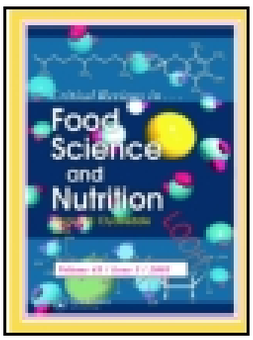

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REVIEW



# Green coffee: economic relevance and a systematic review of the effects on human health

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**ABSTRACT**

Coffee is probably the most popular beverage after water and is an important component in diet and health since its consumption is high worldwide. Globally, it is the most relevant food commodity being just behind crude oil. Besides its pleasant flavor, it is an antioxidant source due to polyphenols, which are protective compounds against several diseases. This study aimed to evaluate the economic relevance and perform a systematic review of green coffee's effects on human health. Databases such as MEDLINE–PubMed, EMBASE, COCHRANE, and GOOGLE SCHOLAR were searched, and PRISMA guidelines were followed. Green coffee is considered a novel food product because consumers usually consume only roasted coffee. It can be marketed as such or as an extract. Due to the content of bioactive compounds, which are partially lost during the roasting process, the extracts are usually marketed concerning the potential regarding health effects. Green coffee can be used as dietary supplements, cosmetics, and pharmaceuticals, as a source of antioxidants. It can benefit human health, such as improvement in blood pressure, plasma lipids, and body weight (thus contributing to the improvement of risk components of Metabolic Syndrome). Moreover, benefits for cognitive functions may also be included.

**KEYWORDS**

Cardiovascular diseases; food industry; glycemia; green coffee; hypertension; obesity

## Introduction

Coffee is the most popular beverage after water and is an essential component in diet and health since its consumption is high over the world. It represents the most important food commodity behind crude oil (Esquivel and Jimenez 2012). According to the International Coffee Organization, the world's ingestion reached about 10.1 million kg in 2019/2020 (International Coffee Organization 2020). In addition to its flavor, which is appreciated worldwide, it is a relevant antioxidant source due to the presence of polyphenols, which can protect against several diseases. The main species of coffee are *Coffea arabica* and *Coffea canephora* that are grown in tropical and subtropical areas. Brazil, Colombia, Indonesia, and Vietnam are the primary coffee producers (Klingel et al. 2020; Morvaridi et al. 2020; Sanlier, Atik, and Atik 2019).

Among components other than caffeine and trigonelline (the most common alkaloids), the chlorogenic acid (CGA) represents a family of phenolic compounds. CGA is formed by the esterification of hydroxycinnamic acids, such as caffeic, ferulic, and *ρ*-coumaric, with quinic acid (Figure 1). The CGA major subclasses in coffee are caffeoylquinic acids (CQAs), dicaffeoylquinic acids (diCQAs), and feruloylquinic acids (FQAs) with several isomers per group (Bosso et al. 2019; Moeenfard and Alves 2020; Monteiro et al. 2007; Morton et al. 2018).

Green coffee can be considered a novel food product since consumers usually use only roasted coffee. This product can be marketed as such or as an extract concerning the potential on health effects (Klingel et al. 2020; Watanabe et al. 2006).

The green coffee compounds are generally associated with reducing oxidative stress and its complications (Nogaim et al. 2020), can be used to treat obesity, and improve insulin response (Asbaghi, Sadeghian, Rahmani, et al. 2020). CGA stimulates Glucose transporter-4 (GLUT-4) expression and peroxisome proliferator-activated receptors and reduces plasma lipids even after the hyperlipidemic diet intake (Craig et al. 2016). It may also reduce the percentage of visceral fat (Roshan et al. 2018) and may play a role in protecting muscle injury after the practice of physical exercises (Bosso et al. 2019). Moreover, caffeine can affect the central nervous system producing stimulating effects (Klingel et al. 2020).

Given the above, this review aimed to evaluate the economic relevance and effects of green coffee on human health.

## Methods

### *Focused question*

This systematic review was performed to answer the focused question*: Can Green Coffee exert beneficial effects on human health?*

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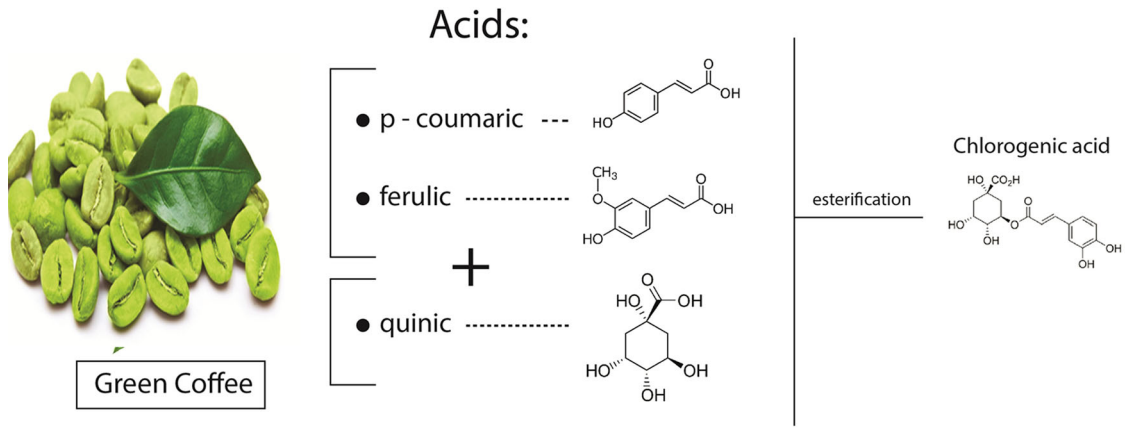



**Figure 1.** Chlorogenic acid formation.

### Language

Only studies in English were selected.

### Databases

This review has included studies in MEDLINE–PubMed (National Library of Medicine, National Institutes of Health), COCHRANE, EMBASE, and Google Scholar databases.

The mesh terms used were green coffee and antioxidant or anti-inflammatory or diabetes or obesity or metabolic syndrome or cancer. The use of these descriptors helped identify studies related to green coffee and its health effects. We have followed PRISMA (Preferred Reporting Items for a Systematic Review and Meta-Analysis) guidelines (Moher et al. 2009) to perform the Systematic review.

Moreover, this study also showed the economic relevance of green coffee. For the search of studies in this matter, we used the descriptors green coffee and economy or dietary supplements or food or cosmetics or pharmaceuticals.

### Study selection

Conferences, abstracts, letters to editors, and other sources were evaluated but not included. Furthermore, other relevant studies about green coffee and human heath were included to help the Introduction and Discussion sections.

The inclusion criteria applied to the systematic review were only human interventional studies.

This systematic review's exclusion criteria were reviews, studies not in English, editorials, case reports, and poster presentations. We also excluded studies with animal models. Figure 2 shows the study selection according to PRISMA guidelines (Moher et al. 2009).

### Data extraction

We did not select a period to perform the search. The retrieved articles were described in Table 1 and showed in Figure 2.

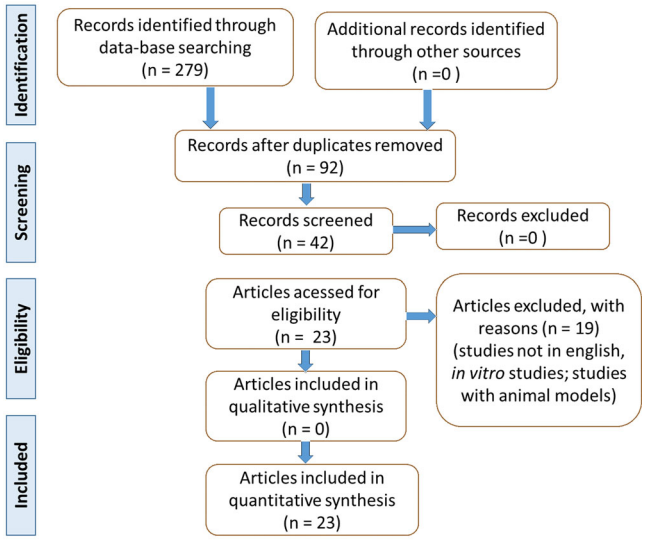



**Figure 2.** The study selection design according to PRISMA guidelines (Moher et al, 2009).

### Search and selection of the relevant articles

The flow diagram represents the selection of the articles, as well as the inclusion and exclusion process.

