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Short review of antioxidant and antidiabetic activities of medicinal plants

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Abstract

Diabetes mellitus being a chronic endocrine disorder has become a major health care problem since the last couple of decades because of the intensive lifestyle intervention. Antioxidants have become a crucial part of our lives for maintaining optimal cellular and systemic health and wellbeing. There is an increased interest in the food industry and preventive medicine in the development of natural antioxidants from plant material. This review deals with medicinal plants with antioxidant and antidiabetic properties used in the traditional Indian system of medicine; also a briefing of their *in vitro* models for evaluating antioxidant and antidiabetic activity has been conducted.

Keywords: Antioxidants, medicinal plants, crucial

Introduction

Plants are an essential and fundamental part in medicine due to their capability of producing secondary metabolites like proteins, steroids, alkaloids, etc. they can be used as an acceptable source for curing many health issues and restoring general health. In the recent decade, the role of antioxidants has been increasingly recognized as a critical influence on the biochemistry of living beings. Any substance that causes delay or prevents oxidative damage to a target molecule is an antioxidant. A number of agricultural and food products have been detected to contain antioxidants also phenols from plants have been seen to be used extensively for food preservation. Antioxidants prevent the oxidation of other chemicals such as nucleic acids, proteins, carbohydrates and fatty acids. Antioxidants act as scavengers as they prevent cell and tissue damage by preventing or retarding the oxidation process. Tissue injury can be caused due to over production of free radicals. Antioxidants are capable of removing these free radicals and preventing them from causing cell damage by terminating reactive radicals, this is done by transferring a hydrogen atom from the antioxidant to the reactive radical intermediate. When cells use oxygen to generate energy free radicals are produced. Metabolism is one such reaction that can lead to the production of free radicals. Although metabolism is an inevitable process and oxygen is the basic requirement for survival, but the paradox is that oxygen is a very highly reactive molecule that can become harmful by producing reactive oxygen species. Free radicals posses an unpaired electron which is why they are highly reactive species and these can react with a stable molecule causing it to become unstable by taking away its electron and making it a free radical, this then leads to a chain reaction, this is where antioxidants come into play and act as a defense factor and subsidize the negative effects caused by free radicals. Free radicals can majorly be of two types: either oxygen derived (ROS, reactive oxygen species) or nitrogen derived (RNS, reactive nitrogen species) and other non radical reactive derivatives are called oxidants. These take place by two methods of enzymatic or non enzymatic reactions apart from the delirious effects that they have they are also involved in some vital actions like destroying bacteria and other foreign matter and in switching certain genes off and on, but if the generation of free radicals increases the production of antioxidants this could be very harmful for the body. These highly reactive species can be initiated by exogenous factors or endogenous metabolic processes in the human body.

Oxidative stress is one of the causes of free radicals and reactive oxygen species (ROS). These can be formed under normal physiological conditions, when not eliminated appropriately they can become harmful. Oxidative stress causes damage to biopolymers including carbohydrates, proteins, nucleic acids, fatty acids, etc. Oxidative damage can lead to break down or hardening of lipids due to lipid peroxidation which results in cell death or makes it non-feasible for the cell to get nutrients or to receive and send signals. Also, it can lead to tissue damage due to cytotoxic

oxygen derived free radicals like superoxide (Jainu & Devi, 2005) [6]. In addition, it can cause inadvertent enzyme activation and cellular system damage. These highly reactive species react with biomolecules in the cells, especially DNA being their most important target and the consequences include mutagenesis which could be simple changes in base pairs or major deletions in DNA leading to various disorders. Oxidative stress results in cell damage or even cell death accelerating ageing and being the cause of a variety of degenerative conditions such as central nervous system disorders, Alzheimer's disease, cardiovascular disease, atherosclerosis, cancer, cataract, diabetes, etc. However, nature has endowed each cell with adequate mechanisms to be able to fight away any harmful effects that are caused by free radicals. Nature has caused our bodies to adapt with a complex network capable of performing several mechanisms to counteract the oxidative stress and prevent the harmful effects; antioxidants are one such substance that is capable of neutralizing free radicals and its effects. These antioxidants can either be naturally produced *in situ* or they can be supplied through external sources like food or supplements (Pham-Huy *et al*., 2008) [5]. Antioxidants play a vital role in the maintenance of optimal cellular and systemic health and well-being. They have preventive roles not only on tissue damage caused by free radicals but also on the nutritional quality of food and the shelf life of processed food and conserves.

