Consumption of Chlorogenic Acids through Coffee and Health Implications

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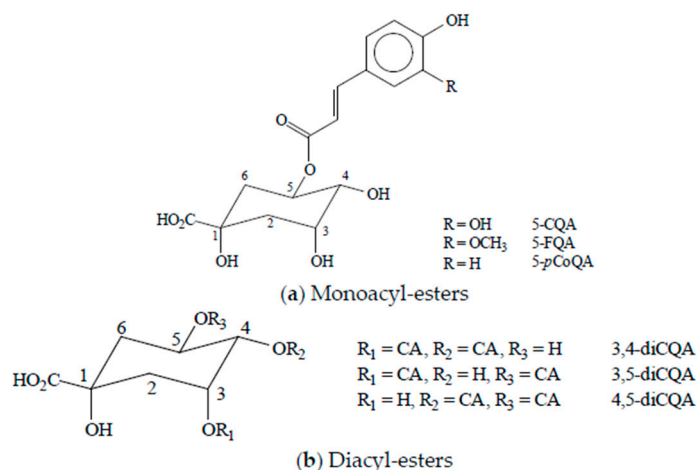* Correspondence: afarah@nutricao.ufrj.br; Tel.: +55-21-39386449

Abstract: Chlorogenic acids (CGA) are the main antioxidant compounds in the Western diet, due to their high concentrations in coffee associated with the high consumption of the beverage. Until about 10 years ago, like many other phenolic compounds, CGA were thought to be poorly absorbed in the human digestive system. Along the years, large amounts of information on the absorption and metabolism of these compounds have been unveiled, and today, it is known that, on average, about one third of the consumed CGA from coffee is absorbed in the human gastrointestinal tract, although large inter-individual variation exists. Considering results from *in vitro* animal and human studies, it is possible to conclude that the antioxidant and anti-inflammatory effects of coffee CGA are responsible for, at least to a certain extent, the association between coffee consumption and lower incidence of various degenerative and non-degenerative diseases, in addition to higher longevity.
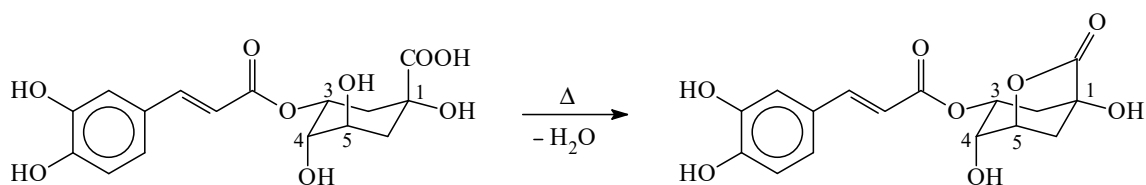
1. Introduction

Chlorogenic acids (CGA), esters of trans-hydroxycinnamic acids and quinic acid (Figure 1), were discovered in 1837 [1]. They were first thought to be caffetannic acid [2], which was in fact a mixture of different acids. Later, CGA were found to be distinct from tannic acid, the latest only found in green coffee. In 1908, 5-caffeoylquinic acid (5-CQA) or chlorogenic acid, numbered according to the International Union of Pure and Applied Chemistry (IUPAC) recommendations [3], was first isolated from a cristaline potassium–caffeine chlorogenate complex by Gorter [2,4], who discovered that this compound was widely distributed in leaves and seeds of numerous plants [5] including phytotherapeutic ones. But at least until the early 1920s substances in coffee other than caffeine were considered to have no biological effects [6]. In 1950, the term isochlorogenic acid was given to another CGA fraction found in coffee which was purified by Corse et al. [7] in 1965 and came to be the mixture of the three main dicaffeoylquinic acids (diCQA) [8]. By the end of the 60s, the neochlorogenic and cryptochlorogenic acids, corresponding to 3-caffeylquinic (3-CQA) and 4-caffeoylquinic (4-CQA) acids, respectively, according to IUPAC [3] as well as the three main feruloylquinic acids (3-FQA, 4-FQA, and 5-FQA) had already been isolated and identified by Nuclear Magnetic Resonance (NMR) spectroscopy [8]. In the late 70s and early 80s, the use of liquid chromatography enabled the identification of nine major CGA and other minor compounds in the coffee matrix [8]. From the beginning of the 90s and on, a new field of research laid in the study of CGA antioxidant attributes and their physiological significance stimulated studies with decaffeinated coffee. Discovered and isolated in the 80s [9], quinic acid lactones or quinides formed by dehydration of the quinic acid moiety during roasting (Figure 2) also gained physiological importance in the 90s [10–14]. Currently, more than 300 major and

minor CGA and related compounds such as dicaffeoylquinic acids (diCQA), diferuloylquinic acids, caffeoylferuloylquinic acids, dimethoxycinnamoylquinic acids, caffeoyldimethoxycinnamoylquinic acids, trimetoxycinnamoylcaffeoylquinic acids; feruloyldimethoxycinnamoylquinic acid, sinapoylquinic acids, sinapoylcaffeoylquinic acids, sinapoylferuloylquinic acids, and related compounds, in addition to a number of new minor *p*-coumaric acid-containing compounds have been described both in coffee [15–24] and in other plant materials [25,26], and a number of potential beneficial effects of CGA have been revealed *in vitro* and in animal studies, corroborating results of epidemiological studies. The aim of this review was to raise the awareness of coffee consumers and not consumers for the high intake of CGA through coffee and for their potential beneficial health effects on health.

Figure 1. Major chlorogenic acids found in coffee. CQA: caffeoylquinic acids; FQA: feruloylquinic acids; *p*-CoQA: *p*-coumaroylquinic acids; diCQA: dicaffeoylquinic acids. When citing other authors, their numbering has been changed for consistency. Numbering follows the International Union of Pure and Applied Chemistry (IUPAC) numbering system [3], which has been recently discussed, in other reviews [23,24].

Figure 2. Formation of 1,5-quinolactone during coffee roasting, exemplified by 3-caffeoylquinide-3CQL. Note: Although under IUPAC rules the numbering system [3] for the lactones is different from the acids, to avoid confusion, the authors used for lactones the same numbering of the carbon atoms as for the acid precursors.

2. Chlorogenic Acids Levels in Coffee Beverages and Estimated Daily Consumption through Coffee

Together with mate (*Ilex paraguariensis*) green coffee seed is the main known source of CGA in nature, especially in *Coffea canephora*, cultivars (Robusta and Conilon), in which contents commonly reach 7–8 g/100 g (dry matter-dm), while in *C. arabica* cultivars 4–6 g/100 g (dm) are more common. However, coffee is mostly consumed after roasting and as CGA are thermolabile compounds, in addition to being isomerized, epimerized, and lactonized, a considerable amount can be lost by degradation during roasting, although part of hydroxycinammic acids can be incorporated into the melanoidins structures formed in Maillard reaction as roasting progresses. Reasonable ranges of contents reported for CGA in laboratory roasted seeds considering various roast degrees are 0.4–2.9 g/100 g (dm) for *C. arabica* and 0.4–5.9 g/100 g (dry basis) in *C. canephora* seeds [27]. The more coffee is roasted the lower is the content difference between species. In medium roasted coffees,

reported CGA contents vary from about 1.7 to 3.5 g/100 g (dm) for *C. arabica* and from 1.0 to 4.3 g/100 g (dm) for *C. canephora*. Reported contents for commercial blends (including lactones) of various roast degrees vary from 0.2 to 3.1 g/100 g (dm) in different countries [27].

