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REVIEW ARTICLE

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Health Benefits of Green Coffee Beans

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ABSTRACT

Green coffee beans are coffee seeds (beans) of Coffee fruits that have not yet been roasted. The roasting process of coffee beans reduces the amounts of the chemical chlorogenic acid. Therefore, green coffee beans have a higher level of chlorogenic acid compared to roasted coffee beans. Chlorogenic acid together with caffeine in green coffee are thought to have many health benefits including anti-obesity,anti-tumour, anti-diabetic, anti-hypertensive, anti-inflammatory and anti-microbial effects.Also green coffee and its active ingradients may provide a non-pharmacological and non-invasive approach for treatment and prevention of some chronic abnormalities as Alzheimer's and Parkinson's diseases. In this review, the health benefits of green coffee and its main components eg. chlorogenic acids will be detailed.

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Introduction

Coffee is a very common plant consumed by many societies all over the world. Moreover, beans of coffee are rich source of phytocompounds with noted high antioxidant activity. The phenolic compounds like chlorogenic acids found in coffee beans have been testified to have many beneficial effects like anti-obesity, anti-diabetic, antioxidant, anti-inflammatory, antimicrobial, antihypertensive, anti-cancer and neuro-protective effects [1-8]. Green coffee beans are unroasted coffee beans. They are naturally green, but the roasting process turns them brown . Coffee beans are rich in antioxidants and other pharmacologically active compounds. Researchers believe that chlorogenic acids mainly and caffeine to lesser extent are responsible for many of the health benefits associated with green coffee beans [9]. Green coffee extract contains chlorogenic acids, which are a group of antioxidant compounds that scientists believe may be responsible for most of its health effects. Because of the chemical changes during roasting, coffee beans have some different effects on the body when roasted or unroasted. Unfortunately, most of the chlorogenic acids are lost when people heat coffee beans to very high temperatures. However, roasted coffee still contains many other healthful compounds. There is much less caffeine in green coffee than in roasted coffee, but green coffee can still cause caffeine-related side effects similar to the regular coffee [10]. There are numerous studies conducted to show the health benefits associated with the consumption of green coffee and its active components. For this reason this article was reviewed to show the health effects of green coffee and the possible mechanisms of action.

Chlorogenic Acids

Chlorogenic acids (CGAs) are important biologically active dietary polyphenols produced by certain plant species and are the major components of green unroasted coffee. The intestinal epithelium is a tissue responsible for the absorption of dietary components, and intestinal epithelial cells are always exposed to high concentrations of dietary polyphenolic compounds, including CGAs, when foods, such as coffee and fruits, are frequently consumed. CGA is absorbed, not only in its intact form, but also in its hydrolysed forms, caffeic acid (CA), Ferulic acid (FA), and quinic acid (QA), by mucosal and/or microbial esterase in the intestinal tract(11). Reduction in the risk of a variety of diseases following CGAs consumption has been mentioned in recent basic and clinical research studies.

Chemical Composition and Metabolism of Chlorogenic Acids

Chlorogenic acids are a family of esters formed between quinic, p-coumaric and trans-cinnamic acids, which are an important group of dietary phenols. There are three major classes of chlorogenic acids present in green coffee beans, namely: caffeoylquinic acid (CQA), di-caffeoylquinic acid (diCQA) and feruloylquinic acid (FQA). Another pivotal component of the green beans is cinnamic (caffeic) acid (CA) [12].

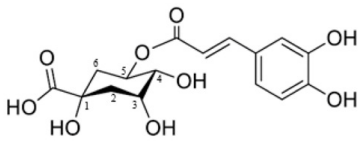

Figure 1: Chemical Structure of Chlorogenic Acid (CQA)

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The most common individual chlorogenic acid is caffeoylquinic acid (CQA), which is still often called chlorogenic acid. Unroasted coffee beans represents the richest dietary source of chlorogenic and caffeic acids [13]. Studies in colostomy patients indicate that about 33% of ingested chlorogenic acid and 95% of caffeic acid are absorbed intestinally. Thus, about two thirds of ingested chlorogenic acid reaches the colon where it may be metabolized by the colonic microflora, resulting in compounds such as hippuric acid, caffeic acid, and ferulic acid .Therefore, it is possible that the positive effects of chlorogenic acid on human health could be due to these metabolites [14]. For instance, it has been suggested that ferulic acid, one of the metabolites of chlorogenic acid, could be the cause of the hypotensive effects observed in humans after consumption of green coffee bean extract (GCBE) , as it is known that ferulic acid can scavenge superoxide anions and has shown hypotensive effects in rats [13]. Green coffee contains also macro nutrients such as carbohydrates, protein, fat, beside the minor components such as caffeine, trigonelin and chlorogenic acid. polypehonic materials found in green coffee especially chlorogenic acid have an important role due to its high antioxidant activity [15].

