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REVIEW: BIOCHEMICAL STUDIES ON CHLOROGENIC ACID & ITS PHARMACOLOGICAL EFFECT

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ABSTRACT: Coffee is one of the widely consumed beverages throughout the world and it has some beneficial therapeutic effect. Chlorogenic acids (CGAs) are the most vital ingredient of coffee beans which has been extensively used in nutraceuticals, pharmaceuticals & medicine. Chlorogenic acid (CGA) is formed from esterification of caffeic acid and (−)quinic acid. CGAs are naturally found as an intermediate in lignin biosynthesis and thus are prevalent in plant kingdom. Emergence of drug resistant microorganism, innumerable side effects of drugs of cancer, blood sugar, obesity etc have triggered the idea to use naturally occurring substances with little or no side effects at all. Most of these may be used as food supplements also in order to get desired results. CGAs are one such phenolic compound found abundantly in plant which has numerous beneficial pharmacological activities. These activities include anti-microbial, anticancer, antioxidant, anti-inflammatory, anti-diabetic, anti-lipidemic antihypertensive and neuroprotective.

KEYWORDS: Chlorogenic acids (CGAs), anticancer, anti-diabetic, anti-inflammatory, anti-lipedemic, antihypertensive and neuroprotective.

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1. INTRODUCTION

Obesity is one of the most serious health issues of 21st century. In 2015, 600 million adults (12%) and 100 million children were obese. Obesity is a medical condition in which excess body fat has accumulated to the extent that it may have a negative effect on health. Obesity is stigmatized in much of the modern world (particularly in the Western world). Changes in the diet and exercising are the mainstream treatments of obesity. However, in modern lifestyle there is very little time for exercising. So dietary supplements must be given to reduce body fats. Side effects with weight loss drugs can

vary depending upon the type of drug you take and how the drug works. Stimulants-type drugs like phentermine can lead to insomnia, increased blood pressure, fast heart rate, restlessness, drug dependence and abuse, and withdrawal symptoms. Drugs that interfere with fat absorption, such as orlistat (Alli), can lead to oily spotting, gas, and soft stools. Diet pills that affect neurotransmitters in the brain, such as Belviq (lorcaserin) or Contrave (bupropion and naltrexone) can be linked with headache, nausea and vomiting, constipation, dry mouth, and dizziness. Thus, researchers have focussed on advancement of anti obesity drugs from plant sources with little toxicity. Drugs extracted from plants sources is of great importance and many plant-derived compounds like polyphenols, flavanoids and terpenoids are of enormous nutritional and medicinal value and comprehensively studied for their potential as beneficial effects on human health. When plant foods are consumed, the bioavailability of plant derived compounds may elicit a variety of important bioactivities. Recently like green tea, extract made from green coffee beans have received much interest from researchers with increasing investigation as a possible health-promoting supplement. Green coffee beans are rich source of chlorogenic acids. Chlorogenic acids (CGAs)are by products of cinnamic acid. Caffeoylquinic acids (CQA)and dicaffeoylquinic acids (diCQA) are the main CGA found in green coffee beans and it is recorded to have strong antibacterial and anti- inflammatory effects. However, the cytotoxicity effect of 5CQA on adipocyte cell lines has not been confirmed. In the present study we have made an attempt to screen antilipogenic activity of 5CQA, a decaffeinated green coffee bean extract. Even though pharmacological industries have produced a number of new antibiotics in the last three decades, resistance to these drugs by microorganisms has increased. In general, bacteria have the genetic ability to transmit and acquire resistance to drugs, which are utilized as therapeutic agents. After the revolution in the “golden era”, when almost all groups of important antibiotics (tetracyclines, cephalosporins, aminoglycosides and macrolides) were discovered and the main problems of chemotherapy were solved in the 1960s, the history repeats itself nowadays and these exciting compounds are in danger of losing their efficacy because of the increase in microbial resistance. Currently, its impact is considerable with treatment failures associated with multidrug- resistant bacteria and it has become a global concern to public health. The problem of microbial resistance is growing and the outlook for the use of antimicrobial drugs in the future isstill uncertain. Therefore, actions must be taken to reduce this problem, for example, to control the use of antibiotic, develop research to better understand the genetic mechanisms of resistance, and to continue studies to develop new drugs, either synthetic or natural. The ultimate goal is to offer appropriate and efficient antimicrobial drugs to the patient. For a long period of time, plants have been a valuable source of natural products for maintaining human health, especially in the last decade, with more intensive studies for natural therapies. The use of plant extracts and phytochemicals, both with known antimicrobial properties, can be of great significance in therapeutic treatments.

