# THE MAGICAL SMELL AND TASTE: CAN COFFEE BE GOOD TO PATIENTS WITH CARDIOMETABOLIC DISEASE?

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**Abstract**

Coffee is a beverage consumed globally. Although few studies have indicated adverse effects, it is typically a beneficial health-promoting agent in a range of diseases, including depression, diabetes, cardiovascular disease, and obesity. Coffee is rich in caffeine, antioxidants, and phenolic compounds, which can modulate the composition of the gut microbiota and mitigate both inflammation and oxidative stress, common features of the burden of lifestyle diseases. This review will discuss the possible benefits of coffee on complications present in patients with diabetes, cardiovascular disease and chronic kidney disease, outwith the social and emotional benefits attributed to caffeine consumption.

**Keywords:** coffee, coffee phytochemicals structure, oxidative stress, inflammation, gut microbiota, burden of lifestyle diseases.

## Introduction

Coffee is one of the most consumed beverages globally [1]. It belongs to the Rubiaceae family, including *Arabica* and *Canephora*, two of the world's most economically important crops [2]. Coffee comprises a host of different forms derived through grinding and roasting, all of which may impart significant chemical and sensory changes associated with its consumption [3; 4].

The biochemical mechanisms underpinning coffee metabolism and any potential beneficial effects it may impart for treating chronic diseases are poorly understood [5; 6].

Coffee is rich in anti-inflammatory and antioxidant compounds, including polyphenols, diterpenes, chlorogenic acid (CGAs), and caffeine [7;4], which have been linked to cardiometabolic protection, including reduced risk of atherosclerosis and other cardiovascular outcomes, stroke brain, neurodegenerative conditions, cardiorenal protection, and antidiabetic effects [8; 6; 9; 10].

However, findings have not proven universal, as heterogeneity has emerged in studies regarding the types of coffee used (caffeinated and decaffeinated), different forms of preparation and degrees of roasting, the presence of isolated compounds and variations in dose and time of intervention [11; 12]. Additionally, polymorphism in cytochrome P450 and the CYP1A2 gene [13] has also focused on explaining these equivocal findings.

Thus, considering that coffee is one of the most widely consumed drinks globally, it is essential to understand coffee metabolism and associated health benefits. In this narrative review, we will discuss the effects of coffee intake on diabetes, cardiovascular disease and, in particular, chronic kidney disease.

## Coffee - a historical perspective

Coffee is thought to have been discovered more than a thousand years ago, circa 575 AD. The oldest story about the emergence of coffee attributes this to Pastor Kaldi, a goat keeper in the Kafa region of Ethiopia, who observed that when his goats consumed a red/yellowish fruit of a particular tree (the coffee bush), they were very agitated [14]. The region propagated this legend, and the local population started to consume the fruit in macerated form, mixed in lard for meals, its leaves in broths, and an alcoholic beverage made from the fermentation of the juice [14]. Consumption of coffee as a stimulant in the broader sense only started circa 1000 AD, when monks used this invigorating drink to remain awake. Subsequently, roasting was developed in the 14th century to give the drink the flavour and aroma that we know today [14].

According to the International Coffee Organization (ICO), the largest coffee-producing countries, in descending order, are Brazil, Vietnam, Colombia, Indonesia and Ethiopia. The largest coffee consumers are the United States, Brazil and Japan, although the European continent remains exceptional for consumption per capita [15].

Although there are many species of coffee-producing plants, *Coffea arabica* (arabica coffee) and *Coffea canephora* (robusta coffee) are the most significant in terms of economic

importance and are thus the most consumed and studied [2]. Differences between *Coffea Arabica* and *Coffea Canephora* are detailed in **Table 1** [16; 17].

Coffee production (**Figure 1**) begins in the field with the harvesting of the fruits, which can be manual or mechanized, and then the seeds are processed (they have a moisture content of around 10% to 12%, which allows transport without loss of quality). Coffee by-products are generated from the separation of the outer layers of the seeds (skin, pulp, mucilage and parchment). From seed processing, green coffee beans are generated and transported to industries that will carry out the next processing steps (roasting, grinding and encapsulation) [229].

The biochemical content of coffee beans (i.e., the content of carbohydrates, lipids, proteins, and minerals) as well metabolites responsible for the taste and aroma may be modulated by the type of harvest [18]. Coffee is composed of a class of complex structures, brown-coloured polymers and macromolecular produced from the Maillard reaction of carbonyl and amino compounds during roasting [227]. The carbohydrate content represents 60% of the total weight of raw coffee beans; in addition, proteins, fats, tannins, caffeine, minerals and other ingredients complete its composition [228]. A detailed description of the coffee composition is addressed in **Figure 2**. Also, the components of the coffee can be influenced by processing, in particular, roasting, which has four stages (drying, developing, decomposing, and completing), responsible for the bean's physic-chemical changes and organoleptic and colour changes, leading to the production of melanoidins, volatile compounds and reduction of polysaccharides and proteins from the Maillard reaction and Strecker degradation [18].

The roasting process can be classified as light, medium, and dark according to the Agtron / SCAA Roast Classification Color Disk system [19]. At high temperatures, coffee roasting can degrade bioactive compounds such as polyphenols. Therefore, roasting time and temperatures are critical for any salutogenic bioactive properties of coffee and influence the quality and composition [3]. After the coffee roasting process, soluble compounds are extracted, and coffee grounds are formed, corresponding to the solid residue. Soluble coffee is produced through coffee grounds from which soluble solids and volatile compounds are extracted, concentrated, and dried [20].

Grinding also interferes with the number of antioxidants extracted during the drink preparation. It has been reported that the storage of whole grains favours lower production of free radicals due to the shorter time of exposure to oxygen [21]. Additionally, the drying process affects coffee properties, such as pH, total titratable acidity, total solids, and total soluble solids.

Additionally, different brewing methods can affect coffee's antioxidant potential. In this case, the preferred brewing method to preserve antioxidant potential is an infusion [22; 23]. Notably, however, Angeloni et al. (2019) have shown that the maximal caffeine and CGA content occurs in espresso coffees, compared to Moka and filtered coffees.

**Coffee - properties, absorption, and metabolism**

The composition of coffee (**Figure 3**) is around 76% water, 10% protein, 8% ash, 2% fibre, and 4% nitrogen extract, represented by tannins, sugars, caffeine, CGAs, caffeic acid, cellulose, hemicellulose, lignin, amino acids, minerals such as calcium, potassium, sodium, iron, magnesium, and others [24]. Coffee also contains fatty elements, such as triacylglycerols, fatty acids, and a fraction of diterpenes known as cafestol and kahweol (not very sensitive to roasting) [24]. Caffeine and CGA are in larger quantities in coffee grains, and both have antioxidant potential [22; 23; 3]. CGAs are widely found in a range of natural substances, including vegetables, cereals and fruits, though coffee contains the greatest CGAs [25] .

CGAs are hydroxyl esters derived from the esterification of quinic acid with cinnamic acids, including caffeic, ferulic and p-coumaric acids [26]. Several isomeric forms of CGAs have been described in coffee, which varies according to the coffee subgroup, extract, cultivation, location and post-harvest procedures, plus washing and drying of beans [26]. Following the bean roast, CGAs are converted into components that contribute to the pigment, flavour and aroma of coffee [7; 26].

CGAs are metabolised by esterases (derived from the gut microbiota in the small intestine) which convert them into caffeic, quinic and ferulic acids, later absorbed intact by paracellular diffusion or by a monocarboxylic acid (MCT) carrier [27]. These compounds are then broken down into glucuronide and sulfate metabolites, which correspond to components circulating in the bloodstream [28].

The bioaccessibility of CGAs is directly related to their concentration in coffee [29], which can be affected by several factors, such as food composition, i.e., fat milk can increase the bioaccessibility of CGAs through a protective effect against degradative reactions or the presence of surfactant content [30].

Caffeine, a methylxanthine, is the best-known bioactive compound in coffee. Its biosynthesis mainly consists of 4 phases (3 methylations and one nucleosidase reaction) via the xanthosine pathway [31].

Ingested caffeine is almost totally absorbed (approximately 99%) following consumption. Within 50 minutes, 20% is absorbed in the stomach, while the remaining 80% is absorbed in the small intestine [32]. Caffeine metabolism can be influenced by several factors, including age, gender, diet, genetics, smoking, medication, presence of comorbidities and environmental factors [33]. In general, caffeine metabolism occurs in the liver, mainly via CYP1A2 (belonging to the Cytochrome P450 family). CYP1A2 can perform 1, 3 and 7-demethylation reactions for caffeine; 7-demethylation of paraxanthin and 1- and 3-demethylation of theophylline. A further three CYP isoforms may also contribute to caffeine metabolism, these being CYP2E1, CYP2D6-Met and CYP3A4 [33; 34]. The coffee compounds have antibacterial, antitumor, antifungal, antioxidant and anti-inflammatory properties, and studies have shown some

effects on cardiometabolic diseases such as cardiovascular diseases, diabetes and chronic kidney disease, as discussed below.

**Antioxidants, anti-inflammatory and anti-adipogenic effects of coffee**

CGAs are potent antioxidants and anti-inflammatory agents. CGA and Kahweol are known to inhibit the nuclear factor-kB (NF-kB) activation pathway, leading to decreased inflammatory cytokine secretion and nitric oxide production [13; 26; 195-197]. Phenolic compounds in coffee and CGAs can attenuate the activity of cyclooxygenase-2 (COX-2) by inhibiting the NF-κB and JNK/AP-1 signalling pathways and consequently reduce the production of eicosanoids, which are active compounds that mediate the inflammatory process [35; 36]. However, the main antioxidant effect of coffee is mediated through a molecular pathway that involves the transport of Nrf2 from the cytosol to the nucleus.

Kolb et al. (2020) have elucidated that the phenolic acids present in coffee can activate the Nrf2 signalling pathways / antioxidant response elements (ARE), then suppress the expression of Keap-1, preventing degradation via ubiquitination by ubiquitin ligase E3 based on Cullin 3 (Cul3) of Nrf2, that enters in the cell nucleus and stimulates the formation of heterodimers with small proteins of the muscle-aponeurotic fibrosarcoma (sMaf) [37]. Antioxidant enzymes, such as superoxide dismutase, catalase, and glutathione peroxidase, are expressed via the Nrf2 pathway, generating a cytoprotective and antioxidant response [37]. Corroborating these findings, recently Toydemir et al. (2021) showed in intestinal epithelial cells that bioactive coffee compounds are effective in activating, through interactions between the pathways, Nrf2 and aryl hydrocarbon (AHR) [38]. AHR is described as a ligand-activated transcription factor that reacts against toxic xenobiotics but also with flavonoids, stilbenes, carotenoids, indoles and tryptophan [39].

