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GREEN COFFEE IN PHARMACEUTICAL INDUSTRY: A BOON TO MANKIND

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ABSTRACT

Coffee is amongst the most sought-after commercial beverages consumed worldwide. Its beneficial effects were related to its constituent caffeine however due to its increasing adverse effects and drug interactions the demand of other constituent i.e., chlorogenic acid (CGA) has increased which is highly present in **green coffee** and has ample of health benefits due to its various therapeutic and pharmacological action, side effects, drug interaction, dosing of green coffee. This review discusses the pharmacognosy, geographical indication, pharmacology, pharmacokinetics, mechanism of action, uses, drug interactions, adverse effects of green coffee.

KEYWORDS- Chlorogenic acid (CGA), coffea arabica, green coffee, anti-obesity, anti-oxidant, protective effects, anti-inflammatory, caffeoylquinic acids (CQA), feruloylquinic acids(FQA)

Introduction

Green coffee beans are originated from dicotyledonous plants which have the coffea fruits bearing coffee seeds. These are dehydrated ripe seeds of Coffea arabica linn of family-rubiaceae and they are unroasted unlike coffee. The green coffee from these beans has a mellow, green and aroma just like beans. It lacks the distinctive aroma of coffee as it develops through the roasting process. The natural occurring polyphenolic constituents are being converted into a convoluted amalgamation of Maillard reaction products during the roasting process. Due to maillard's and strecker's reactions during roasting, bitterness intensifies because of caffeic acid release and generation of lactones and other phenol derivates account for the flavor and aroma. It was originally found in places like India, Brazil, Vietnam, Indonesia, Ethiopia, Mexico, Guatemala and Sri Lanka. Budding, cutting and grafting has been used for propagation except seeds which is the usual way. The average age of these plants is 30 to 40 years but some plantations even range upto 100 and still bearing. Trees start bearing around 3-4 years after planting and around 6-8 start bearing at their full potential. After flowering, fruits tend to mature in 7-9 months. Cherry picked ripe red ones are of the highest quality. Coffee is most commonly consumed beverages worldwide. India lays the 5th largest coffee production in the world has large quantities of green coffee available. It acts for natural antioxidants for nutraceuticals and functional foods as a promising source. Apart from being used for beverages, it also serves as an alternative to drug therapy. It is a good practice to use food components for preventing along with treating hypertension. Caffeine, fixed oil, tannin, and proteins constitute coffee. Caffeine exists as a salt of chlorogenic acid in seeds. Caffeine enhances clinical conditions of diabetic patients and boosts energy dissipation. It also suppresses fat absorption. Caffeine prevents various degenerative diseases. Due to caffeine’s side effects on the cardiovascular system, the central nervous system, the endocrine system and its stimulating effect on the central nervous system have significantly decreased its consumption. The coffee beans roasting minimizes the amount of chemical chlorogenic acid and might experience drastic structural changes such as hydrolysis, heating to a high level can cause polymerization however, these changes may lead to a remarkably different product or activity profile. Conventional structural alterations in coffee beans during roasting include downgrading CGA and trigonelline, loss of proteins and carbohydrates, development of melanoidin. Compared to regular roasted coffee beans, green coffee beans have a higher level of chlorogenic acid which has various health benefits, decaffeinated coffee enhanced with chlorogenic acid uplifting a person’s behavior and attentiveness. The improvement of fat metabolism in the liver is due to CGA and its related compounds. It also changes lipid metabolism and glucose in healthy as well as genetically metabolic-related disorders.[2][6][28][31][32][38]

