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The Pharma Innovation

ISSN (E): 2277-7695
ISSN (P): 2349-8242
NAAS Rating: 5.23
TPI 2022; 11(7): 2970-2976

www.thepharmajournal.com
Received: 29-04-2022
Accepted: 14-06-2022

Akshita Vats
Department of Food Technology and Nutrition, School of Agriculture, Lovely Professional University, Phagwara, Punjab, India

Corresponding Author:
Akshita Vats
Department of Food Technology and Nutrition, School of Agriculture, Lovely Professional University, Phagwara, Punjab, India

Pharmacological properties of Green coffee: A review

Akshita Vats

Abstract
Green coffee is high in carbohydrates, protein, and fat, as well as caffeine, trigonelin, and chlorogenic acid, which are minor components. Natural antixodants include phenols, chlorogenic acids, and brown pigments. Green coffee's high polypehonic materials, particularly chlorogenic acid, play an essential role. Green coffee contains chlorogenic acid and caffeine, which are thought to have anti-obesity, anti-tumor, antidiabetic, anti-hypertensive, anti-inflammatory, and anti-microbial properties. Green coffee and its active constituents may also offer a non-pharmacological and non-invasive treatment and preventative option for some chronic disorders. Green coffee is thought to have impacts on body mass, blood glucose and cholesterol levels, blood pressure, and cardiovascular disease prevention due to the antioxidant action of chlorogenic acid. However, many aspects of these active molecules, such as toxicological effects, dosages, quantities, body utilisation, advantages and disadvantages, and so on, must be investigated. As a result, this article has been updated to consider the health consequences of green coffee.

Keywords: *Coffea arabica, Coffea robusta, Coffea liberica,* bioactive compounds, Caffeine, Chlorogenic acid

Introduction
Coffee is one of the most widely consumed beverages in the world today. It has around 700 compounds that give it its aromatic and distinctive flavour (Cornelis, 2012) [32]. Coffee is a member of the *Rubiaceae* family. It grows in rainy places with typical temperatures of 18-24°C. The most important species of *Coffea* are *Coffea arabica* and *Coffea canephora var. robusta*, which account for 40-60% of global production (Baker, 2014). *Arabica* is typically found in South America (mostly Brazil) and upland and mountainous portions of East Africa, whereas *Robusta* is found in the lowlands of Central and West Africa, as well as South Asia (mostly Vietnam) (International Coffee Organization, 2013) [23].
Green coffee is an unroasted bean from the Coffee fruit that contains more bioactive phytochemicals than roasted coffee beans (Esquivel and Jim'enez, 2012) [38]. Chlorogenic acid (CGA), a polyphenol, is abundant in green coffee beans (Ludwig *et al*, 2014) [24]. The ester of caffeic and quinic acids forms chlorogenic acid, a naturally occurring chemical compound (Upadhyay and Rao, 2013) [43]. Chlorogenic acid contains anti-cancer, anti-inflammatory, anti-lipidemic, anti-hypertensive, and anti-diabetic activities, according to research (Galvez et.al, 2017) [28]. Caffeine, theophylline, theobromine, cafestol, kahweol, tocopherols, trigonelline, chlorogenic acids and their derivatives, are associated to these properties (Skowron et.al, 2015) [25]. Anti-inflammatory and antimutagenic effects of the components help to prevent cancer and chronic disorders. Suárez-Quiroz *et al*., (2013) found that they have antiviral, antioxidant, antibacterial, antifungal, and antimycotoxigenic properties (Brahat *et al*., 2015) [6]. CGAs have also been found to affect lipid metabolism and glucose levels in both inherited diseases and disorders of the metabolism (Naveed *et al*., 2018) [34]. Caffeine reduces oxidative stress and preserves the antioxidant system in hypoxia-induced pulmonary epithelial cells; it is an inhibitor of hydrogen peroxide-induced lipid peroxidation products in human skin fibroblasts, and it prevents tissue lipid peroxidation (Couroucli *et al*., 2014) [49].

Chemical composition of green coffee
The chemical composition of green coffee bean is defined by the amount of caffeine ranging from 1.45%-2.38% in *C. arabica* and *C. canephora* respectively. Green coffee consists of various primary components respectively (Babova *et al*., 2016) [3]. These primary components include polysaccharides, lipids, proteins, chlorogenic acid (CGA), caffeine, simple sugars and free amino acids. Polysaccharides account for nearly half of the dry weight of coffee beans (Wei and Tanokura 2015) [52].