### Quality assessment

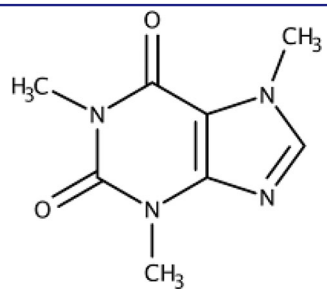
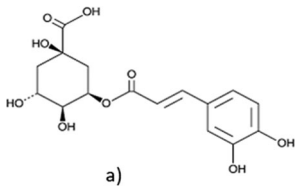
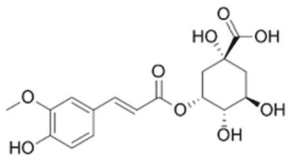
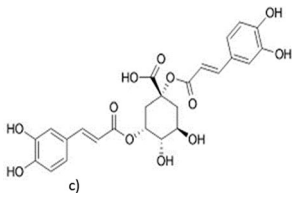
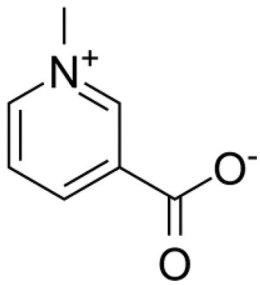
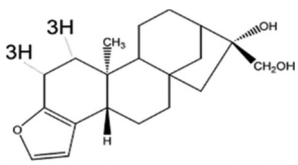
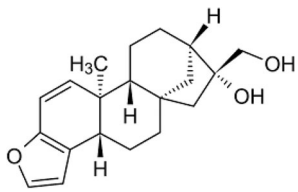
To evaluate the risk of bias related to the selection of the studies, we consulted the Cochrane Handbook for systematic reviews of interventions.

## Results

The selection of the included clinical trials is shown in Figure 2.

Lipid profile parameters were evaluated by five studies (Hosseinabadi et al. 2020; Martínez-López et al. 2019; Haidari et al. 2017; Roshan et al. 2018; Wong et al. 2014). Only one study showed an increase in the HDL-c levels (Hosseinabadi et al. 2020). Two studies showed a significant reduction in LDL-c levels (Martínez-López et al. 2019; Haidari et al. 2017). Three studies (Hosseinabadi et al. 2020;

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

| Bioactive compound | Structure | Functions | Reference |
|---|---|---|---|
| caffeine |  | - ergogenic effects,<br>- augment in alertness and concentration,<br>- reduction in fatigue,<br>- reduction in pain perception,<br>- anti-inflammatory (inhibition of TNF-α, leukotriene synthesis, IL-6, and IL-8. | (Pauwels and Volterrani 2021; Sivalokanathan, Małek, and Malhotra 2021; Stadheim et al. 2015) |
| Chlorogenic acids:<br>- (a) caffeoylquinic acid |  <br>a) | - anti-inflammatory,<br>- antioxidant,<br>- hepatoprotective,<br>- cardioprotective,<br>- chemopreventive,<br>- anti-diabetic,<br>- anti-obesity<br>- anticancer,<br>- neuroprotective effects,<br>- anti-neurodegenerative effects. | (Fukutomi et al. 2021; Pauwels and Volterrani 2021; Socała et al. 2020; Wasim et al. 2020) |
| - (b) feruloylquinic acid |  <br>b) | | |
| - (c) dicaffeoyl-quinic acid |  <br>c) | | |
| trigonelline |  | - anti-inflammatory,<br>- antioxidant,<br>- anti-obesity,<br>- anti-diabetic,<br>- neuroprotective | (Farias-Pereira, Park, and Park 2019; Mohamadi et al. 2018; Sharma et al. 2018) |
| Cafestol and |  | - anti-inflammatory,<br>- anti-angiogenic,<br>- reduction of neoangiogenesis,<br>- reduction of neoangiogenesis | (Moeenfard et al. 2016; Pauwels and Volterrani 2021) |
| Kahweol |  | | |

TNF-α: tumor necrosis factor; IL: Interleukin

Martínez-López et al. 2019; Haidari et al. 2017) showed a reduction in the levels of total cholesterol and triglycerides. Only one study showed a reduction in the levels of VLDL-c (Martínez-López et al. 2019).

Four studies showed a reduction in Body Mass Index (Hosseinabadi et al. 2020; Watanabe et al. 2019; Roshan et al. 2018; Revuelta-Iniesta and Al-Dujaili 2014); two studies showed a reduction in the waist circumference

(Watanabe et al. 2019 and Roshan et al., 2018), two studies found a decrease in the percentage of body fat (Watanabe et al. 2019 and Sarriá et al. 2018). In three studies, the authors found a reduction in body weight (Watanabe et al. 2019; Martínez-López et al. 2019; Roshan et al., 2018).

Seven studies investigated systolic and diastolic blood pressure. Six of them found a significant reduction in both (Martínez-López et al. 2019; Roshan et al., 2018; Revuelta-Iniesta and Al-Dujaili 2014; Yamaguchi et al. 2008; Watanabe et al. 2006; Kozuma et al. 2005). However, one study (Wong et al., 2014) did not show a significant difference between the placebo and the treated group.

The serum glucose levels were significantly lower in the treated group in one study (Sarriá et al. 2018) and did not differ significantly in the two studies (Wong et al. 2014; Beam et al. 2015). The same two studies also did not show the difference in insulin levels.

Liver enzymes and hepatic steatoses were studied in only one study (Hosseinabadi et al. 2020) that did not show a significant difference. Likewise, urinary-free cortisol and cortisol/cortisone ratio were also studied in only one study (Revuelta-Iniesta and Al-Dujaili 2014), and it showed a significant reduction in the treated group.

Resistin and PAI-1 levels were investigated in one study (Sarriá et al. 2018) and showed a significant reduction in the treated group. Likewise, leptin also showed a decrease in one study (Haidari et al. 2017)

Fukagawa et al. (2017) analyzed the effects of green coffee in the skin and significantly reduced clinical skin scores for dryness, reduced skin surface pH, transepidermal water loss, and augmented stratum corneum hydration skin blood flow during local warming.

Two studies evaluated cognitive function. Saitou et al. (2018) did not found significant effects for the Rapid Visual Information Processing measure. On the other hand, Camfield et al. (2013) found that the CGA group showed a significant augment in Cognitrax domain scores for psychomotor speed, motor speed, and executive function compared to placebo and improved the shifting attention test scores. The sleep architecture was investigated by Park et al. (2017) that showed that CGA shortened sleep latency and no effect on sleep architecture, such as rapid eye movement, slow-wave sleep, or waking after sleep onset was seen.

Reyes-Izquierdo et al. (2013) compared the serum level of brain-derived neurotrophic factor (BDNF) between the treated and placebo groups. The treatment with GC caffeine powder and grape seed extract powder increased blood levels of BDNF by about 31%, whereas treatment with coffee fruit concentrate powder increased by 143%.

Olthof et al. (2001) was the only study that measured serum homocysteine levels and found an increase in homocysteine in the group treated with green coffee.

Cardio-ankle vascular index was analyzed in one study (Suzuki et al. 2019), showing that the Green Coffee Extract (GCE) group's Cardio ankle vascular index (CAVI) modification was significantly higher.

Green coffee is relevant for the economy since it can result in novel food products. It can be market in grains, capsules, powder, gum, and oils. These new products can be used for multiple purposes, such as cosmetics, food, and pharmaceutical industry.

## Discussion

### Coffee

The genus *Coffea* belongs to the family *Rubiaceae*, subfamily *Ixoroideae*, and tribe *Coffeeae, including* at least 120 species. The beans obtained from the red fruit are primarily used in the food industry and Medicine and cosmetology (Cheek, Csiba, and Bridson 2002; Socała et al. 2020).

Coffee may present over 2000 different chemical components. A coffee cup can contain 20–675 mg CGA (Ohishi et al. 2021). This mixture of countless bioactive compounds results in many health effects. Isolated or a combination of these compounds are related to different body actions (Farah 2018). However, the amounts of these compounds may differ in other species, cultivation conditions, time of collection, and storage of fruits (Farah and Ferreira 2015). The major components found in coffee are caffeine, CGA, trigonelline, cafestol, kahweol, and melanoidins (Ludwig et al. 2014; Socała et al. 2020).