2. Chlorogenic acid

CGA also called Cyclohexanecarboxylic acid, 3-[[3-(3,4- dihydroxyphenyl)-1-oxo-2-propenyl]oxy]-1,4,5-trihydroxy-, [1S-(1 ,3ß,4 ,5)-(9CI), is a biologically active polyphenol formed by an ester bond between caffeic acid and quinic acid[1]. Chlorogenic acid is formed as the by-product of cinnamic acid and functions as an intermediate in lignin biosynthesis [2]. The term "chlorogenic acids" typically includes at least five groups of isomers including caffeoylquinic acids, dicaffeoylquinic acids, and feruloylquinic acids.Upon oxidation chlorogenic acid dispense green colour hence the name. Isomers of chlorogenic acids are formed by the esterification of the caffeoyl group at different hydroxyl group on the quinic acid ring [3].

Seven such Caffeoylquinolic acid has been reported which are formed by the addition of one or more than one Caffeoyl groups at distinct position of the quince acid ring. These isomers are namely : 1-O-caffeoylquinic acid, 4-O-caffeoylquinic acid, 5-O-caffeoylquinic acid, 1,5-O-di-caffeoylquinic acid, 1,3-O-di-caffeoylquinic acid, 4,5-O-di-caffeoylquinic acid and 1,3,5-O-tricaffeoylquinic acid [4].

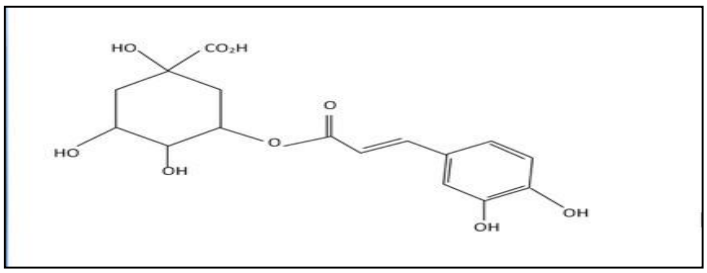

Figure 1: Caffeoylquinolic acid (Chlorogenic acid)

3. Natural occurrence of Chlorogenic acid

Chlorogenic acid is widely distributed in the plant kingdom as an antioxidant. Green coffee and green tea contains a tremendous amount of chlorogenic acid. Others include dicotyledonous plants (*Caprifoliaceae, Compositae, Cruciferae, Cucurbitaceae, Labiatae, Leguminosae, Polygonaceae, Saxifragaceae, Solanaceae, Theaceae, Umbelliferae, and Valerianaceae*), vegetables (Chinese, red, savoy, and white cabbages, carrots, cauliflower, celery, kale, kohlrabi, eggplant, lettuce, onions, peas, sweet peppers, potatoes etc), fruits (blueberries; black, red, and white currants; green, yellow, and red gooseberries, grapefruits, lemons, oranges; strawberries, sweet melons; and watermelons) and medicinal plants (*B. folium, O. folium, and S. herba*) [5-7].

4. Biosynthesis of Chlorogenic acid

Coffee plants especially coffea Arabica synthesise various isomers of chlorogenic acid namely CQA, diCQA, FQA. The most abundant of them is the 5CQA. Structurally, chlorogenic acid is the ester formed between caffeic acid and the 3-hydroxyl of L-quinic acid [8]. The caffeoyl part of 5CQA is formed viathephenylpropanoid pathway derived from phenylalanine (Hahlbrockand Scheel, 1989). The biosynthetic precursor of chlorogenic acid are derivatives of hydroxycinnamoyl-CoA (derived from cinnamic acid) namely, 4-coumaroyl-CoA. Caffeoyl-

CoAor 4-coumaroyl-CoA is combined with quinicacid,which is derived by the shikimic acid pathway(Gamborg, 1967). The hydroxylation of the coumaryl ester, i.e. installing thesecond hydroxyl group, is catalyzed by acytochrome P450 enzyme [9]. The pathway which operates in coffee plants suggested the formation of 5CQA via phenylalanine →5 cinnamic acid → 4-coumaric acid →5 caffeic acid →5 caffeoyl-CoA → 5CQA.One of the first enzymes involved in the conversion of phenylalanine to 5-cinnamic acid is PAL (Phenylalanine ammonia lyase). 4-coumaroylester 3-hydroxylase then catalyzes the conversion of 4- coumaric acid/4-coumaroylester to caffeic acid/ caffeoylester. Other participating enzymes in CQA and FQA biosynthesis include hydroxycinnamoyl-CoA shikimate/quinate hydroxyl cinnamoyl transferases. These enzymes have broad substrate specificity, including p-coumaroyl-CoA, caffeoyl-CoA, and feruloyl-CoA. 5-CQA appears to be formed from caffeoyl-CoA via feruloyl-CoA. Biosynthesis of chlorogenic acids seems to be controlled by the activity of the phenylpropanoid pathway and the shikimic acid pathway [10, 11].