The Green *Robusta* bean has 48 percent polysaccharide, which is mostly made up of arabinogalactan, mannan, and cellulose. *Arabica* and *Robusta* green coffee beans have comparable polysaccharide profiles. The key difference is that *Robusta* beans have a 3 percent higher arabinogalactan content than *Arabica* beans. *Arabica* green coffee beans have a higher sugar concentration than *Robusta* (Murkovic and Derler 2014). Sucrose accounts about 9% of the dry weight of green coffee beans. Sucrose imparts a distinctive aroma and colour to the coffee during roasting. Green coffee beans have much lower quantities of glucose, fructose, and galactose (Oliveira *et al*. 2018). Green coffee beans have a 7-17 percent oil content. *Arabica* has a higher oil content (average 15%) than *Robusta* (mean 10 percent). The coffee oil forms most of the green coffee lipids. Coffee oil consist of triglycerides, phospholipids, sterols, tocopherols, coffee's distinctive diterpenes (cafestol, kahweol), and fatty acid esters (Pimpley *et al*. 2020) [50].

CGAs, such as caffeic, ferulic, and p-coumaric acids, are phenolic compounds synthesized by esterifying cinnamic acids with (-)-quinic acid. 3-, 4-, and 5-caffeoylquinic acids (3-, 4-, and 5-CQA), 3,4-, 3,5-, and 4,5-dicaffeoylquinic acids (3,4-, 3,5-, and 4,5-DCQA), 3-, 4-, and 5-feruloylquinic acids (3-, 4-, and 5-FQA) are the main hydroxycinnamic acids found in green coffee bean extract (Dziki *et al*., 2014) [18]. Other bioactive components found in green coffee include methylxanthines-caffeine (CAF), theobromine, and theophylline (Huck *et al*., 2019) [22]. *C. arabica* contains 3.40%-7.24% chlorogenic acid, while *C.canephora (robusta)* contains 5.17%-14.4% chlorogenic acid (Narita and Inouye 2015).

