, leading to metabolic abnormalities in carbohydrates, lipids and proteins. Free radicals are well known for their dual role as beneficial and toxic components, higher levels of free radicals causing damage to cellular proteins, membrane lipids and nucleic acids leads to cell death. Antioxidants are effective against free radicals by donating their own electrons. There is an increasing evidence confirmed that free radicals plays a crucial role in the pathogenesis of diabetes mellitus. Herbs are the well known source of non toxic antioxidants. The aim of the present review is to establish the role of free radicals in pathogenesis of various diseases with special consideration to diabetes mellitus. Further more recently reported herbs with antidiabetic action having antioxidant capacity is also with in the scope of this article..

1. Introduction

Free radicals are atoms or groups of atoms containing at least one unpaired electron in their orbital and can be formed when oxygen interacts with certain molecules[1]. A free radical is also considered as unstable form of any atom or molecule capable of independent existence that contains one or more unpaired electrons[2]. Free radicals could be produced in biological systems in many different ways such as (a) breaking of covalent bonds by homolitic way (b) losing an electron (c) gaining an electron[3, 4]. There are enormous varieties of free radicals that can be formed inside the body. Amongst those, reactive oxygen species (ROS) and reactive nitrogen species (RNS) are the major components. Free radicals include hydroxyl ($OH^{\bullet}$), superoxide ($O_2^{\bullet -}$), nitric oxide ($NO^{\bullet}$), nitrogen dioxide ($NO_2^{\bullet}$), peroxyl ($ROO^{\bullet}$) and lipid peroxyl ($LOO^{\bullet}$). Moreover oxidants like hydrogen peroxide (H_2O_2), ozone (O_3), singlet oxygen ($1O_2$), hypochlorous acid (HOCl), nitrous acid (HNO_2), peroxynitrite ($ONOO^-$), dinitrogen trioxide (N2O3) and lipid peroxide (LOOH), although are not free radicals, can easily lead to free radical reactions in living organisms[5]. ROS and RNS are generated from either endogenous or exogenous sources. Endogenous free radicals are generated from immune cell activation, inflammation, mental stress, excessive exercise, ischemia, infection, cancer, aging. Exogenous ROS/RNS result from air and water pollution, cigarette smoke, alcohol, heavy or transition metals (Cd, Hg, Pb, Fe, As), certain drugs (cyclosporine, tacrolimus, gentamycin, bleomycin), industrial solvents, cooking (smoked meat, used oil, fat), radiation[1].

ROS and RNS are well recognized for playing a dual role as both deleterious and beneficial species, since they can be either harmful or beneficial to living systems[6]. At low and moderate conditions ROS and RNS plays vital role in maintaining normal physiological functions of the body mainly in the immune system, maturation process of cell structures, cell signaling mechanisms. The harmful effect of free radicals causing potential biological damage is termed oxidative stress and nitrosative stress[7-9]. The defense system of the body against free radicals is antioxidants. They interact with free radicals and stop them before vital molecules are damaged. Antioxidants are manufactured

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within the body and can also be extracted from the food humans eat such as fruits, vegetables, seeds, nuts, meats and oil[10]. Oxidative stress is produced mainly due to the imbalance between the formation of free radicals and antioxidants in the body. Oxidative stress is currently suggested as the mechanism underlying diabetes and diabetic complications[11].

Diabetes mellitus (DM) is a chronic disease caused by inherited and/or acquired deficiency in the production of insulin by the pancreas, or by the ineffectiveness of the insulin produced. Such a deficiency results in increased concentrations of glucose in the blood, which in turn damage many of the body's systems, in particular the blood vessels and nerves. Diabetes affects about 5% of the global population[12]. Diabetes is mainly classified as type I and type II. Type I diabetes is also known as insulin dependent diabetes mellitus (IDDM) or juvenile onset diabetes and type II diabetes is also known as non insulin dependent diabetes mellitus (NIDDM). Although the etiology of this disease is not well defined, viral infection, autoimmune disease, and environmental factors have been implicated[13]. Increased oxidative stress is a widely accepted participant in the development and progression of diabetes and its complications[13]Diabetes is usually accompanied by increased production of free radicals or impaired antioxidant defenses[13](A.C. Martim et al., 2003). Management of diabetes without any side effects is still a challenge to the medical system[14]. Herbal drugs are widely prescribed because of their effectiveness, fewer side effects and relatively low cost. Ample active principles which are derived from plants have established antidiabetic activity. Hence this review focuses on the role of antioxidants in increasing the potential of anti diabetic herbs.