The 5-O-caffeoylquinic acid is the most profusely chlorogenic acid in coffee beans, also named chlorogenic acid (Naveed et al. 2018). Table 1 shows the biological effects of these main compounds.

Many researchers have shown that the consumption of coffee can be related to antioxidant (Bhagat et al. 2019; Nogaim et al. 2020) and anti-inflammatory properties (Cosola et al. 2018; Li et al. 2021; Rajaram, Jones, and Lee 2019), reducing the risk of several metabolic conditions such as obesity (Tamura 2020), diabetes (Ley et al. 2018; Osama et al. 2021), Metabolic Syndrome (Wong et al. 2020), cardiovascular diseases (Gökcen and Şanlier 2019; Nieber 2017), and cancer (Inoue and Tsugane 2019; Oleaga et al. 2012; Pauwels and Volterrani 2021). On the other hand, excessive coffee consumption can lead to undesired effects such as elevation of total cholesterol levels and reduction of HDL-c (high-density lipoprotein), tachycardia, increase in blood pressure, arrhythmia, interference in cognition, headaches, anxiety, insomnia, and hindered sleep quality (Cano-Marquina, Tarín, and Cano 2013; Cornelis and El-Sohemy 2007; Guest et al. 2021; Ran et al. 2021). Specific side effects with the use of green coffee are shown below.

### Green coffee

Green coffee berries present the seed and the silverskin that is removed in other processes. Coffee berries are traded as green coffee in the international market. Still, industrial processing can generate a large number of by-products such as cherry husks and pulps, silver skin, and spent coffee. When green coffee is harvested, the beans can undergo dry or wet processing. In the first, the cherries are spread out immediately after the collection and sun drying. Then, the

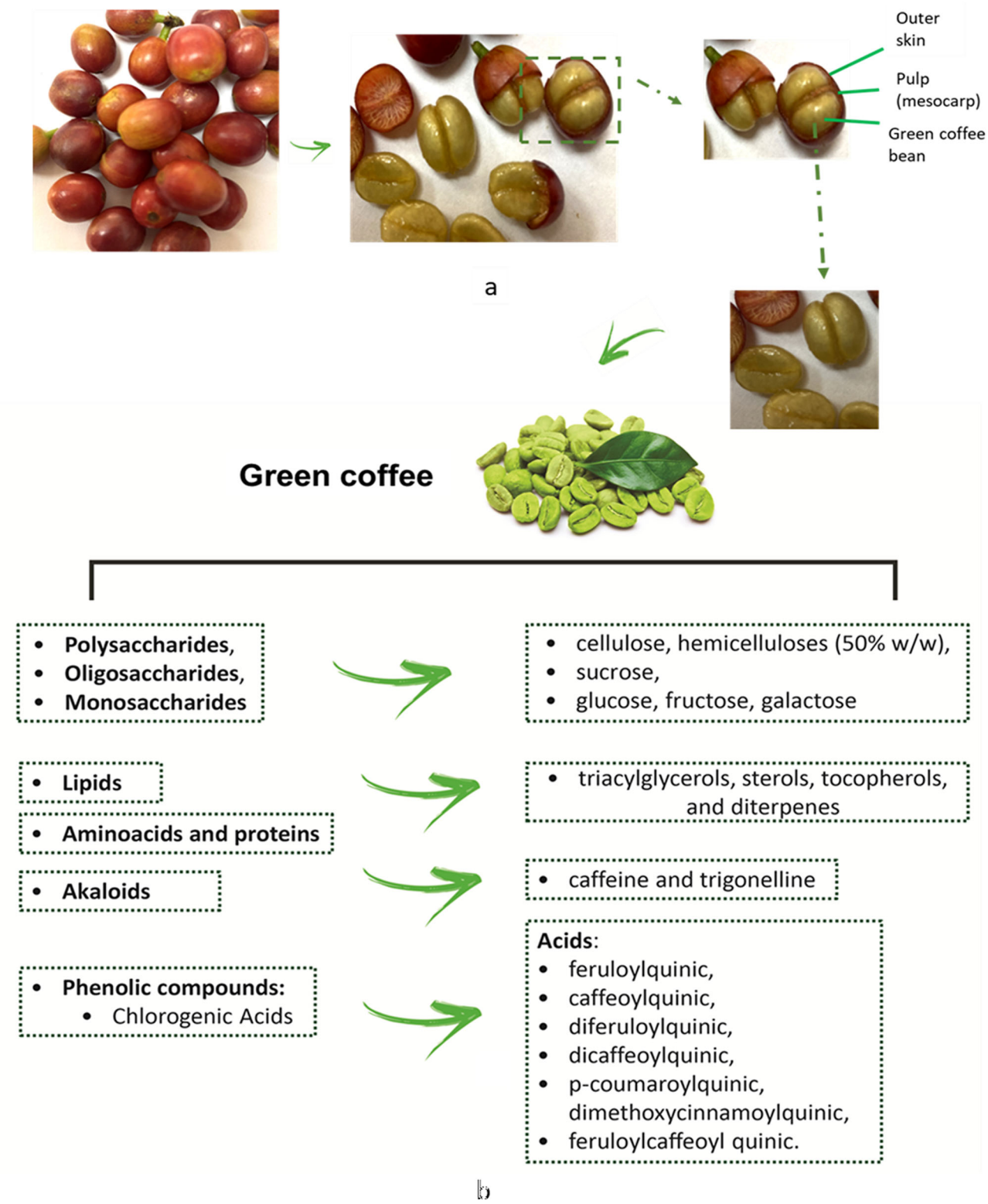



**Figure 3.** a) Coffeeberries and grains. b) Main carbohydrates, lipids, alkaloids and phenolic compounds found in green coffee.

dry pulp and the skin are removed by peeling equipment. The wet processing is differentiated in three ways: pulped natural or semi-dry method (squeeze off the pulp, and all mucilage remains on the parchment and dried on it), semi-washed, and thoroughly washed. In these last subtypes, the mucilage is entirely removed, and in the semi-washed, the process employs brushes and the parchment's friction. In the thoroughly washed process, the mucilage is removed by microorganisms naturally present in the environment of the coffee. After removing the skin, mucilage, pulp, and parchment, green coffee beans remained and traded on the international market. These grains are still covered by skin, and further processing steps can be used to remove it entirely (Esquivel and Jimenez 2012; Klingel et al. 2020).