Assays for detecting antioxidant activity

There are several methods used for analyzing antioxidant activity. The methods can be broadly classified into assays based on Hydrogen atom transfer (HAT) and assays based on Electron transfer (ET). HAT includes inhibition of induced low density lipoprotein autoxidation, oxygen radical absorbing capacity (ORAC), total radical trapping antioxidant parameters (TRAP) and crocin bleaching assays. ET based assays measures the capacity to which an antioxidant can reduce an oxidant based on the color change (when it is reduced) which is related to the concentration of antioxidant present in the sample. The assays include total phenolic content by Folin Ciocalteu reagent (FCR), trolox equivalent antioxidant capacity (TEAC), Ferric ion reducing antioxidant power (FRAP) and total antioxi dant potential assay using a cu (II) complex as an antioxidant and DPPH (2,2-diphenyl-1-picrylhydrazyl) as a stable free radical, ABTS (2,2-Azinobis (3-ethylbenzothiazoline-6 salphonic acid), FOX (ferrous oxidationxylenol orange), FTC (ferrous thiocyanate) and ACA (aldehyde/carboxylic acid) assay.

Direct assays which can measure the scavenging activity of radicals such as hydroxy, peroxynitrate, singlet oxygen, super oxide or anion radical by the sample can be used.

In addition, lipid peroxidation methods help in analyzing antioxidant capacity. Some of the methods include Thiobarbituric acid assay (TBA), Malonaldehyde/high performance liquid chromatography (MA/HPLC), Maloaldehyde/gas chromatography (MA/GC), β-Carotene bleaching and conjugated diene assay.

Medicinal plants with antioxidant activity

***Hibiscus sabdariffa* L.**

The roselle is a species of *Hibiscus* belonging to the Malvaceae family. It is found in Asia (India to Malaysia) and tropical Africa. *Hibiscus* contains polyphenolic compounds, anthocyanins and flavonoids. In addition, a potent antioxidant and cytoprotective agent has been characterized from this shrub known as betaine. Chemical studies have shown presence of high amounts of magnesium, potassium, sodium, calcium, iron, protocatechuic acid, delphinidin, quercetin, sabdaretin and hibiscretin, anthocyanins, ascorbic acid, etc. implying its usefulness as a source of enriching food products low in essential minerals (Abou-Arab *et al*., 2011) [1].

A comparison study using hexane, ethyl acetate and methanol extract of three varieties of sorrel (two red traditional red [TRED] early bearing red [ERED] and one white [WHITE] mature hibiscus variety) for their antioxidant activity, indicating that the methanol extract of the red variety has greater inhibition capability and therefore better antioxidant activity compared to the white variety, TRED having an inhibition capacity of 80%, ERED of 77% and WHITE 56%. The DPPH inhibition of the methanol extract was reported to be 78% (Jakopic *et al*., 2009) [7].

Maturation to have an impact on the phenolic content, although the WHITE variety seemed to behave differently inspite of not having anthocyanins that could be related to the ascorbic acid content of the plant.

Compounds such as delphinidin-3-sambubioside and cyaniding-3-sambudioside which seemed to significantly contribute to the antioxidant activity of the plant have been isolated. Major polyphenols of *H. sabdarifa* were isolated by HPLC techniques of which the components include protocatechuic acid (8.83%), catechin (9.97%), epigallocatechin (EGC) (20.20%) and caffeic acid (18.10%).