Health Benefits of Green Coffee and its Active Components

Weight Loss

Green coffee became popular for weight loss since few years ago, GCBE may be an effective weight loss aid as it was found that the body fat mass of mice fed with GCBE decreased significantly even with a high dietary fat. Also, rats showed a decrease in weight gain, liver weight and supression in rates of adipogenesis [16]. Another study showed that CCBE taken daily for 8 weeks decreased significantly the body weight and BMI in meta-analysis of randomized clinical trial [17]. Decaffeinated green coffee bean extract was found to attenuate diet-induced obesity and insulin resistance in mice [18]. Several studies and reviews have shown that green coffee bean extract (GCBE) may help people to lose weight. In a study done on females with obesity, taking 400 mg of green coffee bean extract for 8 weeks, along with an energy-restricted diet, resulted in more weight loss than following an energy-restricted diet alone [19]. Chlorogenic acid in decaffeinated green coffee supplementation was found to decrease body weight and BMI about twice as much as the placebo by inhibiting adipogenesis and by contributing to the evident loss of appetite, which was evaluated through a scored questionnaire [20]. Also it is suggested that caffeine, chlorogenic acid and other polyphenolic compounds in (GCBE) act synergistically to suppress body weight gain and visceral fat accumulation in mice [21]. GCBE was found to be effective against weight gain and fat accumulation by inhibition of intestinal fat absorption and activation of fat metabolism in the liver. Caffeine was found to be a suppressor of fat absorption, while chlorogenic acid was found to reduce hepatic triglyceride (TG) levels [22]. Further studies were prompted to examine the anti-obesity effect of GCBE on dietary fat absorption using olive oil-loaded mices. The elevated serum TG level was lowered by GCBE and caffeine in olive oil-loaded mices [23]. Phenolic compounds as chlorogenic acid can enhance the enzyme hepatic carnitine palmitoyl transferase (CPT) activity and inhibit the enzyme glucose-6-phosphatase leading to increased fatty acid oxidation, decreased gluconeogenesis and prevention of fat accumulation in liver [24]. On the other hand, it was found that caffeic acid promotes lipolysis in rat adipocytes and reduces adipogenesis, as well as genes and proteins associated with lipid metabolism in white adipose tissue and liver, leading to loss of body weight [25]. A recent study showed that GCE supplementation had a beneficial effect on body weight(BW),body mass index (BMI) and waist circumference (WC), it provided a cost-effective and safe alternative for the treatment of obesity [26]. Another study showed that high fat diet (HFD) induces obesity in male rats, and the administration of GCBE resulted in weight loss in these obese rats [27]. In another study in mice given high fat diet and GCBE at a dose of 100–200 mg/kg BW, showed that GCBE supplementation decreased body weight gain, the observed anti-obesity effect may be due to reduction in triglyceride levels in the blood and liver as a result of suppressing lipogenesis and stimulating lipolysis [28]. The slimming role of CGA was shown to be inhibiting adipogenesis in 3T3-L1 preadipocyes by interrupting insulin signaling through the downregulation of IRS1, and also by contributing to appetite control [29]. CGA showed promises as an anti-obesity agent. It primarily activates the AMP activated protein kinase, inhibits 3-hydroxy 3-methylglutaryl coenzyme-A reductase and strengthens the activity of CPT with more fatty acid oxidation leading to obesity control [30]. GCBE has a potential anti-obesity effect with lowering body fat accumulation by regulating adipogenesis and lipid metabolism-related genes and proteins in white adipose tissues and liver [31]. Another study showed that the use of GCBE supplementation for treatment of obesity gave greater improvements in individuals with a starting BMI ≥25 kg/m2 [32]. Chlorogenic acid can enhance the enzyme hepatic (CPT) activity through the activation of the AMP activated protein kinase, inhibition of 3-hydroxy 3-methylglutaryl coenzyme-A reductase leading to increased fatty acid oxidation and decreased hepatic lipogenesis [33]. Treatment with GCBE was reported to improve body weight, lipid metabolism and obesity-related hormones levels in high-fat fed mice. CGA seemed to be more potent for body weight reduction and regulation of lipid metabolism than caffeic acid [34]. Increased lipid metabolism occurs through the opposing activities of liver X receptor α (LXRα) and peroxisome proliferator-activated α (PPARα), which are nuclear receptor transcription factors that are highly expressed in the liver [35].

Glucose Homeostasis and Anti-Diabetic Effects

A beneficial effects were demonstrated by CGAs on glucose homeostasis leading to hypoglycemic effects with increased insulin sensitivity. Because they can regulate glucose levels and insulin, CGAs could prevent or control type 2 diabetes T2-DM. It is reported that daily consumption of 3 to 4 cups of decaffeinated coffee containing high contents of CGA significantly reduced the risk for T2DM by 30% [36]. Moreover, diabetic animal models have revealed the occurrence of high oxidative stress due to chronic and persistent high blood glucose. Several studies indicate that chlorogenic acids can potentially restore the activity of lipoprotein and lipid metabolism to normal if taken in a dose of more then 400 mg per day, it could also improve insulin sensitivity and secretion leading to correction of glucose levels in the blood [37]. The mechanisms leading to these effects are:

Decreased hepatic glucose production through the inhibition of Glucose -6-Phosphatase System by Chlorogenic Acid. The

hydrolysis of glucose-6-phosphate to glucose and phosphate represents the terminal step of the glucose-producing pathways as gluconeogenesis and glycogenolysis.Glucose-6-phosphate hydrolysis requires the coupled function of glucose-6-phosphatase, a glucose-6-phosphate translocase protein, and a second translocase protein. Chlorogenic acid has been shown to be a specific competitive inhibitor of the glucose-6-phosphate translocase in rat liver microsomes [38]. Moreover, a study reported an inhibitory effect of CGA on the postprandial blood glucose concentration in rats. Through the inhibition of the activities of α-amylase and α-glucosidase leading to reduction in the postprandial blood glucose concentration [39].