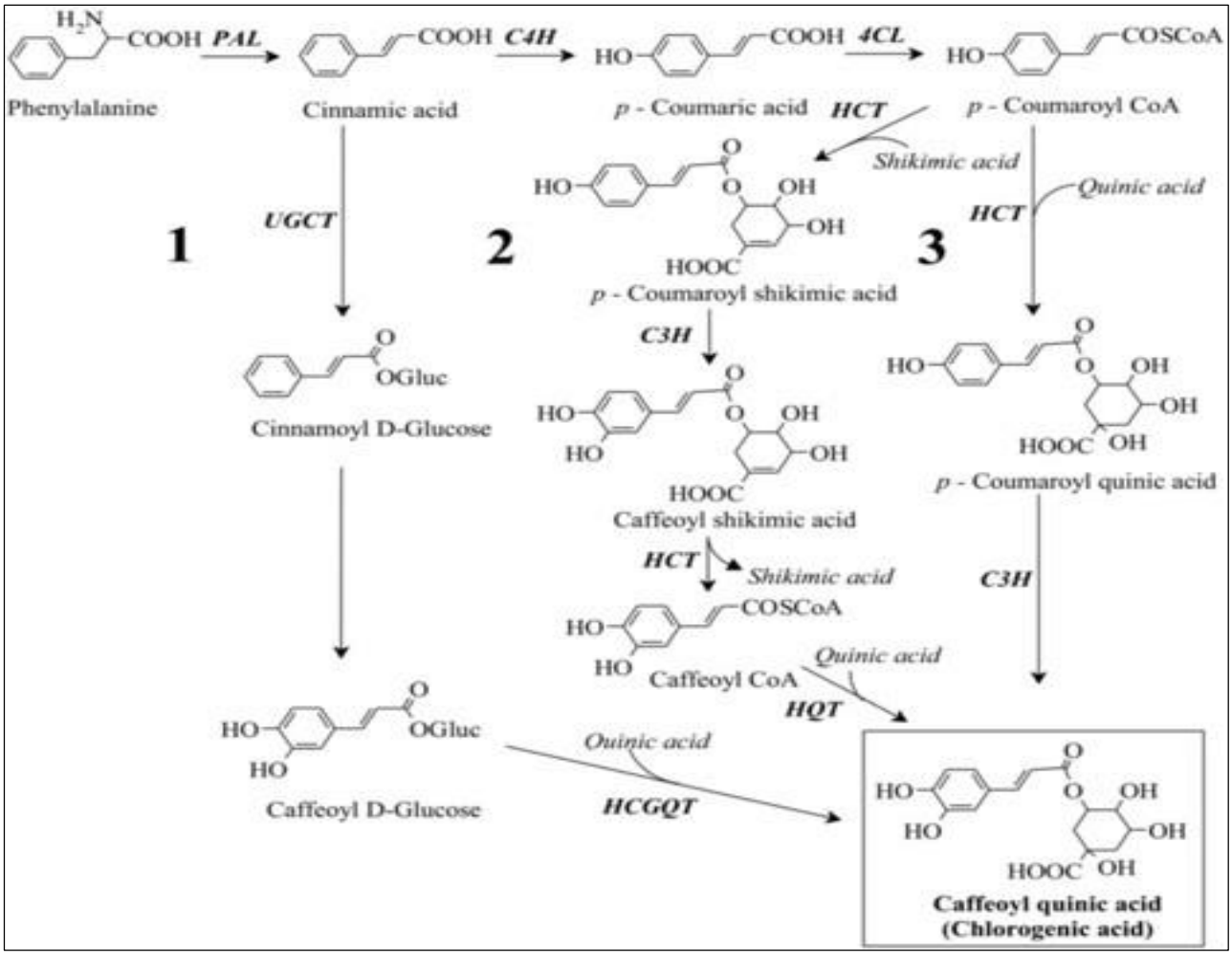

Figure 2: Biosynthesis ofChlorogenic acid [32]

5. Therapeutic / Pharmacological effects of Chlorogenic acid

Chlorogenic acid, like many other plant derived compounds, exerts a wide range of pharmacological activities which can be exploited as therapeutic equivalents to that of commercial

drugs.