In general, the levels of CGA (including their lactones) in coffee brews as reported in the literature may vary largely, from 26 mg/100 mL (including studies that only reported concentrations of the three main CQA isomers) [28,29] to extreme 1141 mg/100 mL (considering unusually concentrated espresso coffees) [30,31], but common values, including caffeoylquinic, feruloylquinic and dicaffeoylquinic compounds, and their main lactones (1,5-caffeoylquinides), range from 50–200 mg/100 mL [32,33]. Percent distribution of CGA compounds in coffee brew, in order of abundance is, on average: 5-CQA (41%–48%), 4-CQA (20%–25%), 3-CQA (17%–20%), 5-FQA (4%–8%), 4-FQA (2%–5%), 3-FQA (1%–4%), 3,4-diCQA (1%–2.5%), 3,5-diCQA (1%–1,5%), 4,5 (~1%), others (<1%) [33,34].

The first variable that leads to such large range of CGA values in coffee brew is the blend. It may contain different percentages of varied types of coffee seeds, including cultivars of *C. arabica* and *C. canephora* species, grown under different edaphoclimatic conditions, and in different degrees of maturation (the latter in the case of a lower quality blend), and processed by a variety of post-harvest methods. All these variables affect coffee chemical composition including CGA content [27]. There are also the roast degrees and roast profiles that will also affect CGA content. The roasted seeds can then be ground to different sizes and the proportion of powder to water classically used can also change dramatically between countries and cultures. For example, while in most European countries, in the USA and Canada the use of ~7 g (1/4 oz) per 100 mL is common for filtered coffees, in Brazil 10 g or more are used. In Italy, the use of 20 g of ground roasted coffee is also not uncommon per 100 mL. In espresso coffee, although traditionally 6–8 g is used for each 25 mL of water, an extreme proportion of 10 g for 25 mL water is nowadays often used by 3rd wave baristas [35,36]. Then, there are a variety of brewing methods where pressure, temperature, and contact time between the water and ground coffee may vary considerably. Despite all variations, domestic brewing can extract considerable amounts of CGA (40%–95%) from roasted coffee [33,37–39] with tendency for lower extraction of diCQA compared to CQA and FQA because of their lower solubility.

In general, considering the different existing brewing methods (Table 1), the values reported for major CGA (CQA, FQA, and diCQA), including the major lactones, in brews prepared at 6%–17.5%, (weight/water volume) using light to dark ground roasted coffees vary as follows: from ~25 to 150 mg/100mL in manually dripped (filtered) brews [33,34,40], from ~35 to 170 mg/100mL in electric dripper (filtered) brews [33,34,41,42], from ~40 to 1000 mg/100 mL in espresso brews [30,32–34,41,42]; from ~55 to 150 mg/100 mL in Italian coffee brews prepared by moka pot [32–34,41,42]; from ~40 to 280 mg/100 mL in French press brews [32,42,43]; about ~110–200 mg/100 mL in Turkish coffee brews [29,34], from ~70 to 230 mg/100 mL in boiled coffee brews [28,33,34,42]; and approximately 35 to 319 mg/100mL in cold-dripped brews [32,34,43,44].

In espresso brews, CGA contents can be much higher than in brews prepared by dripping/filtered or other methods, first simply due to the use of higher proportion of ground coffee per water volume in general. Additionally, the espresso machine may extract CGA more efficiently due to the high pressure applied to the extraction process (commonly 9 bar). In addition to espresso, high concentrations of CGA can be found in brews made using a moka pot, mainly due to water evaporation and brew concentration associated with higher water pressure compared to dripping methods [45]. For cold brews, there are a number of methods in which temperature and infusion times vary considerably. In general, cold brews from short infusion periods and lower temperatures tend to yield lower CGA concentrations in the cup [34,43]. In the same way, higher temperatures up to 95 °C tend to result in greater extraction of CGA [37,38], but keeping coffee brews heated at elevated temperatures may reduce their content in the brew [11,12].

The reported contents of CGA (including lactones) in solid soluble coffee vary largely in the literature, from 0.7 to 9.0 g/100 g (dm) for roasted coffees [37,46–48]; from 10.2 to 21.1 g/100 g (dm) for green (unroasted) coffees that are usually consumed in capsules [34,48], and from 4.6 to 6.7 g/100 g

in blends containing both roasted and unroasted coffees [34,45]. Values in dissolved coffee can be obtained considering that 4 g or less are used per 100 mL cup [49]. After dissolution in hot water, total CGA content should be similar to those in percolated extracts from ground roasted coffees, with potentially higher contents in freeze-dried compared to spray-dried coffees [34]. However, because in many countries soluble coffee is commonly prepared from blends containing high percentage of *C. canephora* seeds, after dissolution in water, such beverages often contain more CGA and lactones than those prepared from ground roasted coffee (with higher percentage of *C. arabica* seeds) and, in this case, daily consumption of CGA would increase through soluble coffee consumption [45]. Table 1 includes values from studies in which quantification of at least the three main coffee CGA (CQA) have been performed in brews.

Table 1. Chlorogenic acids contents in coffee brews obtained by different extraction methods.

