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Antioxidant effect of *Cassia auriculata* (Flowers, Leaves and Seeds) on diabetes: Systematic review

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Abstract

The herbal medicines are selected over modern medicine due to their efficacy, safety and lesser side effects. *Cassia auriculata* is an evergreen shrub that grows in many parts of India and in other countries of Asia. *C. auriculata* has been used medically for many years to treat chronic disorders. It is commonly eradicated by cutting and digging the whole plants and sometime herbicides are used to control. However, it has very good medicinal properties which are widely used in India and popular in indigenous system of medicines like Ayurveda and Siddha. Flower of this plants are used in skin disorders, rheumatism, bark and leaves as astringent and anthelmintic, powdered parts are used for opthalmia, conjunctivitis, diabetes etc. *C. auriculata* is one among the medicinal plant that has been used by human for centuries as a medicinal herb. The whole plant is used for treating diabetes. *C. auriculata* has been reported to produce significant antihyperglycemic effect. Administration of *C. auriculata* has significant antidiabetic effect in streptozotocin (STZ)-nicotinamide induced diabetes. Oxidative stress plays an important role in the development of chronic complications of diabetes and is postulated to be associated with increased lipid peroxidation. Oxidative stress was determined by measuring lipid peroxidative markers and enzymic and non-enzymic antioxidants. Oxidative stress results from an imbalance between the generation of oxygen derived radicals and the organism's antioxidant potential. Thiobarbituric acid reactive substances (TBARS) and hydroperoxides from plasma and tissues (liver and kidney) of diabetic rats were significantly increased and enzymic antioxidants: superoxide dismutase (SOD), catalase, glutathione peroxidase (GPx) and glutathione-S-transferase (GST) and non-enzymic antioxidants: vitamin C, vitamin E, reduced glutathione (GSH) were significantly decreased with significant increase in the level of ceruloplasmin in diabetic control rats. Administration of *C. auriculata* flowers extract (CFEt), *C. auriculata* leaf extract *(*CLEt) and *C. auriculata* seeds extract (CSEt) significantly decreased the levels of TBARS and hydroperoxides accompanied with significant increase in the activities of enzymic antioxidant as well as non-enzymic antioxidants. Sequential metabolic correlation between decreased lipid peroxidation and increased antioxidant activities, stimulated by *C. auriculata,* may be by the possible biochemical mechanism through which glucose homeostasis was regulated.

Keywords: *Cassia auriculata*, enzymic antioxidants, nonenzymic antioxidants, lipid peroxidation, diabetes, streptozotocin

Introduction

While the dietary botanical supplement market is growing, the need for more rigorous clinical and scientific research on herbal and traditional medicine is strongly advocated for larger acceptances and visibility [1]. Traditional herbal medicines have a long history of use and are generally considered to be safer than synthetic drugs. Traditional medicine-inspired approaches remain important especially for the management of chronic diseases as well as to facilitate natural product drug discovery [2, 3].

Medicinal plants are significant component of a nation's natural resources. They contribute significantly to the delivery of basic healthcare services to the rural population. They operate as both medicinal agents and crucial raw materials in the production of conventional pharmaceuticals [4]. The majority of people in underdeveloped nations, including India, still use traditional medicine as their primary method of disease treatment; nevertheless, even among those who have access to western medicine, the use of complementary and alternative medicine is fast rising globally.

For chronic diseases including diabetes and cardiovascular conditions where long-term treatment is needed, co-administration of herbal and modern medicines may pose higher risk of adverse events and hence sufficient evidence of safety is necessary [5]. In such situations, safety pharmacology is useful to predict the adverse drug reactions [6]. Safety pharmacology deals with key aspects that are causal to unknown adverse events and aims at investigating potential undesirable pharmacodynamic effects on physiological functions in the therapeutic dose range. Increasing regulatory concerns in drug development have broadened the scope of safety to include general pharmacology, adverse drug reactions, cardiovascular pharmacology and pharmacokinetic herb-drug interactions [7].

C. auriculata is one such herb, has a reputation for being effective against a number of diseases. It has stunning yellow flowers and is an evergreen plant (Fig.1). Different regions of Asia, particularly India support the growth of this plant [8]. *C. auriculata,*a member of the Fabaceae family, it is a legume shrub. Alternative synonyms for it include Tarwar, Ranwara, Tanner's Cassia, and Avaram senna. It is called as Avaram in Tamil language. Growing between 30 and 60 cm tall, it is a perennial plant. The stem has several branches, is strong and solid, and has a brown colour. The complex, stipulated leaves have a yellowish-green colour. The plant gives out a huge golden flower. Seven to ten seeds make up the fruit, which is a legume. The bark of Tanner's Cassia, one of the most expensive Indian tans, is where the plant gets its name [9].