Studies recently published in 2022 confirm these findings and elucidate the ability of Kahweol [210] and CGAS [2011; 212] to stimulate the NRF2 pathway and inhibit NF-κB signalling pathways.

It is worth mentioning that the coffee roasting process increases the activation capacity of the Nrf2 pathway, with dark roasted coffee being the most potent effector [40; 41]. In keeping with these findings, regular coffee intake increases glutathione levels and improves protection against DNA damage [42].

Other compounds of coffee, such as CGA and caffeic acid, have been shown to reduce the activity of enzymes necessary for lipogenesis: acetyl-CoA carboxylase (ACC), fatty acid synthase (FAS) and stearoyl-CoA desaturase (SCD ) [43; 44]. In addition, it has been shown that they regulate upstream transcription factors for lipogenesis, for example, receptors activated by peroxisome proliferators (PPAR, especially PPARγ), known to regulate adipogenesis [45]. Coffee also reduces lipogenesis via the AMPK pathway [46] and regulates β-oxidation of fatty acids [43; 44; 46]. In this way, it is clear that the antioxidant and anti-inflammatory properties of coffee have the

potential for treating the burden of chronic diseases, such as diabetes, cardiovascular disease and chronic kidney disease (CKD) [47] (**Figure 4**).

**Can coffee change the gut microbiota profile?**

Bioactive compounds from coffee, such as polyphenols, fiber, caffeine, and melanoidins, can interact with the gut microbiota [48; 1; 49]. Studies have shown that coffee can modify some bacterial content and increase the short-chain fatty acid (SCFA) production by microbes in the gut [49; 50]. In human studies and pre-clinical models, coffee intake has been demonstrated to increase the abundance of the *Bifidobacterium spp*.[198] and alter the Firmicutes-Bacteroidetes ratio [37] though some equivocal data exists based on acute low-dose coffee intake [51].

Coffee may improve intestinal permeability and barrier function through increased expression of the occludin and ZO-1 proteins [52; 223;224]. Some gut commensals, including *Escherichia coli, Bifidobacterium lactis and Lactobacillus gasseri*, facilitate the degradation of the coffee in the gut due to cinnamoyl esterase enzyme activity, which acts by cleaving the ester link and releasing the bioactive compounds [53].

Among the polyphenols in the coffee, around two-thirds of the CGA reaches the colon and are metabolised by the gut microbiota releasing several metabolites such as m-coumaric acid, hippuric acids, and benzoic acids, reducing the intestinal pH and modulating the gut microbiota [54; 55]. Previously, Lou et al. (2011) revealed that CGAs could change the cell membrane permeability of the bacteria, acting as antimicrobial [56]. Additionally, other studies have demonstrated in pre-clinical models that CGAs alter the composition of the gut microbiota, decreasing the relative abundance of some pathogens, such as *Enterococcus spp., Wohlfahrtiimonas spp., and Escherichia coli* [55; 57-59]. Besides, a recent animal model study demonstrated that CGA was able to reduce endotoxemia due to altering the gut microbiota profile and increasing the relative abundance of SCFA bacteria producers [223]. Caro-Gómez et al. (2019) found that green coffee extract (equivalent to 220mg/kg CGA) for two weeks in mice promoted beneficial changes in the intestinal microbiota by restoring the number of taxonomic units [60].

Emerging studies on coffee wastes (i.e., coffee pulp and grounds) attempt to decrease garbage production. The coffee pulp contains caffeine, chlorogenic acid, and other compounds. Moreover, a recent study showed that 5% of freeze-dried coffee pulp intervention in rats enriched the abundance of *Clostridium saudiense, Akkermansia muciniphila, Cronobacter malonaticus* and *Cronobacter sakazakii* [199]. Coffee grounds are also rich in two types of dietary fibers, such as galactomannans and arabinogalactans, which have been reported to modify the composition of the gut microbiota by increasing the abundance of Bacteroides and Prevotella [61]. The hydrolysis of the galactomannans from the spent coffee grounds releases mannooligosaccharides (MOS) bioactive entities with the capability to support the growth of Bifidobacteria and increase α-diversity of the gut microbial community [61; 62].

Additionally, the melanoidins possess a prebiotic property [63; 64], possibly mediated by the bacterial production of p-hydroxyphenyl acetic acid and pyrogallol [64].

Recently, Calderón-Pérez and collaborators evaluated, through dietary recalls, the intake of phenolic compounds from coffee and the relationship with the intestinal microbiome in hypertensive and healthy individuals [65]. Coffee phenolic compounds were positively associated with faecal SCFAs, *Bacteroides plebeius* and *Bacteroides coprocola* in hypertensive and healthy individuals. The association was negative between *Faecalibacterium prausnitzii* and *Christensenellaceae R*-7 [65].

**Coffee and Diabetes: could they be allied?**

The first evidence that coffee could have a beneficial effect on glycemic homeostasis emerged in 2002 in a study carried out with healthy individuals who were followed between 1973 and 1977. It was observed that people who consume at least 7 cups of coffee per day have a lower risk of developing diabetes [66]. A subsequent systematic review of the literature confirmed the hypothesis that coffee intake could decrease the risk of developing diabetes [67]. Furthermore, current systematic reviews support these findings [68; 222].

A large-scale meta-analysis included 29 articles with data from 30 prospective studies, with 1 185 210 participants and 53 018 incident type 2 diabetes (T2D) cases by Carlström and Larsson (2018) [47]. The results suggested that the risk of T2D is inversely associated with coffee consumption of 5 cups/day (relative risk (RR): 0.71). The risk of T2D decreased, respectively, by 7% (RR: 0.73) and 6% (0.80) for each cup/day increase of caffeinated and decaffeinated coffee consumption [47].

Bhupathiraju et al. (2014) reported on a large prospective study in which they assessed whether changes in coffee intake affected the subsequent risk of T2D in three groups of men and women in the United States: 48,464 women were followed in the Nurses' Health Study (NHS, 1986-2006), 47,510 women in the NHS II (1991-2007), and 27,759 men in the Health Professionals Follow-up Study (HPFS, 1986-2006) [5]. It was observed that an increase in coffee intake reduced the risk of developing T2D, and a lower coffee intake increased the risk [5]. Coffee intake was also inversely associated with the prevalence of Diabetes mellitus in a Korean cohort studied between 2012-2016 [69]. Indeed, several further studies and meta-analyses have shown that coffee reduces the risk of diabetes [70] and mortality in diabetes [71].

Several hypotheses have been put forward to try to explain the possible effect of coffee in reducing the risk of developing Diabetes. CGAs competitively inhibit glucose-6-phosphate translocase, resulting in decreased intestinal glucose absorption and reduced brush border sodium-dependent glucose transport [72]. CGAs can also act on skeletal muscles, stimulating glucose uptake through AMPK, a protein kinase activated by adenosine monophosphate, resulting in reduced hepatic glucose and fat synthesis [73]. Other mechanisms of action include: modification

of adenosine receptor signalling, inhibition of glucose absorption in the intestine, increasing the formation of GIP-1 and GLP-1 and stimulating the GLUT4 pathway, providing better insulin release from the pancreatic islets and peripheral insulin sensitivity and glucose uptake [67; 74-76] **(Figure 5)**.

In addition, coffee and its components, especially CGAs, can directly interfere with glucose metabolism by intensifying insulin sensitivity [25]. Another possible mechanism of coffee ingestion appears to be the preservation of functional beta cell mass via Nrf2 through increased mitochondrial function and reduction of endoplasmic reticulum stress; also, the coffee components can interact with misfolded peptides, preventing the formation of amyloids (toxic to cells) [77].

Beaudoin et al. (2011) have pointed out that the acute intake of high doses of caffeine (isolated supplementation of ≥ 250 mg of caffeine) administered to healthy individuals reduced insulin sensitivity and increased blood glucose concentration [78]. Decaffeinated coffee is less harmful to glycemic metabolism than caffeine, suggesting that caffeine is responsible for such deleterious effects on glucose metabolism [79]. A recent review has shown that decaffeinated coffee does not acutely affect postprandial glucose when consumed with other foods. The author also reports that decaffeinated coffee can behave like acarbose, a drug used to control glycemia that prevents post-hyperglycemia -prandial and attenuates carbohydrate metabolism [80].

Although, a recent study by Srivastava *et al*. (2022) showed that caffeine statistically reduced sorbitol levels in serum samples immediately and maintained the effect after one h [221]. The noteworthy reduction in sorbitol observed in this study could be virtuous for preventing abnormalities related to sorbitol accumulation, like diabetic neuropathy [221].

Finally, although data in the literature are conflicting, there is sufficient evidence to elucidate the potential protective effect of coffee concerning the development of Diabetes and that its intake can reduce the risk by up to 30% [47] (**Table 2**) [81-93].

**Coffee for cardiovascular health: is it good or bad?**

Coffee has attracted the interest of the scientific community regarding its risks and benefits for the cardiovascular system [8; 94]. Currently, the risk-hazard ratio for the effects of caffeine on the cardiovascular system remains the subject of debate [95; 94].

Several studies have indicated adverse effects from coffee intake, correlating with a higher risk of hypertension, cardiovascular events, acute coronary syndrome, coronary artery disease, and dyslipidemia, especially at higher doses [96-99].

In a meta-analysis of twelve studies from Western countries with a total of 1017 subjects, researchers have shown that coffee intake, in a dose ranging from 2.4 to 8.0 cups/day for 45 days, was associated with an increase in total cholesterol (TC), low-density lipoprotein (LDL) cholesterol and triglycerides. The authors also observed an increase in TC levels, which was more

significant in trials using unfiltered coffee and caffeine [12]. In addition, the result of another meta-analysis with twelve randomised controlled trials corroborated previous findings. In summary, evidence associates the risk of dyslipidemia and CVD with excessive coffee consumption, with doses above 5 to 6 cups/day [100].

Increased blood pressure appears to be an acute effect of caffeine intake that promotes a blockage of adenosine receptors in vascular tissue leading to vasoconstriction [101], and short experimental studies have shown that acute intake raises blood pressure due to increased plasma levels of stress hormones such as cortisol [102]. Despite these findings, long-term coffee intake does not seem to be related to the development of increased blood pressure or hypertension [102].

Miranda et al. (2020) have assessed the association between the risk of hypertension and habitual coffee consumption in a middle-aged Brazilian cohort with 8,780 non-hypertensive participants and followed for 3.9 years (the average total coffee intake was 150 mL/day). At the end of the study, they observed that 1,285 participants developed hypertension, but the relationship between coffee intake and hypertension was directly associated with smokers. Non-smokers, who consumed between 1 and 3 cups/day, had a lower risk of developing hypertension [103]. Recently, a population-based observational study of 1095 adults in Switzerland supported the benefits of habitual coffee consumption as regular drinkers of light (1-3 cups), and moderate (over 3 cups) coffee had reduced arterial stiffness parameter values, as well as central and peripheral BP, when compared to non-habitual patients [200].