2. Role of free radicals in ageing and various diseases

2.1. Ageing

After the reproductive phase of life, the physiological functions of the organism starts to decline and the process is termed is ageing. The "free radical approach" is based on the fact that the random deleterious effects of free radicals produced during aerobic metabolism cause damage to DNA, lipids, and proteins and accumulate over time[4]. Even under ideal conditions, some electrons "leak" from the electron transport chain. These leaking electrons interact with oxygen to produce superoxide radicals, so that under physiological conditions, about 1-3% of the oxygen molecules in the mitochondria are converted into superoxide[4]. The primary site of radical oxygen damage from superoxide radical is mitochondrial DNA (mtDNA)[15]. The cell cannot fix mitochondrial DNA damage as much as it can fix nuclear DNA damage. Hence, wide mtDNA damage accumulates over time and shuts down mitochondria, causing cells to die and the organism to age[4]. Ageing can be correlated with the amount of oxygen consumption by the organism and the rate of ROS production in the organism[11].

2.2. Carcinogenesis

Oxidative DNA damage is one of the vital reasons for cancer development[1]. Oxidative stress induces a cellular redox imbalance. This imbalance is found in various cancer cells and thus may be related to oncogenic stimulation. Oxidative damage modifies the genetic material permanently and is the first cause for the origin of mutagenesis and carcinogenesis. ROS-induced DNA damage involves single- or double-stranded DNA breaks, purine, pyrimidine, or deoxyribose modifications, and DNA cross-links[4]. DNA damage can result in either initiate or arrest transcription, induction of signal transduction pathways, replication errors, and genomic instability, all of which are associated with carcinogenesis[16, 6]. Reactive nitrogen species (RNS), such as peroxynitrites and nitrogen oxides, are also engaged in damaging DNA[17]. In addition to DNA damage, Malondialdehyde and 4-hydroxynonenal, the important end products of lipid peroxidation have also been implicated in the mechanism of carcinogenesis[16]. Many of the biological effects of antioxidants appear to be related to their ability not only to scavenge deleterious free radicals but also modulate cell-signalling pathways[18]. Thus the modulation of cell signalling pathways by antioxidants could help prevent cancer by (i) preserving normal cell cycle regulation; (ii) inhibiting proliferation and inducing apoptosis; (iii) inhibiting tumour invasion and angiogenesis; (iv) suppressing

Table 1
Biomarkers of oxidative damage associated with some human diseases.

Diseases	Biomarker
Cancer	MDA, GSH/GSSG ratio, NO2-Tyr, 8-OH-dG
Cardiovascular disease	HNE, GSH/GSSG ratio, Acrolein, NO2-Tyr, F2-isoprostanes
Rheumatoid arthritis	F2-isoprostanes, GSH/GSSG ratio
Alzheimer's disease	MDA, HNE, GSH/GSSG ratio, F2-isoprostanes, NO2-Tyr
Parkinson's disease	HNE, GSH/GSSG ratio, Carbonylated proteins, Iron level
Atherosclerosis	MDA, HNE, F2-isoprostanes, NO2-Tyr, Acrolein
Diabetes mellitus	MDA, GSH/GSSG ratio, F2-isoprostanes, NO2-Tyr, AGE

Abbreviations: MDA- malondialdehyde; HNE- 4-hydroxy-2-nonenal; AGE- advanced glycation end products; 8-OH-dG- 8-hydroxy-20-deoxyguanosine; GSH- reduced glutathione; GSSG-oxidised glutathione; NO2-Tyr- 3-nitro-tyrosine.

inflammation; (v) stimulating phase II detoxification enzyme activity and other effects[4].

2.3. Cardiovascular diseases

ROS-induced oxidative stress plays a vital role in various cardiovascular diseases such as atherosclerosis, ischemic heart disease, hypertension, cardiomyopathy, cardiac hypertrophy and congestive heart failure[19]. The ROS-induced oxidative stress in cardiac and vascular myocytes has been linked with cardiovascular tissue injury[20]. The major sources of oxidative stress in cardiovascular system involve: (i) the enzymes xanthine oxidoreductase (XOR), NAD(P)H oxidase and NOS (ii) the mitochondrial cytochromes and (iii) hemoglobin[4]. Oxidation of cholesterol component of the low-density lipoprotein (LDL) leads to oxidised LDL by a series of consecutive events. This induces endothelial dysfunction, which promotes inflammation during atherosclerosis and is responsible for hypertension[21].