Species	Country	N	Roast Degree	Amount of Powder to Water	Water Temperature	Brewing Time	5-CQA	Other CGA (CQA, FQA, diCQA, CQL)	Total CGA	Ref.
				per 100 mL				mg/100 mL		
Manual drip										
Arabica	Colombia	1	M	10	100 °C	2 min	75.1	81.7	156.8	[40]
Arabica	Indonesia	1	M	10	100 °C	2 min	73.4	80.4	153.8	[40]
Arabica	Kenya	1	MD	10	100 °C	2 min	31.2	34.2	65.4	[40]
Arabica	Costa Rica	1	MD	10	100 °C	2 min	10.9	62.4	73.3	[40]
Arabica	USA	1	M	7	98 °C	~3 min	35.4	48.3	83.7	[34]*
Blend	Brazil	1	ML	10	95 °C	~2.5 min	39.1	41.5	80.6	[33]*
Blend	Brazil	1	MD	10	95 °C	~2.5 min	9.8	14.4	24.2	[33]*
Electric dripper										
Arabica	Guatemala	1	Nr	6	90 °C	6 min	74.2	92.6	166.8	[41]
Arabica	USA	1	M	7	95 °C	4 min	41.3	54.8	96.1	[34]*
Arabica	Portugal	1	Nr	13.3	100 °C	2.5 min	16.9	46.8	63.7	[42]
Robusta	Portugal	1	Nr	13.3	100 °C	2.5 min	16.4	45.9	62.4	[42]
Robusta	Vietnam	1	Nr	6	90 °C	6 min	43.8	56.6	100.4	[41]
Blend	Brazil	1	ML	10	Nr	~3 min	44.9	85.1	126.6	[33]*
Blend	Brazil	1	MD	10	Nr	~3 min	12.4	21.8	34.2	[33]*
Espresso										
Arabica	USA	1	M	7	90 °C	28 s	40.8	54.6	95.4	[34]*
Arabica	Ethiopia	1	Nr	14	92 °C	30 s	446.0	584	1030.0	[32]
Arabica	Guatemala	1	Nr	17.5	90 °C	24 s	68.9	150.1	150.1	[41]
Arabica	Ethiopia	1	Nr	18	92 °C	25 s	480.0	661.0	1141.0	[32]
Robusta	Vietnam	1	Nr	17.5	90 °C	24 s	37.0	49.5	86.5	[32]
Blend	Portugal	1	Nr	5.3	90 °C	21 s	33.2	88.8	122.0	[42]
Blend	Scotland-coffee shops	20	Nr	Nr	Nr	Nr	45.2–468.2	43.6–449.2	88.8–918.1	[30]
Blend	Brazil	1	ML	10	90 °C	<1 min	26.0	60.5	86.5	[33]*
Blend	Brazil	1	MD	10	90 °C	<1 min	10.3	27.8	38.2	[33]*
Moka										
Arabica	USA	1	M	7	95 °C	10 min	47.0	64.2	111.2	[34]*
Arabica	Guatemala	1	Nr	8	93 °C	10 min	107.2	140.2	247.4	[41]
Arabica	Ethiopia	1	Nr	10	90 °C	Nr	122.0	145.0	267.0	[32]
Arabica	Portugal	1	Nr	13	Nr	Nr	18.8	55.5	74.3	[42]
Robusta	Portugal	1	Nr	13	Nr	Nr	22.5	64.7	87.2	[42]
Robusta	Vietnam	1	Nr	8	93 °C	10 min	62.5	90.4	152.9	[41]
Blend	Brazil	1	ML	10	Nr	~7 min	58.8	88.0	146.7	[33]*
Blend	Brazil	1	MD	10	Nr	~7 min	19.0	35.8	54.8	[33]*

Table 1. *Cont.*

Species	Country	N	Roast Degree	Amount of Powder to Water	Water Temperature	Brewing Time	5-CQA	Other CGA (CQA, FQA, diCQA, CQL)	Total CGA	Ref.
				per 100 mL				mg/100 mL		
				Infusion bag						
Arabica	Japan	4	Nr	2.5	95 °C	5 min	8.9/10.2	22.6/28.6	31.5–38.6	[34]*
				French press						
Arabica	Guatemala	1	Nr	8	98 °C	5 min	85.7	110.8	196.5	[41]
Arabica	Hawaii	2	M	10	98 °C	6 min	Nr	46.0/51.0	46.0/51.0	[43]
Arabica	USA	1	M	7	90 °C	5 min	38.8	49.3	88.1	[34]*
Arabica	Portugal	1	Nr	13	100 °C	2.5 min	16.3	48.1	64.4	[43]
Arabica	Brazil	1	L	10	100 °C	6 min	126.1	124.0	250.1	[32]
Arabica	Mexico	1	L	10	100 °C	6 min	147.6	133.2	280.8	[44]
Arabica	Ethiopia	1	Nr	10	95 °C	5 min	53.0	67.0	120.0	[32]
Robusta	Portugal	1	Nr	13	100 °C	2.5 min	17.3	49.3	66.6	[42]
Robusta	Vietnam	1	Nr	8	98 °C	5 min	36.3	57.6	93.9	[42]
				Aeropress						
Arabica	Ethiopia	1	Nr	6.6	93 °C	1 min	72.0	82	154.0	[32]
				Cold brewing						
Arabica	USA	1	M	7	95 °C followed by 10 °C	12 hr	30.3	33	63.3	[34]*
Arabica	USA	1	M	7	10 °C	12 hr	28.6	30.6	59.2	[34]*
Arabica	Hawaii	2	M	10	25 °C	24 hr	Nr	51.0/52.0	51.0/52.0	[43]
Arabica	Hawaii	2	D	10	25 °C	24 hr	Nr	36.0/39.0	36.0/39.0	[43]
Arabica	Brazil	1	L	10	25 °C	7 hr	112.4	107.7	220.1	[44]
Arabica	Mexico	1	L	10	25 °C	7 hr	85.7	75.9	161.6	[44]
Arabica	Ethiopia	1	Nr	10	25 °C	6 hr	139.0	180.0	319.0	[32]
				Turkish coffee						
Arabica	USA	1	M	7	90 °C	5 min	46.1	64	110.1	[34]*
Blend	Croatia—Local manufacturer	3	Nr	8	98 °C	5 min	79.5–101.3	74.6–99.8	154.1–201.1	[29]

Table 1. *Cont.*

Species	Country	N	Roast Degree	Amount of Powder to Water	Water Temperature	Brewing Time	5-CQA	Other CGA (CQA, FQA, diCQA, CQL)	Total CGA	Ref.
				per 100 mL				**mg/100 mL**		
				Boiled coffee						
Arabica	USA	1	M	7	95 °C	5 min	45.2	59.7	104.9	[34]*
Arabica	Brazil	1	L	10	100 °C	Nr	126.5	169.1	295.6	[28]
Arabica	Brazil	1	M	10	100 °C	Nr	30.7	51.2	81.9	[28]
Arabica	Brazil	1	D	10	100 °C	Nr	8.7	17.4	26.1	[28]
Arabica	Portugal	1	Nr	13.3	100 °C	2 min	19.4	54.9	74.3	[42]
Blend	Brazil	1	ML	10	100 °C	~4 min	96.8	133.8	230.6	[33]*
Blend	Brazil	1	MD	10	100 °C	~4 min	23.6	47.5	71.13	[33]*
				Soluble or instant coffee beverage						
Nr	Portugal	3	Nr	1.3	100 °C	-	6.0–6.8	11.0–15.2	17.0–22.0	[42]
Nr	UK	2	L	0.9	100 °C	-	5.7/7.2	9.0/10.8	14.7/18.0	[50]
Nr	UK	2	M	0.9	100 °C	-	7.1/7.5	10.3/11.7	17.4/19.2	[50]
Nr	UK	1	Green and roasted	0.9	100 °C	-	21.5	22.5	44.0	[50]
				Ready to drink cold coffee beverage						
Nr	Japan	4	Nr		-	-	65.5–74.8	141.0–169.0	206.5–243.8	[34]*

Note: N: number of samples; 5-CQA: 5-caffeoylquinic acid. Other CGA: 3-caffeoylquinic acid; 4-caffeoylquinic acid, 3-feruloylquinic acid; 4-feruloylquinic acid; 5-feruloylquinic acid, 3,4-dicaffeoylquinic acid; 3,5-dicaffeoylquinic acid; 4,5-dicaffeoylquinic acid, 3-caffeoylquinic-1,5-quinide; 4-caffeoylquinic-1,5-quinide. Roast degree: M: medium; ML: medium light; MD: medium dark, D: dark; L: light. Nr: not reported. *Quantification of nine major CGA compounds and two lactones; Blend: blend of *C. arabica* and *C. canephora*.