Other studies have shown benefits from coffee intake on cardiovascular diseases. Nikpayam et al. (2019), in a systematic review of the effects of green coffee extract (GCE) and CGAs, reported that lipid profile was improved and that higher dose and an extended period of supplementation with GCE gave optimal results [70].

A recent systematic review and meta-analysis noted that green coffee bean extract supplements promoted a reduction in C-reactive protein (CRP) levels and that this was more pronounced at doses above 1000 mg/d, duration of intervention less than four weeks, and for unhealthy individuals (dyslipidemia, hypertension, and non-alcoholic fatty liver disease) [104]. Likewise, other recent literature reviews and studies support the salutogenic properties of coffee, such as efficacy in reducing the risk of coronary heart disease, heart failure and arrhythmia [105-107], inverse association with the development of stroke [108-110] and the association between moderate and habitual coffee consumption and reduced risk of developing arterial hypertension [111].

Additionally, coffee can also reduce lipogenesis and be cardio-protective [76]. A study with 57,053 participants from The Danish Diet, Cancer, and Health study with a follow-up of 13.5 years, has observed that coffee intake was inversely associated with the incidence of atrial fibrillation [98]. Indeed, a meta-analysis has shown that interventional studies did not confirm that caffeine intake was associated with ventricular arrhythmias [112].

Equivocal findings for the effects of coffee on cardiovascular health are often confounded through methodological differences. These differences centre on the use of caffeinated or decaffeinated coffee, different forms of preparation (boiled, filtered, espresso), blends, degrees of roasting and the presence of isolated compounds [11; 12].

Concerning the effects of individual coffee components, caffeine seems responsible for blood pressure effects, diterpenoids for the hyperlipidemic effects of unfiltered coffee, and hydroxy-hydroquinones for the production of reactive active oxygen species [113-115]. On the other hand, CGAs seem to balance coffee's adverse health effects due to their antioxidant, antihypertensive, and hypoglycemic properties [116; 114].

Despite these differences, many studies have reported promising salutogenic effects of coffee in controlling body weight [48; 116]; improving flow-mediated vasodilation [117;118]; arterial stiffness [119], improving plasma lipids [11] and blood pressure [120]. More recently, data from 20.487 Italian adults from the Moli-sani study [121], from 679.333 American participants [122], from 468.629 UK participants [201] and from 190.000 Korean participants [202] were analysed and showed that coffee intake was associated with a lower risk of mortality by CVD. **Table 3** summarises studies on the effects of coffee and its compounds on cardiovascular risk parameters [60;116;118;120; 123-142;198;203-209].

**Coffee for chronic kidney disease patients: is it allowed?**

Patients with chronic kidney disease (CKD) present with increased oxidative stress and inflammatory burden, accompanying accelerated biological ageing [143]. Additionally, cytotoxic stress results in the activation of NF-kB, which promotes the activation of the Nod-like receptor pyrin domain containing 3 (NLRP3) via the inflammasome, which is responsible for the release of pro-IL-1β and pro-IL- 18 [143; 144]. Overexpression of NF-κB in CKD is accompanied by diminished expression of Nrf2, resulting in a pernicious cycle between increased oxidative stress and chronic inflammatory burden as the disease progresses [145].

The salutogenic properties of coffee intake may be related to the activation of Nrf2 by CGAs with consequent activation and expression of the HO-1gene in kidneys, which leads to an increase in the antioxidant enzymes and inhibition of ROS production. This mechanism reduces structural damage in the kidney and mitigates oxidative stress, thus improving kidney function [146]. CGAs can also inhibit the nuclear translocation of NF-κB by blocking the channel involved with TLR-4, thus decreasing IκB phosphorylation and the production of pro-inflammatory cytokines [146; 147].

CGAs can also attenuate renal fibrosis by up-regulating the expression of antifibrotic factors such as bone morphogenetic protein-7 (BMP-7) and hepatocyte growth factor (HGF). BMP-7 and HGF can promote the regeneration of renal architecture and inhibit renal fibrosis [148].

In addition, HGF can suppress the expression of transforming growth factor-β1 (TGF-β1) in renal fibrosis, an essential protein involved in the tissue regeneration process [147; 148].

Putative protective effects of coffee intake on kidney function changes are listed in **Table 4** [146-148; 157-161; 213]. In keeping with these salutogenic effects, the Atherosclerosis Risk in Communities (ARIC) study investigated coffee intake in patients with incident CKD using food frequency questionnaires and observed that individuals who took higher doses of coffee had a lower risk of CKD [149]. Also, the intake of more than 2 cups of coffee per day has been reported to reduce the risk of CKD in the general population [150]. Recent systematic and meta-analyses have indicated that coffee drinkers have a significantly lower incidence of CKD than non-coffee drinkers [151-153].

Randomised Mendelian analyzes of 227,666 UK Biobank participants have shown that increased intake of a cup of coffee among regular drinkers leads to a protective effect against CKD in stages 3 to 5 and was associated with a higher glomerular filtration rate [154]. In patients with CKD, an observational study of 4863 adults from the National Health and Nutrition Examination Survey showed that caffeine intake was inversely associated with all causes of mortality in these patients [155].

Another recent meta-analysis concluded that individuals who drink ≥2 cups/day compared to those who drink ≤1 cup/day have a lower risk of incident end-stage CKD and a lower risk of albuminuria. In addition, the risk of death related to CKD was lower in coffee drinkers [10].

Another important finding discussed recently in the literature is the inverse association of coffee consumption with the formation of kidney stones. Researchers have suggested in their studies that coffee consumption [214; 215], as well as its bioactive compound trigonelline [216], was associated with a reduced and lower risk of developing kidney stones.

The mechanisms by which coffee leads to reno-protection are not fully understood [151]. However, the possible explanation may be related to the antioxidant effect of coffee (via caffeine and CGAs), which can alleviate atherosclerotic kidney damage and reduce the development of CKD [151]. Therefore, it is believed that individuals who regularly consume coffee may have less oxidative stress and inflammatory load. Furthermore, recently He et al. (2021), in a review of the literature on coffee metabolites and incidence of CKD, found that glycocenedeoxycholate, a metabolite related to the primary metabolism of bile acids, may favour reno-protection. While the metabolites O-methylcatechol sulfate and 3-methyl catechol sulfate, both associated with benzoate metabolism, were detected as possibly harmful to kidney health [156].

Thus, coffee intake is not contraindicated in patients with CKD and may be associated with renal protection; however, there is no specific recommendation for coffee intake for patients with CKD [152]. The type of coffee is essential, with caffeinated and filtered coffee being recommended, while unfiltered coffee increases the risk of CKD [152]. In addition, caffeine can be

beneficial to CKD patients since it influences stimulus processing, modulates the encoding and long-term retrieval of memories and enhances vigilance [157].

**Coffee and polymorphism**

The impact of coffee intake shows significant inter-individual variation, especially concerning biophysical and genetic parameters, such as weight, gender, the metabolic activity of P450, and genetic polymorphism [162]. Polymorphism describes a phenotypic variation in the DNA sequence in a chromosomal locus resulting from nucleotide changes.

Single nucleotide polymorphisms (SNPs) may account for inter-individual variation in responses to coffee intake and any putative salutogenic or pathogenic properties [163; 217;218]. The risk of developing heart disease, for example, has been reproduced to be affected by a polymorphism associated with coffee. Liu et al. (2020) elucidated that the risk is significantly lower in coffee consumers with TRIB1 (pseudokinase 1) GG genotypes [163]. Another interesting example is the intake of sweetened and unsweetened coffee that could be influenced by the taste's SNP [217; 219].

Some genetic polymorphisms are associated with caffeine, especially in genes that encode cytochrome P450 (CYP1A1, CYP1A2), aryl hydrocarbon receptor (AHR), neuronal cell adhesion molecule, and taste receptor type 2, family member 43 (TAS2R43) loci [13]. Caffeine metabolism may be compromised if there is a substitution of the cytosine nucleotide for adenine in intron 1. The variation of these genes interferes with caffeine metabolism and may be associated with cardiovascular risk [163-166] and the renal sodium tubular resorption pathway [113]. Furthermore, it can be related to the neural responses [167; 168] and taste perception [169; 170], as showed in **Table 5**.

Genes that encode the enzyme cytochrome P450 (CYP1A1, CYP1A2) influence the metabolism of caffeine, so they can divide the population into two groups, "fast metabolisers" (allele *1A) and "slow metabolisers" (allele *1F) [165]. The change in this allele directly interferes with caffeine metabolisation, and "slow" metabolisers may be associated with a greater risk of myocardial infarction and hypertension, indicating a decrease of coffee consumption [171; 172]. Furthermore, Gkouskou et al. (2022) showed that the consumption of coffee in the CYP1A2 rs762551 polymorphism could have a more influence on the body composition in people with obesity predisposition [220].

Furthermore, some studies have tried to relate SNP to coffee consumption and diabetes and heart disease. Individuals are considered to be slow metabolisers, and with high coffee consumption may present a higher chance of having impaired fasting glucose [99]. However, postprandial blood glucose may be more elevated in fast metabolisers than in slow metabolites [173]. Besides, studies show the inverse relationship between coffee consumption and T2D [174; 175].

**Coffee can be dangerous: for whom?**

Coffee also possesses adverse health effects. Coffee intake has been associated with stimulant effects attributed to caffeine, which remains the most widely used psychoactive substance globally [176; 177]. Caffeine is an antagonist of the adenosine A1 and A2 receptors in the brain, which promote sleep [178]. It is used in headache medications and is indicated for athletic performance and night workers to increase alertness and fight fatigue [179; 180].

According to the European Food Information Council (EUFIC), the average caffeine content per 150mL (one cup) of ground toasted coffee is about 85mg, instant coffee is 60mg, and decaffeinated coffee is 3mg. The ideal intake of coffee is 2-3 cups/day, and exacerbated use (5-6 cups/day) may cause toxicity [181].

High caffeine intake delays sleep onset and reduce neurophysiological markers of sleep intensity (177), which is associated with several diseases [182]. Excessive caffeine intake can cause headaches, insomnia, psychomotor agitation, anxiety, lack of attention, gastrointestinal discomfort, irritability, cardiac arrhythmias, and mild hallucinations [177]. Clark & Landolt (2017) have reported in a systematic review that caffeine decreases sleep time, efficiency and quality of sleep, in addition to prolonging sleep latency. In addition, they stated that the effects of caffeine might be more significant on older adults' sleep than on younger adults [176].