A thorough analysis on the anti-inflammatory effect of *H. sabdarifa* polyphenols showed that this plant not only had very strong anti-inflammatory potency but was also capable of significantly decreasing inflammatory markers induced by lipopolysacharides (LPS) such as cyclooxygenase (Cox-2)/inducible nitrous oxide synthase (iNOs), aspartate transaminase (AST), alanine transaminase (ALT) and alkaline phosphatase (ALKP) and inhibiting nitric oxide (NO) and prostaglandin E2 (PGE_2) production. Based on the hypothesis that over expression of Cox-2 or iNOs might be involved in pathogenesis of many diseases, it can be concluded that *H. sabdarifa* can prevent chronic disease progression by regulating the inflammatory. The ethanol extract has been reported to have hypolipemic property by reducing 50% of serum triglyceride in mice fed with hyper caloric diet. Revealed the aqueous extract of *H. Sabdariffa* to protect the kidney from oxidative stress induced by chronic exposure to sub lethal dose of Malathion an organophosphorous pesticide and considered it as a safe and potent natural antioxidant. Clinical studies in Taiwan on human subjects to evaluate the cholesterol reducing capability of *H. sabdarifa* extract (HSE) capsules, indicated significant reduction in the cholesterol within two weeks and brought it down to 2.6% in 4 weeks, suggesting two capsules of HSE per month can significantly lower serum cholesterol. When tested against Cox-1and Cox-2 enzymes the extracts had similar inhibition capacity as Aspirin, therefore it is suggested that sorrel could be effective at promoting good cardiovascular health and reducing blood pressure and preventing hypertension. Administration of ethanol extract of dried flowers revealed hepatoprotective,

hypolipidemic and antioxidantactivity. Survey by Hou *et al* on Dp3-sam anthocyanins isolated from *H. sabdarifa* concluded anti-cancer activity of this phenolic compound. It was reported that the Dp3-Sam induced dose dependant apoptosis in human leukemia cells (HL-60). Considering this, it could be of further interest in cancer chemo preventive studies and therapy. Studies by Oboh indicated neuroprotective activity of *H. sabdarifa* also called as the sour tea, they claim sour tea could prevent and manage neurodegenerative diseases.

***Moringa oleifera* Lam.**

M. oleifera (Moringaceae) is native to the southern foothills of the Himalayas in the northwestern India. *M. oleifera* is rich in compounds like glucosinolates and isothiocyanates, kaempferol, rhamnetin, isoquercitrin, kaempferitin, alkaloids like moringinine and moringine,henicosanoic, palmitic acid, vitamine E, betacarotene, α-linolenic, g-linolenic ad linoleic acid. Presence of trace elements such as magnesium, iron, hydrogen, oxygen, carbon, nitrogen and sulfur has been reported. Using Laser Induced Breakdown (LIB) analysis two new glycoslated carbamate and glycosylated nitrile compounds were isolated namely S-ethyl-N-{4-[(α-Lrhamnosyloxy) benzyl]} thiocarbamate and 2-acetoxy{4[(2′,3′,4′tri-O-acetyl-α-L-rhamnosyloxy) benzyl] acetonitrile}.

The DPPH scavenging activity of mature and tender leaves have been analyzed reporting a slightly higher activity in the mature leaves, with an IC_{50} of 18.5 compared to tender leaves with an IC_{50} of 19.2, also phenolic content being higher in mature leaves compared to the tender leaves. Various agro climatic regions and different solvents used could have an effect on the antioxidant capacity which is directly related to the phenolic content, 80% methanol and 70% ethanol being better solvents. Acetone also proved to be a good solvent and revealed higher phenols flavonoids, flavanols and proanthocyanidins. Although the growing locations as well as the stage of development, genetic variability and post harvest handling, all could have a synergic effect together.

***Clitoria ternatea* L.**

C. ternatea belongs to the family Fabaceae. Various secondary metabolites like polyphenolic flavonoids, anthocyanin glycosides, pentacyclic triterpenoids such as taraxerole and taraxerone, phytosterols, Flavonols, kaempherols, quercetin and myricetin and their glycosides have been isolated from this plant. Antioxidant potential of the methanolic extract of the leaves was investigated and reports indicate an IC of 420 μgml^{-1}. The percentage of its radical scavenging activity has been quite similar to that of BHT (butylated hydroxytoluene).