**Table 2.** Studies showing the effects of green coffeeor its derivatives on human health.

| Reference | Population / Intervention/Comparison | Outcomes | Main conclusions |
|---|---|---|---|
| Studies on green coffee and metabolism | | | |
| (Naylor et al. 2021) | Single center, double-blind, randomized, placebo-controlled crossover study with 21 healthy men (16) and women (5) (45–65 y ) with FMD < 7,5%. Subjects were randomly allocated into A = Placebo, B = 302 mg of DGCE, C = 604 mg, and D = 906 mg) | A significant FMD increase (>1%) was seen at 8.5, 10, and 24 h after ingestion of 302 mg of DGCE (156.4 mg CGAs) comparing to placebo. The differences between the placebo and the other 2 groups were not statistically significant. | The improvement in %FMD with the ingestion of DGCE can be explained partly due to the blood circulation of CGAs and their metabolites. |
| (Hosseinabadi et al. 2020). | Randomized, double-blind placebo-controlled clinical trial with 44 men and 21 women (20–60 y) with NAFLD that were instructed to intake 100 mg of CGA or placebo for 8wk. | GCE supplementation significantly increased the levels of HDL-c and reduced BMI, total cholesterol and triglyceride when compared to the placebo. Hepatic steatosis grade, liver enzymes, and adiponectin levels did not present significant differences between the two groups. | GCE supplementation improved serum lipid profile and BMI in individuals with NAFLD. GCE may be helpful in controlling NAFLD risk factors. |
| (Watanabe et al. 2019) | Randomized, double-blind, parallel controlled trial with 150 healthy and overweight men and women (49.5 ± 8.4 y) (BMI ≥25 to <30 kg/m2) that were randomly allocated to high-CGA (369 mg CGA/serving) or control (35 mg CGA/serving) coffee groups consumed once daily for 12w. | Visceral fat area, total abdominal fat area, body weight, and waist circumference significantly decreased in the CGA group compared with the control group. No severe adverse events occurred | Consumption of high-CGA coffee for 12 weeks by overweight adults might lower visceral fat area, total abdominal fat area, BMI, and waist circumference. |
| (Adamska-Patruno et al. 2018) | Two single-center, randomized, double-blind, placebo-controlled, cross-over studies with 182 healthy men and women (18-64 y) instructed to drink a complex with 600 mg of white mulberry, 1200 mg of white bean extract, and 400 mg of GC or a placebo beverage before two or five standardized meals. | Postprandial glucose and insulin concentrations were lower at 20–35 min after meal intake among subjects in the treated group, and fewer episodes of postprandial reactive hypoglycemia were noted. | The combined formulation decreased the adverse consequences of high glycemic index/glycemic load meal consumption. |
| (Martínez-López et al. 2019) | Randomized, cross-over, controlled study with men and women (18–45 y) which normo (n = 25) and hypercholesterolemia (n = 27) for 8w consuming 6 g/day of soluble green/roasted coffee (35:65) or a control beverage (water or an isotonic drink). After a 3-w wash-out period with the same food restrictions, participants consumed the other beverage during the same 8w intervention period. | The consumption of 6 g/day of soluble green/roasted coffee reduces serum lipids, BP, and body weight effects and increases plasma antioxidant capacity. Inflammatory biomarkers did not show significant changes | Regular consumption of coffee improves cardiovascular health in moderately hypercholesterolemic people. |
| (Roshan et al. 2018) | Randomized, double-blind, placebo-controlled trial. 50 men and women (18-70 y) diagnosed with the MetS and with BMI > 25 kg/m$^2$ were randomly allocated to consume 400 mg of GCE or placebo capsules 2x/d/8w. | After GCE supplementation, SBP, glycemia, waist circumference, and appetite score were significantly reduced compared with the placebo. No difference was observed in HbA1c and lipid profile parameters between the two groups. | GCE administration promoted an ameliorating effect on some of the MetS components such as high SBP, hyperglycemia, insulin resistance, and abdominal obesity. |
| (Haidari et al. 2017) | Randomized, double-blind clinical trial placebo-controlled with 64 obese women (20-45 y) instructed to intake 400 mg of GC bean extract for 8w or placebo. All participants were on an energy-restricted diet. | Serum total cholesterol, LDL-c, leptin, and plasma-free fatty acids significantly decreased in the intervention group. The levels of adiponectin significantly increased in the intervention group. | GC bean extract combined with an energy-restricted diet affects fat accumulation and lipid metabolism and is a cheap method for weight control in obese people. |
| (Sarriá et al. 2018) | Cross-over, randomized, controlled study with 25 normo and 27 hypercholesterolemic men and women (18–45 y) treated with three servings/d of a blend with 510.6 mg of hydroxycinnamic acids and 121.2 mg of caffeine/d versus a control drink during 8w. | SBP and DBP, % body fat, leptin, PAI-1, resistin, glycemia, and triglyceride levels significantly decreased in both healthy and hypercolesterolemic group after coffee consumption when compared to placebo. | Regular consumption of green/roasted coffee blend may be recommended to normo and hypercholesterolaemic subjects. |
| (Wong et al. 2014) | Randomized, double-blind, placebo-controlled cross-over trial with 39 subjects (18–80 y) that consumed a supplement (500 mg of olive leaf extract, 100 mg of GC bean extract and 150 mg of beet powder) or placebo 2x/d/6w, followed by the alternate supplement for a further 6w. | There was no significant effect of the treatment on BP, fasting blood lipids, glucose levels and insulin sensitivity. | The supplementation with a combined formulation did not reduce 24-h BP nor clinic BP nor improve blood lipids, blood glucose, nor insulin sensitivity. |
| (Beam et al. 2015) | Randomized, double-blinded experimental trial in 10 male cyclists (26 ± 5 y) after completed three 30-min bouts of cycling at 60% of peak power output, each participant immediately consumed dextrose 75 g with 5 mg/kg of caffeine, 10 mg/kg of GC bean extract (5 mg/kg chlorogenic acid), or placebo. | No significant effects for blood glucose and insulin were found between the groups. | Caffeine and GCE did not significantly alter post-exercise glycemia and insulin. |

| | | | |
|---|---|---|---|
| (Revuelta-Iniesta and Al-Dujaili 2014) | Randomized, cross-over study with 20 subjects consumed both green and black coffees 40 g/day for 2w. Each group consumed a type of coffee for one week and after washing out, the types of coffee were inverted | After GC intake, SBP arterial elasticity, BMI, abdominal fat, urinary free cortisol, and cortisol/cortisone ratio were significantly reduced. No significant difference was seen in the antioxidant capacity and polyphenol concentration. | GC can be used to reduce cardiovascular risk factors. |
| (Lecoultre et al. 2014) | Randomized, controlled, cross-over trial with 13 healthy men (21–25 y) studied on 5 different occasions, each time with 1 of 5 different dietary conditions (4 g of fructose; roasted caffeinated coffee high in CGA; roasted coffee with a high CGA content; roasted, decaffeinated coffee with regular amounts of CGA; energy-balanced diet without fructose supplementation) over a 28d, with a wash-out period of 4w between each condition. | The comparison with the control diet, the high-fructose diet significantly increased IHCLs and HGP and decreased fasting lipid oxidation. All 3 coffees significantly decreased HGP. Fasting lipid oxidation was increased with caffeinated coffee high in chlorogenic acid and decaffeinated coffee with regular chlorogenic acid amounts. None of the 3 coffees significantly modified IHCLs. | Coffee ingestion reduces hepatic insulin resistance but not the increase of IHCLs induced by fructose overfeeding. |
| (Yamaguchi et al. 2008) | Double-blind, randomized controlled trial, with 183 subjects (91♂; 92♀; 30-65 y) allocated in five study groups: control (beverage was identical to ordinary coffee), zero-dose (0 mg of CGA), low-dose (82 mg of CGA), middle-dose (172 mg of CGA) and high-dose (299 mg of CGA), instructed to drink 1 cup of coffee /d/4w. | CGA has an anti-hypertensive effect in a dose-dependent manner in HHQ-free coffee, and ordinary coffee showed almost no effect. A significant correlation between BP change and the three dose-response patterns was observed. | Coffee with a high concentration of CGA can be an adjuvant to the treatment of BP. |
| (Watanabe et al. 2006) | Randomized, placebo-controlled trial in 28 subjects (11♂, 17♀) with mild hypertension without any treatment that were randomized to receive CGA (140 mg/day) from GCE or placebo once a day for 1/d/12w. | In the CGA group, SBP and DBP decreased significantly during the ingestion period. There was no difference in BMI and pulse rate between the groups and no apparent side effects. | CGA from GCE is effective in decreasing BP and safe for patients with mild hypertension. |
| (Kozuma et al. 2005) | Multicenter, randomized, double-blind, placebo-controlled, parallel-group study in 117 male volunteers (43 ± 9.1 y) with mild hypertension randomized into a placebo and three groups that received 46 mg, 93 mg, or 185 mg of GCE /1xd/ 4w. | SBP in the placebo, 46 mg, 93 mg, and 185 mg groups was reduced by −1.3 ± 3.0, −3.2 ± 4.6, −4.7 ± 4.5, and −5.6 ± 4.2 mmHg from the baseline, respectively. The decreases in SBP in the 93 mg group and the 185 mg group were statistically significant compared with placebo. DBP in the placebo, 46 mg, 93 mg, and 185 mg groups was reduced by −0.8 ± 3.1, −2.9 ± 2.9, −3.2 ± 3.2, and −3.9 ± 2.8 mmHg from the baseline, respectively, and significant effects were observed between the groups. | Daily use of GCE has a blood pressure-lowering effect in patients with mild hypertension. |
| **Green coffee and food intake** | | | |
| (Bobillo et al. 2018) | Prospective cross-over study in 57 normal and overweight subjects; 16 men and 41 women (18–5 0 y) instructed to chewing active gum made with *Garcinia cambogia*, GC extract, and L-carnitine, placebo gum or no gum. The treatments a and b were double-blind, whereas treatment c was open. | It was observed a significant decrease in low-fat sweet snack ingestion in placebo gum and the gum with the compound compared to no use of gum and a decrease in high-fat sweet snack ingestion with the gum with the compound compared to placebo gum and no gum. | Chewing gum with nutraceuticals can aid in the control over snack intake and reduce hunger sensations. |
| **Green coffee and skin** | | | |
| (Fukagawa et al. 2017) | Double-blind, placebo-controlled, randomized design in 49 healthy women (25-40 y) 25–with mildly xerotic skin that received a test beverage with CPPs (270 mg/100 mL/day) or a placebo /8w. | The intake of CPPs significantly reduced clinical skin scores for dryness, reduced skin surface pH, transepidermal water loss, and augmented *stratum corneum* hydration and the skin blood flow during local warming. Moreover, the amounts of FFA and lactic acid in the *stratum corneum* significantly increased after the ingestion of CPPs. | GC improves the permeability of the skin barrier function and hydration and promotes improvement in microcirculatory pattern, resulting in efficacy in alleviating mildly xerotic skin. |
| **Green coffee and BDNF** | | | |
| (Reyes-Izquierdo et al. 2013) | 25 health subjects (18-55 y) consumed a 100 g single dose of whole coffee fruit concentrate powder, GC caffeine powder, grape seed extract powder or GC bean extract powder. | The treatments with GC caffeine powder and grape seed extract powder increased blood levels of plasma brain-derived neurotrophic factor (BDNF) by about 31%, whereas treatment with coffee fruit concentrate powder increased by 143%. | These results indicate that coffee fruit concentrate powder could be used for modulation of BDNF. |
| **Green coffee and cognitive function** | | | |
| (Saitou et al. 2018) | Randomized, double-blind, placebo-controlled, parallel-group with 38 subjects (38♂, 17♀; 50-69 y) instructed to ingest either a | The CGA group showed a significant augment in Cognitrax domain scores for psychomotor speed, motor | CGAs improve cognitive functions, which would help in the efficient performance of complex tasks. |