An important factor that cannot be forgotten is the compounds formed from coffee processing, such as polycyclic aromatic hydrocarbons (PAHs), described in the literature as harmful to health. Considered potentially carcinogenic and genotoxic substances, pollutants PAHs may be present in coffee, a priori, through the roasting process and environmental pollution [183]. The formation of PAHs during coffee roasting occurs from the pyrolysis of coffee macronutrients. The significant health damage related to PAHs is the development of breast, lung and colon cancer [183]. Although a fixed number of residual PAHs in coffee and other beverages has not yet been established, according to the European Commission, a fixed percentage is established for oils and fats (10 μg/kg), cocoa beans and by-products (35 μg/ kg), meat and fish products (30 μg/kg) and infant food and diet foods for particular medical protocols (1.0 μg/kg) [184].

According to the literature, green coffee beans have a low number of PAHs, mainly due to air pollution [185]. Unlike what is observed after the roasting process, including drying and grinding [183]. Thus, although the European Food Safety Authority (EFSA) has considered that coffee is not a relevant source of PAHs, it was clarified that reaching the ideal temperature and roasting time allows for a better quality of coffee, both in terms of characteristics, regarding the production of PAHs, able to reduce or even avoid them. Furthermore, it should be noted that, although more studies are needed, it is highlighted that decaffeinated coffee has a lower content of PAHs [183].

Another relevant problem related to coffee consumption is the stimulation of the secretion of acids in the stomach, damaging the gastric and oesophagal mucosa [186], which is associated with diseases such as peptic ulcers, gastritis, and oesophagal reflux [187]. CGAs, caffeine, pyrogallol, catechol, (β)N-alkanoyl-hydroxytryptamides (C5HT) have been reported as the main culprits for irritating the stomach and stimulating acid secretion [188].

On the other hand, there are other compounds in coffee described as less offensive to the stomach, such as N-methyl pyridinium (N-MP), which are produced from trigonelline during the roasting process and which have been shown to regulate gastrin receptor expression negatively and to possess chemo-preventive and antioxidant properties [188-190]. Thus, it is clear that N-MP's quantitative content for C5HTs and CGAs in a coffee drink will determine gastric acid secretion [188; 191].

Likewise, Boekema et al. (1999), in a review of coffee and gastrointestinal functions, have explained that in addition to promoting gastroesophageal reflux (GER), coffee also promotes stimuli for the release of gastrin, stimuli for gallbladder contractility and motor actions of the colon [192]. Furthermore, corroborating these findings, Vossoughinia et al. (2014), in an epidemiological study on GER and its risk factors, explained that out of 2.500 study participants, 27% had GER with coffee intake as one of the associated risk factors [193]. However, other studies have shown that GER may not induce erosive esophagitis [187;194]. Thus, further studies on the adverse effects of coffee intake and its components are needed.

## Conclusions

Through its constituent components, coffee can exert a series of salutogenic effects, from its antioxidant and anti-inflammatory capacity, in addition to modulating the profile of the intestinal microbiota **(Figure 4)**. It holds promise as a natural medicine for managing and treating cardiometabolic diseases where high inflammatory and oxidative loads prevail. Likewise, it is a new addition to the arsenal of non-pharmacological treatments for controlling diabetes and cardiovascular disease.

According to our literature research, we concluded that safe coffee consumption occurs in doses of 2 to 3 cups/day, which is worth approximately 500ml/day of coffee, and adverse effects were only observed in higher doses. However, we also emphasise that studies analysing coffee intervention in patients with these diseases are limited. Therefore, clinical trials evaluating the intervention of coffee in patients with cardiometabolic diseases should be started as a first step.

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**Table 1:** Features and differences of *Coffea Arabica* and *Coffea Canephora* [16; 17]

| Properties | *Coffea Arabica* | *Coffea Canephora* |
|---|---|---|
| **Production of Chlorogenic Acids (CGA)** | 45 – 50 different CGA derivatives | Between 80 – 90 different CGA derivatives (65 and 55% - 5-CQA) |
| **Acidity (%)** | 5.26 – 5.27 | 6.11 – 6.13 |
| **Caffeine content (g/100g)** | 0.9 – 1.4 | 1.5 – 2.6 |
| **Trigonelline (g/100g)** | 1.0 | 0.7 |
| **Cultivation** | Mild climate with temperatures between 15ºC and 22ºC | Higher temperatures, accepting between 24ºC to 29ºC |
| **Flavor** | Mild, chocolatey flavor | More astringent and bitter taste |
| **Price** | It has prices and greater commercial value for having a balance between desirable chemical compounds, presenting better quality | ↓ price, ↑ industrial yield |

**Table 2:** Studies involving coffee functions on diabetes.

| References | Study/ Sample | Intervention | Results |
|---|---|---|---|
| | | ***Animal Studies*** | |
| Al-Megrin et al. (2020)[81] | Diabetes in Rats (HFD/STZ) | 50 mg $kg^{-1}$ $day^{-1}$ of green coffee (~1 cup/day in a human); 100 mg $kg^{-1}$ $day^{-1}$ of green coffee (~2 cups) for 4 weeks | **In testicular tissue:** ↑ GSH, SOD, CAT, GPx, and GR, ↓ lipid peroxides and NO<br>↓ IL-1*β*, TNF-*α*, Bax, and caspase-3 |
| Kaczmarczyk-Sedlak et al. (2019)[82] | Diabetic rats (STZ) | Caffeine at a dose of 20 mg/kg *for 4 weeks* | In the lenses: ↓ MDA and AOPP↑ GSH, ↓ SOD, CAT and GPx |
| Martina et al. (2019)[83] | Healthy mice | Arabica coffee gayo beans (50 mg, 100 mg, and 200 mg) and Arabic coffee gayo extract (30 mg, 60 mg, and 120 mg) | Both Arabica coffee ↓ blood glucose |
| Shokouh et al. (2019)[84] | Rat model of T2D, the Zucker diabetic fatty (ZDF) rat | 3 groups: control; arabica instant coffee (1.8% *w*/*w*) and robusta instant coffee (1.8% *w*/*w*) for 10 weeks | Coffee groups: ↓ liver TG, postprandial insulin, Cpt1a gene expression in liver<br>Robusta Group: ↑ adiponectin, TC and HDL levels, ↓ Glucose-6-phosphatase, catalytic subunit (G6pc) and mechanistic target of rapamycin (mTOR) gene expression in liver |
| Shokouh et al. (2018)[85] | Sprague–Dawley rats – HFD + 20% W/W fructose in drinking water | 3 groups: Control; coffee (1.18 g of ground medium-roast Ethiopian Arabica) or nutraceuticals (24 mg 5-*O*-caffeoylquinic acid, 12 mg caffeic acid, and 7 mg trigonelline) for 14 weeks | Coffee Group: ↓ plasma glucose, fasting insulin, HOMA-IR, and oral glucose tolerance |
| Folwarczna et al. (2017)[86] | Wistar diabetic rats (STZ and nicotinamide) | Caffeine administered orally (20 mg/kg daily) for 4 weeks | No damage effect on bone turnover markers, mass, mineral density, histomorphometric parameters |
| Folwarczna et al. (2016)[87] | Wistar diabetic rats (STZ and nicotinamide) | Trigonelline (50 mg/kg p.o.) for daily for 4 weeks | In STZ/nicotinamide induced rat: ↑ BMD<br>In STZ group: ↑osteoporotic changes |

| | | | |
|---|---|---|---|
| Fujii et al. (2015)[88] | Male C57BL/6J mice | CPE (0·28 g/kg as polyphenols) with high-fat meal (starch (2 g/kg BW) + trioleate (1 g/kg BW), 33 % (w/w) fat) | ↑ gut-derived active GLP-1 secretion and ↓ glucose-dependent insulinotropic polypeptide release |
| ***Human Studies*** | | | |
| Alperet et al. (2020)[89] | Double-blind randomized placebo-controlled trial / 126 overweight, non-insulin sensitive participants | 2 Groups: Placebo and coffee (4 cups of instant regular coffee) for 24 weeks | ↔ insulin sensitivity, glucose and adiponectin |
| Mansour et al. (2020)[90] | 26 patients TD2 and NAFLD | 4 groups: 200 mg caffeine + 200 mg chlorogenic acid, or 200 mg caffeine + 200 mg placebo (starch), or 200 mg chlorogenic acid +200 mg placebo, or 200 mg placebo + 200 mg placebo for 12 weeks | ↓ body weight in the intervention groups |
| Gao et al., (2018)[91] | Healthy individuals (consumer and non-coffee consumers) | Standard questionnaire on current lifestyle, coffee consumption, tea consumption, smoking, alcohol consumption, physical activity, medical records, family history of diabetes (only first-degree relatives) and education | Coffee consumption was positive associated with the function of pancreatic beta cells<br>Consumers: > levels of fasting insulin, 30 min and 1 hour during the oral glucose tolerance test and ↓ plasma glucose levels. |
| Reis et al. (2018)[92] | Randomized, double-blind crossover study with 17 healthy individuals | Coffee with sugar-free caffeine, coffee with sugar-caffeine, and decaffeinated coffee providing caffeine to the participants at 1,4–2,0 and 0,24–0,33 (mg/kg body weight), respectively | Decaffeinated coffee: effective in improving insulin sensitivity without modifying the levels of incretin hormones |
| Lee et al. (2016)[93] | Pre-diabetic patients with glycated hemoglobin levels between 5.7% to 6.4% | Kaplan-Meier cross-tabulation and survival analyzes were used to compare patients with and without diabetes progression based on the frequency and method of coffee intake | Coffee consumers: ↓ risk of Diabetes and higher effect in coffee sugar free |

**Abbreviations:** HFD: High-Fat Diet; STZ: streptozotocin; TG: triglyceride; TC: total cholesterol; BMD: bone mineral density; HDL: High-density lipoprotein; T2D: type 2 diabetes mellitus; HOMA-IR: Homeostases Model Assessment-Insulin Resistance; CAT: catalase; GSH: glutathione; GPx: glutathione peroxidase; GR: glutathione reductase; SOD: superoxide dismutase; NO: nitric oxide; MDA: malondialdehyde; AOPP: advanced oxidation protein product; GLP-:1Glucagon-like peptide 1; CPE: coffee polyphenol extract; NAFLD: non-alcoholic fatty liver disease; TNF-*α:* tumour necrosis factor-alpha; Bax: : Bcl-2-like protein 4.