In vitro antimicrobial analysis conducted on various extracts of *C. ternatea* flowers proved to be effective against gram negative urinary pathogens. Presence of certain biologically active peptides called cliotides display potent antimicrobial activity. Reports also exist on the anthelmintic activity of methanolic extract of *C. ternatea*.

Hepatoprotective potential of the leaf extract of this plant has been reported against paracetamol induced liver damage in mice. It was observed that previously raised alanine aminotransferase (ALT), aspartate aminotransferase (AST) and Billirubin in the hepatotoxic mice were significantly reduced with administration of the leaf extract; histopathological examination also verified hepatoprotective effect.

Experimented on the leaf and flower of *C. ternatea* and have reported the hypoglycaemic effect on alloxan induced diabetes in rats where in they have suggested this effect to be due to the enhancement of the glycogenesis process. Recently too, streptozotocin induced diabetic wistar rats were analyzed for the effect of the alcoholic root extract of *C. ternatea* on the brain and pancreatic tissue. Results indicated positive impact on cerebral corcital hippocampal CA3 neurons and on the pancreatic tissue of juvenile diabetic rats, therefore justifying its usage as a memory enhancing agent and in promoting excellent intellect.

***Ocimum sanctum* Linn.**

This is one of the wonder herbal drugs in the Indian system of medicine, known as “Tulsi” in Hindi/ sanskrit and “Holy Basil” in English. It belongs to the lamiaceae family. For thousands of years Ayurvedic practitioners have been trying and testing the effects of this plant and have concluded the various uses and benefits of Tulsi although modern science has a different approach to confirm its uses and its efficacy. Therefore, various scientists have conducted preliminary investigations on different extracts of the plant to be able to conclude its efficiency in the traditional system of medication.

Detailed investigation has given us thorough knowledge of the active compounds which include eugenol, ursolic acid, rosmarinic acid, caryophyllene and oleanic acid. Seeds contain fixed oils having linoleic acid and linolenic acid (www.holy-basil.com). Holy basil has been used by traditional practitioners as an anticancer, antiemetic, antidiabetic, expectorant, analgesic, insecticidal, antifungal and anti-stress agent owing most of its healing properties to Eugenol.

This plant has shown very good scavenging activity at very low concentrations. Water and alcohol extracts have been reported to have anti lipid peroxidative activity. Antibacterial activity of Sanctum fixed oil has been proved which is related to the content of linolenic acid present in the plant. Ethanolic extract has been reported to be a better inhibitor of streptococcus mutants and the best zone of inhibition was obtained at 4% concentration of Tulsi extract.

*O. sanctum*is also called as the “queen of plants” due to its diverse bio-pharmacological activities like antiinflammatory, antidiabetic, antibacterial, antiulceric, antimalarial and immunomodulatory properties.

This holy plant has also provided significant liver and aortic tissue protection in cases of hypercholesterolemia – induced peroxidative damage. Recent work conducted on *H. plantanifoluis* concluded that the ethanolic and aqueous hot extracts of leaves have good hypoglycemic and hypolipidemic activity.

***Plumbago zeynalica* L.**

It belongs to the Plumbaginaceae family. It is a herb that grows widely in India and has been used by the rural and tribal for hundreds of years as a traditional medicine. An herbal preparation is derived from the root which is useful in treating arthritis and rheumatism related problems.

Various amino acids have been isolated from the aerial parts of this plant including aspartic acid, tryptophan, tyrosine, threonine, alanine, histidine, glycine, methionine and hydroxyproline using spectral analysis characterized difuran naphthoquinone from the roots of this plant and the compounds identified were naphthoquinones, lapachol, plumbagin, 2-isopropenyl-9-methoxy-1,8-di-oxadi cyclopenta (*b,g*) naphthalene-4,10-dione, 9-hydroxy2-isopropenyl-1,8-dioxa-dicyclopenta (*b,g*) naphthalene-4,10-dione, 2-(1-hydroxy-1-methyl-ethyl)-9methoxy-1,8-dioxa-dicyclopenta (*b,g*) naphthalene4,10-dione and 5,7 - dihydroxy-8-methoxy-2-methyl1,4-naphthoquinone, 3chloroplumbagin, chitranone, zeylalone, isozelalone, plumbazeylone, coumarin, triterpenoids. Plumbagin is a naphthoquinone and most of the work conducted seems to be related to this compound. Researchers believe that the therapeutic effects are mainly related to this quinone.