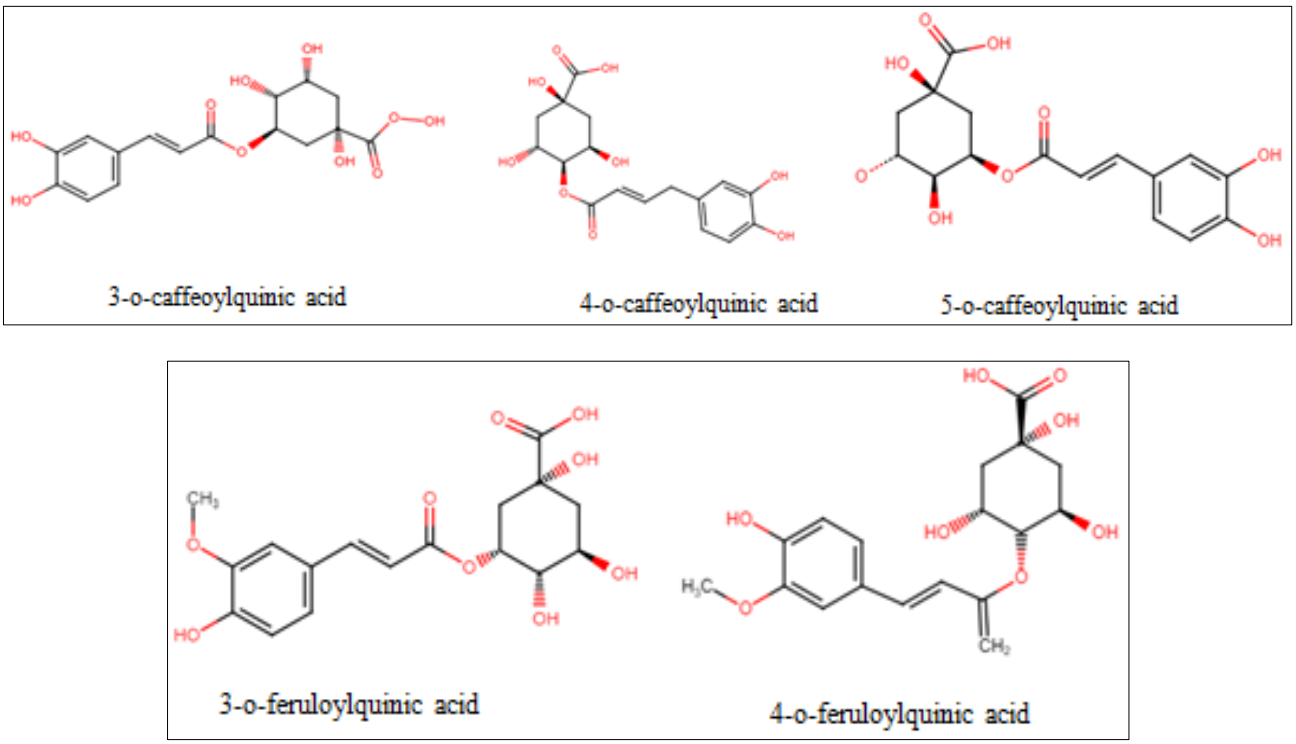

Fig 1: Structures of different chlorogenic acids present in coffee beans.

Caffeine (1, 3, 7-trimethylxanthine) is the most abundant purine alkaloidal component in green coffee beans, accounting for 99.78 % of total methylxanthines. The amount of caffeine in green coffee beans does not change as they age. Caffeine being thermostable, cannot be destroyed or reduced by excessive roasting of the beans (Mussatto *et al*., 2011) [33]. Proteins, sugars, CGA, trigonelline and fat can either be preserved or converted into reactive chemicals after roasting. Some amounts of theophylline, theobromine, paraxanthine, libertine, and methylliberines are also present. *Arabica* coffee has a caffeine concentration of 0.8% to 1.4% (w/w), while *Robusta* coffee has a caffeine content of 1.7% to 4.0% (w/w) (Belitz *et al*., 2009) [5]. Caffeine, an adenosine antagonist with stimulant characteristics, is the main psychoactive component in coffee. It includes monoamine oxidase inhibitors such as carboline and harman, which may be responsible for its psychedelic properties (Berlowitz et.al, 2022) [41]. Cafestol, kahweol, 16-O-methylcafestol, cafestal, and kahweal are among the diterpenes found in green coffee. They account for around 20% of the lipid component. Diterpenes are esterified with saturated long-chain fatty acids in coffee oil (LCFAs) (Berti *et al*, 2020) [15].

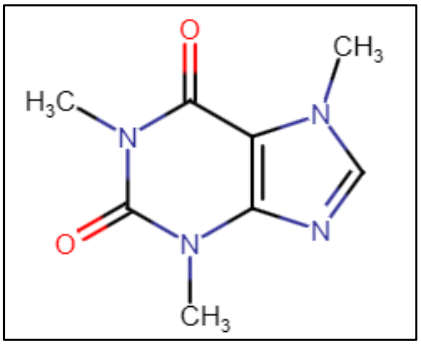

Fig 2: Structure of caffeine.

Green coffee beans are high in minerals like potassium, magnesium, calcium, sodium, iron, manganese, zinc, copper etc. (Mussatto *et al*., 2011) [33]. According to the RDA, one

cup of coffee includes 1–5% magnesium, 1–2% potassium, 1–3 mg nicotinic acid, 6–18% niacin, and 0.1–0.21% vitamin E. (Anonymous, 2021). The second most abundant alkaloid in raw coffee beans is N-methyl-nicotinate, a vitamin B6 derivative. This alkaloid accounts for around 0.6 to 1.0% of the dry matter in roasted coffee (Mizuno *et al*, 2014) [29]. At 230°C roasting temperature, 85% of trigonelline is hydrolyzed to nicotinic acid (Ashihara *et al*. 2014) [21]. Trigonelline is a new phytoestrogen (Allred *et al*., 2009). Coffee beans are also rich in pyridoxine phosphate, another important member of the vitamin B complex.

Proteins make up 8–12% of dried green coffee beans, and the majority of proteins are hydrolyzed to amino acids during maturation, which is sped up by CGA and its derivatives (Gupta, 2016). Alanine, arginine, asparagines, cysteine, glutamic acid, histidine, glycine, isoleucine, leucine, lysine, methionine, phenylalanine, proline, serine, tyrosine, threonine, and vaniline are among the amino acids found in coffee beans (Dong *et al*., 2015) [53]. Coffee has an average amino acid concentration of 4 mg/g in *robusta* coffee and 4.5 mg/g in *arabica* coffee. The presence of free amino acids in green coffee beans contributes to its disagreeable flavour, although roasted coffee does not (Sharma, 2019) [20].