It is a yearly or annual shrub that can be found in open woods in India's hotter regions. Due to the existence of phytochemical components as tannins, saponin, alkaloids, glycosides and volatile oils, plant has significant medicinal effects.

The plant's leaves are astringent, acrid, cooling, diuretic, bitter, opthalmic and vulnerary. The entire plant has medicinal significance from the tip to the root, demonstrating therapeutic properties like anti-microbial, anti-diabetic, hepatoprotective, antiperoxidative, antiviral and antipyretic. The plant's bark is used to cure gout, gonorrhea, and rheumatic pain, while the roots are significant in urinary disorders, fever and other bacterial infections. Leaf properties include constipation and are helpful in digestion. Flower buds are used to treat diabetes [10].

Botanical characters

Flowers: Flowers are bright yellow and irregular and large (5cm). The pedicels are glabrous, and 2.5cm long, the five sepals are separate, concave, membranous and unequal. Two external and three internal sepals, outer ones are longer than the inner ones. The petals 5 in numbers are free imbricate, crisped along the edge and bright yellow veined. The anthers are 10 in numbers also separated by the three stamens barren; the ovary is unilocular, superior with peripheral ovules.

Leaves: Leaves are dull green; these are alternate, stipulate, paripinattly compound leaves with 16-24 pairs of leaflets. Leaves are firm, narrowly rugged, pubescent, and thin, with vertical and linear gland between the leaflets of each pair and shortly stalked, 2-2.5cm long, 1-1.3cm wide. Marginally overlapping, rectangular, dull-witted at both ends, and glabrous.

Fruit: Fruits are pale brown or green in colour and little legume, 7-11cm long, 1.5cm broad, rectangular, long style base, flat, thin, papery, pilose, undulate crimpled and tripped with long style base. It has about12-20 seeds per fruit, each in its distinct cavity.

Parts studied	Chemical constituent
Flowers	Alkaloids, glycosides, saponins, phenols, terpenoids, flavonoids, tannins and steroids [11]
Leaves	O-methyl-d-glucose, resorcinol, alpha-tocopherol- beta –mannosidase and carboxylic acid [12].
Seeds	Palmitic acid, linoleic acid, benzoic acid 2-hydroxyl methyl ester, 1-methyl butyl ester and resorcinol [13].
Roots	Anthraquinone glycosides and flavone glycosides [14].

Table 1. Chemical constituent reported in *Cassia auriculata*

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Figure.1. *Cassia auriculata*

Ayurvedic formulations and preparations

***Diasulin*:** A herbal preparation of *C. auriculata*, *Curcuma longa*, *Gymnema Sylvestre*, *Coccinia indica*, *Momordica charantia*, *Scoparia dulcis*, *Syzygium cumini*, *Trigonella foenum graecum, Tinospora cordifolia*. Diasulin was used in the treatment of diabetes [15].

***Sugnil*:** A polyherbal formulation from a combination of nine Indian medicinal plants, which are *Aristolochia bracteata* (whole plant), *Shorear oxburghii* (gum), *C. auriculata* (flower), C*asearia esculanta* (leaf), *Coscinium fenestratum* (bark), *Curcuma longa* (tubers), *Eugenia jambolana* (seeds), *Gymnema sylvestre* (leaves) and Triphala (fruits). It is used to reduce vascular complications in diabetes mellitus [16].

***Kalpa herbal tea*:** *C. auriculata* is one of the main ingredients of tea and it was used in the treatment of diabetes.

Avaraipanchanga choornam: It has equal quantities of fruits, leaves, roots, flowers and bark to prepare Avaraipanchangachoornam, which is extensively used in the management of diabetes [17].

***Kudineer*:** It is a polyherbal formulation consisting of seven herbal ingredients, *viz*., *C. auriculata, C. fistula*, *Syzygium Jambos, Olax scandens, Saussurea lappa*, *Terminalia arjuna* and *Cyperus rotundus*. Useful in the treatment of diabetes and antimicrobial and fungal infection [18].

***Talapotaka churna*:** It is a poly-herbal preparation contains *C.auriculata*, *Emblica officinalis*, *berberis aristata* and *Curcuma longa*. It is useful in reducing blood glucose level hence this churna is used to treat diabetes [19].