(*continued*)

**Table 2.** Continued.

| Reference | Population / Intervention/Comparison | Outcomes | Main conclusions |
|---|---|---|---|
| | CGA-added beverage (300 mg) or a placebo daily 30–60 min before bedtime for 16w. | speed, and executive function compared to placebo and improved the shifting attention test scores. CGA increased plasma levels of apolipoprotein A1 and transthyretin (putative biomarkers for early-stage cognitive decline). | |
| (Camfield et al. 2013) | 60 healthy individuals (≥50 y) used 6 g of a decaffeinated GC blend or 540 mg pure CGA or placebo in a double-blind acute cross-over design. | No significant effects were found for the Rapid Visual Information Processing measure, although significant effects were found amongst inspection time measures. | The use of GC improves mood but not cognitive function. |
| **Green Coffee and Cardio-Ankle Vascular Index** | | | |
| (Suzuki et al. 2019) | Randomized, double-blind, placebo-controlled pilot study with 16 healthy Japanese men (36-56 y) instructed to drink 100 mL of a beverage (∼300mg as CGA) or placebo 1xd at bedtime/2w. | The CAVI modification was significantly greater in the GCE group. Besides, FMD increased, and SNA decreased in the GCE group. | Ingestion of GCE for 2w may improve arterial stiffness as assessed by the CAVI. |
| **Green coffee and sleep architecture** | | | |
| (Park et al. 2017) | Placebo-controlled, double-blinded, cross-over intervention study with healthy 4 men and 5 women (25 ± 7 y) instructed to drink a beverage with 600 mg of CGA or placebo for 5d. On the fifth night, the participant stayed in a whole-room metabolic chamber to measure energy metabolism. | CGA shortened sleep latency and no effect on sleep architecture, such as rapid eye movement, slow-wave sleep, or waking after sleep onset was seen. CGA augmented fat oxidation (but did not affect energy expenditure), and enhanced parasympathetic activity assessed from heart-rate variability during sleep. | CGA intake significantly increased fat oxidation during sleep, suggesting that it could be beneficial to prevent obesity and shortened sleep latency and did not adversely affect sleep quality. |
| **Green coffee and homocysteine** | | | |
| (Olthof et al. 2001) | Cross-over study with 20 healthy men (10) and women (10); 24 ± 8 y instructed to ingest 2 g (5.5 mmol) of CGA, 4 g of black tea solids containing 4.3 mmol of polyphenols and comparable to 2 L of strong black tea, 440 mg (0.7 mmol) of quercetin-3-rutinoside, or placebo. Each participant received each of the 4 treatments / 7d, in random order. | Total plasma homocysteine 4–5 h after supplement intake was 12% higher after CGA and 11% higher after black tea than after placebo. Total homocysteine 20 h after supplement intake was 4% higher after CGA and 5% higher after black tea than after placebo. Quercetin-3-rutinoside did not significantly affect homocysteine concentrations. | CGA raises total homocysteine concentrations in plasma. |

BDNF: brain-derived neurotrophic factor; BMI: body mass index; BP: blood pressure; CAVI: cardio-ankle vascular index; FFA: Free Fatty Acids; CGA: chlorogenic acids; CVD: Cardiovascular Disease; CPPs: Coffee polyphenols; DBP: diastolic blood pressure; DGCE: decaffeinated green coffee; FMD: flow-mediated dilation; GC: green coffee; GCE: green coffee bean extract; HbA1c: glycated Hemoglobin; HDL: High-Density Lipoprotein HGP: hepatic glucose production; IHCLs: intrahepatocellular lipids; LDL-c: Low-Density Lipoproteins; MetS: Metabolic Syndrome; NAFLD: nonalcoholic fatty liver disease; PAI-1: Plasminogen activator inhibitor-1; RHR: reactive hyperemia ratio; SBP: systolic blood pressure; SNA: SNA: sympathetic nervous activity.

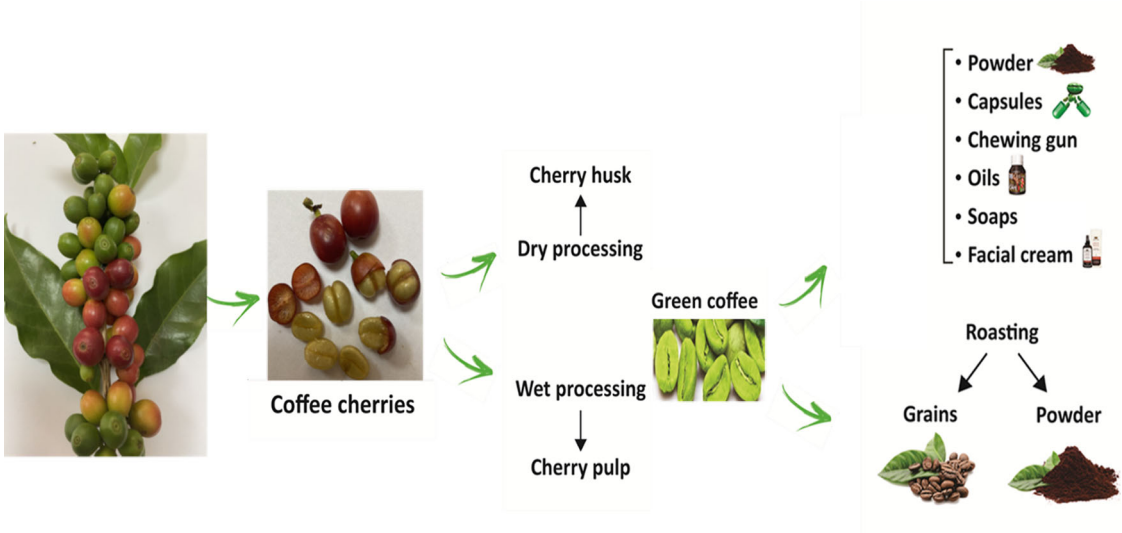



**Figure 4.** Types of coffee processing and products that can be marked.

Green coffee main compounds (Figure 3) are mainly insoluble polysaccharides (~50% w/w) (but also present sucrose, fructose, glucose, galactose, and arabinose), and also present oils and waxes (8%–18% w/w), proteins (9%–12% w/w), and minerals (3%–5% w/w). The polyphenolic compounds are also present, and CGA represents up to 12%. Caffeine (1-4%) and trigonelline (0.8%) are present, but caffeine is in prominence, and its content is related to its quality due to its bitterness. Trigonelline can undergo degradation during the roasting process, resulting in *N*-methylpyridinium (Arya and Rao 2007; Asbaghi, Sadeghian, Nasiri, et al. 2020; Klingel et al. 2020; Ky et al. 2001; Lang et al. 2008; Romualdo et al. 2019). The lipids from green coffee include mainly triacylglycerols, sterols, diterpenes, and tocopherols (Speer and Kölling-Speer 2006). Cafestol is one of the most abundant diterpenes found in coffee. Kahweol is another relevant compound, and its concentrations may differ substantially in different species of coffee. Table 2 shows some of the main compounds of green coffee and its effects on human health.