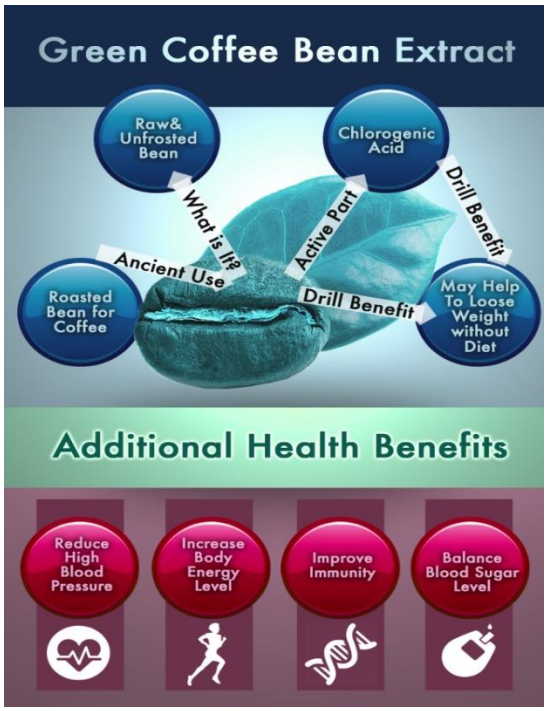

Fig 1. Green Coffee Beans Extract Health Benefits

An ester of caffeic acid and quinic acid constitutes chlorogenic acid. It is biologically active dietary polyphenol and the major polyphenolic synthesis discovered in coffee. The dicaffeoylquinic acids, caffeoylquinic acids (CQA), p-coumaroylquinic acids, feruloylquinic acids(FQA), and mixed diesters of caffeic and ferulic acids with quinic acid, each group with at least three isomers are considered the main groups of CGA found in green coffee beans. CGA may be hydrolyzed, isomerized or depraved into low molecular weight compounds during coffee processing. Roasting at high temperatures also produce remodeled part of CGA into quinolactones along with other compounds, melanoidins. CGA plays a vast role in the development of flavor, pigments, and taste of coffee beans, which defines the quality and recognition of the beverages. The connection between the formation of the CGA and the essence of coffee beans. They are known to be a significant determinant of coffee flavor and adds to the concluding acidity and bestow astringency and tartness to the beverage. It is the most ample isomer among caffeoylquinic acid isomers (3-,4- and 5-CQA), which are nowadays known as 5-CQA as per the guidelines of IUPAC. It is smoothly solvable in alcohol, acetone, organic solvents such as ethanol, DMSO (Dimethyl sulfoxide), dimethyl formamide. Solubility of chlorogenic acid in these solvents is approx 25mg/ml. Water solubility is 3.44mg/ml. Melting point 205-209 C with pka- 3.33(strongest acidic) and -3.2(strongest basic).[5][14][21][30][32][38][39]

Drug Profile:

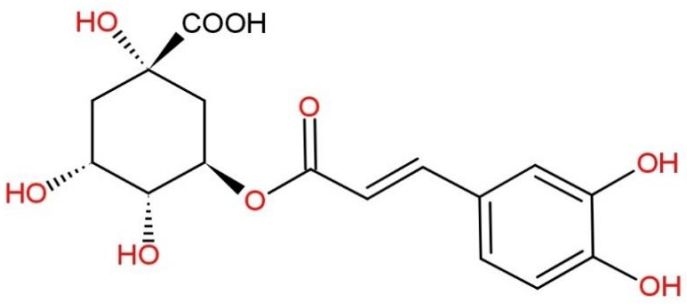

FIG 2. CHLOROGENIC ACID

CHLOROGENIC ACID

Molecular Mass: 354.31g/mol

Formula: $C_{16}H_{18}O_9$

Boiling point: 665°C

Density: 1.28g/cm

Melting point: 207 to 209°C [405 to 408°F; 480 to 482 K]

IUPAC name: (19,3R,4R,5R)-3-{[(2E)-3-(3,4-dihydroxyphenyl) prop-2 enoyl]oxy}-1,4,5-trihydroxycyclohexanecarboxylic acid

Storage: -20°C

Stability: ≥ 2 years

Protein binding: The phosphorescent quenching of human serum albumin (HSA) by CGA forms due to CGA-HSA complex. Binding parameters indicate CGA binds to HSA with the binding connections of the order 104 1 moll. The thermodynamic parameter research unveiled that the binding was portrayed by negative enthalpy and positive entropy changes and the electrostatic interactions play a significant role in CGA-HSA connection. Site I (subdomain II A) of HSA binds specifically with CGA. The tying distance r (3.10 nm) between the donor (Trp - 214) and acceptor (CGA) was obtained according to luminous reverberation energy transfer.[40]

Toxicity: Chlorogenic acid is delicate to people and results in causing asthma, dermatitis, but no this reaction to the oral of CGA. It can be quick no sensitization substances by small intestinal secretions conversion to. The toxicity of CGA is very little, LD50 is better than 1g/kg to young rats, intraperitoneal injection of better than 0.25g/kg.[38][39]

Excretion: urinary discharge rate method, the total elimination rate constant k of CGA is 0.7667.[41]

Half-life: half lifetime t(1/2) of CGA is 0.91 hours (urinary excretion rate method).[41]