Reduced Carbohydrate Absorption in the Digestive Tract

Chlorogenic acid was found to lower blood sugar levels and reduce insulin spikes. It was found that CGA caused a significant reduction in the plasma glucose peak in the oral glucose tolerance test, most likely by attenuating intestinal glucose absorption by reduction of sodium-dependent glucose transport in the brush border membrane vesicles isolated from rat small intestine [40]. Glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) are intestinal hormones that augment insulin secretion after oral glucose consumption [41]. Consumption of green decaffeinated coffee with an oral glucose load was found to decrease plasma concentrations of GIP, which is secreted in the proximal small intestine, and to increase plasma concentrations of GLP-1, which is secreted in the distal small intestine, suggesting that chlorogenic Acid or other Phenolic compounds may slow intestinal glucose absorption [42]. GLP-1 was found also to suppresse hepatic lipogenesis via activation of the AMPK pathway leading to hepatic protection from steatosis. AMP activated protein kinase (AMPK) is a master sensor and regulator of cellular energy balance. It is activated by various pharmacological, pathological, and metabolic stressors such as metformin, thiazolidinediones, hypoxia and exercise. Activation of AMPK leads to translocation of GLUT4 from intracellular membranes to plasma membranes, thus increasing glucose transport [43].

Decreasing Insulin Resistance

Chlorogenic acid (CGA) is a novel insulin sensitizer that potentiates insulin action similar to the therapeutic action of metformin through stimulation of intermediary molecule thus enhances the activation of AMP-activated protein kinase AMPK [44]. It is highly possible that this molecule could be the anti-diabetic adipokine called adiponectin, which has been reported to be decreased in obesity, insulin resistance and T2DM. Adiponectin has also been shown to reverse insulin resistance [45]. More over, Adiponectin was found to enhance hepatic insulin action and increase fatty acid oxidation [46]. Consistent with this, restoration of adiponectin levels in vivo by CGA showed improved glycemia, insulin sensitivity and fatty acid metabolism [19]. Moreover, adiponectin has been demonstrated to activate AMPK via Calcium/Calmodulin-dependent Kinase Kinase (CAMKK) [47]. Therefore, restoration of adiponectin in vivo by CGA was found to enhance the activation of AMPK and resulted in the above-mentioned beneficial metabolic alterations [48].

Increased Glucose Uptake

It was found that 1 gm of CGA caused a significant reduction in early fasting glucose and insulin responses to glucose in overweight men during an oral glucose tolerance test [49]. Besides, other studies demonstrated that CGA stimulates skeletal muscle GLUT4 expression by upregulating mRNA levels of GLUT4, Consequently CGA will increase the uptake of glucose in myotubes CGA causes stimulation of glucose uptake in both insulin-sensitive and insulin-resistant adipocytes, it is unlike thiazolidinedione (TZD) or insulin, does not induce obesity or other side effects [50,51].

Stimulation of Insulin Secretion

It was found that CGA stimulates insulin secretion from the INS-1E insulin-secreting cell line and rat islets of Langerhans [52]. Also, CGA was found to stimulate GLUT4 translocation to the plasma membrane in white adipose tissue and decrease in the regulation of genes involved in adipogenesis as WNT10b, galanin-mediated and TLR-2- TLR4-mediated proinflammatory pathway [53]. All these actions of CGA will improve fasting glucose levels, glucose tolerance, insulin sensitivity and dyslipidemia. All these suggest that CGA could be the main component that contributes to the beneficial effect of green coffee in prevention of T2DM.

Hypotensive Effect

The blood pressure lowering effect of green coffee bean extracts (GCE) was first reported in 2002, when water-soluble GCE was found to decrease the blood pressure significantly in spontaneously hypertensive rats (SHR) [54]. It was found that CGA is responsible for this reduction in blood pressure due its active metabolite ferulic acid (FA) . After the injection of atropine sulphate (5mg/kg SC) the depressor effect of FA was attenuated which suggested that the hypotensive effect of FA in SHR might be mediated via the muscarinic acetylcholine receptors [55]. GCBE was found to improve the vasoreactivity in human which is proved by a clinical trial which showed that the intake of GCBE lead to decreased plasma homocysteine level which is an atherogenic stimulus, reduces protein C activation by arterial and venous endothelial cells, so it is considered as a landmark of cardiovascular risk [56,57]. When compared with other CGA metabolites, ferulic acid had the greatest effect on BP reduction [58]. In aortic rings pre-contracted with phenylephrine (an alpha-adrenergic neurotransmitter agonist), the administration of ferulic acid greatly increased NO bioavailability and enhanced acetylcholine-induced endothelial-dependent vasodilation [59].

These findings in animals were later confirmed by studies in human patients with mild hypertension. After consumption of GCE for 28 days, Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were reduced in a dose-dependent manner [60]. In another randomized, double-blind placebo-controlled clinical trial, when 480 mg per day of GCE was given in the CGA-treated group, BP was decreased significantly by 8/7 mm Hg at week 4 and by 10/7 mm Hg at week 12 from baseline [61]. Also, a recent findings sshowed that 2-week ingestion of GCBE may improve the arterial stiffness as assessed by cardio-ankle vascular index [62]. A significant reduction in SBP and DBP was found in hypertensive

patients when green coffee in a dosage of 400 mg per day for 4 weeks was administered The results of that study support the use of GCBE supplementation for the improvement of blood pressure indices [63]. Several mechanisms by which CGAs or CGA metabolites cause hypotension have emerged:

Inhibition of NADPH oxidase expression and activity, therefore reducing free radical production [64].