In addition to all exposed possibilities of variations before or during beverage preparation, the serving size (a cup of coffee) reported in scientific publications vary from about 25 mL for an Italian espresso up to 600 mL (20 oz) for a filtered brew in the US. The standard American cup, however, is often mentioned as being equivalent to about 237–250 mL (8 fluid oz) [36]. The European traditional cup has been defined in different studies including that of Floegel et al. [51] as containing 150 mL. Finally, the different analytical methods may cause discrepancy in the reported compositional results, especially the least sensitive and specific methods, along with the fact that many reports only consider 5-CQA or the three main CQA isomers. Thus, instead of standard values to represent the chemical composition of a cup of coffee, including CGA content, a range of values seems to be more reasonable. Despite the large increase in consumption of espresso and other concentrated coffees around the world in the last few years, manual or electric dripping with paper or nylon filters are still the most used coffee preparation methods worldwide, including in the US, Canada, Brazil, Central America, and Nordic countries such as Finland, Sweden, Norway, and Denmark. Having said that, based on the value of 100 mg CGA/100 mL as the average of commonly reported contents in filtered coffee (prepared at 6–13.3%) [33,34,40–42] (Table 1), the amounts of ingested CGA per serving of 25 to 600 mL can be estimated in approximately 25 to 600 mg. However, it is also possible to hypothesize that in the case of regular coffees, caffeine helps to regulate the amount of coffee consumed, i.e., strong (concentrated) coffees are commonly used for small servings and week coffees used for large servings.

About the daily CGA intake through coffee, because of the high coffee consumption, in many regions of the world this beverage is the main dietary source of CGA and antioxidants in general [52]. Among exceptions are countries or regions where maté tea is heavily consumed, like the southern regions of Brazil, Argentina, Uruguay, and Paraguay, or places where *Camellia sinensis* tea is mostly consumed, like in the UK and some Asian countries. Exceptions also include the case of coffee abstainers from all over the world [34]. Going from one extreme to another, Nordic countries have the highest daily coffee *per capita* consumption according to the International Coffee Organization (ICO) [53], and therefore probably the highest CGA consumption through coffee, while consumption in Asian countries, especially in Japan, is the lowest [53], with weak brews (about 2.5%) resembling tea infusions. However, it should be noted that coffee consumption in China and Japan is increasing [53] and so is CGA consumption.

Considering the consumption of one to three cups of filtered coffee per day in modest coffee drinkers, (being the latest the amount recommended by several epidemiological studies) [54–56] and considering the average amount of 100 mg CGA per 100 mL serving estimated above for filtered coffees, modest coffee drinkers might consume 100–300 mg CGA/day. Heavy consumers of filtered coffee, considering six 100 mL cups a day, therefore, might reach 600 mg CGA/day. It is important to note that manually dripped or filtered coffees used for estimates contain the lowest amount of CGA among all methods, and therefore the consumption of larger servings than those used for calculations or even coffees extracted by other methods might considerably increase CGA daily intake. Nevertheless, as aforementioned, in the case of regular coffees, caffeine should help regulate the amount of coffee consumed per serving, while for decaffeinated coffee (about 12% of world coffee consumption) [57], CGA consumption can be higher.

Considering a few reports on the estimated *per capita* consumption of coffee brew in different countries, using the same rational as above we can estimate CGA consumption as 120 mg/day for Spain [58], 215 mg/day for Brazil [59], 237 mg/day for Poland [60], 368 mg/day for Iceland [61], 480 mg/day for Norway [62], and 594 mg/day for Finland [63].

3. Bioavailability of Chlorogenic Acids and Lactones and Interaction with Other Food Components

Studies on the metabolism and bioavailability of trans-hydroxycinnamic acids (initially limited to caffeic acid) and CGA started in the 50s, in the same period when the first isomers were discriminated [64]. Although urinary metabolites had already been identified since at least 1957 [65],

until the last decade animal and human studies failed to detect intact CGA in plasma or serum after 5-CQA or coffee intake. In most studies, after 5-CQA or coffee intake, only small amounts of caffeic acid, a hydrolysis product of both CQA and diCQA, had been identified and quantified in murine or human plasma and urine. Therefore, it was generally concluded that less than 1% of CGA ingested was absorbed in animals and humans [66–68] and that almost the whole ingested amount was degraded during digestion, metabolized by the intestinal microflora, and/or excreted with feces [45]. In later studies, considerable amounts of 5-CQA in addition to two CQA, three diCQA, and two FQA compounds were identified in human plasma after consumption of roasted and green coffee extracts [69,70]. Other human studies followed, with improved analytical methodologies and use of synthetic metabolites standards, confirming the absorption and partial bioavailability of CGA, identifying new compounds and specifying forms of conjugation [45,71–75]. Considering human studies, maximum plasma concentration (C_{max}) of CGA and metabolites vary with dose, individual, and with analytical methodology applied in the studies, ranging from nM to low μM levels [45,69–75]. Today, a large amount of knowledge about CGA metabolism has been accumulated, despite the controversies about results involving the distribution of CGA subclasses (diCQA for example) and individual isomers in human fluids, most probably due to analytical circumstances involving enzyme treatment, acyl-migration, hydrolysis or degradation [34,45,76]. It has been estimated that on average, a third of the amount of CGA consumed is absorbed throughout the digestive tract, with a very large variability among individuals [34,45]. Absorption initiates early in the stomach but occurs mostly in the intestine by passive diffusion, and also with probable involvement of monocarboxylic acid transporter (MCT) [77–80] and perhaps of bilitranslocase (an anthocyanin transporter) [78]. Partial intestinal hydrolysis, predominant phase two metabolism (mostly involving sulfation and glucoronidation) and entero-hepatic circulation have been reported [69–75]. The unabsorbed portion of CGA, as with other polyphenols, is extensively hydrolyzed by gut bacteria, serving as potential prebiotic for beneficial bacteria [81–83]. These colonic metabolites can be absorbed and excreted in urine [69–71]. More studies are needed on the bioavailability of lactones, but partial absorption [72,84,85] and partial degradation [71] of the main lactones have been reported in human and *in vitro* studies (for detailed information on *in vitro*, animal and human studies involving CGA and lactones, including pharmacokinetics, liver metabolism, etc., see References [34,45]).

Regarding possible CGA interaction with food components, the interaction between polyphenols and different dietary components has been extensively reported [86]. An important interaction occurs with proteins, especially casein and albumin. When consumed simultaneously with milk, 5-CQA, and hydroxycinnamic acids may interact with whey proteins such as β-lactoglobulin and with casein [87]. These complexes may not be susceptible to proteolysis by gastrointestinal enzymes such as trypsin, chymotrypsin, pepsin, and pancreatin impeding the release of phenolic compounds from the protein complex, and consequently, their absorption [87,88]. This event is not exclusive of coffee polyphenols; it has also been observed in various human studies involving tea [89] and cocoa polyphenols [90].