**Table 3:** Studies involving coffee and functions on cardiovascular risk parameters.

| References | Study/ Sample | Intervention | Results |
|---|---|---|---|
| | | ***Animal studies*** | |
| Ramos et al. (2022)[208] | 24 High-fat diet-induced obese rats | 4 groups for 56 days: control (CT-); coffee (CT+) 3.9 g of freeze-dried coffee/kg of diet; high-fat (HF-); or high-fat + coffee 3.9 g of freeze-dried coffee/kg of diet (HF+) diet | **High-fat diet with coffee group**: ↑ hepatic GST activity and TNF, ↓ IL6. |
| Cavalcanti et al. (2022)[198] | 28 High-fat diet-induced obese rats | 4 groups for 56 days: control group: AIN-93G diet; high-fat group (**HF-**): AIN-93G diet with 58% of fat; coffee group (**CF+**): AIN-93G diet with 3.9 g of freeze-dried coffee solution (FCS)/kg of diet; and high-fat + coffee group (**HF+**): AIN-93G diet with 58% of fat (51.9% of lard and 6.1% of soy oil) and 3.9 g of FCS/kg of diet. | **FCS**: ↑ HDL-C, ↑fecal and cecal *Bifidobacterium* spp. |
| Park (2021)[207] | 20 Sprague-Dawley male rats | 2 groups: water control group and coffee containing javamide-I/-II group for 20 weeks. | No differences were found in plasma LDL, HDL, total cholesterol, CRP, E-selectin, TNF-α and MCP-1 concentrations. |
| Ilmiawati et al. (2020)[226] | 25 High-fat diet-induced obese rats | 4 groups: HFD and GCE at 10, 20, and 40 mg/kg body weight (BW)/day, respectively, and a control group for 13 days. | **GCE (10, 20, and 40 mg/kg BW):** ↓ body weight, serum total cholesterol and triglycerides levels<br>**GCE (40 mg/kg BW):** ↓ TNF-α, LDL-cholesterol levels |
| Caro-Gómez et al. (2019)[60] | 24 $ApoE^{-/-}$ mice | Atherogenic diet without or with GCE by gavage (equivalent to 220 mg/kg of CGA) for 14 weeks | **GCE:** ↓fasting glucose, insulin resistance, serum leptin, liver triglycerides, weight gain, adiposity, inflammatory infiltrate in adipose tissue<br>Modulated hepatic IL-6 |
| Bhandarkar et al. (2019)[130] | 72 Male Wistar rats | 6 groups: corn starch diet (C); C + 5% green or decaffeinated green coffee; high-carbohydrate high-fat diet (H) or H + 5% green or decaffeinated green coffee - 8 weeks. | **Green coffee** ↓ BW, SBP, inflammation in the heart and liver and diastolic stiffness |
| Van Rymenant et al. (2017)[129] | Male Swiss mice, *soluble guanylate cyclase (sGC) alpha 1 subunit knockout (sGCα1 (−/−) mice and their control mice sGCα1 (+/+) with a 129SvJ background*. | 3 groups: Cumulative concentration–response ($1.10^{-7}$–$3.10^{-5}$ M) curves for FA and FA-sul were established, exposing the tissues in 10-min intervals.<br>***In vivo*:** Injection in jugular vein w/<br>- FA 11.42 µg/kg and 114.2 µg/kg<br>- FA-sul, doses were 16.13 and 161.3 µg/kg | - FA-sul caused significant concentration-depend relaxations in all three tissues.<br>***In vivo***<br>- FA-sul: ↓ MAP;<br>- FA-sul induced vasorelaxation: amplified w/ endothelium denudation and L-NAME treatment, only in aortae and femoral arteries;<br>- ODQ ↓FA-sul-induced relaxations |

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| ***Human studies*** | | | |
| García-Cordero et al. (2022)[210] | Randomized, double-blind crossover study with 29 adults overweight/obese | 3 groups: green coffee polyphenols (GCP) (300 mg), beta-glucans (BG) (2.5 g) or GCP/BG (300 mg + 2.5 g) twice a day for 8 weeks | No changes in any of the body composition parameters in any group |
| Schüttler et al. (2022)[209] | Randomized, double-blind crossover study with 16 healthy adults | In session 1, 750 mL of a commercial energy drink (containing 32 mg caffeine/100 mL (0.03%), 0.4% taurine, 11 g/100 ml sugar).<br>In session 2, 3 cups of coffee (containing 80 mg caffeine/cup) | **Coffee:** did not alter ECG-based biomarker periodic repolarization dynamics and heart rate |
| Lara-Guzmán et al. (2021)[203] | Randomized, controlled clinical trial with 25 healthy subjects | 3 groups: coffee beverage (400 mL/day) containing 787 mg (coffee A) or 407 mg (coffee B) of chlorogenic acids and control group (without coffee) for 8 weeks. | **Coffee Groups:** free fatty acids and oxysterols decreased |
| Naylor et al. (2021)[206] | Double-blind, randomized and crossover trial with 21 healthy adults | 3 different doses of decaffeinated green coffee extract (302, 604, and 906 mg) and a placebo. | Flow-mediated dilation increased after consumption of 302 mg decaffeinated green coffee extract. |
| Martini et al. (2021)[204] | Three-arm, crossover, randomized trial, 21 healthy volunteers | 1 cup of espresso coffee/day or 3 cups of espresso coffee/day or 1 cup of espresso coffee + 2 cocoa-based products containing coffee, twice per day. 1 month each step. | No effects on inflammatory markers, trimethylamine N-oxide, nitric oxide, blood lipids, markers of glucose/insulin metabolism and blood pressure |
| Sarriá et al. (2020)[205] | Randomized, controlled and crossover intervention, hypercholesterolemic and normocholesterolemic adults | Coffee group (green/roasted coffee blend containing 74.2 mg/g (dry matter) of total hydroxycinnamic acids (mainly chlorogenic acid) and 20.2 mg/g (dry matter) of caffeine) or a control group (isotonic drink, free of sugar, polyphenols and methylxanthines) three times a day for 8 weeks. | **Coffee group:** Body weight, body fat percentage and BMI were significantly reduced after consumption of the coffee blend without the influence of the group<br><br>**Coffee group:** Waist circumference, waist/hip ratio and waist/height showed a slight reduction only in hypercholesterolemic volunteers |
| Watanabe et al. (2019)[116] | Randomized, double-blinded, parallel between-group comparison trial with 150 healthy and overweight participants | 2 groups: instant coffee high-CGA (369 mg CGA/serving) or control (35 mg CGA/serving) for 12 weeks | **high-CGA Group:** ↓Visceral fat area, total abdominal fat area, BW, WC |

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| Kajikawa et al. (2019)[131] | Single-blind, randomized, placebo-controlled, crossover-within-subject clinical trial of 37 patients with borderline or stage 1 hypertension. | Study 1 group: a single intake of beverage A (CGA: 412 mg, hydroxyhydroquinone: 0.11 mg, caffeine: 69 mg) or beverage B (CGA: 373 mg, hydroxyhydroquinone: 0.76 mg, caffeine: 75 mg) with crossover. Study 2 group was randomized to single intake of beverage A or beverage C (CGA: 0 mg, hydroxyhydroquinone: 0.1 mg, caffeine: 59 mg) with crossover | **Beverage A:** ↑ postprandial flow-mediated vasodilation, ↓ circulating 8-isoprostane levels |
| Suzuki et al. (2019)[118] | Double-blind, placebo-controlled pilot study with 16 healthy Japanese men | 2 groups: test beverage cGCE (100-mL containing 300 mg of CGA) and placebo for 2 weeks | **CGA group:** ↑ endothelium-dependent FMD, ↓ sympathetic nervous activity; ↑ CAVI change |
| Martínez-López et al. (2019)[132] | Randomized, cross-over, controlled study with 25 and 27 hypercholesterolemic subjects | 6 g/ day of soluble green/roasted (35:65) coffee (445.2 mg CQAs and 121.2 mg of caffeine) or control beverage | **Green/roasted coffee:** ↓ TC, LDL-C, VLDL-C and triglycerides; ↑ plasma antioxidant capacity; ↓ MDA, protein carbonyl groups |
| Roshan et al. (2018)[133] | Randomized, double-blind, placebo-controlled trial with 43 patients with the Mets and BMI over 25 kg/m2 | 2 groups: 400 mg of decaffeinated green coffee bean extract or placebo twice per day for 8 weeks | **Decaffeinated green coffee bean extract group:** ↓ SBP, fasting blood glucose, WC, appetite score |
| Sarriá et al. (2018)[120] | Crossover, randomized, controlled study was performed in 25 normocholesterolaemic and 27 hypercholesterolaemic subjects | A green/roasted coffee blend providing 510.6 mg hydroxycinnamic acids and 121.2 mg caffeine/ day 3X/day, control drink for 8 weeks | **Coffee:** ↓ SBP, DBP, % body fat, ↓ Glucose concentration, insulin resistance, ↓ triglyceride levels |
| Boon et al. (2017)[134] | Randomized, Placebo controlled, Crossover trial, 11 healthy participants, regular coffee consumption | 3 treatments tested: (i) 18g of caffeinated coffee (dark roast and ground for espresso) with 300mg CGA (200mL); (ii) 18g decaffeinated coffee (same variety of coffee w/ the caffeine removed) with 287mg CGA (200mL); (iii) control - consumed twice, 2 hours apart, with the 2º beverage consumed simultaneously with a 75g glucose load, with 1 week washout | - **caffeinated coffee** - improvement in endothelial function<br>↔ BP and NO production |