Directly scavenging free radicals through strong anti-oxidant effect [65].

Stimulation of NO production by the endothelial-dependent pathway [66].

Inhibition of angiotensin-converting enzyme in the plasma, and possibly in the organs and tissues eg lungs [67].

Anti-inflammatory effect of CGAs is also likely to be relevant to the integrity of overall vascular function and BP regulation in the long run [68].

Anti-Dyslipidemic and Anti-Atherosclerotic (Cardio-Protective) Effects

Dyslipidemia is characterized by elevated levels of total or low-density lipoprotein cholesterol (LDL-C), triglycerides, and/or low levels of high-density lipoprotein cholesterol (HDL-C). Lipid profile is influenced by several factors including genetics, lifestyle and dietary factors. Hypercholesterolemia together with increased LDL-C levels are the major risk factors for the development of atherosclerosis, cardiovascular disease and nonalcoholic fatty liver disease [69]. CGAs are found to affect lipid metabolism, as shown in a study investigated the effects of CGA in vivo, by using obese, hyperlipidemic, and insulin resistant Zucker rats. The authors reported that CGA significantly lowered fasting cholesterol and triglycerides concentrations in their plasma and liver specimens [70]. In another study, it was found that CGA can potentially ameliorate lipid abnormalities in experimental T2DM rats [71]. It is currently believed that oxidative modification of low-density lipoproteins (LDL) by free radicals is a key early event in the pathogenesis of atherosclerosis [72]. Chlorogenic acid was found to reduce LDL oxidation susceptibility and decreasing LDL-cholesterol and malondialdehyde (MDA) levels leading to protection against cardiovascular disease [73]. It was reported that CGA is possibly effective against weight gain and fat accumulation by inhibition of intestinal fat absorption and activation of fat metabolism in the liver it also caused a reduction in the level of hepatic TG in mice [21]. CGA also lowered triglycerides (in plasma, liver, and heart) and cholesterol (in plasma, adipose tissue, and heart) concentrations. CGA significantly inhibited fatty acid synthase, 3-hydroxy-3-methylglutaryl CoA reductase, and acyl-CoA cholesterol acyltransferase activities, with increased fatty acid beta-oxidation activity [34]. Recent clinical trial demonstrated that GCBE supplementation decreased serum total cholesterol (TC), low density lipoprotein-cholesterol (LDL-C) levels and plasma free fatty acids in obese women [19]. CGA was found to Inhibit the intestinal absorption of cholesterol and its hepatic biosynthesis through inhibition of the key enzyme activities. The inhibitory effect of cholesterol absorption include decreased cholesterol micelles formation and inhibition of pancreatic lipase , while a stronger inhibitory effect on the enzyme 3-hydroxy-3-methylglutaryl-CoA HMG-CoA reductase in the liver will affect cholesterol biosynthesis [37]. Another investigation demonstrated that supplementation with chlorogenic acid caused a significant reduction in serum free fatty acid, total cholesterol, triglyceride, and a significant increase in HDL-C levels through activation of AMPK in a rat model of dyslipidemia [74]. The regular consumption of a green coffee beverage was found to decrease cholesterol in hypercholesterolemic subjects with higher cardiovascular risk it was found that, the visceral fat area, total abdominal fat area and body weight also decreased significantly in the overweight men and women [75]. It is consequently postulated that hypocholesterolemic effect is the primary beneficial effect given by CGA, which leads to further secondary beneficial effects such as atheroscleroprotective, cardioprotective, and hepatoprotective functions. It suggested that the hypocholesterolemic functions of CGA are most likely due to the increase in fatty acid utilization in the liver via the upregulation of peroxisome proliferation-activated receptor α (PPAR-alpha) mRNA. These results indicated that CGA may modify lipid metabolism, which may be attributed to PPAR-α facilitated lipid clearance in the liver and improved insulin sensitivity [76]. Another study investigated the effect of CGA on lipid metabolism of hyperlipidemic mice. It was found that the contents of serum TC, TG, LDL-C levels, and liver TC were significantly lower. Furthermore, malondialdehyde (MDA) contents in serum and liver were decreased, and activities of antioxidant enzymes were increased. Arteriosclerosis index (AI) was also lower than that of the model group. The results indicated that CGA could effectively reduce the blood and liver lipid accumulation and regulate lipid metabolism by improving their antioxidant activities [77]. Many metabolic disorders as metabolic syndrome and diabetes mellitus are associated with dyslipidemia which is a significant risk factor for cardiovascular complications. CGA was found to decrease lipids, lipoproteins, low density and very low-density lipoproteins (LDL and VLDL), respectively, and to increase the concentration of high-density lipoproteins (HDL) in diabetic rats [78].In a recent study, CGA and its metabolites CA, and FA showed anti-obesity activity and hypocholesterolemic effect as well as decreased fatty acid biosynthesis [79]. In addition, the activity of 3-hydroxy 3-methylglutaryl coenzyme A (HMG-CoA) reductase increased significantly in the liver and kidney whereas the activities of lipoprotein lipase (LPL) and lecithin cholesterol acyl transferase (LCAT) were decreased significantly in the plasma of diabetic rats [37]. Administration of CGA remarkably reduced the changes in lipids, lipoproteins, and lipid metabolising enzymes in T2DM rats. Indicating that CGA can potentially ameliorate lipid abnormalities in experimental T2DM leading to renal and hepatic protection [44]. So Green coffee extract may regulate adipogenesis, as well as genes and proteins associated with lipid metabolism in white adipose tissue and liver, leading to decreased body fat with increasing metabolic rate, energy expenditure, lipid oxidation, and lipolytic activities [18].

