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Chlorogenic acid intake guidance: Sources, health benefits, and safety

doi: 10.6133/apjcn.202210/PP.0002

Published online: October 2022

Running title: Chlorogenic acid intake guidance

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ABSTRACT

Chlorogenic acid (CGA) is widely present in plant foods and has attracted much attention due to biological activities such as those which are antioxidant, anti-inflammatory, antibacterial, and antiviral. It plays a role in regulating glucose and lipid metabolism, improving insulin resistance, and reducing the risk of type 2 diabetes and cardiovascular diseases. The estimated dietary intake of CGA is 5 to 1000 mg/d. Based on the data from population intervention studies, daily oral doses of CGA at 13.5mg to 1200 mg can reduce fasting blood glucose (FBG), improve glucose tolerance, enable weight loss /prevent weight gain, and improve blood pressure in hypertensive patients. Daily intake of 200 mg or more may reduce FBG, with a dose-effect relationship in the range 13.5-500 mg/d. Therefore, a specific proposed level (SPL) of CGA to improve FBG could be ≥ 200 mg/d. Data insufficiency does not allow formulation of a tolerable upper intake level (TUIL) for CGA.

Key Words: Chlorogenic acid, acyl quinic acid, caffeoylquinic acid, specific proposed level, tolerable upper intake level

INTRODUCTION

Chlorogenic acid (CGA), also known as acyl quinic acid, or coffee tannic acid, is a phenolic acid that is found ubiquitously in plant foods, especially vegetables, fruits, and coffee beverages. CGA was first identified by Robiquet and Boutron in 1837, its terminology developed by Payen in 1846. In 1854, Ludwig and Kromeyer found that CGA in sunflower seeds, and then that it was widely present in plants. In 1909, crystalline CGA was first isolated and extracted from green raw coffee beans by Gorter K. In 1932, Fischer first determined CGA structure to merit the 3-O-caffeoylquinic acid (3-CQA) descriptor 1, later named 5-O-caffeoylquinic acid (5-CQA) by the International Union of Pure and Applied Chemistry (IUPAC).

In 1921, Oparin suggested that CGA was a respiration-pigment. In 1951, Joslyn and Ponting attributed the browning of fruit after cutting or damage to the oxidation of CGA, not tannic acid. By 1995, the importance of CGA, derived from cinnamic acid, as a dietary antioxidant was recognized.¹ More recently CGA (mainly 5-CQA) has been shown to have a variety of biological activities including those which are antioxidant, anti-inflammatory, antibacterial, and anti-viral. Population-based epidemiological studies, intervention studies, and animal experiments indicate that CGA can regulate glucolipid metabolism. It can improve insulin resistance, reduce the risk of type 2 diabetes and cardiovascular diseases, protect

organs such as nerves, liver, lungs, eyes, and joints from oxidative and inflammatory damage, inhibit carcinogenic effects of chemical carcinogens, and protect DNA. CGA, as a natural antioxidant, is used in cosmetics in Europe and the United States.

CHEMICAL STRUCTURES AND PHYSICOCHEMICAL PROPERTIES

Chemical structure

CGA is a phenolic acid condensed from caffeic acid (3,4-dihydroxycinnamic acid) and quinic acid (1L-1,3,4,5-tetrahydroxycyclohexane carboxylic acid). It is one of the main derivatives of trans cinnamic acid. The system name is called 1,3,4,5-tetrahydroxycyclohexane carboxylic acid-3-(3,4-dihydroxyl) β -phenyl acrylicoate. The chemical name of IUPAC codes is 5-o-caffeoylquinic acid, and the chemical name before is 3-o-caffeoylquinic acid, alias coffee tannic acid. The molecular formula of CGA is C₁₆H₁₈O₉, the relative molecular mass is 354.3, and its chemical structure is shown in Figure 1.