Taking a special look at CGA in green coffee, it is possible to include feruloylquinic, caffeoylquinic, diferuloylquinic, dicaffeoylquinic, p-coumaroylquinic, and other acids as found in Figure 3. Esterification reactions can result in many isomers and free phenolic acids, including ferulic, caffeic, and dimethoxycinnamic acids (Alonso-Salces, Guillou, and Berrueta 2009; Martínez-López et al. 2019).

Green coffee extracts are obtained from water or alcohol extraction processes, resulting in novel food products (Marcason 2013). These products can be market for ingestion in powder, capsules, chewing gum, and oils and products aimed at esthetics such as soaps, body and facial creams, and oils for body massage (Figure 4).

### *Chemical composition of green coffee for roasted*

The most used way to consume coffee is in the roasted form used for the drink. However, scientists' attention has turned to the composition and beneficial effects of green coffee. For these reasons, several researchers have investigated the difference in chemical composition between green and roasted beans.

During the roasting process, carbohydrates, proteins, phenols, and free amino acids are reduced, while the levels of lipids and caffeine remain practically unchanged (Farah et al. 2006; Hu et al. 2019; Wolska et al. 2017), corroborating the results presented by Mehaya and Mohammad (2020) for the caffeine contents, while Sualeh, Tolessa, and Mohammed (2020) say that during coffee roasting, caffeine is kept chemically stable, except for a minimal reduction. As for lipids, more recently, Moeenfard and Alves (2020) observed relative stability for cafesterol and kakweol esters in green and roasted coffee beans of different varieties.

Arabinogalactans (62%), galactomannans (24%), and glucans, respectively are the polysaccharides identified and quantified on green coffee beans. In roasted grains, galactomannans (69%) and arabinogalactans (28%). CGAs are phenolic compounds representing 5 to 14% (Nunes and Coimbra 2001).

Studies show that edaphoclimatic conditions and the genetics of coffee can impact the composition of green beans. Harvesting, post-harvesting, roasting, and storage of roasted coffee, are responsible for the production or degradation of several compounds such as carbohydrates, lipids, caffeine, and acids (Kitzberger et al. 2013; Kitzberger, dos Santos Scholz, and de Toledo Benassi 2014; Rosa et al. 2016).

Coffee bioactivity is related to CGAs, caffeine, trigonelline, and melanoidins, in addition to diterpenoids, especially cafestol and kahweol and their derivatives (Bizzo et al. 2015; Dong et al. 2015; Montenegro et al., 2021). Ribeiro et al. (Ribeiro, de Souza Rocha, and Prudencio 2021) evaluated sources of bioactive peptides in protein extracts of green and roasted coffee beans and found that 11S coffee globulin is a precursor of bioactive peptides. CGAs are phenolic compounds that represent 5 to 14% of the constituents found in green coffee beans, including, as mentioned before, caffeoylquinic, tipfeoylquinic, feruloylquinic, p-cumaroylquinic acids, and mixed esters of caffeic and ferulic acids with quinic acid, with at least three isomers by group (Babova,

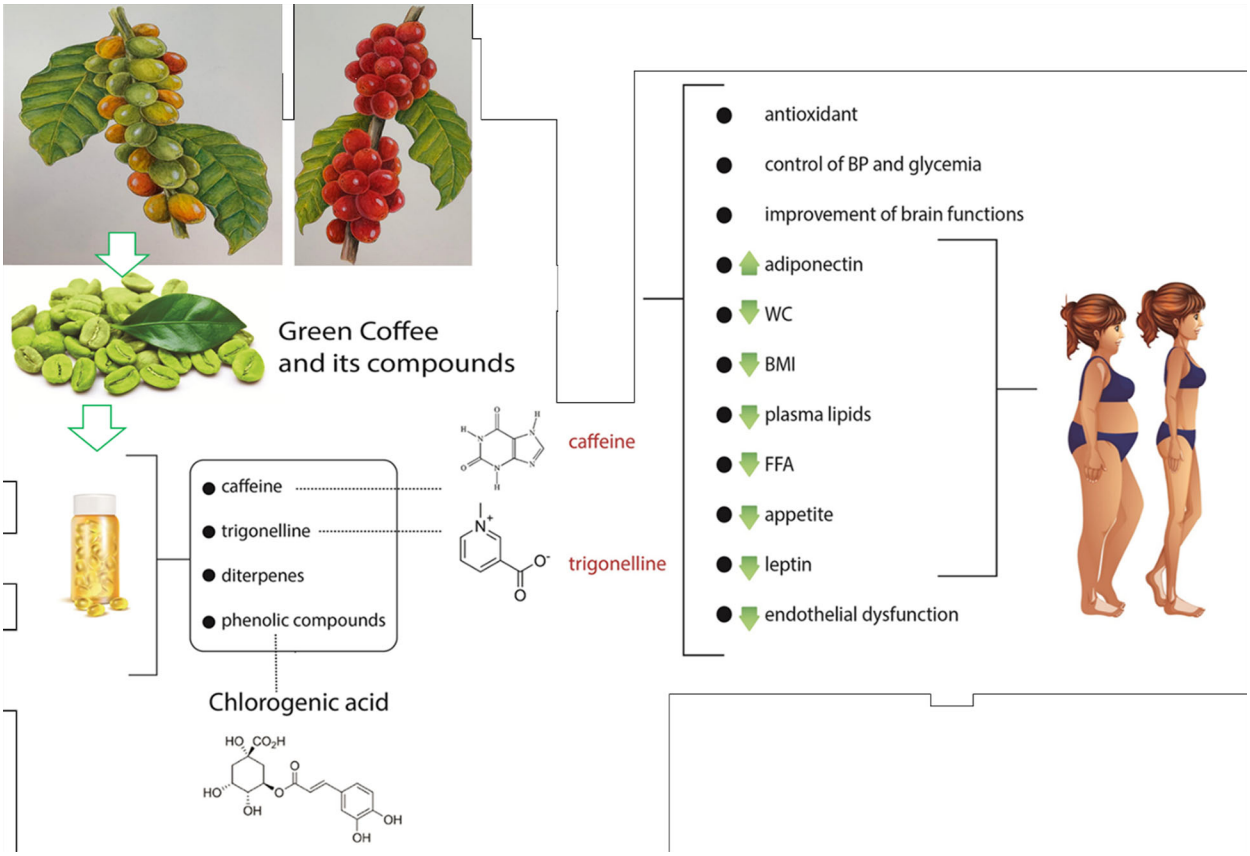



**Figure 5.** Some effects of green coffee on human health. BP: Blood pressure; WC: Waist circumference; BMI: Body Mass Index; FFA: Free fat acids.

Occhipinti, and Maffei 2016; Badmos, Lee, and Kuhnert 2019).

During coffee processing, CGAs can be partially isomerized, hydrolyzed or degraded to low molecular weight compounds. The high temperatures observed in the roasting process mainly lead to the decomposition of sugars and decarboxylation of carboxylic acids. It is also observed rearrangement and reactions between amino acids and sugars via Maillard and Strecker reactions form numerous compounds of very different chemical classes, resulting in melanoidin (Alafeef, Ariffin, and Zulkurnain 2020; A. Gloess et al. 2018; Poisson et al. 2017). CGAs are primarily hydrolyzed to quinic acid and caffeic acids through mechanisms already described, which by pyrolysis form volatile phenolics. Cinnamic acids produce vinyl-phenols by decarboxylation (Hertz-Schünemann et al. 2013; Preedy 2014; Upadhyay and Mohan Rao 2013).

Roasting is a critical process for the sensory quality of the final drink. The pyrolytic process at this stage causes the water contained inside the grains to convert to steam and form a wide variety of volatile compounds (Cheng et al. 2016; A. N. Gloess et al. 2014).