Anti-oxidant Effects

Oxidative stress is related to several chronic diseases, degenerative diseases, cancer, and aging. Antioxidants are valuable compounds

that inhibit/reduce the effects induced by free radicals and oxidizing agents. GCBE contains high percentage of total polyphenol antioxidants. This extract is a potent antioxidant, also a highly bioavailable ingredient for adding increased functionality to nutrition based products [80].

The antioxidant Activity of green coffee constituents like CGA, CA, and FA have been revealed to be an effective antioxidants in human studies. The possible reason for the potent activity of these phenolic acids is due to its capability to induce upregulation of cytoprotective enzymes [81]. Phenolic compounds are well known antioxidants that show various health benefits. CGA and its metabolites are of special interest due to their unique properties and their ability to fight oxidative stress by acting as a metal chelator, reducing lipid peroxidation, inhibiting NAD(P)H oxidase activity, and scavenging free radicals [82]. Ferulic acid (FA) in a combined form with metformin was found to improve the symptoms of diabetes in obese rats through alleviation of lipid peroxidation in diabetic rats by changing the expression of proinflammatory cytokines, apoptosis, and altering oxidative stress [83]. In Isolated rat hepatocytes (Ex vivo) Polyphenols including CGA, CA was found to induce hepatoprotective effects in different models of rat hepatocytes [84]. It was found that dietary intervention rich in CGA has been used as an effective therapeutic agent for prevention of diabetic nephropathy by inhibiting oxidative stress and inflammation through modulation of the Nrf2/HO-1 and NF-κB pathways [85]. Also, when diabetic rats fed with CGA, the lipid hydroperoxide was decreased, and the antioxidants such as reduced glutathione and vitamins C and E were increased [86]. In the methamphetamine-treated rats, CGA was able to reduce the oxidative stress by increasing liver superoxide dismutase and glutathione peroxidase activities and inhibiting lipid oxidation [87]. CA was found to reduce the oxidative stress in mouse hippocampus indicating that CA has the ability to maintain brain health through its antioxidant capacity [88]. Antioxidant activity of FA is one of the most well-known activities. Because it is mainly responsible for the free radical scavenging activity, this facilitates FA to protect lipids and deoxyribonucleic acid against oxidation through ROS. In addition to ROS, FA is also reported to enhance the expression level of superoxide dismutase, catalase, and antioxidant enzyme. Recently, scientists reported the high efficacy of FA and its derivatives in reducing cyclooxygenase (COX) activity and xanthine oxidase effect. It is believed that FA inhibit a number of oxygen species produced by the enzyme-catalyzed transformation [89]. Reactive oxygen species (ROS), including superoxide (O_2^-), hydrogen peroxide (H_2O_2), and hydroxyl anion (OH^-), and reactive nitrogen species, such as nitric oxide (NO) and peroxynitrite ($ONOO^-$), are biologically important O_2 derivatives that are increasingly recognized to be important in vascular biology through their oxidation/reduction (redox) potential. A positive relationship between oxidative stress and blood pressure were demonstrated in some models of experimental hypertension. For example, an upregulation of reactive oxygen species appeared to precede the development of hypertension and an antioxidant regimen arrested the process [90]. NAD(P)H oxidase-derived superoxide had a pivotal role in the regulation of vascular tone in health and disease [91]. It was found that continuous ingestion of CGAs for 8 weeks reduced NAD(P)H-dependent superoxide production in the aorta of SHR, with inhibition of p22phox gene expression [67]. Caffeic acid in particular had been shown to attenuate the proliferation of vascular smooth muscle cells to Ang. II stimulation in SHRsp leading to hypotensive effect [92]. In vascular smooth muscle cells, caffeic acid decreased the protein and enzymatic activity levels of Rac1 GTPase, a partner of NAD(P)H oxidases, either in the presence or absence of Ang. II [93].