Plants: Chlorogenic acid is detected in the bamboo (Phyllostachys edulis) and in plants such as the shoots of common heather (Calluna vulgaris).[39]

Food: Chlorogenic acid and the associated compounds crypto chlorogenic acid, and neochlorogenic acid have been observed in the leaves of Hibiscus sabdariffa. Isomers of chlorogenic acid are observed in potatoes. The flesh of eggplants, peaches, prunes and coffee beans have chlorogenic acid is present in them.[39]

PHARMACOLOGY- Phenolic acids have attained considerable recognition due to their numerous biological, practical, and pharmacological effects nowadays. Chlorogenic acid is an essential and biologically dynamic dietary polyphenol, playing many valuable and healing roles such as antioxidant action, antibacterial, antiviral, cardioprotective, anti-inflammatory, antipyretic, neuroprotective, hepatoprotective, anti-obesity, antimicrobial, antihypertension, free radicals scavenger and a central nervous system stimulator.[1][9][12][15][16][17] CGA can perform significant roles in lipid and glucose metabolism control and thus help in the treatment of various disorders such as hepatic steatosis, cardiovascular disease, diabetes, obesity.[1][3][22][26] CGA induces hepatoprotective effects by preserving animals from chemical or lipopolysaccharide-induced cuts or injuries. The hypocholesterolemic influence of CGA transpires by modifying the metabolism of nutrients, including amino acids, glucose, and fatty acids. [27][30][32][36]

PHARMACOKINETICS OF CGA - Most of the CGA metabolites are isoferulic, ferulic, and caffeic acid which can be noticed in blood circulation. The small intestine physiologically absorbs 1/3rd of eaten or ingested CGAs in beverages and foods which can be estimated by HPLC in the forms of 5-CQA, 4-CQA, and 3 CQA in plasma. The other two-thirds are transported into the large intestine where phenolic acid becomes considerably metabolized by

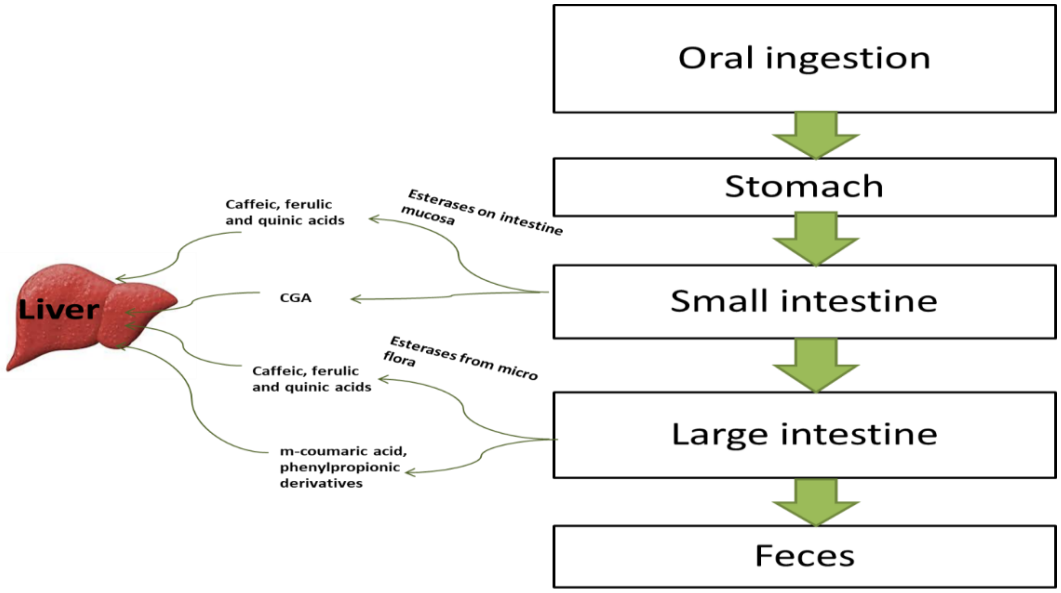

Fig 3. CGA Effect on Small and Large Intestine and Liver, Absorption of CGA when passing through Human Digestive Tract

gastrointestinal microflora and gets absorbed. The breakdown of quinic acid from feruloyl quinic acid (FQA) and CQA and the following release of ferulic acid and caffeic acid happens biochemically inside the small intestine. The colon plays an important role in the transformation of both caffeic and ferulic acid to dihydroferulic acid and also plays an influential role in its absorption. [5][7][13]