Studies carried out by BAUER et al. (Bauer et al. 2018) showed that the roasting process reduced the bioactive properties of extracts obtained from green grains of *Coffea canephora*. However, the drying performed by spray or freezing did not show a reduction in any sample.

Studies show that the roasting process causes a significant decrease in trigonelline content (Franca, Mendonça, and Oliveira 2005). However, during roasting, trigonelline undergoes demethylation and forms niacin (approximately 20 mg 100 g-1 of roasted coffee) (Trugo and Macrae 1984).

Some authors (Lima et al. 2010) verified the reduction of the coffee drink's in vitro antioxidant activity in the decaffeination process. The roasting process enhanced the scavenging activity of free radicals and the reducing power of beverages. However, regardless of the analyzed process (roasting or decaffeination), the coffee drinks evaluated showed antioxidant activity.

In addition to the phenolic compounds, which are partially destroyed in the roasting, other antioxidant compounds, such as melanoidin, can be formed, making it possible to maintain or even increase the antioxidant activity. However, the roasting intensity is a decisive factor in the process because, with its increase, there will be more significant destruction of the phenolic compounds that the formation of others may not compensate. Consequently, coffees from light roasting have a higher antioxidant capacity (Lakenbrink et al. 2000). According to Hečimović et al. (2011), coffee beans obtained by light roasting showed greater antioxidant capacity than green coffee beans, and the intensified roasting resulted in a reduction in its oxidizing potential.

According to Barbosa et al. (2019), the composition of raw coffee can be a measure of the sensory quality of the coffee drink. These are relevant information for producers and industry since green beans are used for commercialization and buying coffee. According to the researchers, coffees

**Table 3.** Descriptive table of the biases of the included randomized clinical trials.

| Study | Question focus | Appropriate randomization | Allocation blinding | Double-blind | Losses (<20%) | Prognostics or demographic characteristics | Outcomes | Intention to treat analysis | Sample calculation | Adequate follow-up |
|---|---|---|---|---|---|---|---|---|---|---|
| (Naylor et al. 2021) | Yes | Yes | Yes | Yes | Yes | No | Yes | Yes | No | yes |
| (Hosseinabadi et al. 2020) | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| (Watanabe et al. 2019) | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| (Adamska-Patruno et al. 2018) | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | No |
| (Martínez-López et al. 2019) | Yes | Yes | No | No | Yes | Yes | Yes | Yes | No | Yes |
| (Roshan et al. 2018) | Yes | Yes | Yes | Yes | Yes | No | Yes | Yes | No | Yes |
| (Haidari et al. 2017) | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| (Sarriá et al. 2018) | Yes | Yes | No | No | Yes | Yes | Yes | Yes | No | Yes |
| (Wong et al. 2014) | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| (Beam et al. 2015) | Yes | Yes | Yes | Yes | Yes | Yes | Yes | No | No | Yes |
| (Revuelta-Iniesta and Al-Dujaili 2014) | Yes | Yes | No | No | Yes | Yes | Yes | Yes | No | Yes |
| (Lecoultre et al. 2014) | Yes | Yes | No | No | Yes | Yes | Yes | Yes | No | Yes |
| (Yamaguchi et al. 2008) | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| (Watanabe et al. 2006) | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | No | Yes |
| (Kozuma et al. 2005) | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | No | Yes |
| (Bobillo et al. 2018) | Yes | Yes | No | No | Yes | Yes | Yes | Yes | No | Yes |
| (Fukagawa et al. 2017) | Yes | Yes | Yes | Yes | Yes | No | Yes | Yes | No | Yes |
| (Saitou et al. 2018) | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | No | Yes |
| (Camfield et al. 2013) | Yes | Yes | No | No | Yes | Yes | Yes | Yes | Yes | Yes |
| (Suzuki et al. 2019) | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | No | Yes |
| (Park et al. 2017) | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | No | No |
| (Olthof et al. 2001) | Yes | Yes | No | No | Yes | Yes | Yes | Yes | No | No |

with lower quality scores were related to high levels of caffeine, protein, CGAs, and total titratable acidity (ATT) in green coffee beans. High concentrations of sucrose, ATT, and cafestol/kahweol ratio in green coffee beans were generally associated with higher scores for coffee preparations.

Liu et al. (2019) demonstrated that the treatment of green beans of *Robusta* coffee with acetic acid altered its aromatic profile after roasting. Vinson, Chen, and Garver (2019), using the High-Efficiency Liquid Chromatography (HPLC) method to measure caffeine and chlorogenic acid levels of dietary supplements, showed that only 28% of the products complied with the legislation.

## *Importance of coffee in the economy: food and cosmetics industry*

In 2019/2020, coffee production in the world was 168.5 million 60 kg bags. The world production for the 2020/21 crop year (July/20 to June/21) is estimated at 171.6 million bags, representing an increase of 1.8%. Coffee is considered one of the most popular drinks globally, with traditional, organic, decaffeinated, and flavored flavors available on the market in the coffee market chain (Manzo 2014; Samoggia and Riedel 2018).

During the last decade, consumers have shown an interest in natural products, promoting a growing demand for extracts obtained from coffee as alternative raw material sources. The inclusion of components with antioxidant, immunomodulatory or photoprotective functions has been used in cosmetic formulations, the pharmaceutical industry, food, and nutraceuticals (de Melo Pereira et al. 2020; Iriondo-DeHond et al. 2019; Nzekoue et al. 2020; Rodrigues et al. 2016a). Besides, sustainability issues lead to the study of new cosmetic ingredients obtained from by-products (Naveed et al. 2018; Rodrigues et al. 2016b).

The cosmetics industry is interested in green coffee oil, composed mainly of triglycerides and fatty acids, which has, among other properties, skin moisture retention and potential action to prevent photoaging (Del Carmen Velazquez Pereda et al. 2009). The study conducted by Castro et al. (Castro et al. 2018) found that *Coffee arabica* green coffee residue extract showed potential as a raw material for dietary supplements, cosmetics, and pharmaceuticals, as a source of antioxidants. Murthy and Naidu (2012) tested different coffee by-products and found antioxidant activity levels ranging from 61% to 70%.

## *Green coffee and health effects*

Several studies have shown the effects of green coffee or its derivatives on human health (Nieber 2017) (Figure 5). The consumption of this product can affect body weight, waist circumference, glycemia, HbA1C, blood pressure, BDNF, homocysteine levels, skin, cognitive functions, and sleep architecture. Table 2 shows the description of the Clinical Trials that investigated the use of green coffee or its compounds and included in this review. The risk of bias of these included studies is shown in Table 3.

Hyperglycemia, obesity, hypertension, high levels of triglycerides, and low levels of HDL-c are included in the Metabolic Syndrome, one of the most prevalent conditions globally and corresponds to a set of diseases whose basis is insulin resistance. Metabolic Syndrome is an important condition to develop heart conditions that represent the leading cause of death worldwide (Tofano et al. 2020). The use of green coffee can reduce Metabolic Syndrome risk factors, as shown by the study of Watanabe et al. (2019), Adamska-Patruno et al. (2018), Martínez-López et al. (2019), Roshan et al. (2018), Haidari et al. (2017), Sarriá et al. (2018), R. Wong et al. (2014), Beam et al. (2015), Revuelta-Iniesta and Al-Dujaili (2014), Lecoultre et al. (2014), Yamaguchi et al.

(2008), Watanabe et al. (2006), Kozuma et al. (2005). However, in the study of Adamska-Patruno et al. (2018), Martínez-López et al. (2019), Sarriá et al. (2018), and Wong et al. (2014), the group that used green coffee also ingested other components such as roasted coffee, mulberry, white bean extract, beet powder, and olive leaf extract.

An interesting differential of Beam et al. (2015) study is the measurement of the dose according to the weight of each participant. Some studies present biases since they include a small number of participants observed in the pilot investigation of Revuelta-Iniesta and Al-Dujaili (2014) in a population of twenty subjects. Moreover, the authors did not inform the participants' age, and the intervention was not blinded. In the study performed by Lecoultre et al. (Lecoultre et al. 2014), only ten subjects completed the study protocol.

Homocysteine can contribute to CVD due to several different mechanisms such as the augment in endothelial dysfunction, the proliferation of vascular smooth muscle cells, oxidative damage, the increase in collagen synthesis, and deterioration of arterial wall elastic material (Zhang et al. 2014). The study of Olthof et al (Olthof et al. 2001) showed that high doses of CGA can raise total homocysteine levels, and it can be partly responsible for the higher homocysteine concentrations observed in coffee drinkers.