CGA in natural plants is often accompanied by isomers (Figure 1). The isomers that have been isolated include CGA (3-CQA), neochlorogenic acid (5-CQA), cryptochlorogenic acid (4-O-caffeoylquinic acid, 4-CQA), isochlorogenic acid A (3,5-O-dicaffeoylquinic acid, 3,5-CQA), isochlorogenic acid B (3,4-O-dicaffeoylquinic acid, 3,4-CQA), isochlorogenic acid C (4,5-O-dicaffeoylquinic acid, 4,5-CQA) and cynarin (1,3-O-dicaffeoylquinic acid, 1,3-CQA; 1,5-O-dicaffeoylquinic acid, 1,5-CQA). The synthetic pathways and the biological activities of these isomers are similar. The most common and widespread monomer of CGA is 5-CQA, currently the only commercially available pure CGA.

Physicochemical properties

CGA is a white powder, which is easily oxidized, unstable to alkali and readily decomposed by being heated, but not easily decomposed by ultraviolet irradiation (UVA, UVB). Its hemihydrate is needle crystal and becomes an anhydrous compound at 110°C. The melting point is 208°C (205-209°C), and the specific optical rotation is -36° (c=1, H₂O). The solubility of CGA in water at 25°C is 4% (25mg/mL) which increases in hot water. As a polar organic acid, CGA is easily soluble in polar solvents such as ethanol and acetone, slightly soluble in ethyl acetate, but insoluble in weak polar solvents such as chloroform and ether.

ABSORPTION AND METABOLISM

Metabolic studies in humans show that CGA can be absorbed through the gastrointestinal tract and be well utilized. Its absorption pathways include: (1) In the human stomach and/or

upper gastrointestinal tract, partially whole 5-CQA (about 33%) is absorbed into the bloodstream without hydrolysis; (2) A small amount of 5-CQA (about 7%) is absorbed by the small intestine through passive diffusion, including as the hydrolysates caffeic acid and quinic acid; (3) Colonic microbiome mediated absorption of 5-CQA metabolites; (4) Whole 5-CQA and its metabolites enter the blood and are absorbed and/or metabolized in the liver. There are large individual differences in the absorption, metabolism, and utilization of CGA in the human body; dihydroxy caffeic acid-O-sulfate in urine may be used as a sensitive biological indicator for evaluating the intake of CGA.²⁻⁷

In healthy individuals, a single intake of CGA 1-2 g (2.8-5.5 mmol) or coffee beverage containing 1.2 g (3.4 mmol) of CGA or green coffee beans containing 146-170 mg (412-450 μmol) of CGA showed that one-third (29.1%-33.1%) could be absorbed into the bloodstream through the upper gastrointestinal tract and small intestine. The peak blood concentration can be reached by about 1 to 2.5 hours after ingestion, mainly 5-CQA, and a small amount of 3-CQA and 4-CQA. The remaining CGA enters the colon, where it is decomposed into caffeic acid and quinic acid through the action of intestinal microorganisms, and then further metabolized into dihydroxy caffeic acid, dihydroxy ferulic acid, ferulic acid, iso-ferulic acid and other metabolites in the blood, reaching peak blood concentration in 5h after ingestion.

After entering the blood, CGA is bound to the specific subregion IIA of human serum albumin (HSA) and transported under physiological conditions. Its metabolites are transported in blood in the form of glucuronic acids and sulfates, such as dihydroxycaffeine-3-O-sulfate or uronates.⁷ CGA entering the body is further metabolized in the liver mainly through the action of NADPH-cytochrome P450 I phase. Metabolites excreted in urine include hippuric acid (50%, 95% CI:37.2-61.8), protochlorogenic acid (5-CQA, 1.7%), dihydroxy caffeic acid, erucic acid, gallic acid, p-hydroxybenzoic acid, vanillic acid, caffeic acid, ferulic acid, isoferulic acid and coumaric acid, accounting for 5.5% of the total intake of CGA, indicating that CGA and its metabolites may not be excreted mainly in urine. Bile and other digestive juices may be the main excretion pathways of circulating CGA and its mixtures.