Anti-inflammatory Effects

Since inflammation is correlated with and influenced by various cytokines and chemokines, reduction of those markers should decrease the degree of overall inflammation. Coffee beans are potentially beneficial substances because they contain compounds which all have anti-inflammatory effect leading to reduction of most inflammatory markers. Amonge those anti-inflammatory compounds flavonoids as CGAs and their metabolites together with the extracts of green coffee showed strong anti-inflammatory effect in various animal models [94]. Green coffee promotes a lower risk of chronic inflammatory conditions through reducing pro-inflammatory cytokines, and increasing serum levels of anti-inflammatory factors like adiponectin and interleukins [95]. In another study it was found that oral administration of 40 mg/kg CGA to lipopolysaccharide (LPS)-induced arthritis in rats caused inhibition of pro-inflammatory cytokines, thereby exhibiting the enhanced healing of tissue damage caused by inflammation [96]. Also, CGA was found to protect against trinitrobenzene sulfonic acid-induced colitis in mice through decreasing neutrophil infiltration and inhibiting nuclear factor kappa B (NF-κB) pathway [97]. CGA, Caffeine and CA were found to modulate inflammatory process, to accelerate wound healing in neuropathic pain and to reduce inflammation in animal models [98]. In another study, the effects of CA on cardiac tissue of diabetic mice has been shown to provide anti-inflammatory, antioxidative, triglyceride-lowering, and anticoagulatory protection of cardiac muscle of diabetic mice. Hence, the supplement of CA is helpful for the prevention/attenuation of **diabetic cardiomyopathy** [99]. In an excision wound model, FA-treated wounds were found to epithelize faster compared with diabetic wound control group [100]. In **diabetic nephropathy**, hyperglycemia increases the inflammatory responses in kidney tissues leading to accumulation of pro-inflammatory cytokines with the induction of serious changes in the glomerular filtration rate , endothelial cell permeability and generation of ROS/free radicals .Recent researches concluded that, daily intake of green coffee is recommended as part of an adjuvant nutritional plan directed to protect from diabetic progressive renal damage due to its anti-inflammatory and anti-oxidant effects [101]. It was reported that CGA is useful for protecting against chronic and acute inflammation associated diseases due to its potential therapeutic value. The most important mechanisms involved in mediating the anti inflammatory effect of it is the inhibition of inflammatory proliferation by suppressing tyrosine protein kinase-1, and inhibition of the release of proinflammatory cytokines (IL-1β &TNF-α) and other inflammatory cells [102]. In experimental acute L-arginine induced pancreatitis, treatment with CGA has clearly inhibited the production of IL-8 and the up-regulation of IL-8 mRNA expression. In fact, IL-8 plays an essential role for development of acute pancreatitis. The level

of circulating IL-8 is up-regulated in acute pancreatitis, and the change of its level affects its clinical course [103].

Anti-cancer Effects

The phenolic compound 5-CQA which is the most abundant chlorogenic acid present in green coffee was found to reduce the occurrence of chemical carcinogenesis in in vitro and in vivo models of cancer. Also high concentrations of 5-CQA was found to inhibit the growth activity of a colon cancer cell line (HT-29) and an oral cancer cell line (SCC-25), suggesting that the intake of unroasted or less roasted coffee may be associated with the prevention of oral and colon cancer [104]. The anti-cancer activity of green coffee extract on mouse and human was studied. It was found that, decaffeinated water-soluble green coffee bean extract used on human and mouse cancer cell lines. It was found that the CGA complex induced apoptosis by DNA fragmentation, PARP-1 cleavage, caspase-9 activation, and down regulation of Bcl-2, an antiapoptotic protein and up regulation of pro-apoptotic protein BAX [105]. 5-CQA was reported to inhibit the proliferation of A549 human cancer cells in vitro, moreover, suggesting that 5-CQA has potential chemoprotective activity against environmental carcinogen-induced carcinogenesis, which can be attributed, at least in part, to modulatory effects on the induction of cellular phase 2 detoxifying enzymes (such as GST and NQO1) and inhibition of ROS-mediated MAPK, AP-1, and NF-κB activation [106]. The dual signaling mechanism associated with mediating the effects of 5-CQA has been shown to affect the fate of cells: stimulating antiapoptotic signaling in the oxidative stress-induced normal cells as well as inducing proapoptotic signaling in cancer cells. In chronic myeloid leukemia (CML) cell lines and clinical leukemia samples, 5-CQA showed quite pharmacological and biological effects, including induction of cell apoptosis, early accumulation of intracellular ROS, disruption of mitochondrial membrane potential (MMP), activation of caspases and other apoptotic pathways, which may be attributed to preferential killing of Bcr-Ab+ cells [107]. Furthermore, In cancer cells, 5-CQA was found to stimulate proapoptotic signaling pathways, and to induced cell undergoing apoptosis progress. On the other hand, 5-CQA suppressed risk stress factors induced apoptosis in normal cells, promoted cellular survival by increasing antiapoptotic molecules [108]. Another study showed that 5-CQA affected melanogenesis and tyrosinase activity inhibited B16 melanoma cell proliferation and suppressed melanogenesis through the inhibition of enzymatic oxidation of a diphenol, especially activated by 8-methoxsalen (8-MOP) [109]. In addition, 5-CQA was shown to inhibit glioblastoma growth, at least in part, by reducing M2 phenotypic macrophage and stimulating M1-polarized macrophage in vivo and in vitro, which is mediated via inhibition of signal transducer and transcription activator 6 (STAT6) and promotion of STAT1 [110]. Another study found that the simultaneous application of 5-CQA and its microbial metabolites enhanced antitumor activities in Caco-2 cells through the increase of antiproliferative effects, and induction of apoptosis [111]. Moreover, some studies showed that CGA has the ability to induceapoptosis and cellular DNA damage in cancer cells without disturbing normal cells [112]. Also, it was demonstrated that CGA had a significant role in the treatment of 4T1 BC tumors in BALB/c mice [113]. Also, CGA was found to induce apoptosis and inhibition of proliferation in human acute promyelocytic leukemia HL-60 cells [114]. While other studies showed that CGA may inhibit the development of cancer cells by inhibiting signaling pathways, such as COX-2, NLRP3 and NF-kappaB signaling pathways [115]. CGA from green coffee beans was found to inhibit colo-rectal cancer (CRC) cells. It induced ROS production and inhibited cell viability in human colon cancer cells. So it may be considered as a potential treatment against CRC [116]. On the other hand, CGA was shown to suppresse esophageal squamous cell carcinoma progression in vivo and vitro by downregulation the expression of BMI1 and SOX2 [117]. Also, CGA was found to suppress the proliferation of cancer cells in breast cancer, lung cancer as well as hepatocellular carcinoma in vivo and vitro [118-120]. Therefore, the above studies indicated that consumption of CGA can be, at least in part, associated with cancer prevention. Hence CGA can act as a good dietary, chemopreventive as well as therapeutic agent for the prevention of cancer.