Formulation	Used to treat
Avaraikudineer	Diabetes, fungal and microbial infection
Kalpa herbal tea	Diabetes
Talapotakachurna	Diabetes and obesity
Diasulin	Diabetic
Sugnil	Diabetic
Avaraipanchangachoornam	Diabetes and obesity

Table 2. Uses of ayurvedic formulations of *Cassia auriculata*

Medicinal uses

Flowers are used for spermatorrhea, dried powder of flowers mixed with goat milk and taken orally to prevent white discharge in Kancheepuram district of Tamil nadu. Flowers are also used as food stuff by tribal people of Andhra Pradesh. Flowers are mixed with whole plant of *Enicostema axillare* and fruits of *Cuminum cyminum*, given to cattle along with grass for three days prevent heat diseases. Other parts are used in urinary discharges and cures tumours, skin diseases and asthma. Powder of bark is used for fixing teeth and decoction for chronic dysentery and various skin disorders and body odour widely used in Rheumatism, Conjuctivitis and diabetes [20].

It is reported for treating ulcer, leprosy and liver disease [21]. The antidiabetic, hypolipidemic and antioxidant and hepatoprotective [22] effect of *C. auriculata* have been reported. It was also observed that flower and leaf extract of *C. auriculata* shown to have antipyretic activity [23].

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Effect of CSEt, CLEt and CSEt on lipid peroxidative markers

Lipid peroxidation is a free-radical mediated propagation of oxidative insult to PUFAs involving several types of free radicals and termination occurs through enzymatic means or by free radical scavenging by antioxidants [24]. lipid peroxidation end products measured as TBARS and HP were increased in plasma and tissues of STZ - nicotinamide induced diabetic rats, which might be due to relatively high concentration of easily peroxidizable fatty acids in tissues. During diabetes, liver showed a relatively severe impairment in antioxidant capacity than kidney. The kidney exhibits a characteristic pattern of changes during diabetes. The increase of oxygen free radicals in diabetes could be primarily due to increase in blood glucose levels, which upon autoxidation generate free radicals and secondarily due to the effects of diabetogenic agent STZ [25]. Drugs with antioxidant properties may supply endogenous defense systems and reduce both initiation and propagation of ROS [26]. Administration of *C. auriculata* flowers extract (CFEt), *C. auriculata* leaf extract (CLEt) and *C. auriculata* seeds extract (CSEt) reduced the lipid peroxidative markers in plasma and tissues of diabetic rats[28-30].

Effect of CFEt, CLEt and CSEt on enzymic and non-enzymic antioxidants

Free radical scavenging enzymes such as SOD, catalase and GPx are the first line of defense against oxidative injury. SOD catalyzes to scavenge the excess of superoxide anions and convert them to H_2O_2. The primary role of catalase is to scavenge H_2O_2 that has been generated by free radicals or by SOD in removal of superoxide anions and to convert it in to water. Gpx works in tandem with catalase to scavenge excess of H_2O_2 as well as lipid peroxidation in response to oxidative stress. A decrease in the activity of SOD and catalase was observed in liver and kidney of diabetic control rats. SOD and catalase are the two major scavenging enzymes that remove toxic free radicals *in vivo*. It is well documented that the activity of SOD is low in diabetes mellitus [31]. Reduced activities of SOD and catalase in liver and kidney have been observed during diabetes and this may result in a number of deleterious effects due to the accumulation of $O_2^{\bullet-}$ and H_2O_2 [32].

Any compound, natural or synthetic, with antioxidant properties might contribute towards the partial or total alleviation of oxidative damage. Therefore removing $O_2^{\bullet-}$ and $^{\bullet}OH$ is probably one of the most effective defenses against diseases [33]. Treatment with CFEt, CLEt and CSEt increased the activities of SOD, catalase in the diabetic rats when compared to diabetic control rats. This clearly shows that CFEt, CLEt and CSEt possesses free radical scavenging activity, which could exert beneficial action against pathologic alterations caused by the presence of $O_2^{\bullet-}$ and $^{\bullet}OH$ [34]. CFEt, CLEt and CSEt effectively scavenges peroxyl radicals ($ROO^{\bullet}$) and reduce the singlet-oxygen induced peroxidation at levels [35]. Administration of CFEt, CLEt and CSEt significantly reversed the changes to near normal levels in the circulation and tissues of diabetic rats. Because of these activities, it was expected that CFEt, CLEt and CSEt might decrease the utilization of enzymic antioxidants and reduce the free radical mediated inactivation of enzyme proteins and thereby maintaining the activities of enzymic antioxidants [36].