In vitro antioxidant and Total Phenolic Content (TPC) assay conducted on methanolic extract of the roots indicated *P. zeynalica* to be a potent radical scavenger. The inhibition percentage by DPPH method was seen to be 88.45% compared to ascorbic acid (96.5%). Aqil and Ahmad reported antibacterial activity of this plant were able to isolate and evaluate the compounds that were the cause of the antimicrobial property such as neoisoshinanolone and 1-epineo-iso-shinanolone from the roots of *P. zeynalica*.

***Capparis zeylanica* Linn.**

It is a type genus from the Capparacceae family. This plant is commonly known as “Indian Caper”. Traditionally it is used as an antidote to snake bite, to cure swelling of testicle, small pox, boils, cholera, colic, hemiplagia, neuralgia, sores, pneumonic and pleurisy. Whole plant showed the presence of saponin, phydroxybenzoic, syringic, vanillic, ferulic and pcoumaric acid. Leaves and seeds showed presence of ß-carotene, thioglycoside, glycocapparin, n-tricortane, a-amyrin and fixed oil.

Phytochemical analysis have showed the presence of carbohydrates, glycosides, alkaloids, phytosteroids, flavonoids, saponins, tannins, phenolic compounds, fixed oils and fats. Reports confirm presence of all eleven essential elements in the *C. zeylanica* plant except for chloride. Haque *et al* using various techniques were able to isolate a new fatty acid from the chloroform extract of the roots and with NMR techniques characterize it as E-octadec7-en5ynoic acid.

The percentage of inhibition of DPPH radical was 87.12 in comparison with ascorbic acid having an inhibition percentage of 96.5%. Antimicrobial activity of the petroleum ether, chloroform, ethanol and aqueous extracts has been reported although this research did not attain any antifungal activity. Methanolic extract of *C. zeynalica* has been proposed to have antidiarrheal properties therefore suggesting its usage in the pharmaceutical industry for diarrhea related problems, as it has the capacity to increase the absorption of water and electrolytes from the gastrointestinal tract.

***Anisomeles malabarica* (L) R.BR.**

Belongs to the family Lamiaceae. The plant is reported to possess anti-cancer, anthelmintic, antiallergic, antianaphylactic, antibacterial, anti-carcinomic, antiedemic, antihistaminic, anti-inflammatory, antileukemic, antinociceptive, antiplasmodial, antiseptic and antipyretic properties. Preliminary phytochemical analysis has revealed presence of alkaloids, flavonoids, tannins, saponins and glycosides. Earlier phytochemical studies on the leaves of *A. malabarica* have shown the presence of ß-sitosterol, ovatodiolide, anisomelic acid, malabaric acid, anisomelol and triterpene betulinic acid. Two apigenin glucosides were reported from the stems of *A. malabarica* and identified as apigenin-7-*O*-beta-D-(4”,6”-di-*O*-P-coumaroyl) glucoside and its 2”,6”-isomer by spectral studies.

Antioxidant activity of the ethyl acetate extract of *A. malabarica* tested using DPPH assay indicated an IC_{50} of 205.86% μgml^{-1} which was quite close to vitamin E radical scavenging activity. The methanolic extract recently analyzed produced similar results with an IC_{50} of 206.86 $\mu g\ ml^{-1}$. Although antioxidant studies done by the same method using the same solvent for extraction (methanol) produced results indicating higher IC_{50} value (252 μgml^{-1}), in this case the scavenging activity was compared to that of rutin.