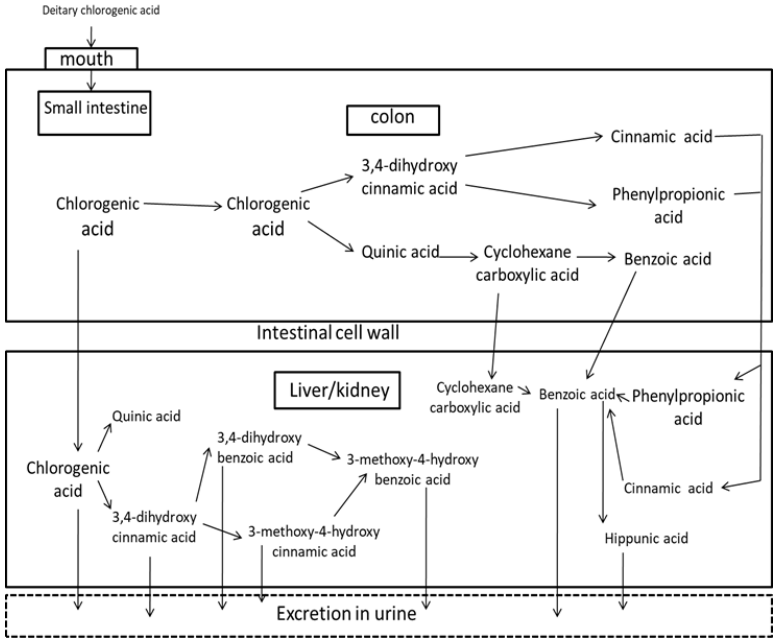

Fig 4. Metabolic Pathway of CGA in Humans

Mechanism of Action Of CGA

CGA has several forms of actions that exercise their productive activities during metabolic syndrome. [26] [32] CGA hinders oxidative stress-induced interleukin(IL)-8 generation in intestinal epithelial cells, thus defeating serious cellular injury and inflammatory intestinal diseases. [9][10] CGA restrains the hepatic Peroxisome Proliferators'-Activated Receptor y (PPARy), which promotes the FA (ferulic acid) uptake into liver cells. Thus the device of action of CGA was that CGA scavenges Reactive Oxygen Species (ROS) produced by administrating a high-fat diet, which represses the representation of redness or inflammation, leading to decline of fectinsulin resistance, fat accumulation and body weight, while hindrance of PPARy obstructs the liver steatosis.[26-27][31][33]

Few of these mechanisms have been associated with the anti-inflammatory and anti-oxidant characteristics of CGA. Oxidative pressure which is concentrated in fat has also been thought of as a prime initiator of the obesity-associated metabolic syndrome. Furthermore, chronic inflammation is also linked to metabolic syndrome. Chlorogenic acid selectively restrain hepatic glucose-6 phosphatase which is a rate-limiting enzyme included in gluconeogenesis.[9][26][32]

Orally administered CGA is metabolized to FA in the liver or kidneys. FA, a metabolite of GCE holding CGA, lowers Blood Pressure (BP) and updates vasoreactivity by working straight on the blood vessels as the agent is beneficial not only for anticipating and advancing hypertension but also for restricting arteriosclerosis. A metabolite of CGA, ferulic acid, regulates blood pressure, and works on the Nitric oxide derived from the vascular endothelium.[4][26][34-35] Blood Pressure is similar to oxidant stress so oxidant stress rises and antioxidant mechanism activities are decreased in hypertensive patients.[26][34]

The antioxidant property and metabolites of CGA enhance endothelial dysfunction, lessen blood pressure, and may also help to check stroke and other coronary heart diseases.[26][34] Chlorogenic acid fundamentally exercises its effects by repressing the enzyme α-glucosidase, which is accountable for dividing carbohydrates. It lessens the uptake of glucose and carbohydrates during digestion by doing so.[31] Chlorogenic acid has a moderate psychostimulatory outcome, one-third of caffeine and negotiated by its breakdown products, caffeic acid, and m-coumaric acid.[36]

Chlorogenic acid may also functions as:

- By Hindering 11-βHSD1 (11β-hydroxysteroid dehydrogenase type1) enzyme which is involved in producing hormones that levitate blood pressure. By stimulating the GABAa receptor by connecting to the benzodiazepine site which ends in decreased levels of anxiety.[1][36] Rising Glucose- Like Peptide 1 (GLP) hormone that raises blood insulin levels and drops glucose.[26-27][31]
- Stimulating Peroxisome Proliferator-Activated Receptor alpha (PPAR-alpha), leading to enhanced heat generation and body fat decline.[23][24][25] Reducing body fat content by lowering levels of triglycerides, LDL (low density lipoprotein) cholesterol, and VLDL (very low density lipoprotein).[3][12] Restraining the retention and production (by hindering fatty acid synthase) of fats, while improving their breakdown (by stimulating beta-oxidation).
- Hindering HMG-CoA (β-hydroxy-β-methylglutaryl-CoA), the enzyme capable of the generation of cholesterol and the central objective of statin drugs.[3][12] Advancing the continuance of dopamine-producing brain cells through the repression of microglial activation.[32]
- Hindering acetylcholinesterase, producing improved perception, consciousness, and memory. Chlorogenic acid prevents the adverse effects of the bacteria and reduces bacterial number by inhibiting the bacterial enzyme sortase A and kills bacteria by disrupting their bacterial membranes.[9]
- The antioxidant activity may be assigned to the increased production of antioxidant proteins such as glutathione and vitamins C and E. Additionally, chlorogenic acid reduces oxidative stress[10] by lowering the

levels of oxidative proteins and reactive oxygen species. CGA possesses potent antioxidant activity by increasing superoxide dismutase, catalase, and glutathione, and decreasing lipid peroxidation.[37][36]

- The topical application of chlorogenic acid have shown some evidences of prevention from skin tumor growth.[10] Topical application of chlorogenic acid can increase the process of excision wound healing by its ability to increase collagen synthesis through upregulation of key players such as tumor necrosis factor-α and transforming growth factor-β1 in different phases of wound healing as well as by its antioxidant potential.[37]
- In cell-based studies, chlorogenic acid reduces the formation of the following cancer types by inhibiting the pathways involved in tumor progression [activator protein-1, nuclear factor kappaB, mitogen activated protein kinase (AP-1, NF-kappaB, MAPK)] and destroys the cells by increasing the production of reactive oxygen species (ROS) and blocking potentially cancer-inducing proteins extracellular signal-regulated protein kinases 1& 2 (ERK1/2): lung , colon , breast , liver.[1][10][11][36]