2.4. Neurological Diseases

Oxidative stress has been investigated in neurological diseases including Alzhiemer's disease, Parkinson's disease, multiple sclerosis, amyotropic lateral sclerosis (ALS), memory loss and depression[21]. The brain is particularly vulnerable to oxidative damage because of its high oxygen utilisation, its high content of oxidisable polyunsaturated fatty acids, and the presence of redox-active metals (Cu, Fe). Oxidative stress increases with age and therefore it can be considered as an important causative factor in several neurodegenerative diseases, typical for older individuals[4]. The production of ß-amyloid, a toxic peptide often present in the brain of Alzheimer's patients, is due to oxidative stress and plays a vital role in neurodegenerative diseases [21]. Apolipoprotein E, a lipid transport molecule that has been linked to the pathogenesis of Alzhimer's Disease, has been found to be subject to free radical attack and a direct correlation exists between apolipoprotein E peroxidation and Alzheimer's disease[22]. A majority of studies explored the effect of oxidative stress that contributes to the cascade of events leading to dopamine cell degeneration in parkinsonism disease[23].

2.5. Pulmonary disease

There is now substantial evidence that inflammatory lung diseases such as asthma and chronic obstructive pulmonary disease (COPD) are characterized by systemic and local chronic inflammation and oxidative stress[21]. Oxidants may play a role in enhancing inflammation through the activation of different kinases and redox transcription factors such as NF-kappa B and AP-1[21].

2.6. Rheumatoid arthritis

Rheumatoid arthritis is an autoimmune disease that causes chronic inflammation of the joints and tissue around the joints with infiltration of macrophages and activated T cells[24]. The pathogenesis of this disease is linked predominantly with the formation of free radicals at the site of inflammation. Oxidative injury and inflammatory status in various rheumatic diseases was confirmed by increased levels of isoprostanes and prostaglandins in serum and synovial fluid compared to controls[4]. T cells isolated from the synovial fluid of patients with rheumatoid arthritis showed signs of decreased intracellular GSH level, impaired phosphorylation of the adaptor protein linker for T-cell activation (LAT) and the "primed" CD45RO phenotype[25]

2.7. Nephropathy

Oxidative stress plays a role in a variety of renal diseases such as glomerulonephritis and tubulointerstitial nephritis, chronic renal failure, proteinuria, uremia. Free radical producing heavy metals such as Cd, Hg, Pb, As and transition metals such as Fe, Cu, Co, Cr induced different forms of nephropathy and carcinogenicity in the body. The nephrotoxicity of certain drugs such as cyclosporine, tacrolimus (FK506), gentamycin, bleomycin, vinblastine, is mainly due to oxidative stress via lipid peroxidation[21]

2.8. Ocular diseases

Oxidative stress play a vital role in the formation of cataract in the eyes. Free radicals act upon the crystalline proteins in the lens which can cross-link and aggregate, leading to the formation of cataracts[26]. In the retina, long-term exposure to radiation can inhibit mitosis in the retinal pigment epithelium and choroids, damage the photoreceptor outer segments, and has been associated with lipid peroxidation[27, 21].

2.9. Free radicals and diabetic mellitus

Diabetes mellitus is mainly classified in to type 1 (T1D) and type 2 (T2D) Diabetes mellitus. T1D involves the autoimmune destruction of insulin-producing pancreatic beta-cells via auto-aggressive T-cells and pancreatic macrophage infiltration[28, 29]. Genetic and environmental factors, which both remain undefined, are thought to act together to trigger the autoimmune disease[30]. Variations in the human leukocyte antigen (HLA) region located on chromosome 6 may account for more than 50% of familial aggregation in T1D [31, 29]. When the two haplotypes DR4-DQ8 and DR3-DQ2, are present in the same individual it increases the risk for T1D and the gene encoding insulin, located on chromosome 11, is another susceptibility factor, which contributes to 10% of genetic susceptibility to T1D[29]. There are several short versions of tandem repeats in the insulin promoter that are associated with a higher risk for T1D, while the long versions seem to provide protection[32]. Whole genome scans have led

to the identification of two important negative regulators of T-cell activation, cytotoxic T lymphocyte antigen4 (CTLA4) and the PTPN22 variant of the lymphoid tyrosine phosphatase encoding gene.[29]