The following are the therapeutic uses if chlorogenic acid:

a) Chlorogenic acid as an anti-diabetic and anti-obesity supplements

Metabolic disorders of glucose and lipids are intertwined with occurrence amelioration of obesity, diabetes, hepatic steatosis, cardiovascular disease, and cancer. Intracellular glucose and lipid metabolic homeostasis is thus indispensable for basic functioning of cells and thus of organism [12]. Chlorogenic acid or CGA has been postulated to modulate glucose and lipid metabolism in vivo in both healthy and genetically metabolic disordered conditions [13-15].

The following table summarizes the mode of action of CGA on glucose and lipidmetabolism:

Table 1a: Effect of Chlorogenic acid on glucose metabolism

Effect On Glucose Metabolism	
Effects	Mode of action
Hypoglycemic and Antidiabetic Effect	In a research conducted by Bassoli et al it was found that CGA encouraged the reduction in the plasma glucose peak by attenuating intestinal glucose absorption demonstrating the effect of CGA as a glycaemic index lowering agent thus reducing the liability of T2 diabetes mellitus [16].Anti diabetic effect is endeavoured by stimulating uptake of glucose in both insulin-sensitive and insulin-resistant adipocytes by enhancing the uptake of 2-[N-(7-nitrobenz-2-oxa-1,3-diazol-4-yl)amino]-2-deoxy-d-glucose(2-NBDG)[17].
Stimulation of Insulin Secretion	In a study conducted by Touch et al., it was recounted that CGA increased glucose uptake in L6 muscular cells and also stimulates insulin secretion from the INS-1E insulin-secreting cell line and rat islets of Langerhans[18].
Improving Glucose Tolerance and Insulin Resistance	CGA improves Glucose tolerance and Insulin resistance by the following mechanism: - Improvement of Cellular Mechanisms - Inhibition of the Activity ofα-Glucosidase - Alteration of GIP Concentrations - Activation of AMPK - Inhibition of HMG CoA Reductase - Strengthening the Activity of Carnitine PalmitoylTransferase - Inhibition of G-6-Pase Expression and - Up regulation of Expression of Hepatic PPAR-α[19].

Table 1b: Effect of Chlorogenic acid on lipid metabolism

Effect On Lipid Metabolism	
Effects	Mode of action
Lowering Serum and Hepatic CG and TG Levels	CGA are hypoglycemic agents and may affect lipid metabolism by decreasing plasma cholesterol, triacylglycerol and liver triacylglycerolsconcentrations significantly [13].
Reducing LDL Oxidation Susceptibility and Decreasing LDL-Cholesterol and MDA Levels	CGA sway the effects of cardiovascular risk by reducing LDL oxidation susceptibility and decreasing LDL-cholesterol and malondialdehyde (MDA) levels [20-21].
Inhibiting Fat Absorption and Activating Fat Metabolism in the Liver	CGA inhibits fat absorption and activation of fat metabolism in liver [22].
Improvement of Obesity- Related Hormones Levels	Chlorogenic acid significantly inhibited fatty acid synthase, 3-hydroxy-3-methylglutaryl CoA reductase, and acyl-CoA cholesterol acyltransferase activities, while they increased fatty acid beta-oxidation activity and peroxisome proliferator-activated receptors alpha expression in the liver compared to the high-fat group [23].