The principal sugars contained in green coffee include sucrose, glucose, fructose, arabinose, galactose, and mannose, which contribute to its bland flavour (Sharma, 2020) [20]. Carbohydrates make up about half of the dry weight of green coffee beans, with arabinogalactan accounting for up to 17% of that (Chen *et al*., 2015) [55]. It is made up of beta 1–3-linked galactan main chains with arabinose (pentose) and galactose (hexose) residues on the side chains. In mature brown to yellow coffee beans, the side chains of polysaccharides have fewer residues of galactose and arabinose. This makes green coffee beans more resistant to physical deterioration and less soluble in water (Simoes *et al*., 2019). Free monosaccharides can be found in mature brown to yellow-green coffee beans. Mannitol is an efficient scavenger of hydroxyl radicals generated in biological membranes by lipid peroxidation (Ghimire *et al*, 2018) [4]. Dry green coffee contains lipids in levels ranging from 11.7 to 14 g/100 g. (Tesgay *et al*., 2020). Green coffee oil is obtained from C. arabica before roasting and contains 75 percent triacylglycerols, 13.54% unsaponifiable matter, and 0.24% wax (1/3N). The most frequent fatty acids detected in green coffee oil are linoleic and palmitic acids (Wagemaker *et al*., 2011) [51]. The volatile compounds contained in green coffee beans include short-chain fatty acids (SCFAs), aldehydes, and nitrogen-containing aromatic molecules, which are pyrazine derivatives (Abdelwareth, 2021) [2]. Green coffee beans have an unpleasant odour and taste because of the presence of the volatile molecules.

Green coffee and pharmacological effects

- **Reduction in obesity and weight**

Obesity is defined as irregular fat build-up or an excess quantity of body fat in respect to globally determined standards (Gómez *et al*., 2017) [1]. Obesity is considered as a severe public health issue worldwide (Clark, 2017) [9]. Diabetes, non-alcoholic fatty liver disease (NAFLD), coronary artery disease, hypertension, cancers, and mental health concerns have all been linked to obesity and overweight people with these chronic disorders (Steele *et al*., 2018). Fat accumulation inhibition, the potential to reduce body weight and body mass indices (Haidari *et al*., 2017), blood pressure mitigation (Onakpoya *et al*., 2015), and postprandial glucose metabolism modulation through intestinal absorption reduction are all putative positive biological effects of GCE and CGA consumption. The green coffee beans activates the liver, causing it to create more bile and speed up the metabolic process while also releasing glucose into the bloodstream (Nakrani *et al*, 2021) [35]. Caffeine also slows fat absorption by releasing fatty acids from stored body fat. CGA helps the liver process fatty acids more efficiently and lowers hepatic triglyceride levels, leading in weight loss (Roshan *et al*., 2018) [42]. Green coffee bean extract decreases hepatic triglyceride levels while chlorogenic acid suppresses fat absorption (Farah, 2019) [13]. Other phenolic components in green coffee beans, such as neochlorogenic acid and feruloylquinic acid, increase the activity of hepatic carnitine palmitoyltransferase (CPT) (Shimoda *et al*., 2006) [46]. In addition to suppressing hepatic triglyceride accumulation, antiobesity effects are mediated by changes in plasma adipokine levels, body fat distribution, and downregulating fatty acids and cholesterol biosynthesis and upregulating fatty acids oxidation and expression of PPAR in the liver (Cho *et al*., 2010).

- **Decrease in blood glucose level (Type 2 diabetes)**

According to Sarriá *et al*. (2016) [59], the global prevalence of Type 2 diabetes is increasing, with an estimated 366 million individuals suffering from the condition by 2030. Caffeine, found in green coffee, is a glucose stimulant and mitochondrial activator. Caffeic acid reduces oxidative stress and promotes axon regeneration when combined with trigonellin dentrit (Maki *et al*., 2019) [30]. Chlorogenic acid, on the other hand, is required for glucose homeostasis and the decrease of oxidative stress. Green coffee extract may protect cells from oxidative stress, lower triglycerides, glucose, and oxidised glutathione levels, have an anti-diabetic effect, and even be helpful in preventing and treating type 2 diabetes in rats fed a high-fat diet (Budryn *et al*. 2017).