Type 2 diabetes mellitus (T2D) is the most common endocrine disorder worldwide, covering 90-95% of all diabetes cases[33]. The classification and pathogenesis of T2D involves abnormalities in glucose and lipid metabolism, inadequate insulin secretion from pancreatic beta-cells and resistance to insulin activity[33]. Insulin resistance and impaired glucose tolerance (IGT), both conditions preceding the development of T2D are closely related to obesity[34]. The contribution of excess visceral fat to the development of insulin resistance, due to pronounced lipolysis and the subsequent release of free fatty acids that can directly block insulin signaling pathways, is well established[35, 29]. Increasing environmental pressure may widen the susceptibility profile of T2D[29]. Increased oxidative stress has been proposed to be one of the major causes of the hyperglycemia-induced trigger of diabetic complications. Hyperglycemia in an organism stimulates ROS formation from a variety of sources. These sources include oxidative phosphorylation, glucose autooxidation, NAD(P)H oxidase, lipooxygenase, cytochromes P450 monooxygenases, and nitric oxide synthatase (NOS)[4].

Under normal conditions, the key sites of superoxide formation in the mitochondrial membrane are complex I and the ubiquinone-complex III interface, where the presence of long lived intermediates allows reaction of electrons with molecular dioxygen[36, 4]. However, diabetes alters the primary sites of superoxide generation so that complex II becomes the primary source of electrons that contribute to superoxide formation under diabetic conditions[37, 4]. Another source of ROS in diabetes is NAD(P)H. Several lines of evidence support that NAD(P)H oxidases are a major source of glucose induced ROS production in the vasculature and kidney cells, confirming thus NAD(P)H as a mediator of diabetic complications[38]. Since hyperglycemia-induced oxidative stress occurs in non nucleated cells lacking mitochondria and the NAD(P)H oxidase (erythrocytes), another mechanism of ROS formation in such cells must exist. A possible explanation for such behaviour is glucose auto-oxidation, Glucose itself, as well as its metabolites, is known to react with hydrogen peroxide in the presence of iron and copper ions to form hydroxyl radical[4].

In addition to ROS, RNS have been implicated as one of the sources of nitrosative stress in diabetes. NO can react with superoxide forming peroxynitrite, a highly reactive oxidant linked with many disease states including diabetes [39]. In addition to that, Xanthine oxidase (XO) has been proposed to be a major source of ROS in diabetes mellitus , treatment of non-insulin dependent diabetes patients with the XO inhibitor allopurinol reduces the level of oxidised lipids in plasma and improves blood flow. Next to that, lipooxygenases catalyse the conversion of arachidonic acid into a broad class of signalling molecules, such as leukotrienes, lipoxins, and hydroxyeicosatetraenoic acid. Thus diabetes is also associated with increased lipoxygenase expression, resulting in eicosanoid formation[4].

In T2D, certain oxidative stress related defect(s) in oxidative phosphorylation machinery and mitochondrial -oxidation lead to excess accumulation of intracellular triglyceride in muscle and liver and subsequent insulin resistance[40]. The oxidation of long-chain fatty acids is central to the provision of energy for the organism and is of particular importance for cardiac and skeletal muscle[4]. When pancreatic β-cells are no longer able to compensate for insulin resistance by adequately increasing insulin production, impaired glucose tolerance appears, characterized by excessive postprandial hyperglycemia . Insulin resistance in skeletal muscle and abnormal pancreatic β-cell function are earliest detectable defects preceding hyperglycemia even 10 years before diabetes is diagnosed and those dysfunctions are due to the oxidative stress[4].

It was demonstrated that pancreatic islets contain relatively small amounts of the antioxidant enzymes CuZn-SOD, Mn-SOD, catalase, and glutathione peroxidase (GPx), due to the low level of antioxidant enzyme expression and activity, the β-cells are at a greater risk of oxidative damage than tissues which have higher levels of antioxidant protection. Consideration of antioxidants in clinical treatment as adjunct therapy in type 2 diabetes is warranted because of the many reports of elevated markers of oxidative stress in patients with this disease, which is characterized by imperfect management of glycemia, consequent chronic hyperglycemia, and relentless deterioration of β -cell function[4] . Generally, antioxidant treatment can exert beneficial effects in diabetes, with preservation of in vivo β -cell function. Antioxidant treatment suppresses apoptosis in β -cells without changing the rate of β-cell proliferation, supporting the hypothesis that in chronic hyperglycemia, apoptosis induced by oxidative stress causes reduction of β -cell mass[4] . Hence from the above evidences suggesting that the antioxidants can also be the potential agents to treat diabetes mellitus.