Confirming such *in vitro* findings, the urinary recovery of CGA and metabolites was evaluated after simultaneous consumption of water, instant coffee dissolved in water or in whole milk. The amount of CGA and metabolites recovered 24h in urine after consumption of the mixture of milk and instant coffee (on average, 40% of the amount consumed) was consistently lower in all subjects compared to plain coffee (average of 68%), indicating that adding coffee to milk quantitatively altered the absorption and/or the metabolism of CGA from coffee [91]. On the other hand, in another study [92], the addition of 10% whole milk or a pre-mixed non-dairy (fat rich) creamer with sugar to coffee did not increase or decrease CGA area under the curve in plasma, in despite of a delay in CGA appearance observed in the creamer test. The use of low amount of milk may have spared CGA's bioavailability in the first treatment. The second treatment contained more than one variable, which makes difficult to discuss. In contrast with the later study, a more recent *in vitro* study investigating the bioaccessibility of coffee CGA [93] also reported that the addition of milk to coffee decreased CGA bioaccessibility and that casein bound 5-CQA with high affinity. Different percentages of different

bovine milk types (whole, semi skimmed, and skimmed) were tested and the presence of fat (50% whole milk, 50% semi skimmed or 25% whole milk) strongly increased the bioacessibility of CGA.

A more recent study evaluated whether the simultaneous consumption of coffee and solid foods affected the absorption and bioavailability of CGA determined by the area under the curve of plasmatic CGA and metabolites' concentration [94]. Subjects consumed plain instant coffee, or coffee with either a high-carbohydrate meal (bread rolls and honey) or a high-fat meal (bread roll and peanut butter) containing the same amount of CGA (3.1 mg CGA/kg body weight). The authors observed significantly lower CGA bioavailability after consumption of a high-fat meal (which in fact also contained carbohydrate) compared to pure instant coffee. The high carbohydrate meal did not change CGA bioavailability compared to plain coffee but produced differences in the kinetic of release. The consumption of both meals with coffee delayed the appearance of colonic metabolites in urine. The effect of fat and sugar on CGA–protein interaction or in CGA absorption is still not clear and deserves further investigation.

Based on the urinary excretion of CGA and primary metabolites after coffee and a soy–coffee beverage consumption by humans [95], soy protein and/or other substances present in soymilk seem to also bind CGA (although to a lower extent compared to cow's milk), decreasing their absorption in the upper digestive tract, which corroborates *in vitro* results on interactions between CGA and soy protein [95–97].

Regarding the effect of coffee matrix variation, no difference has been observed in the 24 h human urinary recoveries of CGA and metabolites after the beverage consumption of green and roasted coffee extracts [98] and of green coffee and green mate extracts [99]. More studies on matrix effect are needed comparing the bioavailability of CGA from different food sources.

The interaction between polyphenols and different dietary components decreasing the bioavailability of the later has also been extensively reported [86]. Polyphenols can form complexes with metal cations through their carboxylic and hydroxylic groups, and thus interfere with the intestinal absorption of minerals. Numerous experiments in both humans and animals have shown that polyphenols strongly inhibit iron absorption [100]. The study of Gutnisky et al. [101] also reported an intense inhibitory effect of CGA from maté (*Ilex paraguarensis*) in the absorption of non-heme iron in rats. Such inhibitory effect has also been observed in coffee and attributed to GCA [102]. This finding is supported by the report on formation of a CGA chelate with iron which decreased induced lipid peroxidation in bovine liver microsomes [103].

4. Effects of Chlorogenic Acids on Human Body and Health

Along the past few years, a number of epidemiological studies have associated moderate coffee consumption, independently of caffeine, with the reduction in the relative risk of development of chronic degenerative diseases and death [54–56,104–108]. The beneficial effects of coffee can be attributed to the joint action of many bioactive compounds [109]. It is likely that most contributions to decreased risk of certain diseases are caused by synergistic or additive effects of the various compounds present in coffee [35]. However, *in vitro* and animal studies have linked certain compounds to specific mechanisms. In the case of CGA, most contribution to coffee's health effects are related to their antioxidant and anti-inflammatory activities [110–113] which include mechanisms involving signal transduction [114,115].

Because only a few CGA compounds are commercially available or synthesized in laboratories, studies on the biological properties of FQA, *p*-CoQA, CFQA, and minor CGA compounds are missing. Most biological activities reported for CGA are related to CQA compounds, especially 5-CQA. There are also some studies investigating the effects of synthesized CQL and diCQA, the latest being also present in considerable amounts in some types of propolis and other medicinal plant material. The CGA contribution to the preventive or healing effect of coffee will be briefly presented below.

Antioxidant Activity

Coffee is the main source of antioxidant compounds in the diet of many populations [35,52] owing mainly to the high concentration of CGA and lactones in the brew associated with its high consumption. The high contribution of coffee and CGA to the dietary intake of antioxidative compounds is described in several reports from different countries. Based on the association of their official food consumption database or other types of surveys with the *in vitro* antioxidant capacity of foods, coffee was found to be the main percent contributor to total dietary antioxidant capacity, i.e., Brazil (66%); Norway (64%); Italy (38% for women and 27% for men); Spain (45%); Japan (56%), and Czech Republic (54.6% for women and 43.1% for men) [35,52].

Oxidative stress is related to several degenerative diseases, cancer development, aging, and death [116,117]. Chemical-based assays, cell-based assays, and animal models have been established to investigate the antioxidant activity of CGA [111]. CGA are known to have similar antioxidant activity to ascorbic acid [118]. They are able to quelate transition metals such as Fe^{2+} to scavenge free radicals and interrupt free radical chain reactions [119]. In addition, they have been able to prevent low density lipoprotein (LDL) oxidation induced by different oxidizing agents [120,121] and prevent DNA damage *in vitro* [122]. The main CGA in coffee 5-CQA was able to scavenge 1,1-diphenyl-2-picrylhydrazyl (DPPH) radicals, superoxide anions ($O2^-$), hydroxyl radicals (·OH), and peroxylnitrite ($ONOO^-$) [123–125] and to protect DNA from damage caused by oxidative stress in different studies [111,126]. Caffeic acid, one of the first and main CGA metabolites, as well as other phenolic derivatives, have also been reported to have important antioxidant activity [127,128].