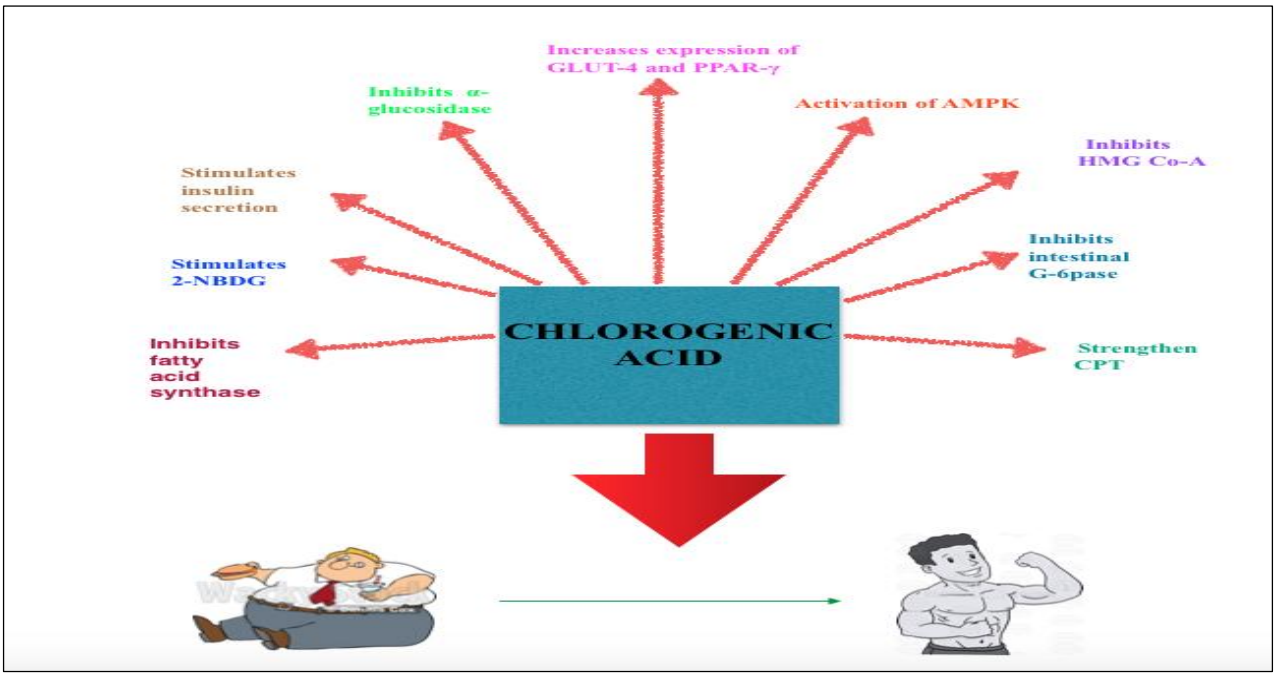

Figure 3: schematic diagram on effect of Chlorogenic acid on glucose and lipid metabolism

Abbreviations: 2NBDG-2-[N-(,3-diazol-4-yl) amino]-2-deoxy-d-glucose; AMPKAMP activated

protein kinase; HMG Co-A-β- hydroxyl-β-methyl glutaric acyl coenzyme A reductase; G-6pase-glucose-6-phosphatase; CPT- carnitine palmitoyl transferase.

a) Chlorogenic acid as an anticancerous supplement

In recent years, the cogency of chlorogenic acid in anti cancerous activity which is customarily accompanied with low toxicity has been widely studied. Yuan Yan *et al.,*, designed an experiment using human HCC cell lines, HepG2 and Hep3B, and observed the 5-FU-induced inhibition of HCC cell proliferation. The combined treatment of 5-FU with CGA enhanced this inhibition. 5-FU stimulated the overproduction of ROS, and the combination of 5-FU and CGAled toanevenmore prominent overproduction of ROS. Moreover, the combination of 5-FUandCGA led to inactivated ERK1/2. CGA could enhance the 5-FU-induced inhibition of HCC cell proliferation by the inactivation of ERK1/2 through the overproduction of ROS [24]. Apoptosis can be divided into caspase-dependent and -independent and mitochondria- dependent and -independent signal pathways [25, 26]. Chlorogenic acid induced apoptosis through the activation of caspase-3 [27]. It has also been reported that agents which induce apoptosis can be divided into mitochondria-dependent and - independent pathways [26]. Chlorogenic acid induced apoptosis in U937 cells through a mitochondria-dependent pathway [27]. CGA potentially affect the cell survival by disrupting the mitochondrial structure and metabolism [28, 29]. LDH assays have been used to determine cell-mediated cytotoxicity and also to identify mediators that induce cytolysis [30]. LDH is a soluble cytoplasmic enzyme that is present in most of the cells and is released into blood stream or extracellular space when the plasma membrane is damaged. The leakage of LDH is another marker of cytotoxicity; treatment of HCT-116 cells with CGA7 resulted in insignificant concentration dependent increase in the LDH levels in cell culture supernatant. This indicates that the cytotoxicity of CGA7 against HCT-116 cells might be attributed to the cell membrane destructive effects of CGA7 [2]. CGA7 induced activation of PARP-1, and caspase 9 (the proteins which are activated during apoptosis) in a dose dependent manner [2]. PARP-1cleavage is reported as a marker for apoptosis and is one of the important targets for caspases [31, 33]. In the study conducted by K. Goutham chandra et al., it was observed PARP-1 cleavage and Caspase 9 activation demonstration that CGA7 triggers activation of mitochondrial pathway of apoptosis [2].