3. Herbs possess anti diabetic activity along with anti oxidant potential

3.1. Acacia Arabica

Acacia Arabica belongs to the family Leguminosae. Seeds and bark of the plant was demonstrated for its antihyperglycemic and antioxidant activity. Seeds showed hypoglycemic effect by initiating the release of insulin from pancreatic β- cells[41]. Hydroalchoholic and chloroform extracts of bark showed antidiabetic and antioxidant activity in alloxan induced diabetic rats[42, 43].

3.2. Aegle marmelos

Aegle marmelos (L.) correa ex Roxb. belongs to the family Rutaceae. Aqueous extract of leaf showed anti hyperglycemic activity in Streptozotocin induced diabetic rats[44]. Leaf extract increases glucose uptake in glucose induced hyperglycemic rats[45].

3.3. Allium cepa

Allium cepa L. belongs to the family Amaryllidaceae. Fruits of *Allium cepa* reported for its strong antidiabetic and antioxidant activity. Aqueous extract of fruits demonstrated anti diabetic, hepatoprotective and antioxidant activity on alloxan induced diabetic rabbits[46].

3.4. Aloe vera

Aloe vera (L.) Burm.F. belongs to the family Aloaceae. Hypoglycemic activity of the whole plant studied on normal fasted rats, oral glucose loaded rats and streptozotocin induced diabetic rats[47]and leaf pulp extracts are studied in type I and type II diabetic rats and its activity may be due to carbohydrate hydrolyzing enzymes and antioxidant activity [48].

3.5. Alpinia galangal

Alpinia galangal Willd belongs to the family zingiberaceae. Dried rhizomes of this plant showed antidiabetic and antioxidant potential. Ethanol extract of dried rhizomes showed potent free radical scavenging activity and antidiabetic activity in both *invitro* and invivo models. Further it demonstrated inhibition of α-glucosidase enzyme[49].

3.6. Ampelodesma mauritanica

Ampelodesma mauritanica Durand. belongs to the family Poaceae. Roots of this plant were reported for its strong antioxidant and antidiabetic activity. Methanolic extract of roots showed antioxidant effect and antihyperglycemic effect in normal glycemic mice[50].

3.7. Annona squamosa

Annona squamosa L. belongs to the family Annonaceae. Leaves of Annona squamosa is known for its strong antioxidant activity. Ethanolic extract of leaf lowers blood glucose level in normal, streptozotocin diabetic rats and alloxan treated rabbit[51].

3.8. Artanema seamoides

Artanema seamoides Benth. belongs to the family Scrophulariaceae. Aerial parts of the plant studied for its antidiabetic and antioxidant activity. Methanol extract of aerial parts demonstrated antidiabetic activity by sensitizing the insulin receptor or stimulating the secretion of insulin from beta cells of islets of langerhans in pancreas of steptozotocin (STZ) induced diabetic rats and it was supported by improved in vivo antioxidant status[52].

3.9. Asparagus racemosus

Asparagus racemosus Willd belongs to the family Liliaceae Ethanol extract of the whole plant demonstrated antidiabetic, antioxidant and antihyperglycemic activity in streptozotocin (STZ) induced diabetic rats[53].

3.10. Asystasia gangetica

Asystasia gangetica belongs to the family Acanthaceae. Leaves of *Asystasia gangetica* were reported for its antioxidant and antidiabetic activity. 70% ethanolic extract of leaves showed potent antioxidant and antidiabetic activity in alloxan induced diabetic albino rats[54].

3.11. Basella subra

Basella subra belongs to the family Basellaceae. Antidiabetic and antioxidant studies were performed on the leaves of *Basella subra*. Aqueous extract of leaves effectively reduced the oxidative stress induced by streptozotocin (STZ) and potential reduction in blood sugar level[55].

3.12. Benincasa hispida

Benincasa hispida belongs to the family Cucurbitaceae. Hydroalchocolic and chloroform fruit extracts of *Benincasa hispida* demonstrated antidiabetic activity in alloxan induced diabetic rats[42, 43]and it was found to be effective in oxidative stress by decreasing malondialdehyde levels and increasing superoxide dismutase and vitamin C levels[56].