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| Zuchinali et al. (2016)[135] | Randomized double-blinded clinical trial, Crossover design, 51 patients w/ predominantly moderate-to-severe left ventricular systolic dysfunction | 5 doses of 100mL decaffeinated coffee mixed with: I. 100 mg of caffeine; or II. lactose powder (placebo). 1-hour intervals between doses. *The protocol was repeated after a 1-week washout period, and a crossover washout after 7 days.* A Treadmill-teste was performed for 10 min. | ↔ VPBs or SVPBs (isolated, couplets, or nonsustained tachycardia), and in mean HR;<br>↔arrhythmias<br>**Treadmill test**: ↑peak SBP and DBP in the caffeine group. |
| Ward et al (2016)[136] | Double-blind, Randomized, Placebo controlled crossover trial, 14 healthy subjects | 4 Treatments: (i) 1 g maltodextrin (control group), (ii) 450 mg purified 5-CGA + 1 g maltodextrin, (iii) 900 mg purified 5-CGA + 1 g maltodextrin, or (iv) 200 mg purified (−)-epicatechin + 1 g maltodextrin (positive control). All participants completed all 4 treatments, in a random order, with a minimum 1-week washout between visits. | - ↔ peak FMD response for either dose of 5-CGA or the epicatechin, at 1h or 4h post-treatment;<br>- ↑ continuous FMD response: 450 mg and 900 mg of 5-CGA at 1h, and 900 mg 5-CGA at 4h;<br>- ↔ BP |
| Zimmermann-Viehoff et al. (2016)[137] | Three-arm within-subjects, Cross-over, 77 healthy subjects, Habitual Consumers and Non-habitual consumers | 3 sessions, randomized order the subjects consumed an equivalent amount of: 1) A triple espresso; 2) Decaffeinated espresso; 3) Warm water. *Interval of at least 48h between the sessions.* | ↔ on vagal activity;<br>Consumption of decaffeinated espresso ↓ vagal activity in habitual coffee consumers. |
| Agudelo-Ochoa et al. (2016)[138] | Randomized Controlled Clinical Trial, Single-blinded, 74 healthy subjects, Habitual coffee drinkers | 3 groups: Control Group *(no coffee consumption, no placebo)*, 2 groups that drank 400mL coffee/d w/ 1 of 2 CGA contents: medium CGA content (420 mg) or high CGA content (780 mg), for 8 weeks | - After coffee consumption (1 h and 8 wk): ↑caffeic, and ↑ ferulic acid in the coffee-drinking groups.<br>- 1h after coffee intake, AC: ↑in the MCCGA, ↑ in the HCCGA;<br>- After 8 weeks: ↔ lipid, FMD, NO, SBP and DBP. |
| Jokura et al (2015)[139] | Single-blind, Randomized, Placebo-controlled, Crossover trial, 19 healthy male adults | 2 groups consumed a teste meal with: CPE beverage (185 mL) with 355 mg of CQAs and placebo beverage (without CQAs). *Each beverage contained 54.9 mg of caffeine.* | - 30 min after the CPE beverage: ↓dROM;<br>- 60 min after CPE beverage: ↓postprandial decline in FMD, and returned to baseline level by 120 min after the CPE beverage;<br>- after CPE beverage: ↑ Peak blood active GLP-1 levels;<br>- 120 min after CPE beverage: ↑ postprandial FMD |
| Noguchi et al. (2015)[140] | Double-blind, Placebo-controlled, Crossover, 27 healthy subjects | 2 protocols w/ interval of more than 2 days, crossover manner: Instant coffee of a 2g w/ or without caffeine was prepared w/ 150 ml hot water. | **Caffeinated coffee intake:** ↑SBP, ↑DBP, ↑MBP, ↑ vascular resistance of the finger vascular bed, ↑post-occlusive reactive hyperemia of finger blood, ↓finger blood flow |

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| Ochiai et al. (2014)[141] | Randomized Acute Clinical Intervention, Cross-over design, 14 healthy men | 2 groups: 225 mL of a 75-g Glu-equivalent test solution, either alone (Glu) or w/ CPP (600 mg CQAs; Glu + CPP) | **Glu + CPP:** ↑ RHI, at 1.5h after ingestion;<br>- Both groups: ↑SBP; ↑ blood Glu, ↑insulin; ↑*Glu- dependent insulinotropic polypeptide;* ↑*glucagon-like peptide 1 levels;* ↑*urinary hydrogen peroxide levels.* |
| Kempf et al. (2014)[142] | Randomized controlled trial, 114 overweight subjects | 2 groups received coffee pads w/ 7.5g: dark-roasted (D-) coffee *(study blend)* or medium-roasted (M-)coffee (market blend). | - M-coffee: ↑HDL cholesterol; ↑adiponectin;<br>- D-coffee: ↑triglycerides;<br>- Both groups: ↑NMP; |

**Abbreviations:** CGA: chlorogenic acids; BW: body weight; GCE: green coffee extract; SBP: systolic blood pressure; DBP: diastolic blood pressure; WC: waist circumference; CAT: catalase; cGCE: CGA-enriched green coffee bean extract; FMD: flow-mediated dilatation; CAVI: cardio-ankle vascular index; Mets: metabolic syndrome; CQAs: Caffeoylquinic acids; 3,5-DCQA: 3,5-dicaffeoylquinic acid; 5-CQA: 5-caffeoylquinic acid; AC: antioxidant capacity; Ach: acetylcholine; ADP: Adenosine 5`-diphosphate; BP: blood pressure; CA: caffeic; CPP: coffee polyphenols; CPE:Coffee polyphenol extract; CPP: coffee polyphenols; CQAs: Chlorogenic acids; DBP: diastolic blood pressure; DHCA: dihydrocaffeic acid; dROM: diacron-reactive oxygen metabolites; eNOS: endothelial nitric oxide synthase; FA: Ferulic acid; FA-sul: Ferulic acid-4-O-sulfate; FMD: flow-mediated dilation; GCBE: green coffee bean phenolic extracts; Glu: Glucose; GSH: glutathione; HAECs: human aortic endothelial cells; HCCGA: high CGA content; HR: heart rate; L-NAME: n ω-nitro-l-arginine methyl ester; MAP: mean arterial pressure; MCCGA: medium CGA content; MDA: malondialdehyde; NMP: N-methylpyridinium; NO: nitric oxide; NOS: NO-Synthase; NOx: S-nitrosothiols, nitrite and nitroso species; ODQ: 1H- [1,2,4]oxadiazolo[4,3-a]quinoxalin-1-one; PE: phenylephrine; RHI: reactive hyperemia index; SBP: systolic blood pressure; sGC: soluble guanylate cyclase; SNP: sodium nitroprusside; SOD: superoxide dismutase; SVPBs: supraventricular premature beats; TEA: Tetraethyl ammoniumchloride; TG: trigonelline; VPBs: ventricular premature beats; YMPE: yerba mate phenolic extracts.

**Table 4.** Studies involving coffee consumption and its effects on kidney diseases.

| References | Study/Sample | Intervention | Results |
|---|---|---|---|
| | | ***Animal Studies*** | |
| Yunus et al. (2020)[148] | Unilateral ureteral obstruction -induced kidney fibrosis mice model | CGA (14 mg/kg/d) intraperitoneally for for 7-14 days | ↓ Myofibroblast and Fibrosis Area Fractions in the kidney<br>↑ HGF mRNA expression |
| Arfian et al. (2019)[147] | Kidney ischemic/reperfusion mice | CGA intraperitoneally for 2 days:<br>Group 1: 3.5 mg/kg; Group 2: 7 mg/kg; Group 3: 14 mg/kg | Group 2 and 3: ↓ tubular injury, myofibroblast numbers<br>Group 3: ↑ kidney function, SOD-1 mRNA expression<br>↓ Cr; TLR-4, NF-$\kappa$B, TNF-$\alpha$ and MCP-1 mRNA expressions<br>All the groups: ↓ vimentin and TGF-$\beta$1 mRNA expressions |
| Bao et al. (2018)[146] | STZ + HFD-induced diabetic nephropathy rats | CGA at a dosage of 10 mg/kg daily for 8 weeks | ↓ diabetic renal damage, CrCl and urea and proteinuria<br>↓ glomerular hypertrophy and mesangial matrix expansion<br>↓ phosphorylation of IκB, nuclear translocation of NF-κB and IL-6, TNF-α and IL-1β production<br>↑ nuclear translocation of Nrf2 and the expression of HO-1 |
| Suzuki et al. (2017)[159] | obese diabetic rat model | Group 1: sedentary; Group 2: exercise; Group 3: 90.7 ± 4.7 mg/kg/day of caffeine; Group 4: exercise plus 90.7 ± 4.7 mg/kg/day of caffeine | Group 1 and 2: ↑ diabetic nephropathy progression<br>Group 3: ↓ insulin resistance<br>Group 3 and 4: ↑BP, urine volume, electrolyte excretion, CrCl, insulin sensibility; ↓ albuminuria |
| Ye et al. (2016)[158] | STZ-induced diabetic nephropathy rats | CGA for 6 weeks<br>Group 1: 5 mg/kg; Group 2: 10 mg/kg; Group 3: 20 mg/kg | All the groups: ↓ albuminuria, Cr and urea, MDA and COX-2 expression<br>↓ mesangial cell proliferation and mesangial expansion in the kidney; ↑ GSH-Px levels in the kidney<br>Group 2 and 3: ↑ SOD and CAT levels in the kidney<br>Group 3: ↓ blood glucose |
| | | ***Human studies*** | |
| Komorita et al. (2022)[214] | Multicenter prospective study; 3,805 with T2D and eGFR ≥60 mL/min/1.73 m2 | Coffee consumption was assessed using a frequency of consumption questionnaire, and participants were divided into four groups: no cup of coffee, less than one cup a day, one cup a day, or two or more cups a day. | Higher coffee consumption: ↓ the risk of decline in eGFR. |

| | | | |
|---|---|---|---|
| Aoun et al. (2021) [161] | Randomized multicenter clinical trials/ 139 HD patients | Group A: 80mL of regular coffee; Group B: 80mL of decaffeinated coffee (placebo), during dialysis, in 12 consecutive dialysis sessions | ↔ headache and hypotension |
| Caetano et al. (2019)[160] | Cross-sectional, multicenter study/ 373 HD patients | Group 1: no coffee<br>Group 2: 1–2 cups of coffees/d<br>group 3: 3 or > cups/d | Group 1: ↑ dialysis adequacy, ↓ DBP, ↓K<br>Group 2: ↓ body cell mass index, albumin and interdialytic weight gain and lean tissue index<br>Group 3: ↑ K, P, DBP, albumin and interdialytic weight gain<br>↑ body cell mass index and lean tissue index<br>↓ dialysis adequacy |
| Nikić et al. (2014)[157] | Cross sectional Study/ 86 HD patients | The habitual coffee use and the average daily caffeine intake estimated by a dietary questionnaire | 78% consume black coffee daily in low to moderate dose<br>Habitual drinkers: 25% normal mental performance<br>Non- habitual drinkers: 16% normal mental performance Regular drinkers:<br>↑ scores on attention and concentration test. |

**Abbreviation:** STZ: streptozotocin; T2D: type 2 diabetes; HFD: high- fat diet; eGFR: estimated glomerular filtration rate; PD: peritoneal dialysis; HD: hemodialysis; Cr: creatinine; BP: Blood pressure; CrCl: creatinine clearance; Nrf2: nuclear factor erythroid-derived 2-related factor 2; HO-1: heme oxygenase-1; NF-κB: nuclear factor kappa beta; CGA: Chlorogenic acid; IL: Interleukin; TNF: Tumoral necrosis factor; MCP-1: Monocyte Chemoattractant Protein-1; TGF-β1: Transforming growth factor-β1; TLR: Toll like receptor; HGF: hepatocyte growth factor; MDA: Malondialdehyde; GSH-Px: glutathione peroxidase; CAT: catalase; SOD: superoxide dismutase; COX-2: cyclooxygenase-2; DBP: diastolic blood pression; K: potassium.