Neuroprotective Effect

Neurological degenerative disorders (NDDs) are highly correlated with inflammation and accumulation of oxidative stress-induced damage [121]. Phenolic compounds like CGAs especially 5-CQA are thought to be strong antioxidant and anti-inflammatory agents, which can cross the blood–brain barrier (BBB) to act directly and/or indirectly to protect the central nervous system [122]. long-term follow-up studies indicated that CGAs (mostly 5-CQA) lower the risk of NDDs such as ischemic stroke [123], Alzheimer's disease (AD) with low cognition, and Parkinson's disease (PD) [124,125]. It was believed that 5-CQA act as a potential cognitive-enhancing therapeutic agent. As well as, it is demonstrated that CGA exerts its neuroprotective effects against AD by inhibiting the activity of two key enzymes, namely acetylcholinesterase (ACHE) and butyrylcholinesterase (BCHE), as well as by suppressing oxidative stress-induced neuronal damage [126]. Another in vitro study focused on PD indicated that CGA is a strong therapeutic or preventive agent against PD onset, which acts by suppressing the interaction between oxidized dopamine and alpha-synuclein in catecholaminergic PC12 (rat pheochromocytoma) cells [127]. In rat primary hippocampal neuronal cells, treatment with CGA was shown to protect neurons against aluminum chloride (AI)-induced oxidative stress by upregulating nuclear factor, erythroid 2 like 2 (NFE2L2, also known as NRF2) and phase 2 enzymes [128]. Another in vitro study showed that CGA significantly suppresses NO production and tumor necrosis factor (TNF) release, and also prevents microglial activation-induced neurotoxicity and ultimately promotes dopaminergic neuron survival in an LPS-induced inflammation model in primary microglia [129]. CGA could be considered as a candidate neuroprotective agent against proinflammatory factor-induced neurodegenerative diseases, by suppressing the nuclear factor kappa-B (NF-κB) anti-inflammatory signaling pathway [130]. It was found that, CGA significantly lowered hypoxia- and NO-induced retinal cell by preventing the downregulation of thymus cell antigen -1(THY1) in mice subjected to crush injury of the optic nerve. This indicates that CGA may prevent retinal degeneration [131]. The preclinical protective benefits of CGA against stroke either in mouse or rat model may be attributed

to the inhibition of neuronal cell death and protection against cortical neurons injury by preventing the glutamate-induced increase in intracellular Ca2+ concentration and maintaining intracellular redox homeostasis [132]. Also, another study in a rat model of cerebral ischemia (CI) demonstrated that CGA reduces brain injury, brain edema, sensory-motor functional deficits, and BBB damage by enhancing free-radical scavenging activity [133]. Furthermore, a recent study showed that CGA reduces brain damage, nerve damage, and volume of cerebral infarction and neuronal apoptosis by regulating the NFE2L2 signaling pathway in CI-reperfusion (CI/R)-induced oxidative stress in rats [134]. CGA was found to improve the spatial memory and prevent the degeneration of hippocampal CA1 pyramidal cells in CI/R rats, which may be attributed to increased expression of Bcl2 and platelet endothelial cell adhesion molecule [135]. Also, intranasal administration of CGA (10 mg/kg b.w.) was found to reduce significantly the cerebral infarction area, Evans blue extravasation and restored the brain water content compared with ischemia group. These findings suggest that the treatment with CGA confers neuroprotection in global ischemic insult by inhibiting and downregulating the different molecular markers of cerebral ischemia [136]. Spinal cord injury was shown to be alleviated by administration of CGA via TLR4/NF-κB and p38 signaling pathways due to its anti-inflammatory activity [137]. Moreover, a recent randomized controlled trial investigated the protective effects of CGA against mild cognitive impairment (MCI), demonstrated the improvement of cognitive functions (executive and attention function) in patients with MCI [138]. FA which is a metabolite of CGA showed neuroprotective effects through its strong anti-oxidant action and could be potentially used as a therapeutic molecule for nucleus pulposus regeneration. Also, the protective effects of FA ethyl ester against the amyloid beta peptide (1- 42)-induced oxidative stress and neurotoxicity have been evaluated and reported. Ferulic Acid was found to Improve the cognitive skills through the activation of the haeme oxygenase system in Rats. So it may be considered as a new drug to treat **Alzheimer's disease** and other oxidative stress-related diseases [139]. Ferulic acid was found to provide neuroprotection against oxidative stress-related apoptosis after cerebral ischemia/reperfusion injury by inhibiting ICAM-1 mRNA expression in brains of rats. These results showed the promising neuroprotection effect of CGA, CA, and FA which gave a great hope for treatment of pateints with **Alzheimer's disease** (AD) [140]. AD is a neurodegenerative disorder, involves brain insulin signaling cascades and insulin resistance (IR). Because of limited treatment options, new treatment strategies are mandatory. GCBE rich in CGA was reported to attenuate IR and improve brain energy metabolism, so GCBE can be used as a prophylactic strategy to delay the onset of AD or combined with pioglitazone (PIO) as a strategy to retard the progression of AD [141]. Another study showed a neuroprotective effect of CGA and its metabolites against glutamate induced excitotoxicity and oxidative stress in rat cortical neurons [142]. On the other hand, Oxidative stress in the brain is due to ROS accumulation, which is an important factor in the brain aging process. Dopaminergic neurons are vulnerable to oxidative products, and oxidative damage plays a critical role in the pathogenesis of **Parkinson's disease** PD [143]. So increased oxidative stress and reduced activities of antioxidant enzymes were observed in these cases, and these effects were found to be prevented by the anti-oxidative role of CGA in animal experiments and cellular models.