The second line of defense consists of the non-enzymic scavengers such as GSH, ascorbic acid and α-tocopherol, which scavenge residual free radicals escaping from decomposition process mediated by the antioxidant enzymes. Moreover, enzymic antioxidants are inactivated by the excessive levels of free radicals and hence the presence of non-enzymic antioxidants is presumably essential for the removal of these radicals [37].

GSH is the most important biomolecule, which participates in the elimination of reactive intermediates by reducing hydroperoxides in the presence of GPx. GSH also functions as a free radical scavenger and in the repair of radical caused biological damage [38]. Decreased glutathione levels in type 2 diabetes have been considered to be an indicator of increased oxidative stress [39]. The decrease in the GSH level represents the increased utilization in trapping the oxy radicals. GPx and GST catalyse the reduction of H_2O_2 and hydroperoxides to non-toxic products [40]. Previous studies reveal that the activities of GPx and GST were significantly decreased in diabetic rat tissues. [34-36]. The decreased activities of these enzymes result in the involvement of deleterious oxidative changes due to the accumulation of toxic products. Administration of CFEt, CLEt and CSEt increased the content of GSH in the liver of diabetic rats.

Vitamin C is an excellent hydrophilic antioxidant in plasma, because it disappears faster than other antioxidants when plasma is exposed to ROS [41]. Studies involving different types of oxidative stress have shown that under all types of oxidative damage it would be helpful in prevention of diseases in which oxidative stress plays a causative or exacerbation role [42]. The observed significant decrease in the level of plasma vitamin C could be due to the increased utilisation of vitamin C as an antioxidant defense against ROS or to a decrease in the GSH level, since GSH is required for the recycling of vitamin C [43].

Vitamin E is an important lipophilic antioxidant, which has an effective role in maintaining the cell structure against oxidative damage through blocking the chain reaction of free radicals [44]. Low levels of plasma antioxidants have been implicated as a risk factor for the development of diabetes [45]. Both vitamin C and vitamin E are known to prevent detectable lipid peroxidation, and under physiological conditions, it has been suggested that vitamin C helps to recycle vitamin E from its radical form [46]. Oral administration of CFEt, CLEt and CSEt to diabetic rats restored the level of vitamin E to near normal. It is likely that increased level of vitamin E may be due to increased levels of GSH.

Ceruloplasmin forms a major part of the extracellular antioxidant defense. It inhibits iron and copper dependent lipid peroxidation and also has a $O_2^{\bullet -}$ scavenging activity [47]. The level of ceruloplasmin has been reported to increase under disease condition that leads to the generation of oxygen products such as $O_2^{\bullet -}$ and H_2O_2 [48]. Further, increase in ceruloplasmin is an indication of increased antioxidant defense to compensate the loss of other antioxidant enzymes. Administration of CFEt, CLEt and CSEt to diabetic rats restored the level of ceruloplasmin. The observed increase in the level of plasma ceruloplasmin in diabetic rats may be a protective response to an increase in circulating unbound Fe^{2+}, which would act as a catalyst for further free radical induced lipid peroxidation.

Administration of CFEt, CLEt and CSEt significantly decreased the levels of lipid peroxidation products in diabetic rats. CFEt, CLEt and CSEt effectively scavenges peroxyl radicals ($ROO^{\bullet}$) and reduce the singlet-oxygen induced peroxidation at levels similar to those of resveratrol [49]. In fact, CFEt, CLEt and CSEt has a free hydroxyl group in the 4' position, exert a significant antioxidant activity. The trans isomery and the double bond in the stilbenic skeleton also play a vital role in antioxidant property [50]. Few studies have focused on the effect of metformin on improvement of antioxidant status [51] and decrease in lipid peroxidation markers in type 2 diabetic patients [52].

Conclusion

C. auriculata has been used by human for centuries as a medicinal herb. *Cassia* revealed that the plant is the source of many therapeutically important chemical constituents. Ethnobotanical, ayurvedic and folklore claims indicate the traditional medicinal system of India. *C. auriculata* is the main ingredient in various herbal formulations such as avarai kudineer, talapotaka churna, sugnil, Kalpa herbal tea, avarai panchanga choornam and diasulin. The plants with antidiabetic activities provide useful sources for the development of drugs in the treatment of diabetes mellitus. CFEt, CLEt and CSEt regulates the glucose homeostasis, which inturn prevents the increased oxidative stress from glucose autoxidation and also from the direct or indirect inhibition of free radical generation mediated by CFEt, CLEt and CSEt. Since the study of the antioxidant status is considered to be a reliable marker for evaluating the antiperoxidative efficacy of the medicinal plants and its active constituents, these findings are suggestions of possible antioxidant and antidiabetic effect of whole plant of *C. auriculata*.

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