Green coffee beans reduces the incidence of diabetes mellitus, and various mechanisms of action have been hypothesised, although the actual target site and mechanism are yet unknown. By acting as an alpha-glucosidase inhibitor, chlorogenic acid appears to reduce, but not stop, glucose absorption from the human stomach, lowering the insulin surge after meals in type 2 diabetic patients (Peterson and Shulman, 2018) [31]. Chlorogenic acid also affects gluconeogenesis and glycogenolysis by blocking the enzyme glucose-6-phosphatase. When glycogenolysis is prevented, the body obtains energy from fat cells, lowering blood sugar levels and lowering body weight (Narita and Inouye 2015). Coffee chemicals also decrease the absorption of glucose in the intestine by modulating the levels of glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-I (GLP-I), which enhance insulin secretion following oral glucose consumption (Reis *et al*., 2018) [7].

- **Antioxidant effect**

Caffeine, a key component of coffee, is a powerful antioxidant with the ability to prevent oxidative DNA damage, alter the apoptotic response, and regulate the cell-cycle checkpoint function (Banerjee *et al*., 2014). Furthermore, the coffee constituents cafestol and kahweol are two diterpenes that have been demonstrated to have a wide

spectrum of bioactive activities, resulting in a reduction in carcinogen-induced genotoxicity (Ferk *et al*., 2014) [16].

Green coffee contains chlorogenic acid, a phenolic molecule with antioxidant properties and the potential to trap superoxide anions or hydroxyl radicals. This chemical offers numerous health benefits, including the ability to scavenge free radicals *in vitro* and limit the spread of oxidative processes (Castro *et al*., 2018) [8]. Cholorogenic acids are excellent scavengers of reactive oxygen species (ROS). ROS are formed physiologically through numerous cellular processes such as aerobic metabolism, and when the number is high enough, they should be hazardous. Even though ROS are known to be detrimental, they must be present at a particular level to maintain cellular homeostasis via redox cell signalling (Priftis *et al*., 2018) [39]. During the interval of coffee drinking, oxidative DNA damage was reduced, glutathione levels and glutathione reductase activity were raised, according to a study (Bakuradze *et al*., 2011).

- **Anti-cancer effects**

Coffee is categorised as noncarcinogenic to humans by the International Agency for Research on Cancer, 2016. Several studies have found a link between coffee drinking and a lower risk of certain malignancies. Many research on coffee's anti-cancer capabilities have identified kahweol as one of the primary chemicals responsible for cancer chemoprevention (Park *et al*., 2016) [14]. The antioxidant kahweol protects DNA from oxidative stress caused by hydrogen peroxides by cleaning reactive oxygen species and triggering hemoxygenase-1 to manage intracellular reactive oxygen species (ROS) (Cárdenas *et al*., 2014).

Hypermethylation of DNA is a prevalent trait in tumour cells and a crucial epigenetic mechanism for inhibiting a variety of genes, including tumour suppressor proteins, DNA repair enzymes, and receptors (Lahtz and Pfeifer, 2011). Caffeic acid inhibits DNA methylation in human cancer cells and is linked to the inactivation of several tumor-related pathways, including cell cycle regulation, inflammatory and stress responses, and apoptosis (Yu *et al*. 2011).

A cup of coffee consumed daily reduces the risk of death due to cancer by 3% (Happonen *et al*. 2008), while moderate coffee consumption protects against cancers of the kidney (Lee *et al*. 2017) [4], liver (Larsson and Wolk 2007), pancreas (Ran, Wang and Sun 2016), colorectal (Schmit *et al*. 2016), breast (Jiang, Wu and Jiang 2013) [53], and prostate (Tverdal 2015).

- **Hepatic Disorders**

According to epidemiological research, drinking coffee can help avoid cirrhosis of the liver and other chronic diseases. Serum gamma glutamyl transferase and alanine amino transferase (ALT) activities have been shown to be negatively correlated with coffee use (Dranoff, 2018) [27]. Coffee is a complex "blend" of a large number of chemical moieties, and any of these may be responsible for its protective effects on liver (Maki *et al*., 2019) [30]. In addition to purging lipids, bad cholesterol, and other detrimental toxic compounds from the liver, cafestol and kahweol also lower the toxicity of a number of carcinogens.