Antimicrobial Effects

Anti-Bacterial

It has been reported that CGA may be a broad-spectrum antimicrobial natural agent due to its broad-spectrum activity against viruses, bacteria, molds, yeasts, and amoebas [144]. CGA showed an effective growth inhibitory effect against certain pathogenic bacteria, by increasing plasma membrane permeability of bacterial cell, leading to plasma membrane barrier dysfunction, as well as leakage of nucleotides This is the possible mechanism by which CGA disrupted the membrane barrier might involve the perturbation of the membrane lipid bilayer, resulting in cell leakage and dissipation of the membrane electrical potential [145]. Anti-Bacterial Activity of GCBE was studied on salmonella enterictidis and staphylococcus aureus by using four concentration 20%, 15%, 10%, 5% in which GCBE showed inhibitory concentration at 20% by disc diffusion activity [146]. In periodontal disease, it was found that pure green coffee extract can be used successfully against periodontogenic bacteria like Porphyromonas gingivalis, Prevotella intermedia, Fusobacterium nucleatum and Aggregatibacter actinomycetemcomitans [147]. Various studies showed that CGA inhibited microorganisms that grow throughout human gastrointestinal tract, from the mouth to colon [148]. In another research, CGA and CA present in GCBE showed growth inhibitory effect against pathogens such as Staphylococcus aureus, Enterococcus faecalis, Listeria monocytogenes, Pseudomonas aeruginosa, Escherichia coli, and Salmonella choleraesuis [149]. Also, CGA effectively inhibited the growth of bacterial strains such as Shigella dysenteriae and S. pneumonia by provoking irreversible permeability changes in the cell membrane, causing cell death [150]. Also it was found that green coffee CGAs have an important antibacterial, antifungal, and anti-mycotoxigenic effects. FA showed bacteriostatic and bactericidal activities against Escherichia coli [151]. The antimicrobial mechanisms of CGA included binding to and disruption of the outer cell membrane followed by the release of cytoplasm macromolecules which leading to cell death [152]. CA was found to inhibit the growth of Pseudomonas Aeruginosa bacteria as it caused increased intracellular membrane permeability, induced the exfoliation of outer membrane, and disturbed the intracellular metabolism leading to Damage of intracellular and outer membranes as well as disruption of cell metabolism resulted in cell death eventually [153]. CGA showed in -vitro antibacterial and antibiofilm activities against bacterial isolates of a Stenotrophomonas maltophilia including the resistant strain to trimethoprim/sulfamethoxazole [154]. In another study, CGA showed antimicrobial effect against Gram-positive pathogenic bacteria [155]. FA showed bacteriostatic and bactericidal activities against Escherichia coli, also it is considered as a novel candidate of bacterial growth inhibiting agent against Listeria monocytogenes [156].

Anti-viral Infections

CGA and CA have been reported to possess anti-hepatitis B virus activity [157]. In another study, CGA showed significant

antiviral effects against several viruses, including HIV [158], Adenovirus, Herpes Simplex virus [159,160]. It also inhibits the inflammation caused by viral infections [161]. CGA was reported to be a potential inhibitor of influenza virus H1N1, H5N1 and H7N9 [162-164). It was reported that CGA could recover cell viability and increase the survival rate in H1N1-infected mice [162]. Previous studies have demonstrated the antiviral effects of CA against influenza virus H3N2 [165]. In-vitro study showed an inhibitory effect on replication and viability of enterovirus 71 by CGA acid [166]. CGA was found to possess a strong anti- viral effect in-vitro and could inhibit the development of Porcine reproductive respiratory syndrome virus PRRSV [167].

Anti-fungal Effects

It was found that CGA exhibited antimycotic activity against certain fungal pathogens by damaging the cell membrane structure It was found that CGA causes damage in fungal membrane lipid bilayers, leading to leakage of ions and other materials as well as forming pores and dissipating the electrical potential of the membrane, without any human erythrocyte hemolysis or any other side effects [168]. The in-vitro antifungal activity of CGA against pathogenic yeasts was determined. It is highly effective against some strains such as Candida albicans, Trichosporon beigelii, and Malassezia furfur, exist in humans as commensals and are superficial contaminants that can cause a variety of serious infections [168]. CGA present in GCBE exerted antifungal property on Aspergillus genus as Aspergillus flavidus, Aspergillus nominus, Aspergillus ochraceus, Aspergillus parasiticus and Aspergillus westerdijkiae [169]. While another results indicated that chlorogenic acid exhibits antifungal activities against certain pathogenic fungi as Candida albicans without any side effects [170].

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