Cell culture experiments have shown antioxidant properties of specific CGA at both the cellular and molecular levels [111]. In the human keratinocyte cell line (HaCaT cells), 5-CQA was found to protect against H_2O_2-induced UVB-mediated oxidative stress [124]. In a culture of mesenchymal stem cells of bone marrow under oxidative stress, 5-CQA suppressed reactive oxygen species increased by activation of Akt phosphorylation and increased the expression of *FOXO* (Forkhead box proteins) family genes. These proteins are a family of transcription factors that play important roles in regulating the expression of genes involved in cell growth, proliferation, differentiation, and longevity [126]. CGA (5-CQA) also reduced apoptosis in primary cortical neurons by upregulating antioxidant enzymes such as NADPH:quinine oxidoreductase 1 [129]. The same compound, as well as 3-CQA and 4-CQA were found to protect murine adrenal cells against hydrogen peroxide-induced apoptosis by suppressing the mitochondrial membrane depolarization caused by oxidative stress [130]; moreover, both 5-CQA and 3,5-diCQA exerted protective effect against generation of t-butyl hydroperoxide-induced reactive oxygen species in model liver cancer HepG2 cells [131]. Feeding diabetic rats with 5-CQA effectively reduced lipid hydroperoxide production and increased the level of non-enzymatic antioxidants such as reduced glutathione and vitamins C and E [132,133]. Other studies have shown that 5-CQA can alleviate the oxidative stress induced by methamphetamine in rats by restoring liver superoxide dismutase and glutathione peroxidase activities and by preventing the accumulation of lipid peroxidation [134]. As aforementioned, there is strong evidence that CGA are effective in protecting against oxidation reactions *in vivo* by upregulating redox-related nuclear transcription factors involved in the expression of antioxidant enzymes [111].

Despite the high antioxidant activity of coffee or its capacity to upregulate antioxidant enzymes, in addition to any other health attribute it might have, it is noteworthy mentioning that this does not mean that CGA from coffee or coffee itself can replace the intake of antioxidants from other foods, as each has its own specific bioactivity [35].

Anti-Inflammatory Effect and Wound Healing

Oxidative stress and chronic inflammation are closely related physio-pathological events [135]. Experimental data show the simultaneous existence of low-grade chronic inflammation and oxidative stress in many chronic diseases like diabetic complications, cardiovascular and neurodegenerative diseases, alcoholic liver disease, and chronic kidney disease [136–138]. Inflammation is a complex

physiological reaction to tissue injury caused by exogenous or endogenous sources [111]. Exaggerated or unregulated prolonged inflammatory process can induce tissue damage and is the cause for many chronic diseases [139].

Most evidences to date show that 5-CQA exerts anti-inflammatory activity by downregulating pro-inflammatory cytokines, through modulation of key transcription factors, such as tumor necrosis factor-alpha (TNF-α), and interleukins such as IL-8 [111,140]. A cell study conducted on murine RAW 264.7 macrophages indicated that 5-CQA decreased lipopolysaccharide (LPS)-induced upregulation of cyclooxygenase (COX-2) at protein and mRNA levels suggesting that 5-CQA could exert anti-inflammatory effects through inhibiting prostaglandin E2 (PGE2) production [141].

In animal studies, the oral administration of 5-CQA protected against trinitrobenzenesulfonic acid-induced colitis in mice by reducing neutrophil infiltration and inhibiting the NF-κB (factor nuclear kappa B) pathway [142]. A similar effect was also observed in the dextran sulfate sodium-induced colitis model in mice [136]. In both cases, suppression of pro-inflammatory cytokines was observed. CGA (5-CQA) could effectively prevent mice from concanavalin A-induced hepatitis, which might have resulted from the activation of Toll-Like Receptor (TLR) 4 signaling, downregulating the expression of adhesion molecules, and also alleviating the infiltration and activation of hepatic leukocytes and the production of pro-inflammatory cytokines [143].

The reduction of inflammation resulting in enhanced wound healing has also been reported for CGA in different studies [111]. In a study with diabetic rats, the oral administration of 5-CQA enhanced hydroxyproline and decreased malondialdehyde/nitric oxide levels in wound tissues, in addition to elevating reduced-glutathione [143,144]. Another *in vivo* study using a mice skin excision wound showed that topically administrated hydrogels containing 5-CQA reduced significantly the wound area size in the inflammatory phase, enhancing the wound healing process [145].

Antimutagenic and Anticarcinogenic Effects

This activity is partly related to CGA antioxidant activity, since the overproduction of oxygen free radicals lead to oxidative damage of DNA which is primarily responsible for promoting various types of cancer as breast, bladder, colon, liver, pancreatic, prostate, and skin cancers [146]. Dietary polyphenols, including CGA, can prevent the initiation step of cancer by inhibition of DNA-damage caused by free radicals or carcinogenic agents [147]. In fact, epidemiological studies show an inverse association between coffee consumption and the risk of certain types of cancer. Such effect has been related to CGA intake [148–150].

The anti-mutagenic property of CGA and their metabolites has been demonstrated decades ago [151]. Recent studies have confirmed these findings and elucidated several mechanisms of chemo-preventive action [35]. They include modulation of expression of enzymes involved in endogenous antioxidant defenses, DNA replication, cell differentiation and ageing [147,152,153], metal chelation, inactivation of reactive compounds, and metabolic pathway changes [154]. In the colon, for example, 5-CQA may inactivate free reactive radicals from diet and as a result help preventing colon cancer [155]. In epithelial JB6 cells from mice, 5-CQA decreased reactive oxygen species generation and stimulated glutathione-*S*-transferase activity, providing a protective role against carcinogens [152]. Coffees rich in CGA induced chemo preventive phase II-enzymes via the Nrf2/ARE pathway (important mechanism for protecting cells and tissues from carcinogenesis and carcinogenic metabolites) *in vitro* and *in vivo* [156].

Hepatoprotective Effect

Hepatic injury may result from many different causes, including viral hepatitis, iron overload, obesity, and excessive alcohol consumption [111]. The beneficial impacts of coffee on liver diseases in general have been reported in several studies [157–159]. They include hepatitis B and C [160] and cirrhosis [158]. Additionally, according to meta-analysis of 16 human studies, coffee consumption (2 cups/day) reduces the risk of developing liver cancer by 40% as compared to no coffee

consumption [161,162]. Proposed protective mechanisms are prevention of cell apoptosis and oxidative stress damage due to activation of natural antioxidant and anti-inflammatory systems [163,164]. Such protective mechanisms have been linked mainly with CGA [165] and caffeine [166] among other coffee compounds. In general, experimental data suggest that the hepatoprotective activity of CGA is probably associated with an inflammatory response inhibition [167] and anti-viral activity [160].

Xu et al. [168] administered intraperitoneal 5-CQA to C57BL/6J mice (with lipopolysaccharide-induced inflammatory liver injury) and observed that the expression of TNF-α was markedly inhibited, suggesting anti-inflammatory effect of 5-CQA on acute liver injury. Yun et al. [164] examined the effects of 5-CQA on hepatic ischemia/reperfusion (I/R) injury in rats. In 5-CQA treated rats, the levels of serum TNF-α, inducible nitric oxide synthase and cyclooxygenase-2 protein was significantly reduced, and hepatic histology was improved, suggesting the positive effect of CGA on I/R-induced liver injury.