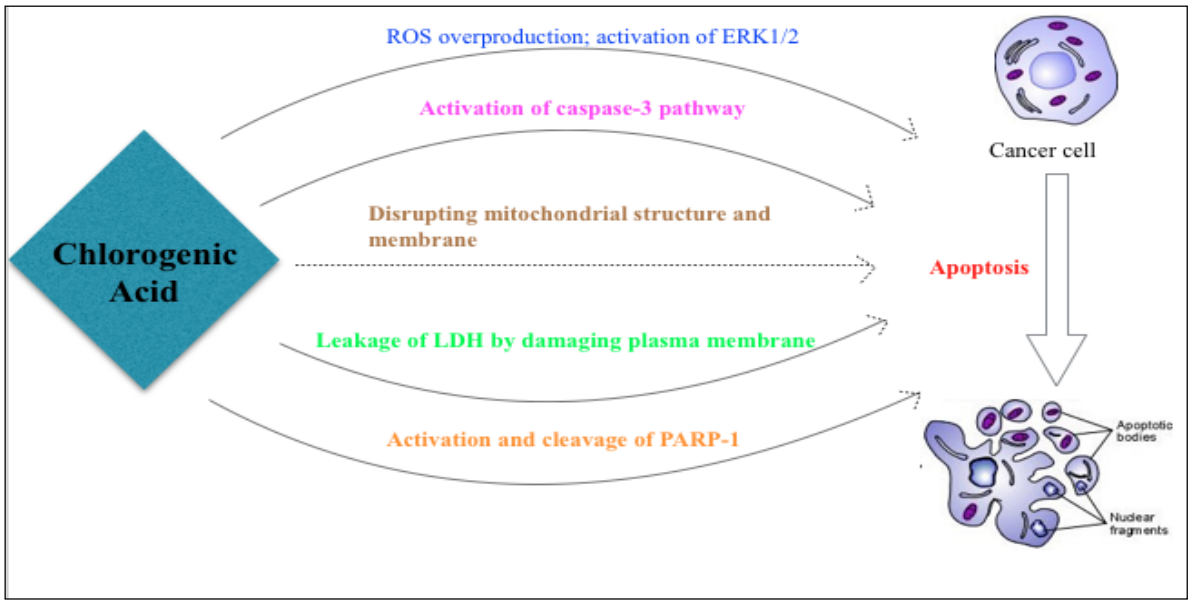

Figure 4: Chlorogenic acid induced apoptosis.

b) Chlorogenic acid as an antibacterialsubstance

Chlorogenic acid (CGA) which is a nonvolatile organic acid found in coffee, inhibit thegrowth of some Gram-positive microorganisms such as *Staphylococcus aureus, Bacillus cereus, Lactobacillus bulgaricus, Streptococuslactis and Streptococcus faecalis*and Gram-negative bacteria like *Escherichia coli, Salmonella typhi*and *Pseudomonasauerginosa.* The outer membrane of Gram negative bacteria consists of lipopolysaccharides and carbohydrates and requires divalent cations to maintain the integrity of the cell membrane. Chlorogenic acid because of its negative surface charge, binds to the OM by electrostatic interactions and chelate Mg2+, disrupting the OM, leading to the loss of the barrier function. Chlorogenic acid probably acts on the plasma membrane by increased permeabilization. Chlorogenicacidfirstdisruptsthecellmembrane permeability andthen depolarizes thebacterialcell membrane. Nucleotide leakage experiments elucidated that chlorogenic acid increased the membrane permeabilization, and caused the leakage of nucleotide[31].

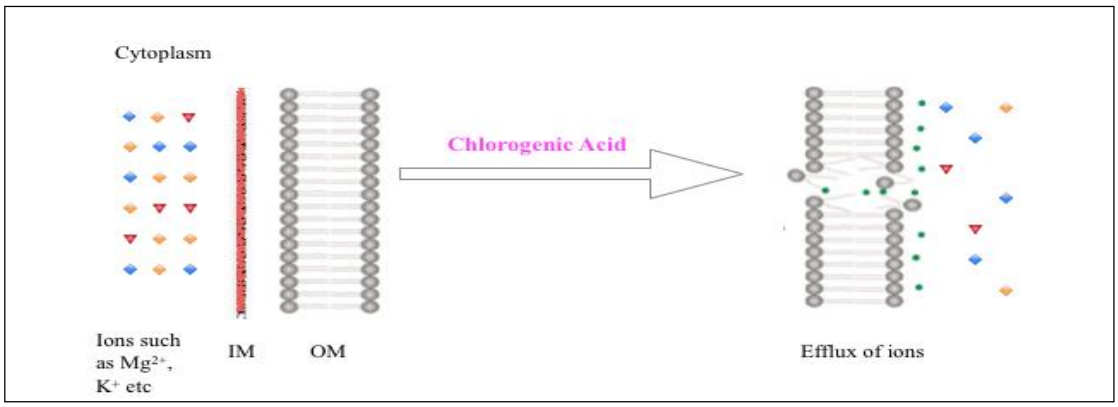

Figure 5: Chlorogenic acid induced membrane permeabilization.