CAVI reflects the stiffness of the entire aorta and the femoral, popliteal, and tibial arteries and measures the increase in arterial stiffness occurring from end-diastole to end-systole, and it may be associated with cardiovascular risk (Matsushita et al. 2019). Arterial stiffness changed along with improvement of Endothelium-dependent flow-mediated dilation and suppression of SNA (sympathetic nervous activity) in healthy men ingesting green coffee extract for only two weeks. These results suggest that the effects of CGAs on vascular function partially contribute to the decrease of CVD (Suzuki et al. 2019).

Xerotic skin can be caused by decreased stratum corneum's water holding capacity, leading to a reduction in lipids and NMFs (natural moisturizing factors), and is observed frequently even in healthy individuals (Hashizume 2004). It is characterized by roughness and the scaling, flaking, and cracking of the skin. Thus, it is important to treat dry skin conditions to prevent serious skin diseases and maintain good skin health (Rawlings and Harding 2004). Green coffee can improve epidermal permeability barrier function, *stratum corneum* hydration, and microcirculatory function, leading to efficacy in treating xerotic skin, as shown by the study performed by Fukagawa et al. (2017).

BDNF is a member of the nerve growth factor-related family, and it is involved in the development, maintenance, and function of the central nervous system. This protein leads to the survival of nerve cells by playing a role in the growth, maturation, and maintenance of these cells (Rodríguez-López et al. 2013). The use of coffee fruit concentrate powder, including green coffee components, increased the blood level of BDNF during the first sixty minutes after treatment with a dose of 100 mg, as shown by the study of Reyes-Izquierdo et al. (2013). However, other components found in the coffee fruit concentrate powder may have interfered with the study results.

Cognitive function includes a wide range of brain functions, such as attention, language, memory, and executive function, crucial for our daily activities (Meguro 2008). The results of Saitou et al. (Saitou et al. 2018) showed that CGAs found in green coffee could improve cognitive functions, including attention and motor speed, which may facilitate the efficient performance of complex tasks observed in the neuropsychological tests. On the other hand, CAMFIELD et al. (Camfield et al. 2013) suggested that green coffee can only improve mood, not cognitive functions.

Green coffee compounds such as CGA can act in many physiological systems, suggesting a link between sleep, autonomic nervous system, and energy metabolism (Hirotsu, Tufik, and Andersen 2015). Park et al. (2017) demonstrated that the ingestion of CGA stimulated fat oxidation without an adverse effect on sleep architecture; instead, it shortened sleep latency. The intake of CGA augmented parasympathetic performance during sleep, but its effects on sleep and fat oxidation remain to be evaluated.

In summary, we can say that the use of GC can help prevent various metabolic disorders such as Metabolic Syndrome and its cardiovascular complications since this product is related to the reduction of body weight, decreases the levels of serum lipids, body fat and abdominal fat, reduces hepatic steatosis, decreases leptin expression, controls blood pressure, and increases adiponectin production. Therefore, its use in clinical practice can help prevent the diseases that kill the most in the world, namely CVD. In addition, it may also have benefits in preventing other chronic-degenerative diseases as it has the effect of increasing the antioxidant capacity. Furthermore, it also shows positive effects on cognition, executive function and improves BDNF levels. With these results, we can say that different professionals in the medical field can consider CG.

## Adverse effects of green coffee

The studies included in this review varied regarding the presence or absence of adverse effects after green coffee consumption. Watanabe et al. (2019) noticed 72 adverse events in the control group and 63 in the CGA group. However, the symptoms were considered to be mild and temporary. Moreover, the number of adverse events did not differ significantly between the placebo and experimental groups.

In the study performed by Roshan et al. (2018), one patient reported stomach irritation after consuming the capsules and dropped out of the study. Another patient in the same study reported dizziness, which increased the time gap between the two doses taken per day.

Wong et al. (2014) reported four adverse events during the 12-week intervention. Complaints were vivid dreams (n = 1), gastrointestinal discomfort (n = 1), increased headache frequency and severity for a preexisting migraine sufferer (n = 1) and improved taste (n = 1).

One volunteer reported dizziness and nausea immediately after ingesting the green coffee, and another reported an

increase in libido in the study performed by Revuelta-Iniesta and Al-Dujaili (2014).

No adverse effects were reported by Saitou et al. (2018); Park et al. (2017); Fukagawa et al. (2017); Yamaguchi et al. (2008); Watanabe et al. (2006), Kozuma et al. (2005) studies.

The subsequent studies did not report whether or not there were any adverse effects: Suzuki et al. (2019); Martínez-López et al. (2019); Bobillo et al. (2018); Sarriá et al. (2018); (Haidari et al. (2017); Beam et al. (2015); Camfield et al. (2013); Lecoultre et al. (2014); Reyes-Izquierdo et al. (2013); Olthof et al. (2001).

### *Safety of green coffee and green coffee extract*

Besides being responsible for producing the primary physical, chemical, and organoleptic characteristics of coffee, the roasting process also results in undesired toxic compounds such as acrylamide and furan (Schouten, Tappi, and Romani 2020). The green beans

In a recent study on coffee by-products, Klingel et al (Klingel et al. 2020) cited toxicity no side effects of green coffee. The acute use of 2 g/kg bw or a subacute use of 75 mg/kg bw showed no toxicity, but an increase in the relative weight of the thymus and heart without histopathological changes was observed (de Oliveira et al. 2020).

Another concern is caffeine, which is recognized to interfere with the central nervous system and is popularly used as and stimulating. However, overdosing is related to adverse events, and the maximum recommendation is 400 mg/day (EFSA Panel on Dietetic Products, Nutrition and Allergies 2015).

The study of Vaclavik et al. (2013) showed that the presence of mycotoxins should be considered mainly in the production of extracts. These authors showed the presence of ochratoxin A (36.9 $\mu$g/kg), ochratoxin B (20.2 $\mu$g/kg), fumonisin B1 (415.0 $\mu$g/kg), and mycophenolic acid (395.0 $\mu$g/kg) in green coffee extracts.

## Future perspectives for green coffee

The various industrial branches (food industry, pharmaceuticals, cosmetics, and others) have turned their attention to replacing conventional materials with natural products. The search for natural sources for inputs and raw materials has aroused great interest due to their added value and low levels of side effects for health.

Due to its nutraceutical properties, green coffee can be considered a supporting agent in treating metabolic diseases such as obesity, diabetes, and cardiovascular complications (Asbaghi et al. 2021). Also, due to its antioxidant and anti-inflammatory properties, green coffee can be used in the cosmetics industry (for example, it can benefit skin properties such as hydration, permeability barrier function, and microcirculatory function (Fukagawa et al. 2017), and as photoprotection. In the food industry, it can be used as a source of bioactive compounds for the nutritional improvement of several products (de Melo Pereira et al. 2020).

These new possibilities for the application of green coffee open up infinite possibilities for studies that will help in the industrial and technological applications of green coffee. First, however, it is important to evaluate the impact of various parameters on the quality and composition of green coffee. It is crucial to investigate the effects of extraction, sample preparation, technology, and other issues that must be considered in obtaining an adequate strategy to ensure the deactivation and/or prevention of toxic substances as well as the balance of sensory characteristics.

## Conclusion

Most of the clinical trials included in this review showed that green coffee could benefit human health. These benefits are related to improved blood pressure, plasma lipids, and body weight, thus contributing to the improvement of Metabolic Syndrome's risk components. Also, other effects have been shown, including benefits for the skin and cognitive functions.

## Limitations

This study has limitations due to the high heterogeneity of the studies included in the systematic review. It is challenging to compare studies that used patients of different ages, with variations in the dose administered, formulations, and ways of delivery. Besides, some studies used green coffee associated with other substances, making the comparison challenging to perform. Moreover, small-sample studies can present bias in the results.

## Author's contributions

HB and SMB designed the manuscript and wrote the final version. HB, SMB, RAG, and AMO contributed to the literature survey and reviewed the final version of the manuscript. We are responsible for the accuracy of the contents of this paper, and we do not have a financial interest.

## Disclosure statement

The authors declare no conflict of interests or funding support.

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