3.13. Cassia auriculata

Cassia auriculata (L.) belongs to the family Leguminosae. Aqueous flower extract of this plant suppresses enhanced gluconeogenesis during diabetes and enhance utilization of glucose through increased glycolysis[57]and it also inhibits the alpha glucosidase enzyme[58].

3.14. Cinnamomum tamala

Cinnamomum tamala Fr. Nees belongs to the family Lauraceae. Leaves of *Cinnamomum tamala* were studied for its antioxidant and antidiabetic activity. Aqueous extract of leaves showed antihyperglycemic as well as antioxidant activities in streptozotocin (STZ) induced rats[59].

3.15. Dodonaea viscose

Dodonaea viscose Linn. belongs to the family Sapindaceae.

Leaves and aerial parts were reported for antioxidant and antidiabetic activity. In STZ induced diabetic rats, D. viscosa reduced glucose levels in dose dependent manner. Altered levels of lipids, TBARS, non enzymatic and enzymatic antioxidant levels were restored[60].

3.16. Eucalyptus camaldulensis

Eucalyptus camaldulensis Dehnh. belongs to the family Murtaceae. Leaves of *Eucalyptus camaldulensis* were studied for its carbohydrate hydrolyzing enzymes inhibition potential and for its antioxidant activity. The essential oil isolated from the plant demonstrated antioxidant activity and the same inhibited alpha amylase and alpha glucosidase inhibition[61].

3.17. Eucalyptus globules

Eucalyptus globules belongs to the family Myrtaceae. Aqueous extract of leaves of *Eucalyptus globules* restores the antioxidant power, due to the improved hyperglycemia in streptozotocin (STZ) induced diabetic rats and it reduce the plasma glucose level too[62].

3.18. Eugenia jambolanum

Eugenia jambolanum belongs to the family Myrtaceae. Ethanolic extract of seeds of *Eugenia jambolanum* showed hypoglycemic, better glucose tolerance activity and increases the tissue antioxidant levels in streptozotocin (STZ) induced diabetic rats[63].

3.19. Eurphorbia hirta

Eurphorbia hirta belongs to the family Euphorbiaceae. Stems of *Eurphorbia hirta* reported for its strong antioxidant and antidiabetic activity. Ethanol and petroleum ether extracts of stems showed antioxidant, antihyperglycemic and hyperlipidemic activity[64].

3.20. Ficus racemosa

Ficus racemosa Linn belongs to the family Moraceae. Fruits of *Ficus racemosa* is known for its strong antioxidant potential and the same was studied for its antidiabetic activity. Ethanolic extract of fruits demonstrated hypoglycemic activity and *invitro* antioxidant activity[65].

3.21. Glinus oppositifolius

Glinus oppositifolius belongs to the family Molluginaceae. Methanol extract of leaves of *Glinus oppositifolius* showed moderate antioxidant activity and significant antihyperglycemic activity in alloxan induced diabetic rats [66].

3.22. Gymnema sylvestre

Gymnema sylvestre belongs to the family Asclepiadaceae. Ethanol extract of leaves exhibited strong antioxidant activity and hypoglycemic activity in streptozotocin (STZ) induced diabetic rats[67]. The leaves extract of *Gymnema sylvestre* stimulates *invitro* insulin secretion using MIN6- β -cell line and isolated human islets of langerhans. Aqueous leaf extract of the same plant showed hypolipidemic and hypoglycemic activity in alloxan induced diabetic rats at 400 and 800 mg/ kg B.W[68].

3.23. Hippophae rhamnoides

Hippophae rhamnoides L. belongs to the family Elaeagnaceae. Aqueous extract of seeds of *Hippophae rhamnoides* demonstrated the antihyperglycemic, antioxidant activity in streptozotocin (STZ) and high fat diet induced type II diabetic rats[69].

3.24. Hybanthus enneaspermus

Hybanthus enneaspermus (Linn) F. Muell belongs to the family Violaceae. Alcoholic extract of the whole plant of *Hybanthus enneaspermus* reduced the blood glucose level in streptozotocin (STZ) induced diabetic model and it also showed antioxidant activity[70].

3.25. Hyptis suaveolens

Hyptis suaveolens belongs to the family Lamiaceae. Leaves of *Hyptis suaveolens* were studied for its antioxidant and antidiabetic potential. 50% ethanolic extracts of leaves demonstrated anti hyperglycemic activity and antioxidant activity in streptozotocin (STZ) induced diabetic rats[71].