MECHANISMS OF ACTIONS OF CGA

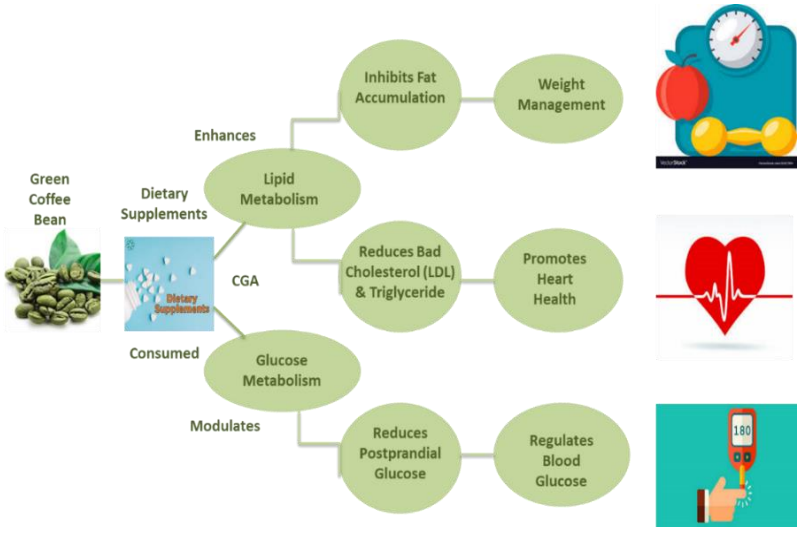

Fig 5. MOA of CGA: Enhances Lipid Metabolism and Modulates Glucose Metabolism

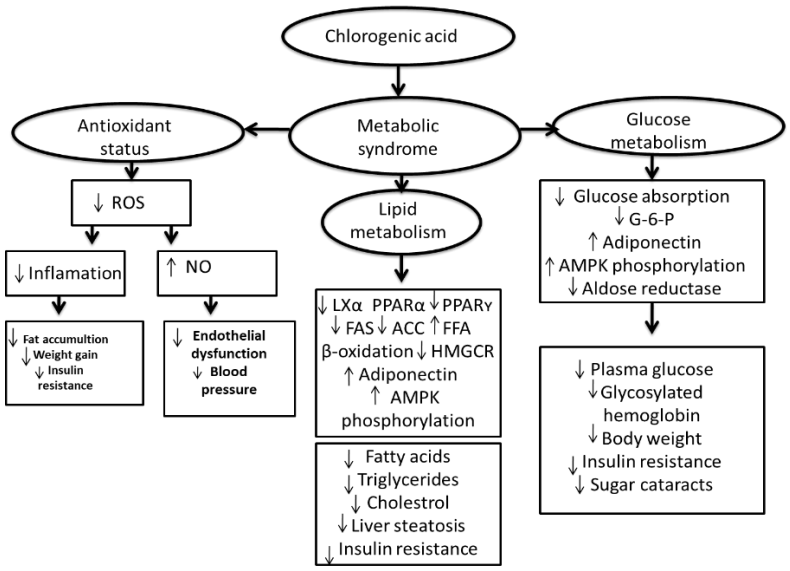

Fig 6. MOA of CGA: Antioxidant, Metabolic Syndrome, Glucose Metabolism, (AMPK= AMP-activated protein kinase, ACC= Acetyl-CoA carboxylase, FFA= Free Fatty Acid, FAS= Fatty Acid Synthase, G-6-P= Glucose-6-Phosphatase, HMGCR= 3-hydroxy-3-methylglutaryl CoA reductase, NO= Nitric Oxide, LXR α = Liver X receptor α , ROS= Reactive Oxygen Species, PPAR α = Peroxisome Proliferator-activated receptor α, PPARγ= Peroxisome Proliferator-activated receptor γ)

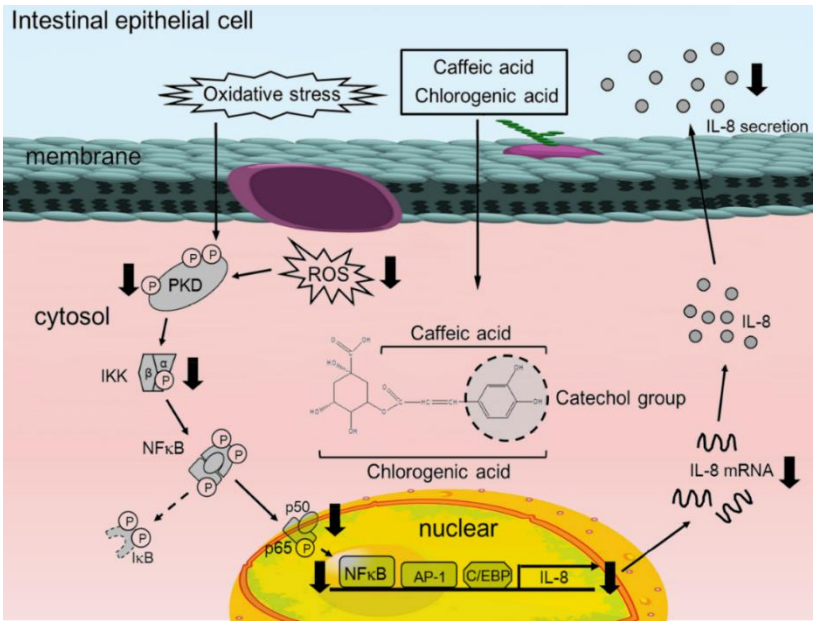

Fig 7. The Anti-Inflammatory Mechanism of Action of Chlorogenic Acid & Caffeic Acid (Intestinal Epithelial Cell)

