CHLOROGENIC ACID: A PHARMACOLOGICALLY POTENT MOLECULE

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Abstract: Chlorogenic acid (CGA; (1S,3R,4R,5R)-3-[(2Z)-3-(3,4-dihydroxyphenyl)prop-2-enoyl]oxy)-1,4,5-trihydroxycyclohexanecarboxylic acid) is a naturally occurring polyphenol mostly present in vegetables and fruits. CGA is a prominent component of Traditional Chinese Medicines and is known for various pharmacological activities such as antioxidant, antimicrobial, anti-inflammatory and hepatoprotective etc. This minireview is an attempt to summarize the available literature in the last decade and to point out future perspectives in this area of research.

Keywords: chlorogenic acid, oxidative stress, antioxidant, inflammation

Chlorogenic acid (CGA) is a biologically active polyphenol which is soluble in ethanol and acetone and is marketed as svetol. It is generally used as an ingredient in chewing gum and mints and is naturally present in different fruits such as peach and prunes (1, 2) and vegetables such as potato (3). CGA has also been found as a phenolic component of bamboo (4), green coffee bean extract (5) and tobacco (6). A family of esters of hydroxycinnamic acids (including ferulic acid, caffeic acid and p-coumaric acid) with quinic acid is also some times refered as chlorogenic acids (7, 8).

Synthesis of CGA

The esterification of caffeic acid with L-quinic acid yields CGA (Fig. 1) (9).

Pharmacological importance of CGA

CGA is known to exhibit a range of pharmacological activities such as anticancer, antioxidant, anti-inflammatory, cardiovascular, hepatoprotective, renoprotective, anti-diabetic and anti-lipidemic. Pharmacological properties exhibited by CGA are summarized in Table 1.

Encapsulated CGA possesses remarkable antioxidant activity

Although CGA is a good antioxidant agent (8, 20); its unstable nature, on exposure to light and heat, limits its industrial applications, especially in the food industry. However, recently, this problem has been eradicated by the use of encapsulation technology. A study conducted on the determination

Figure 1. Synthesis of chlorogenic acid
of antioxidant activity of CGA encapsulated with β-cyclodextrin (β-CD) (inclusion ratio = 79.86 ± 1.92%) and hydroxypropyl-β-cyclodextrin (HB-β-CD) reported that the encapsulated CGA possesses an efficient antioxidant activity in grape juice. The complex of CGA/HB-β-CD is described to possess better antioxidant activity compared to CGA/β-CD complex and CGA alone; this enhanced activity can be attributed to the interactions and stabilization of radical species with the guest molecule (scavenger). The technological modifications in the formation of CGA/β-CD inclusion complex results in the reduced freedom of rotation for quinic acid moiety, which is due to the penetration into the cavity of β-CD; this was evident by the reported downfield shift of protons of quinic acid moiety in proton NMR of the CGA/β-CD complex formed. On the other hand, a little to no change in the NMR data was reported for caffeic acid moiety, present in chlorogenic acid, before and after complexation with β-CD. From the reported NMR it can be stated that quinic acid moiety was included in the β-CD cavity. No new peaks were reported in the proton NMR of formed complex, which signifies that chlorogenic acid was in a state of rapid exchange among free state and complex state. Also, storage stability was reported to be increased in an inclusion complex of β-CD and CGA (10).

Another major hurdle in the use of CGA for certain applications is its hydrophobic nature. This problem has been solved in a research where the structure of CGA was modified and converted to chlorogenic laurate (CGL) in order to improve its liposolubility profile. Interestingly, this structural modification was reported to enhance antioxidant activity (EC50 for CGA = 112.3 µg/mL and for CGL = 70.5 µg/mL) (11). In another study, a dose of CGA (100 mg/kg body weight) was given to mice for 8 days; it is reported that CGA reversed lipid peroxidation, inactivation of cytochrome P450 and increased cellular defense (21).

**CGA suppresses DSS-induced colitis**

It has been reported that a compound possessing good antioxidant activity normally shows good anti-inflammatory activity as well (22). Recently, in an *in vivo* study conducted on C57BL/6 mice, an anti-inflammatory activity of CGA was reported on dextran sulfate sodium-induced (DSS-induced) colitis. CGA was stated more potent to suppress DSS-induced colitis than its hydrolyzed derivative (caffeic acid) which has well established anti-inflammatory activity; *in vitro*, CGA was reported to inhibit H2O2- and tumor necrosis factor (TNF-α)- induced interleukin-8 (IL-8) production (12). A water extract of *Trachelospermum jasminoides* was studied in λ-carrageenan-induced paw edema in ICR mice and an anti-inflammatory response has been reported; besides other phenolic compounds, CGA has also been found in the extract analyzed by HPLC analytical plot and is a possible inhibitor of inflammatory mediators, TNF-α and NO production (13). Apart from these, the inhibition of cyclooxygenase-2 (COX-2), inducible nitric oxide synthase (iNOS) with lack of cytotoxic effect, attenuation of IL-1β and IL-6 along with TNF-α in a dose dependent manner and inhibition of nuclear factor-κB (NF-κB) by CGA is reported in a recent studies (23, 24).