3.26. Lagenaria siceraria

Lagenaria siceraria (Mol.) Standley belongs to the family Cucurbitaceae. Methanolic extract of aerial parts of *Lagenaria siceraria* demonstrated antidiabetic activity by sensitizing the insulin receptor or by stimulating the secretion of insulin from β cells of islets of langerhans in pancreas of streptozotocin (STZ) induced diabetic rats and this was supported by improved in vivo antioxidant status [72].

3.27. Momordica charantina

Momordica charantina Linn. belongs to the family Cucurbitaceae. Fruit extracts of *Momordica charantina* alleviate oxidative stress induced by diabetes through antioxidant activity and it reduces the blood glucose levels in the same model[73].

3.28. Morinda tinctoria

Morinda tinctoria belongs to the family Rubiaceae. Aqueous extract of fruits of *Morinda tinctoria* controlled blood glucose level, improved plasma insulin, lipid metabolism and is beneficial in preventing diabetic complications from lipid peroxidation and improved the antioxidant systems in streptozotocin (STZ) induced diabetic rats[74].

3.29. Morus alba

Morus alba belongs to the family Moraceae. Leaves of *Morus alba* were studied for its antioxidant and antidiabetic activity. 90% ethanolic extract of leaves exhibited significant antioxidant and antidiabetic activity in alloxan induced diabetic rats[54].

3.30. Nepeta cataria

Nepeta cataria L. belongs to the family Limiaceae. Aerial parts of Nepeta cataria demonstrated *invitro* antioxidant and invivo anti diabetic activity in STZ induced diabetic rats. It inhibits the carbohydrate hydrolyzing enzymes such as alpha amylase, alpha glucosidase and β galactosidase significantly[76].

3.31. Ocimum sanctum

Ocimum sanctum belongs to the family Labiatae. Leaves of *Ocimum sanctum* is known for its potent antioxidant property. Various phytoconstituents isolated from the same showed highly potent antioxidant activity. Ethanolic extract and various fractions showed antidiabetic and antihypercholesterimic effect along with anti oxidant activity [77].

3.32. Polyalthia longifola

Polyalthia longifola Var. belongs to the family Annonaceae. The stem bark of *Polyalthia longifola* was studied for its antioxidant and antidiabetic activity. Methanol extract of stem bark showed good antihyperglycemic and antioxidant activity in streptozotocin (STZ) induced diabetic rats[78].

3.33. Potentilla chinesis

Potentilla chinesis belongs to the family Rosaceae. Whole plant of *Potentilla chinesis* studied for its antioxidant and antidiabetic activity. Trans-tiliroside an isolated constituent from the whole plant showed significant anti hyperglycemic, anti hyperlipidemic and antioxidant activities[79].

3.34. Prosopis cineraria

Prosopis cineraria belongs to the family Fabaceae. Bark of *Prosopis cineraria*was demonstrated for its antioxidant and antidiabetic activity. Ethanolic extract of bark normalize serum lipid profile parameters, glucose level and enzymatic and non enzymatic antioxidant levels in alloxan induced diabetic rats[80].

3.35. Pterocarpus marsupium

Pterocarpus marsupium Roxb. belongs to the family Fabaceae. Wood and bark of *Pterocarpus marsupium* was studied for its antioxidant and antidiabetic potential. Ethanol extract of wood and bark showed antioxidant, antidiabetic and antihyperlipidemic activity in alloxan induced diabetic rats[81].

3.36. Punica granatum

Punica granatum belongs to the family Punicaceae. Flowers of *Punica granatum* were demonstrated for its antioxidant and antidiabetic activity. Aqueous extract of flowers ameliorates blood glucose, lipid parameters and oxidative stresses in streptozotocin (STZ) induced diabetic rats[82].

3.37. Salacia reticulate

Salacia reticulate belongs to the family Hippocrateacaea. 50% ethanolic extract of roots of the plant investigated for its protective effect on plasma lipid peroxide levels and on anti-oxidant enzyme superoxide dismutase (SOD) and it showed antioxidant and antidiabetic effect in streptozotocin (STZ)induced diabetic rats[83].

3.38. Scoparia dulcis

Scoparia dulcis belongs to the family Scrophulariaceae. 95% of ethanolic extract of aerial parts showed antidiabetic activity at a dose of 100 & 200 mg/kg body weight in the alloxan induced diabetic rat models and the same showed potential antioxidant effect in in vitro models of free radical systems[84].