The anti-fibrotic effect of 5-CQA oral administration on CC14-rats with induced cirrhosis was investigated by Shi *et al.* [169]. CGA (5-CQA) reduced liver fibrosis as well as the expression of collagens I and III. Consistently, rats treated with 5-CQA displayed reduced levels of vascular endothelial growth factor, tissue growth factor-β and α-smooth muscle actin, thus indicating that 5-CQA was able to counteract liver fibrogenesis in rats. Successively, the same authors further extended their findings on the anti-fibrotic effects of 5-CQA in the same experimental model by showing that 5-CQA treatment reduces the expression of inflammatory cytokines, TLR 4, myeloid differentiation factor 88, inducible nitric oxide synthase, and activation of cyclooxygenase-2 and nuclear factor-κB [170]. These are just a few among the many positive studies on the hepatoprotective effect of coffee and CGA.

Anti-Diabetic Effect

Epidemiological studies suggest that coffee consumption prevents or delays the onset of type 2 diabetes [171,172]. Studies concluded that daily consumption of 3–4 cups of coffee a day might exert such health effects by reducing oxidative damage, body fat mass, and energy/nutrient uptake [173,174]. These beneficial effects have been attributed mainly to CGA and derivatives [175] as well as trigonelline [176,177]. They appear to target preferentially hepatic glucose metabolism by improving whole body insulin sensitivity [178–180]. Additionally, a synthetic derivative of 5-CQA (S3483) inhibited the glucose-6-phosphate system and subsequently delayed glucose absorption in the intestine [111,181]. Other proposed mechanisms observed *in vivo* and *in vitro* are related to the regulation of key enzymes of glucose and lipid metabolism, such as glucokinase, fatty acid synthase, and carnitine palmitoyl transferase [182]. CGA lactones have also been able to increase hepatic and muscle glucose utilization among other mechanisms that result in lowering the blood glucose levels in rats [183].

Cardioprotective and Antihypertensive Effects

Cardiovascular diseases are the leading cause of death in the world according to the World Health Organization (WHO), with 13.2% and 2% of deaths due to ischaemic and hypertensive cardiovascular diseases, respectively [184]. Key mechanisms for cardiovascular protection are high antioxidant and anti-inflammatory properties which improve endothelial dysfunction and reduce insulin resistance. CGA exhibit both of these properties and a number of *in vitro* studies have demonstrated a positive role against endothelial dysfunction [111]. Another mechanism for CGA protective effects on vascular endothelial function is the release of vasoactive molecules such as nitric oxide [185] and decrease in plasma total homocysteine levels [186]. Additionally, studies indicate that 5-CQA and caffeic acid have beneficial effects on cardiovascular diseases via suppressing P-selectin expression on platelets. Potential effects on P-selectin expression were suggested to derive from their significant involvement in platelet activation [187]. In respect to effects of CGA on blood pressure, several mechanisms have been proposed, including the stimulation of nitric oxide production through the

endothelial-dependent pathway [188], reduction of free radicals through inhibiting NAD(P)H oxidase expression and activity [189], and inhibition of angiotensin-converting enzyme [111].

Antiobesity and Anti-Metabolic Syndrome Effects

The oxidative stress accumulated in fat tissue has been proposed as an early initiator of the obesity-associated metabolic syndrome [190,191] which is defined as a group of interconnected physiological, biochemical, clinical, and metabolic factors that increase the risk of cardiovascular diseases, type 2 diabetes, and all-cause mortality [192]. Chronic inflammation has also been associated with the underlying cause of dysregulation of adipocytokines and development of metabolic syndrome [112,193]. CGA exert both antioxidant and anti-inflammatory properties, being promising candidates to help prevent and fight metabolic syndrome.

Habitual coffee consumption (1–4 cups/day) has been inversely associated with metabolic syndrome [194,195]. Moreover, epidemiological evidence suggests that the consumption of coffee is inversely associated with weight gain [196]. In two prospective cohort studies, the consumption of both regular and decaffeinated coffees was associated with body weight loss [196,197], which suggests a positive effect of non-caffeine coffee compounds on weight reduction, with CGA being the strongest candidate [198]. In fact, decaffeinated green CGA-rich coffee extracts have been marketed for such purposes.

Several mechanisms related to the antioxidant and anti-inflammatory properties of CGA have been proposed to explain how these compounds exert positive effects over metabolic syndrome [191]. Ma et al. [199] found that 5-CQA treatment in obese mice fed a high-fat diet greatly inhibited the diet reduced expression of macrophage marker genes *F4/80*, *Cd68*, *Cd11 b* and *Cd11c* in adipose tissue, aand of and pro-inflammatory mediator genes (*TNF-α* and *MCP-1)* in macrophages. In addition, the authors observed that 5-CQA inhibited hepatic peroxisome proliferator-activated receptor γ (PPARγ), which promotes fatty acid uptake into liver cells. The mechanism proposed was that 5-CQA scavenges reactive oxygen species (ROS) generated by consumption of high-fat diet, which suppresses the expression of inflammation, and consequently reduces fat accumulation, weight gain, and insulin resistance, while inhibition of PPARγ prevents and improves liver steatosis [191]. Furthermore, 5-CQA has been observed to have an impact over important transcription factors and enzymes that regulate lipid metabolism, which has been associated to positive effects on obesity and dyslipidemia [191,200]. The anti-obesity properties of CGA have also been linked to the metabolism of glucose [200,201]. CGA (5-CQA) was responsible for a significant improvement in glucose tolerance that might be a consequence of reduction in body mass index and its effects on body weight [202]. In mice, 5-CQA has been suggested to reduce body weight by inhibiting hepatic triglyceride accumulation [203]. The mechanism via enhanced lipolytic activity in the adipocyte tissue has also been related to the effects on adipocyte metabolism and weight reduction [111,204].

Recently, 5-CQA showed promising effects in modulating lipid metabolism and decreasing obesity in high-fat diet induced rats, which could be attributed to the reduction in hepatic lipogenesis and hepatic fatty acid uptake, as well as the enhancement of hepatic fatty acid β-oxidation. The mechanism of 5-CQA action was associated with upregulation of peroxisome proliferator-activated receptorα (PPARα) expression and downregulation of liver X receptor α (LXRα) expression. Additionally, enhancement of the antioxidant activity and clearance of free fatty acids also contributed to the effect of 5-CQA [205].

Neuroprotective Effects

Alzheimer's disease is the most frequent cause of dementia, leading to a progressive cognitive decline. While there is currently no medication against Alzheimer's disease [182], several studies have observed an inverse association between regular coffee consumption and development of Alzheimer's disease [35,36]. The mechanisms of coffee protective effect are believed to be related to the anti-inflammatory effects of caffeine and CGA on the A1 and A2 receptors as well as to the

reduction of toxic β-amyloid peptide deposits in the brain, a pathological characteristic in patients with Alzheimer's disease [206–209]. Other proposed mechanisms could be the inhibition of the enzyme's acetylcholinesterase and butyrylcholinesterase in the brain (given that such inhibition retards acetylcholine and butyrylcholine breakdown), and prevention of oxidative stress-induced neurodegeneration due to its high antioxidative activity [206–208].