Abbreviations: IM- Inner membrane, OM- outer membrane.

c) Chlorogenic acid helps to regulate blood pressure in hypertensivepeople

In a clinical trial conducted by Takuba *et al.,* Chlorogenic acid in which a depressor effect of CGA was shown in patients with mild hypertension. The resulting hypotensive effect of CGA was due to NO mediated vasodilation [33] thus inducing muscle cell relaxation and blood vessel dilation. NO deficiency leads to hypertension and CGA intake improves NO bioavailability in hypertensive patients[34].

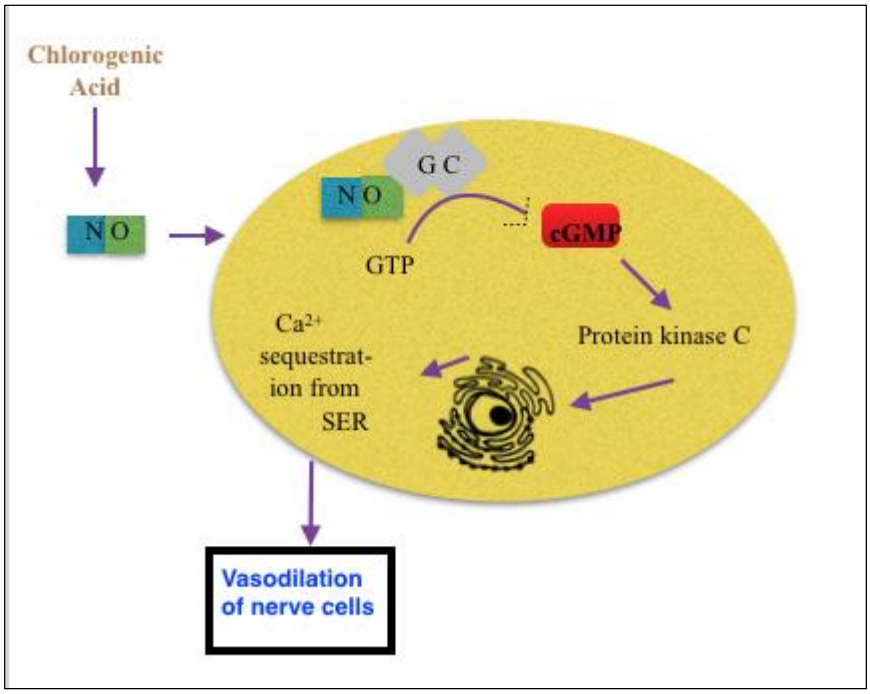

Figure 6: Vasodilation induced by CGA in smooth muscle cell

Abbreviations: NO- Nitric oxide, GC- Guanylyl cyclase, cGMP- cyclic Guanosine monophosphate, SER- Smooth endoplasmic reticulum.

d) Chlorogenic acid as an anti-inflammatoryagent

In a study conducted by S.J Hwang *et al.,* CGA treatment was given to inflamed RAW 264.7cells. [RAW 264.7 cells were previously swollen from treatment with lipopolysaccharide. In contrast to normal cells, CGA treatment to LPS-induced inflammation cells reduces inflammation by decreasing NO production mediated by down-regulation of iNOS. In addition to reducing NO concentration it also suppresses pro-inflammatory cytokines such as IL-1b, TNF-a, and IL-6, as well as the chemokine CXCL1 through down-regulation of NF-KBand inhibition of Ninj1, which is important for leukocyte infiltration [35]. Thus, Chlorogenic acid is a conjectural anti-inflammatory drug for regulating the adhesion and trafficking of leukocytes in leukocyte-mediated inflammatory diseases.

e) Chlorogenic acid has Neuroprotectiveeffects.