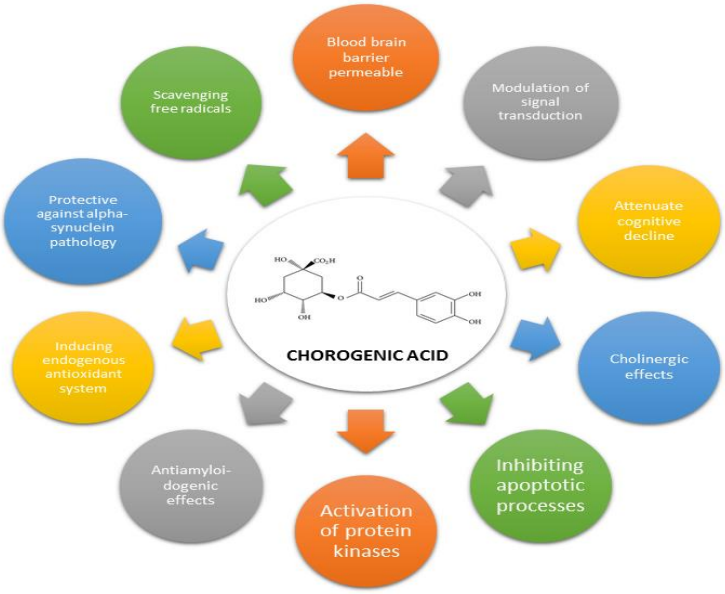

Fig 8. Protective Effects of CGA in the Central Nervous System

Side Effects:

Their extract dose up to 480 mg daily is considered safe with oral route being the safest route. There is less amount of caffeine present in green coffee than in regular coffee, however it still can cause **caffeine-induced side effects** similar to

normal coffee. Caffeine can lead to insomnia, nervousness, restlessness, digestive problems, nausea, vomiting, increased heart and breathing rate, and various other side effects.[8] Large amount of coffee intake may also lead to headache, anxiety, agitation, tinnitus, and irregular heartbeats.[1]

Some Considerable Precautions:

Abnormally high levels of homocysteine: Consuming a high dose of chlorogenic acid for a short period of time can lead to elevated plasma homocysteine levels, which may be associated with cardiac problems.[4][35]

Diabetes: Caffeine should be consumed with caution if a person have diabetes because it has been reported to be related with increase or decrease in blood sugar. Blood sugar of such patient should be monitored carefully.[35]

Glaucoma: Consumption of "green coffee contained caffeine" can increase pressure within the eye although the time duration for the increased pressure ranges within 30 minutes to 90 minutes.[35]

Hypertension: Intake of caffeine is also related to hypertension.. Although, this effect may be less in people who consume "green coffee contained caffeine" or caffeine from some other sources regularly.[26][34]

Thinning bones (osteoporosis): Caffeine from green coffee generally increases flushing out of calcium through urine that makes a person calcium deficit. A person with osteoporosis, should limit the caffeine consumption to less than 300mg/day. However, consumption of calcium supplements [23][26][32] may help to build up for lost calcium. So, a healthy person who is taking sufficient amount of calcium through his/her diet or supplements can take caffeine up to 400mg/day, i.e. 20 cups of green coffee, without increasing their chances of getting osteoporosis. Postmenopausal women with an inherited condition related to defective Vitamin D metabolism should consume caffeine cautiously. [35]

Drug Interactions:

- **Moderate**

  Be careful while taking these drugs with caffeinated green coffee

- **Adenosine**

  The caffeine present in green coffee may block the effects of adenosine. Adenosine is generally used by doctors to do a cardiac stress test. One should avoid consumption of green coffee or other caffeine-contained products at least 24 hours before a cardiac stress test.[35]

- **Alcohol**

  Consumption of green coffee along with alcohol increases caffeine levels in bloodstream and can lead to caffeine related side effects including jitteriness, headache, and tachycardia.[35

- **Clozapine**

  The body breaks down clozapine to lower down its levels in the body. The caffeine present in green coffee decreases the body breakdown mechanism of clozapine and therefore consumption of green coffee increases the effects and side effects of clozapine within the body.[35]

- **Disulfiram**

  The body breaks down caffeine in green coffee to decrease its levels it the body. Disulfiram can decrease simultaneously with the decrease in caffeine in the body. Consuming green coffee along with disulfiram might elevate the effects and side effects of green coffee including jitteriness, hyperactivity, irritability, and others.[35]

- **Ephedrine**

  "Green coffee contained caffeine" and ephedrine both act as stimulant drugs, however consuming green coffee with ephedrine may result in too much of stimulation which may further, sometimes can cause serious side effects and cardiac problems so it is advisable not to take caffeine-contained products and ephedrine together at the same time.[35]

- **Estrogens**

  The body breaks down the caffeine in green coffee to lower down its levels. Estrogens can decrease the body breakdown mechanism of caffeine. Consumption of estrogen pills and green coffee together can lead to jitteriness, headache, tachycardia and other side effects so while consuming estrogen pills caffeine intake should be limited.[35]

- **Lithium**

  Body gets rid of lithium naturally, however the caffeine in green coffee might interact with serum lithium levels. If you take caffeine containing products and lithium together, withdraw caffeine intake gradually as sudden changes in caffeine levels can fluctuate lithium levels and can increase the side effects of lithium.[35]