Emerging evidence from animal models also link CGA to prevention against other neurodegenerative diseases and ageing [210,211]. Although the involvement of coffee polyphenols in human cognitive function has not been well studied, the number of findings on the *in vitro* neuroprotective effects of polyphenols in general is rapidly increasing [212]. Shen et al. [213] reported that the intraperitoneal injection of 5-CQA decreased oxidative damage in rat brain cerebellum exposed to methotrexate, a drug with severe side effects used to treat certain types of cancer, psoriasis, and rheumatoid arthritis. They found that 5-CQA pre-treatment attenuated lipopolysaccharide (LPS)-induced IL-1β and (TNF-α) release in the substantia nigra, thereby pointing to the neuroprotective effects of 5-CQA on pro-inflammatory cytokine-mediated neurodegenerative disease. In another study by Taram et al. [214], the neuroprotective effects of 5-CQA and major metabolites caffeic and ferulic acids were investigated in primary cultures of rat cerebellar granule neurons and it was suggested that caffeic acid displays a much broader profile of neuroprotection against a diverse range of stressors than its parent 5-CQA or ferulic acid. The authors concluded that caffeic acid is a promising candidate for testing in pre-clinical models of neurodegeneration.

The anxiolytic and mood-elevating properties of 5-CQA have been reported. The anti-anxiety effect was blocked by flumazenil, suggesting that such an effect by 5-CQA is dependent on its activity on GABAA-benzodiazepine receptors [215]. Also, CGA' positive effects on inflammation are consistent with those outlined in the neuroinflammatory hypotheses of depression and with the effects of current antidepressant therapies. In the same way, due to the aforementioned positive CGA effects on the central nervous system, they may play a part in decreasing depressive symptoms. However, to date, there is insufficient evidence to confirm this hypothesis [216].

Regarding CGLs, they hold the same antioxidant property as their CGA precursors and as they are less polar, they should be more permeable to the blood–brain barrier. They have been shown to bind to specific sites in the brain, including μ-opioid receptors [13,14]. A significant correlation between CGL concentration in coffee and neuron cell survival in a hydrogen peroxide-induced neuron death model has been reported [217], suggesting a possible contribution of CGL to the increased neuron protective effects.

Antimicrobial Effect

A number of studies have reported antimicrobial (bacteriostatic and bactericidal) effects of 5-CQA and coffee extracts on various types of detrimental microorganisms that may grow in different parts of the body, from oral bacteria causative of caries to detrimental intestinal bacteria. Roasted *C. arabica* and *C. canephora* extracts and brews showed antibacterial activity against *Streptococcus mutans* and other oral types of bacteria [218,219]. CGA (5-CQA) was shown to contribute to such activity, with minimum inhibitory effect (MIC) varying in the different studies from 0.8 to 5.0 mg/mL [218,219]. Bactericidal effect was found against the intestinal bacteria *Stenotrophomonas maltophilia* resistant to trimethoprim/sulfamethoxazole [220], *Helicobacter pylori* [221], *Staphylococcus epidermidis* [222], *Streptococcus pneumoniae*, *Staphylococcus aureus*, *Bacillus subtilis*, *Escherichia coli*, *Shigella dysenteriae*, *Salmonella Typhimurium* [223], *Klebsiella pneumonia* [224].

In addition to 5-CQA, bacteriostatic and bactericidal effects of CGA colonic metabolites (ferulic, isoferulic, benzoic, and hydroxybenzoic acids) have been observed against *Escherichia coli* [225,226]. Minimum inhibitory effect for caffeic acid and other CGA metabolites varied from 0.6 to 80 mg/mL in different studies for different types of microorganisms [221–224]. The mechanism for antimicrobial action of 5-CQA has been suggested to be binding to the outer cell membrane and disruption of it, exhaustion of intracellular potential, and release of cytoplasm macromolecules, leading to cell

death [223]. Especially in the context of knowledge about the positive effects of 5-CQA against detrimental colon microflora, it has been suggested that the potent and selective antimicrobial effect of 5-CQA makes it suitable as an ideal food preservative and additive [113].

CGA can also exert antifungal effects against *Candida albicans* by disrupting the fungi's cell membrane [227]. Both caffeic acid and 5-CQA are known to have multi-antiviral activities against Herpes simplex virus (HSV) types 1 and 2 [228], HIV virus [229], and adenovirus [230]. Potent antiviral activity of 5-CQA against Ebola virus have also been observed [231,232].

Potential Prebiotic Effect

The consumption of prebiotic foods or compounds stimulate the growth of probiotic and other health promoting colonies in the intestine, with special emphasis given to *Bifidobacterium* and *Lactobacillus* spp. [233,234]. Therefore, indirectly, the literal benefits of prebiotics to health are the same as those of probiotics, such as production of short-chain fatty acids which decrease the luminal pH, stimulating the growth of beneficial intestinal bacteria and suppressing pathogenic bacteria [233,234], stimulating the immune system [235,236], preventing colon cancer [237], increasing calcium absorption [238], and preventing diabetes [239–242]. Furthermore, dietary supplementation with prebiotics may reduce or retard the accumulation of advanced glycation end products (AGE) formed via Maillard reaction in individuals at risk of type 2 diabetes, and also, improve and restore microbial balance within the gastrointestinal tract, potentially reducing AGE absorption [243].

Reported data suggest that the unabsorbed portion of CGA and caffeic acid in the human gastrointestinal tract serves as a substrate for beneficial intestinal bacteria, stimulating their growth [35,244,245]. While the bifidogenic effect of CGA seems to be a consensus [246,247], CGA effect on the multiplication of *Lactobacillus* spp. is somewhat controversial, suggesting growth of selected strains [226,247]. In most studies evaluating the prebiotic effects of 5-CQA, increase in short-chain fatty acids production has been observed [246]. However, differently from the classical prebiotic frutooligosaccharide, incubation with 5-CQA has promoted the growth of *Firmicutes* and *Bacteroides*, and of *Clostridium coccoides–Eubacterium rectale* groups as well [247]. Also, the effect of 5-CQA on the growth of *E. coli* does not seem to be clear, being effective in decreasing the number of colonies in just a few studies [223]. In conclusion, the number of studies on the prebiotic effects of CGA is small but the existing data are promising, although not all the effects observed for classical prebiotic compounds are observed. The physiological and clinical outcomes from such differences need to be evaluated. Also, the prebiotic effect of CGA compounds other than 5-CQA needs to be evaluated.

5. Concluding Remarks

The contribution of CGA to the daily polyphenol and antioxidant intake for coffee drinkers is quite relevant. Several studies have demonstrated that CGA are partially bioavailable and potentially beneficial to human health. However, considering that their concentration in coffee beverage depends on a number of factors, that a considerable inter-individual variability occurs in the metabolism of these compounds in humans, and that the ingested amount necessary to promote each of their potential health benefits is still unknown, more studies are needed in order to establish a daily dietary recommendation aiming at specific health benefits. Studies are also needed to elucidate the mechanisms involved in the absorption and metabolism of individual major and minor CGA compounds from coffee. Because only a few CGA are commercially available or synthesized in laboratories, studies on the bioavailability and biological properties of CGL, FQA, *p*-CoQA, CFQA (caffeoyl-feruloylquinic acid), and other minor CGA compounds are missing. Lastly, studies on the interactions of food components with CGA are also needed.

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