Table 1: Main bioactive compounds of green coffee and their effects on human health

Bioactive compounds	Functions	References
1. Caffeine	• Ergogenic effects, • Augment in alertness and concentration, • Reduction in fatigue, • Reduction in pain perception, • Anti-inflammatory (inhibition of tnf-a, leukotriene synthesis, il-6, and il-8).	Pauwels and Volterrani 2021 [37]; Sivalokanathan, Małek, and Malhotra 2021 [45]; Stadheim *et al*., 2015 [48]
2. Chlorogenic acid	• Anti-inflammatory, • Antioxidant, • Hepatoprotective, • Cardioprotective, • Chemopreventive, • Anti-diabetic, • Anti-obesity • Anticancer, • Neuroprotective effects, • Anti-neurodegenerative effects.	Fukutomi *et al*., 2021 [17]; Pauwels and Volterrani 2021 [37]; Socała *et al*, 2020 [47]; Wasim *et al*., 2020
3. Trigonelline	• Anti-inflammatory, • Antioxidant, • Anti-obesity, • Anti-diabetic, • Neuroprotective	Farias-Pereira, Park, and Park 2019 [14]; Mohamadi *et al*., 2018; Sharma *et al*., 2018 [20]
4. Cafestol and Kahweol	• Anti-inflammatory, • Anti-angiogenic, • Reduction of neoangiogenesis,	Moeenfard *et al*., 2016; Pauwels and Volterrani 2021 [37]

Green coffee and its toxicity

As mentioned above green coffee have various health benefits. The presence of chlorogenic acids is primarily responsible for the physiological characteristics of green coffee beans (CGAs) (Nieber, 2017). However, there are certain studies that reports about the adverse effects of CGA (Fan *et al*., 2009) [12]. According to Du *et al*. 2013, a high dose of CGA given to male Wistar rats could cause an inflammatory reaction as seen by the elevated leukocyte count, elevated cytokine levels, and depleted antioxidant status. In a different investigation, it was discovered that CGA had a prooxidant impact that increased the production of

intracellular reactive oxygen species (ROS), which in turn caused myeloid leukaemia cells to undergo apoptosis (Rakshit *et al*., 2010) [40]. In this study, we investigated the *in vivo* toxicity of a standardised green coffee bean extract that had 50% CGA in it. Based on assessments of acute and sub-chronic toxicity, the extract's safety was determined.

Green coffee use in excess has numerous negative effects. Although it has less caffeine than normal coffee, it is still best to limit your intake (Bhatt, 2020). Too much green coffee consumption can have a number of negative side effects, such as restlessness, insomnia, anxiety, irregular heartbeat, nausea, upset stomach, nervousness, exhaustion, headaches, faster breathing, agitation, and diarrhoea. Additionally, it is not a good idea to consume green coffee extract if you are nursing or pregnant (Prakasan, 2017). Consuming too much green coffee may cause the body to lose calcium through the urine, resulting in a calcium deficit. It might eventually lead to serious illnesses like osteoporosis (Anonymous, 2019).

Conclusion

Coffee is one of the most popular beverages in the world, and it is well-known for being a good source of antioxidants in the human diet, which helps to avoid oxidative stress-related disorders. As a result, it's recommended as a weight-loss supplement and as a component of other weight-loss supplements. The efficacy of green coffee beans and its potential side effects have been a source of debate, as there have been reports of both unpleasant occurrences and no side effects. There has been a link found between the amount of coffee eaten and the risk of death. "Coffee may offer potential health advantages, but further research is needed," the Harvard School of Public Health said after a 22-year study. Coffee's negative effects are more common when it's consumed in excess, and many of the health hazards are caused by caffeine, which may be avoided by drinking decaffeinated coffee. In addition to adequate and balanced nutrition, 3-4 cups of green coffee per day may have health benefits. However, the amount of caffeine consumed should be carefully monitored, and no more than the daily maximum safe dose of 400 mg for adult subjects set by the European Food Safety Authority should be consumed.

Green coffee beans contain the most CGA, and its promising pharmacological activities, such as antioxidant activity, the ability to increase hepatic glucose utilisation, suppression of fat absorption, enhancement of fat metabolism in the liver, inhibition of HIV-1 integrase, antispasmodic activity, inhibition of carcinogenicity of carcinogens, antihypertensive effect, and several other desirable pharmacological effects, suggest that GC should be exploited. As a result, evaluating green coffee's nutraceutical qualities is primarily motivated by the need to discover new and promising sources of natural oxidants and nutraceuticals. Further experimental and clinical investigations addressing the different bioactive components responsible for desirable and undesired effects, underlying processes, and dose- and time-dependent effects are needed to assess the health hazards and advantages of coffee and caffeine use. Genetic heterogeneity in relation to food intake, chronic diseases, and genetic polymorphisms in phase I and phase II biotransformation enzymes could aid in identifying genotypes that are more vulnerable to negative or positive impacts. Because coffee is one of the most popular global beverages, more study should be focused on adverse outcome pathways and harmful consequences, if any, following long-term intake in children, adolescents, and pregnant women.

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