***Cassia occidentalis* Linn.**

It belongs to the Caesalpiniaceae family. The plant is used to cure sore eyes, haematuria, rheumatism, typhoid, asthma, disorders of haemoglobin and for cure of leprosy. A decoction of the plant is used in hysteria, in dysentery and other stomach troubles, for application to sores, itch and inflammation of the rectum. The plant is employed in dropsy, and as a vermifuge. Along with other plants, it is made into an ointment used for skin diseases. Preliminary phytochemical studies have reported the presence of alkaloids, glycosides, proteins, amino acids, sterols, carbohydrates, phenolic compounds, flavonoids, saponins and tannins. A wide range of chemical compounds such as achrosin, aloe-emodin, anthraquinone, anthrone, apigenin, auranthiobtusin, campesterol, cassiollin, chryso-obtusin, chrysophanic acid, chrysarobin, chrysophanol, chrysoeriol etc. have been reported to be isolated from this plant.

***Cassia auriculata* L.**

Belonging to the family Fabaceae, *C. auriculata*is mainly found in the central and southern parts of India. It has been used since ages in the traditional medicine for treatment of rheumatism, conjunctivitis, diabetes, etc. The root is used for treating skin diseases including leprosy. The plant has been reported to contain polysaccharides, flavonoids, tannins and fatty oils.

C. auriculata has a significant effect on rats treated with streptozotocin to induce diabetes. The best effect was observed at 0.45 $gmkg^{-1}$ body weight of the streptozotocin (STZ) diabetic rats. Its effects in comparison to Glibenclamide were almost similar. It is also reported that this plant reduces levels of serum and tissue lipids and has a beneficial effect on plasma insulin. Similar studies conducted on STZ induced diabetic rats indicated that *C. auriculata* leaves posses potent antihyperglycemic and hypolipidemic activity.

In alcohol treated rats which were induced with liver damage significant lipid lowering effect was reported and it was also seen to have reversed steatosis in the liver and spongiosis in the brain.

***Curculigo orchioides* Gaetrn.**

Better known as golden eye grass or "Kali Musli" in India, belongs to the family Hypoxidaceae, the plant is native to India, and has a special position in the Ayurvedic system of medicine. Amongst the few of its medicinal attributes *C. orchioides* is used along with other preparations to cure blindness and white eye spots on the eye ball. It is also used on cuts and wounds because of its anti-infective potency, also seen as useful in some cases of asthma. It is prescribed in the treatment of gonorrhea, diarrhea, piles, jaundice, bronchitis, indigestion, vomiting, gleet, etc. It is also used in Persian traditional healing systems.

The methanolic extracts of the rhizomes of *C. orchioides* proved to have potent antioxidant activity against liver damage induced rats using CCl_4. It was seen that the normal functioning of antioxidant enzymes like super oxide dismutase (SOD), catalase (CAT) etc. were regained after being treated with the methanol extract, revealing its efficiency in combating with the oxidative stress due to hepatic damage. *C. orchioides* rhizome extract showed significant antimicrobial activity against pathogenic gram positive and gram negative bacteria.

Conclusion

As the global scenario is now moving towards using nontoxic plant products having medicinal uses thorough research into this gold mine of centuries old knowledge should be emphasized. Presence of such medicinal plants that are rich in phytochemical constituents could reveal a new era of investigation for isolation of these useful compounds. Most of the plants considered in this study proved to have good to moderate antioxidant activity, *Ocimum sanctum*, *Hibiscus sabdariffa*, *Capparis zeylanica*, *Cassia occidentalis* being some of the most frequently used plants for their healing properties. In most of the research conducted it has been seen using methanol as a solvent for extraction produces better scavenging abilities, indicating the better capability of methanol to extract the phenols which is directly proportional to the antioxidant activity, although some scientists differ in their opinion about the extraction procedure choosing water over alcoholic solvents. In most of the plants investigation is conducted on the aerial parts of the plants mostly indicating leaves to be better parts for antioxidant studies. Majority of the medicinal plants seemed to be used for cure of diabetes, diarrhea asthma and skin diseases; leaving many areas open for investigation. A drug development program should be undertaken to develop modern drugs with the active constituents that could be used to cure these diseases directly. The work done to exploit their therapeutic utility to combat diseases, and production of drugs with better economic and therapeutic utilization seems insufficient giving us the possibility for profound advanced research in this field

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