**CGA is an active agent against cardiovascular problems**

CGA is a biologically effective component of Chinese folk medicine used against cardiovascular disorders as it reduces heart triglyceride levels (25). Cardiac hypertrophy is considered as one of the major reasons for heart failure. In a recent study, CGA has been found effective against isoproterenol (Iso)-induced hypertrophy in cardiomyocytes; the number of reactive oxygen species (ROS) increases in the Iso-induced cardiac hypertrophy and CGA has the ability to reduce this pathological condition by scavenging ROS (14). Increased cholesterol level (hypercholesterolemia) is considered as one of the
Chlorogenic acid: a pharmacologically potent molecule

Major reasons for heart diseases as well; CGA is well known to reduce heart cholesterol (25); in this regard a pre-clinical study was conducted on rats for 28 days; this study reports that CGA has the ability to control elevated levels of cholesterol significantly if taken up as a dietary ingredient (26).

In contrast to above reports, an increase in plasma concentration of homocysteine is reported in the blood with increased intake of coffee and black tea containing CGA; high concentration of homocysteine in plasma may cause cardiovascular disease (27).

Hepatoprotective nature of CGA
CGA possesses hepatoprotective nature (26). In a recent study conducted on tetrachlorobenzoquinone (TCBQ, a metabolite of an environmental pollutant pentachlorophenol)-induced liver damage in mice; the CGA pretreatment was reported to be effective in suppressing TCBQ-induced oxidative stress and therefore, possessing hepatoprotective nature (15). Moreover, in vitro a protecting property of CGA was reported at a dose of 300 or 500 mg/kg against CCl4-induced acute liver injury in male Sprague Dawley rats (16).

Renoprotective activity of CGA
Cisplatin (CP), an antineoplastic drug, is famous for various solid tumor treatments and is known to cause nephrotoxicity through various mechanisms, including inflammation, necrosis and apoptosis (17). Recently, in vivo study was conducted on intraperitoneally administrated with CP male BALB/cN mice; CGA pretreatment was reported to attenuate 4-hydroxynonenal expression, which is an indicator of renal oxidative stress, moreover, CGA was also described to attenuate heme oxygenase 1 and cytochrome P450 E1 overexpression as a result of CP administration; also CGA has been reported to inhibit advanced glycation end products (AGEs) with an IC50 value of 148.32 µM; these AGEs play a vital role in the development of chronic diabetic complications (28), these results established renoprotective activity of CGA (18). CGA is known to reduce triglyceride levels in the liver as well (25).

CGA holds anti-diabetic and anti-lipidemic activity
Diabetes is a common disease of the modern age and its major possible causes are obesity and lifestyle. CGA is abundantly found in our daily food like coffee and its consumption is advantageous because it can help in lowering the blood sugar level as well as to improve the lipid profile. Recently, in studies conducted on Leprdb/db mice, CGA has been reported to inhibit gluconeogenesis by affecting expression and activity of enzyme glucose-6-phosphatase (G6Pase), moreover, it improves skeletal muscle glucose uptake by increasing expression and translocation of glucose transporter type 4 (GLUT 4); a 2.5-fold increase in glucose transport was described as an additive action of CGA with insulin; on treatment with CGA a vacuolar degeneration has been reported in Hep G2 cells (human liver carcinoma cell line) resulting in reduction of lipid accumulation (19).

CGA reduces body weight
According to another study, performed at a clinical trial level on 12 subjects, the CGA plays a significant role in body weight reduction. The coffee products were tested on volunteers and it was reported that coffee containing enriched CGA caused 6.9% reduction in glucose absorption compared to control (29). The reduction in glucose absorption is attributed with alteration in glucose uptake pattern in small intestine, which is caused by antagonistic effect of CGA on glucose transport (30). CGA has been reported as a specific inhibitor of G6Pase translocase (an enzyme which regulates homeostasis of glucose in blood) in microsomes of rats (31). Another aspect studied was the effect of enriched coffee with CGA on 30 overweight individuals. The reported reduction in body mass was 3.17 times higher in individuals who used CGA enriched coffee compared to control (29).

CGA can alter body fat in high-fat diet; this has been reported in a study conducted on mice. The mice were given 0.02% (w/w) dose of CGA, which resulted in a pronounced body fat reduction, decrease in weight and decrease in plasma leptin as well as insulin levels compared to control. Plasma adiponectin elevation, fatty acid β-oxidation activity increment and peroxisome proliferator activated receptors an expression enhancement in liver were caused by CGA. Further, the reduction in synthesis of fatty acids, 3-hydroxy-3-methylglutaryl CoA reductase, acetyl CoA and cholesterol acyltransferase was reported (25).

CONCLUSION
The literature reveals the biological applications of CGA, however, some adverse effects have also been reported in the case of high dose administration of CGA, like its role as an anti-inflammatory agent is pre-established but simultaneously, it can cause inflammation and behaves as a double-edge
sword; CGA is present in ample amount in Chinese herbal injections and medicines, therefore, a careful dose selection is required while prescribing it (32).

Moreover, an increased level of plasma homocysteine is reported in the users of coffee and black tea containing CGA as a major polyphenol, this increased level is thought to be a risk factor in various cardiovascular diseases (33). Therefore, a careful study to investigate the amount of CGA which is useful for the humans is required.

REFERENCES


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