**Table 5**. Polymorphism associated with caffeine [113; 163-170]

| Gene | Polymorphism | Alteration |
|---|---|---|
| CYP1A2 | rs762551*1A allele or rs762551*1F allele | Enzyme activity – divided individuals in “caffeine fast metabolizers” or “slow caffeine metabolizers” |
| CYP1A2 | rs762551*1F allele | More effect of caffeine in blood pressure by renal sodium tubular reabsorption pathway |
| CYP1A1 | T3801C | Higher enzyme activity and blood pressure changes |
| AHR | rs4410790 | Neural response to coffee consumption. |
| POR | rs17685 | Increased POR expression and potentially weakens the DNA binding of several transcriptional regulatory proteins. |
| ABCG2 | rs1481012 | Encodes a xenobiotic efflux transporter |
| TAS2R43<br>TAS2R38<br>CA6 | rs71443637<br>rs713598, rs17266866 e rs10246939<br>rs2274333 | Perception of bitter flavor |
| TRIB1 | rs17321515 | Risk of cardiovascular disease and changes in plasma levels of cholesterol. |

**Figure 1.**

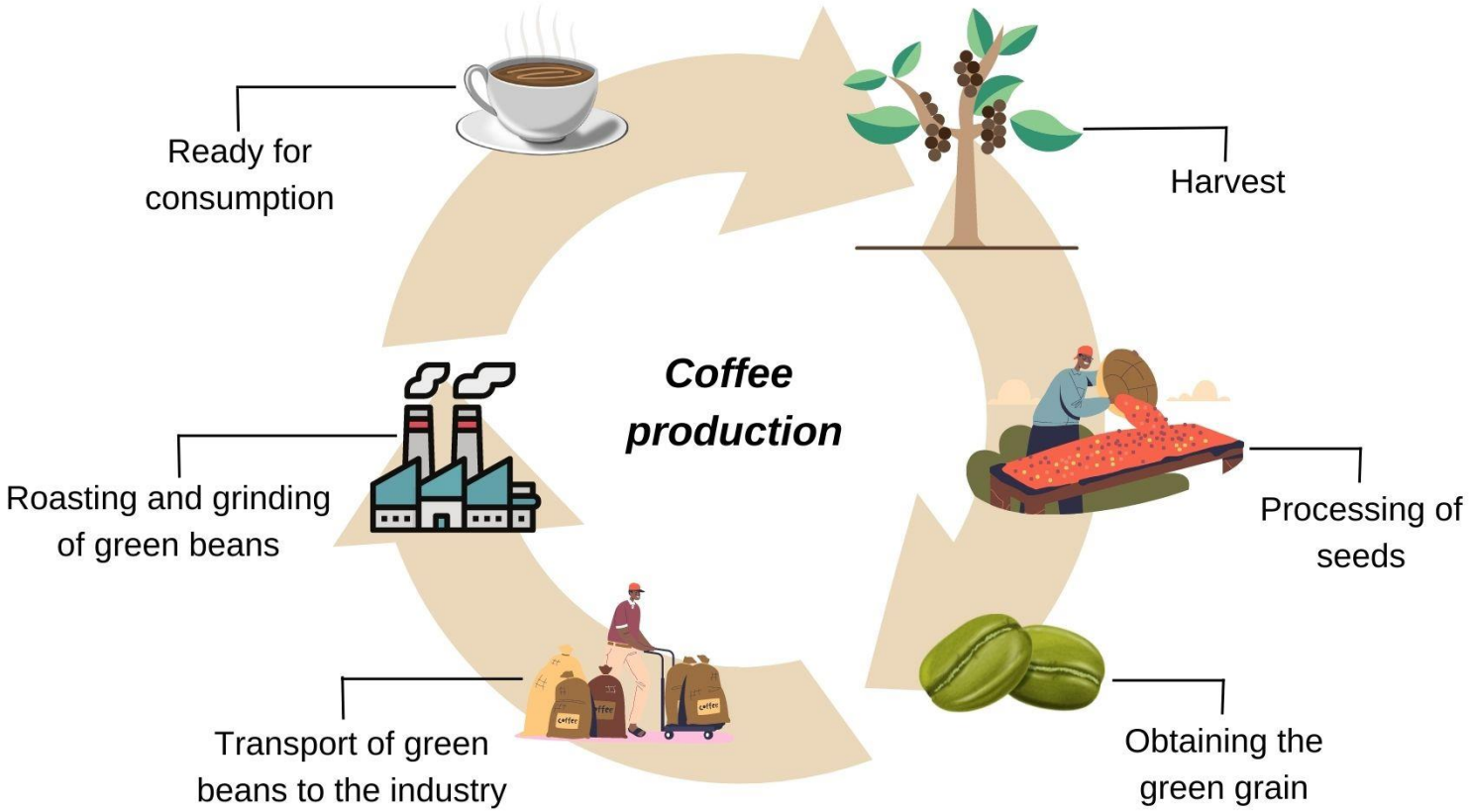
Ready for consumption
Harvest
Coffee production
Roasting and grinding of green beans
Processing of seeds
Transport of green beans to the industry
Obtaining the green grain

**Figure 2.**

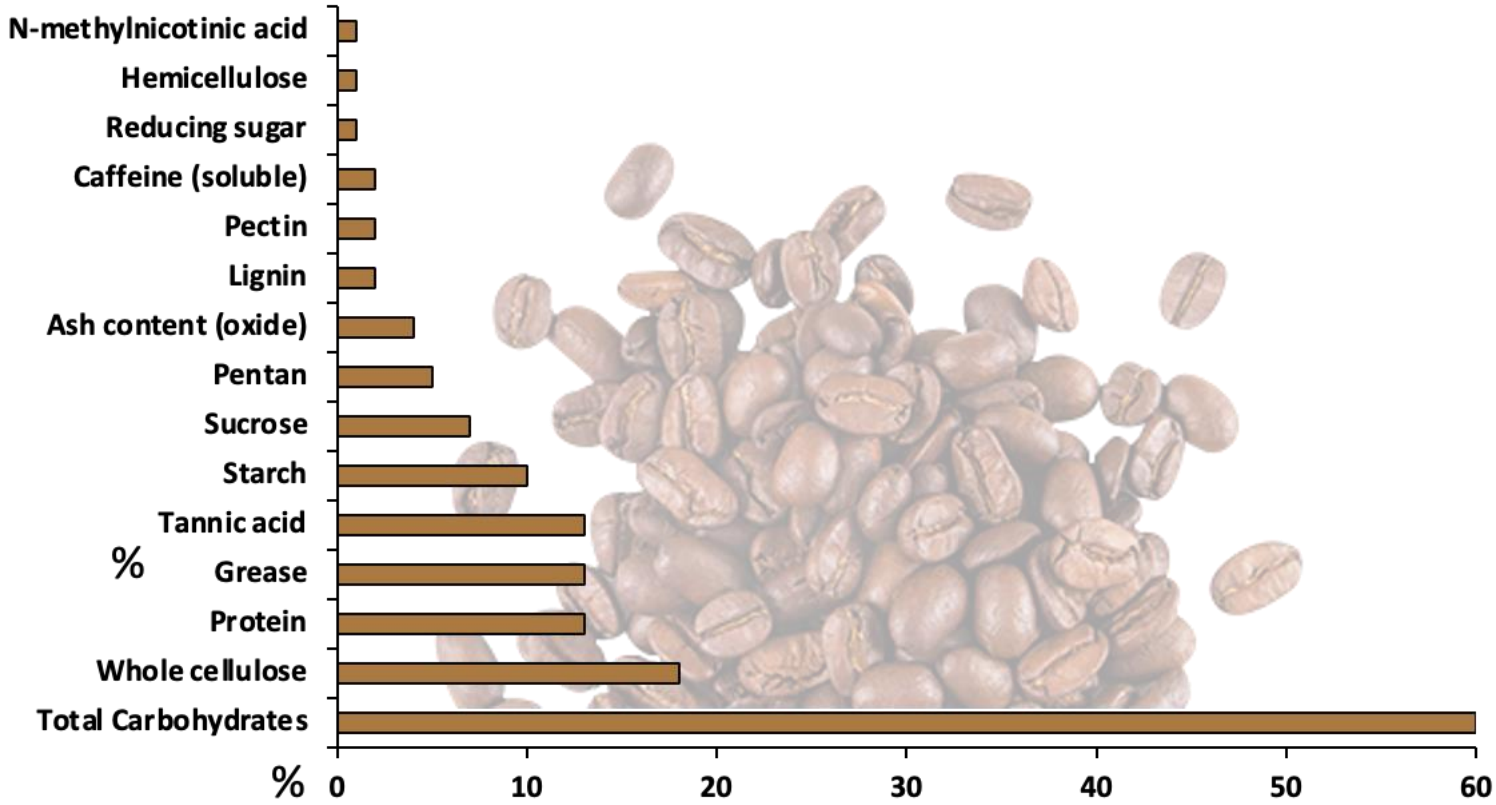
N-methylnicotinic acid
Hemicellulose
Reducing sugar
Caffeine (soluble)
Pectin
Lignin
Ash content (oxide)
Pentan
Sucrose
Starch
Tannic acid
Grease
Protein
Whole cellulose
Total Carbohydrates
%
%
0
10
20
30
40
50
60

**Figure 3.**

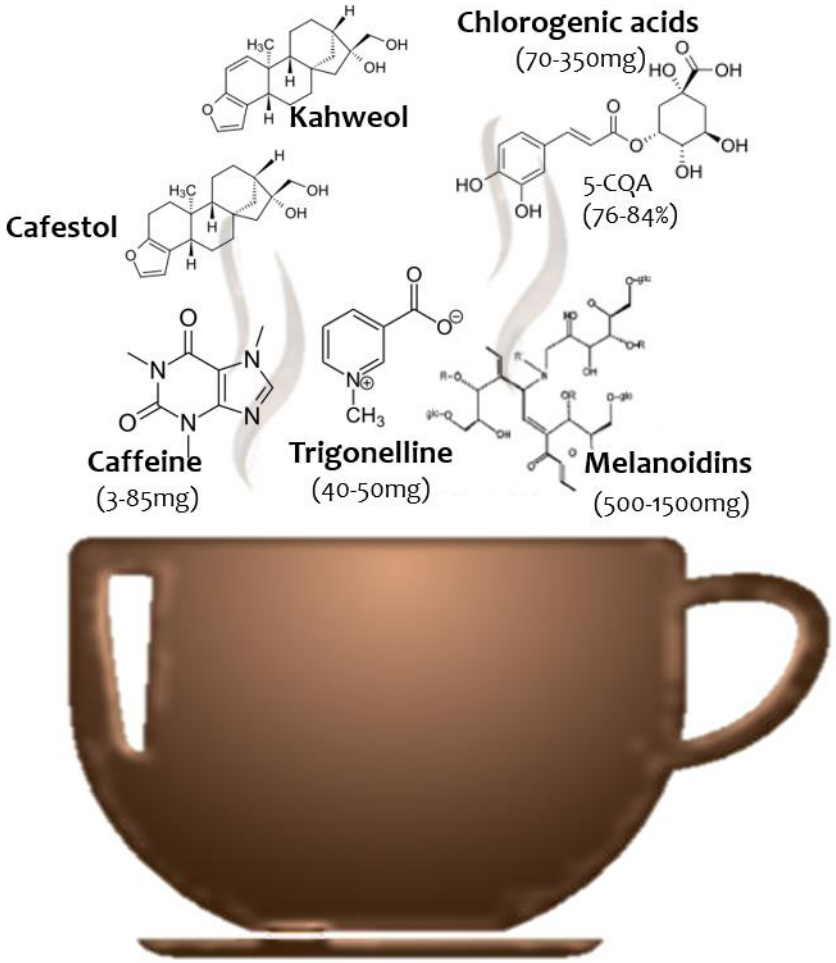
Chlorogenic acids
(70-350mg)
Kahweol
Cafestol
5-CQA
(76-84%)
Caffeine
(3-85mg)
Trigonelline
(40-50mg)
Melanoidins
(500-1500mg)