Chlorogenic acid can convalesce brain function and neurodegenerative disorders. In a study conducted by S.H Kwon *et al.,* scopolamine-induced amnesic mice were treated with chlorogenic acid. CGA administration significantly inhibited acetylcholinesterase in hippocampus and frontal

cortex in a dose dependant manner. Moreover, the antioxidant property of CGA ameliorated the oxidative stress which significantly contributes to the perturbations and calcium homeostasis andsubsequent apoptosis as seen in Alzheimer's patients [36]. In a study conducted by Shen et al.,, CGA significantly suppressed NO production and TNF- α release in LPS-stimulated primary microglia. In addition, CGA decreased LPS-stimulated phosphorylation and degradation of inhibitory kappa B-alpha (IκBα), and prevented translocation of nuclear factor-kappaB (NF-κB). Furthermore, CGA prevented neurotoxicity caused by microglial activation and ultimately improved survival of dopaminergic (DA) neuron [37]. Chlorogenic acid prevented the toxic effects of alpha-synuclein, the protein implicated in the destruction of dopamine-containing neurons and the development of Parkinson's disease [38].

Table 2: Summarization on the therapeutic effect of Chlorogenic acid

Main role	Effects	Molecular mechanism
Anti diabetic and Anti obesity	**Hypoglycemic and Antidiabetic Effect**	⏎[N-(7-nitrobenz-2-oxa-1,3-diazol-4-yl)amino]-2-deoxy-d-glucose(2-NBDG)
	Stimulation of Insulin Secretion	↑ Insulin
	Improving Glucose Tolerance and Insulin Resistance	✓ AMPK; ✕HMG Co-A; ✕G-6-Pase; ✓PPAR-α .
	Lowering Serum and Hepatic CG and TG Levels	↓ cholesterol, triacylglycerol and liver triacylglycerols
	Reducing LDL Oxidation Susceptibility and Decreasing LDL-Cholesterol and MDA Levels	↓ LDL-cholesterol and malondialdehyde (MDA)
	Inhibiting Fat Absorption and Activating Fat Metabolism in the Liver	↓fat absorption; ↑fat metabolism
	Improvement of Obesity-Related Hormones Levels	↓ fatty acid synthase, 3-hydroxy-3-methylglutaryl CoA reductase, and acyl-CoA cholesterol acyltransferase
Anti cancerous	**Apoptosis by ROS overproduction**	↑ROS; ✓ERK 1/2

	Apoptosis by caspase pathway	↑Caspase 3; ↓ Caspase 9.
	Apoptosis by mitochondria dependent pathway	☒ mitochondrial membrane & metabolism
	Apoptosis by damaging plasma membrane	⦸↑ LDH &☒plasma membrane
Antibacterial	**Permeablization of membrane**	☒Outer membrane ⦸ Mg2+
Lowering blood pressure	**Vasodilation**	↑ NO production
Anti-inflammatory	**Suppression of pro-inflammatory substances**	↓NO production; downregulation iNOS;↓IL-1b , TNF-a , and IL-6 & chemokine CXCL1; down regulation NF- KB; ✕Ninj1

Symbolic representation: (↑) increase; (↓) decrease;(↩) uptake; (⦸) leakage/chelate; (☒) disruption; (✕) inhibition; (✓) activation.

2. CONCLUSION

Our present study strongly suggests a generalized relation of the naturallyoccuring compound in green coffee beans, chlorogenic acid and its beneficial biological activity. The presence of chlorogenic acid, a phenolic compound, in green coffee possessesanti-oxidant, antibacterial and lipolytic activity. Chlorogenic acid has many freehydroxyl groups which is responsible for its remarkable antioxidation properties.Chlorogenic acid is capable of scavenging ROS and thus reducing oxidative stresses thuscan render a wide variety of pharmacological activity such as cardioprotective,renoprotective, hepatoprotective etc. Green coffee bean extract also inhibits the growthof pathogenic microorganism as was observed during antibacterial study. Like antibioticschlorogenic acid inhibits the growth of microorganism by altering membranepermeability. In Well diffusion antibacterial assay clear zone of inhibition can beobserved. Chlorogenic acid is both effective against Gram positive and Gram negativepathogenic bacterial strains. The lipolytic assay of purified sample exhort the fact thatchlorogenic acid also possess lipolytic activity and thus theorising the fact thatconsumption of green coffee will allow an individual to lose weight faster than usual and also renders the patient free from diabetes. Chlorogenic acid have huge impact on fatmetabolism. It inhibits the expression of certain enzymes of different lipid biosyntheticpathways such as HMG Co-A reductase, fatty acid

synthase and acyl Co-Aacyltransferase as well as induces lipid catabolism in liver. Thus chlorogenic acid couldact as a dietary supplement which can implement a wide variety of health benefits toindividuals such as antidiabetic, antiobese, anticancerous, antibacterial, reduceshypertension, anti-inflammatory and also has neuroprotective effects.

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CONFLICT OF INTEREST

Author doesn't have any conflict of interest regarding this present study.

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