- **Medications for asthma (Beta-adrenergic agonists)**

  Green coffee contains caffeine. Caffeine can act as a cardiac stimulant. Some anti-asthmatic medications are also cardiac stimulant. Consumption of caffeine and anti- asthmatic medications together may increase stimulation potential and can lead to cardiac problems.[35]

- **Medications for depression (MAOIs)**

  "Green coffee contained caffeine" may stimulate the body after its consumption. Medicines used for depression might also result in stimulation of the body. Consumption of green coffee and some medicines of depression may increase stimulation and can cause serious side effects including tachycardia, hypertension, nervousness, and others.[35]

- **Medications for blood clotting (Anticoagulant / Antiplatelet drugs)**
- "Green coffee contained caffeine" can suppress blood clotting. Taking green coffee along with medications can decrease clotting potential of the body leading to increased bruising and bleeding.[35]
- **Pentobarbital**

  The stimulant effect of caffeine in green coffee can result in blockage of sleep-inducing potential of pentobarbital.[35]

- **Stimulant drugs**

  Stimulant drugs stimulate the sympathetic branch of the autonomic nervous system however acts by charging up the nervous system, stimulant medications can make you feel jittery and experience an increase in heartbeat. "Green coffee contained caffeine" can also increase the nervous system. Consumption of green coffee along with stimulant drugs might cause serious problems including tachycardia and hypertension. Intake of stimulant drugs along with green coffee should be avoided.[35]

➢ **Minor**

- **Medications for diabetes (Antidiabetic drugs)**

  Caffeine in green coffee might elevate blood sugar levels. Anti- diabetic medications are taken to lower down blood sugar levels. Caffeinated green coffee might decrease the effectiveness of anti-diabetic medications by increasing blood sugar levels in the body.. Therefore, decaffeinated green coffee should be consumed.[32]

- **Medications for high blood pressure (Antihypertensive drugs)**

  Green coffee decreases blood pressure. Taking green coffee along with anti-hypertensive drugs might cause your blood pressure to go too low. [26][34-35]

➢ **Some other interactions**

- **Bitter orange**

Bitter orange when consumed in combination with caffeine or caffeine-containing herbs, it may elevate the blood pressure and heart rate in absolute healthy adults with normal blood pressure, thus leading to possibility of serious cardiac problems. Hence, this combination should be avoided. [35]

- **Calcium**

High caffeine consumption from foods and beverages including green coffee (which contains caffeine) increases the amount of calcium flushed out in the urine. [35]

- **Ephedra (Ma huang)**

Green coffee contains caffeine, which is a stimulant. Consuming green coffee with ephedra, also a stimulant, might increase the risk of serious or life-threatening side effects such as hypertension], heart attack, stroke, seizures, and death. Consumption of caffeine with ephedra and other stimulants should be avoided.[35]

- **Iron**

Some components of green coffee like catechins may cause prevention and inhibit the iron absorption from food and digestion. Theoretically, this may lower down iron levels in the body to extremely low levels.[35]

- **Magnesium**

Consumption of large amount of green coffee can increase the amount of magnesium being flushed out in the urine.[35]

- **Interactions with foods are not known.**

DOSING: Drink green coffee preferably an hour before or after meals to maximize nutrient intake, however the appropriate dose of green coffee depends on several factors such as the user's age, health, and various other conditions. At present there is not sufficient scientific information to determine an appropriate range of doses for green coffee (in children/in adults). It should be taken into consideration that natural products are not always necessarily safe and dosages are equally important. Before consumption be sure and careful to follow relevant directions written on the product labels and the pharmacist or physician or other healthcare professional should be consulted before using it.[18]

Conclusion:

Green coffee health benefits are mostly due to its the bioactive constituent 'Chlorogenic acid' which is highly available in unroasted green coffee beans. CGA is the promising source for natural antioxidants for functional foods and nutraceuticals and can be used as an alternative to drug therapy, it is advisable to use food components for the prevention along with the treatment of hypertension. Green Coffee consumption might have a role in the reduction of cardiovascular risk factors. CGA consumption has shown anti-obesity and anti-inflammatory effects. Chlorogenic acid is an important and biologically active dietary polyphenol and plays several important therapeutic roles and is thought to have various health benefits. Side effects of green coffee consumption are mainly due to the presence of caffeine in it.

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