**Figure 4.**

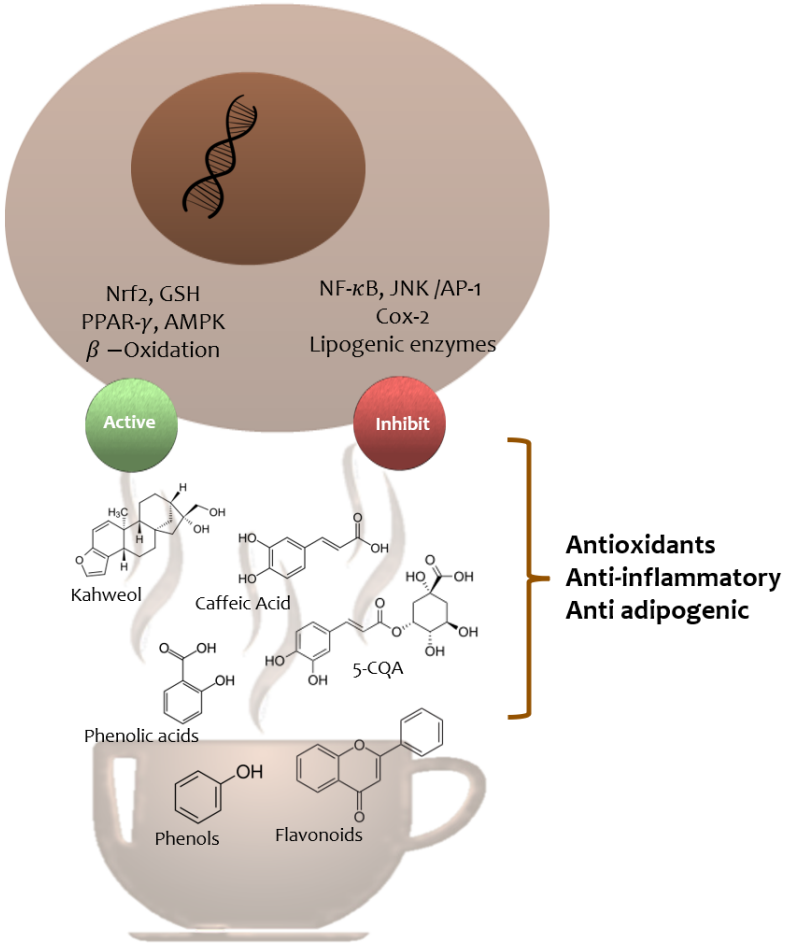
Nrf2, GSH
PPAR-γ, AMPK
β −Oxidation
NF-κB, JNK /AP-1
Cox-2
Lipogenic enzymes
Active
Inhibit
Kahweol
Caffeic Acid
5-CQA
Phenolic acids
Phenols
Flavonoids
Antioxidants
Anti-inflammatory
Anti adipogenic

**Figure 5.**

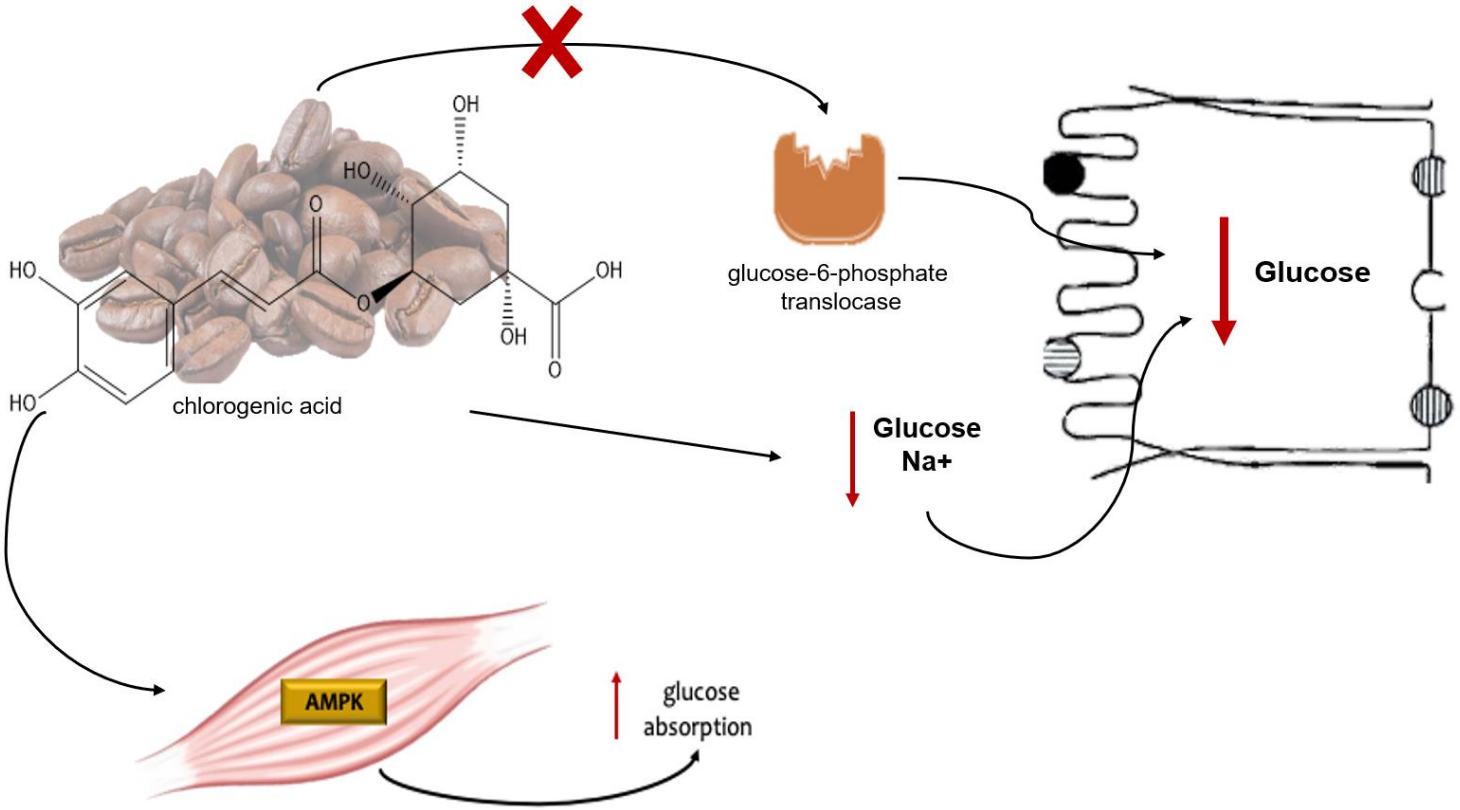
chlorogenic acid
glucose-6-phosphate translocase
Glucose
Glucose Na+
AMPK
glucose absorption

**Figure 1 legends. Coffee production steps.** 1- harvest the fruits in the field; 2- Seed processing to separate the outer layers (skin, pulp, mucilage and parchment; 3- Obtaining the green bean; 4- Transport to industries; 5- Roasting, grinding and encapsulation in industries; 6- Ready-to-drink coffee is distributed to the commercialization centers.

**Figure 2 legends. The main chemical composition of raw coffee beans.** Coffee beans contain a variety of ingredients that make up the total weight of raw coffee beans, such as carbohydrates (60%), Reducing sugar (1%), Sucrose (7%), Pectin (2%), Starch (10%), Pentan (5%), Hemicellulose (15%), Whole cellulose (18%), Lignin (2%), Grease (13%), Protein (13%), Ash content (oxide) (4%), Tannic acid (13%), N-methylnicotinic acid (soluble) (1%) and Caffeine (soluble) (1~2%).

**Figure 3 legends. The usual composition of a cup of coffee (100mL).** The composition can change according to blend, roasting degree, grid, and method of preparation. The most common CGA isomer is 5-caffeoylquinic acid (5-CQA) (35-175mg), found in green beans. But, 3-caffeoylquinic acid (3-CQA), 4-caffeoylquinic acid (4-CQA), 3,4-Dicafeoylquinic acid (3,4-diCQA), 3,5-Dicafeoylquinic acid ( 3,5-diCQA) and 4,5-Dicafeoylquinic acid (4,5-diCQA) are also present in coffee. 3-feruloylquinic acid (3-FQA), 4-feruloylquinic acid (4-FQA), 5-feruloylquinic acid (5-FQA), 3-p-coumaroylquinic acid (3- p -CoQA), 4 -p-cumaroylquinic acid (4-p-CoQA), and 5- p -coumaroylquinic acid (5-p-CoQA) are also detected in coffee, but in smaller quantities. Soluble fiber (200-800 mg), protein (100 mg), lipids (0.8 mg), minerals (250-700 mg) and niacin (10 mg) are also found in coffee.

**Figure 4 legends. Potential antioxidant and anti-inflammatory effects of coffee compounds.** Abbreviations: Nrf2: erythroid-related nuclear factor 2; GSH: glutathione; PPAR-γ: Peroxisome Proliferator-Activated Gamma Receptor; NF-kB: nuclear factor kappa B; JNK: c-Jun N-terminal kinase; AP-1: activator protein 1; Cox-2: Cyclooxygenase-2.

**Figure 5 legends. Possible mechanism of protection of coffee against the development of Diabetes through chlorogenic acids.** CGAs competitively inhibit glucose-6-phosphate translocase, resulting in decreased intestinal glucose uptake and brush border sodium-dependent glucose transport. CGAs can also act on skeletal muscles, stimulating glucose uptake through AMPK, adenosine monophosphate-activated protein kinase, resulting in hepatic reduction of glucose and fat synthesis. Abbreviations: CGAs: chlorogenic acid; AMPK: proteína quinase ativada por adenosina monofosfato.