3.39. Shorea tumbuggaia

Shorea tumbuggaia Rox. belongs to the family Dipterocarpaceae. Leaves of *Shorea tumbuggaia* were studied for its antioxidant and antidiabetic activity. Alcoholic extract of leaves showed significant antihyperglycemic, hypolipidemic and anti oxidant effects in alloxan induced diabetic rats[85].

3.40. Strychnos nuxvomica

Strychnos nuxvomica Linn. belongs to the family Loganiaceae. Methanol extract of seeds showed potential antidiabetic and antioxidant activity in alloxan induced

diabetic models[86]. The antidiabetic activity produced by the extract may be due to its antioxidant activity and in addition to that it may be due to increased uptake of glucose at the tissue level or by an increase in pancreatic beta cell function or due to inhibition of intestinal absorption of glucose.

3.41. *Tectona grandis*

Tectona grandis Linn. belongs to the family Verbanaceae. Bark of *Tectona grandis* was investigated for its antioxidant and antidiabetic activity. Ethanolic extract of bark reported for its potent *invitro* antioxidant potential and marked hyperglycemic activity in alloxan induced diabetic rats[87].

3.42. *Tephrosia Purpurea*

Tephrosia Purpurea belongs to the family Fabaceae. Aqueous extract of seeds of *Tephrosia Purpurea* reported for its strong antioxidant and antidiabetic activity in streptozotocin (STZ) induced diabetic rats. It reverts back the level of hexokinase and glucose-6-phosphatase in liver of diabetic animals[88].

3.43. *Terminalia arjuna*

Terminalia arjuna Roxb. belongs to the family Combretaceae. Methanol extract of leaf demonstrated remarkable antihyperglycemic activity in streptozotocin (STZ) induced diabetic rats and the action is plausibly due to its underlying antioxidant role[89].

3.44. *Terminalia superba*

Terminalia superba belongs to the family Combretaceae. Roots of *Terminalia superba* was studied for its antioxidant and carbohydrate hydrolyzing enzyme inhibition potential by in vitro models. Hydroethanolic extract showed in vitro antioxidant activity and alpha amylase inhibition activity significantly[90].

3.45. *Thespesia populnea*

Thespesia populnea belongs to the family Malvaeceae. Bark and leaves ethanolic extract possess strong antidiabetic activity against streptozotocin (STZ) induced diabetic rats and also showed the possible mechanism due to inhibition of generation of free radicals[91].

3.46. *Tinospera cordifolia*

Tinospera cordifolia belongs to the family Menispermaceae. Stem of *Tinospera cordifolia* was investigated for its antioxidant and antidiabetic activity. Aqueous extract of stem showed its preventive role against fructose induced insulin resistance and the same reduced the oxidative stress [92].

3.47. *Uncaria callophylla*

Uncaria callophylla belongs to the family Rubiaceae. Methanol extract of stems of *Uncaria callophylla* showed strong antioxidant and antidiabetic activity along with alpha glucosidase inhibition also[93].

3.48. *Uncaria longiflora*

Uncaria longiflora belongs to the family Rubiaceae. Stem and leaves of *Uncaria longiflora* investigated for its antioxidant and antidiabetic activity. Methanol extract of stem and leaves showed strong antioxidant and antidiabetic activity and Methanol extract of stem inhibited the alpha glucosidase enzyme[93].

3.49. *Viscum album*

Viscum album belongs to the family Loranthaceae. Aqueous extract of leaves of *Viscum album* reduced the blood glucose level and increases the antioxidant power of alloxanized rats at the dose of 500 mg/ kg and 1000 mg/ kg b.w.[94].

3.50. *Zingeber officinale*

Zingeber officinale Roscoe belongs to the family Zingeberaceae. Sesquiterpene isolated from the rhizome of *Zingeber officinale* reported for its antidiabetic activity through reducing oxidative stress, increase the insulin level and decrease the fasting glucose level in streptozotocin (STZ) induced diabetic rats[95].

4. Conclusion

This review highlights the importance of antioxidant property in the medicinal plant to attenuate its anti diabetic activity. The number of studies in this area is quite high although most of the studies have been done on the extract level. Enormous numbers of studies are to be done in isolated antioxidant compounds on various diabetic models for better understanding of its mechanism of action. This review may thus be an initiative for such studies.

Conflict of interest statement

The authors report no declarations of interest. The authors alone are responsible for the content and writing of the paper.

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