The absorption, metabolism, and utilization of CGA may be affected by human health state, intestinal microflora and cooking conditions of foods. It is stable in gastric juice, and 5-CQA absorbed through the small intestine may be stored in the liver. The absorption and metabolism of different CGA isomers in humans are different. For example, the ratio of 5-CQA, 4-CQA and 3CQA in the tested samples is 1.2:1.0:1.1, while the ratio in plasma is 6.0:1.4:1.0, indicating that 5-CQA is metabolized more slowly than 4-CQA and 3CQA.

There is difference between individuals in bioavailability of CGA. The concentration (%) of CGA in plasma is 33.1 ± 23.1 on average, and its range is 7.8%-72.1%. However, individual difference is not dependent on age, sex, body weight or body mass index (BMI). Human studies show that the plasma CGA increases 2h and 6h after the fasting intake of cherry tomato (containing 31mg CGA) cooked for 15min at 100°C and is significantly higher than that of uncooked panica (containing 46mg CGA),⁸ suggesting that the degree of cooking may affect CGA absorption.

BIOLOGICAL ACTIVITY AND FUNCTIONS

Glycolipid metabolism, diabetes prevention and management

The findings of many population-based randomized controlled trials (RCTs) show that oral CGA can improve glucose tolerance and plasma insulin in the healthy, the overweight and obese, and those with impaired glucose tolerance.⁹ As an adjunctive therapy for diabetes, CGA derived from plant extracts may benefit for glycolipid metabolism with reduced fasting blood glucose (FBG) as well as plasma C-reactive protein (CRP), with improved liver function.¹⁰ The mechanisms of action are several: CGA can 1) inhibition of α -glucosidase activity to reduce sugar absorption; 2) inhibition of glucose-6-phosphatase to reduce the output of liver glycogen; 3) upregulation of GLUT4 and GLUT2 to accelerate sugar transport; 4) increased adiponectin to improved insulin sensitivity; 5) competitive inhibition of α -amylase to delay the rise in blood glucose; 6) increased fatty acid beta oxidation by activating the AMPK pathway, with down-regulation of LXR α , PPAR γ , and ACC, and up-regulation of peroxisome proliferator-activated receptor alpha (PPAR α).¹¹⁻¹⁴

Weight loss and weight gain prevention

A systematic review and meta-analysis of 15 RCTs showed that the intake of green coffee extract (GCE) containing CGA could reduce body weight and body mass index (BMI).¹⁵ The mechanisms may be 1) to inhibit the accumulation of triglycerides in liver and changing blood adipokine status, down-regulating lipogenesis-related genes, and up-regulating the expression of fatty acid oxidation-related genes; 2) to regulate the activities of fat metabolism-related enzymes, such as inhibiting fatty acid synthase, acetyl-CoA carboxylase; 3) to enhance expression of PPAR- α and β -oxidation activity of fatty acid in liver; 4) to inhibit fat absorption; 5) to reduce food intake and increase energy expenditure.^{16,17}

Blood pressure lowering and improved cardiovascular health

In a multicenter, double-blind, randomized, placebo-controlled trial, 117 participants with mild hypertension were treated orally with green coffee bean (not roasted) water extract containing different doses of CGA (0, 25, 50 and 100 mg) for 4 weeks. At the end of 2 and 4 weeks, blood pressure in the CGA group decreased significantly, and showed a significant dose-effect and time-effect relationship.¹⁸ In the other two RCTs, 28 patients with mild hypertension and 20 healthy men with a decreased vasodilation response were given an oral green coffee bean aqueous extract containing 140 mg CGA for 4 months respectively.^{19,20} The vascular reactivity of those who took CGA was significantly improved, and blood pressure was significantly reduced at 1 to 4 months; serum homocysteine decreased, and no adverse reactions were observed.

CGA may play a role in the prevention and management of cardiovascular disease (CVD). The mechanisms by which CGA improves CVD are several and include that it can 1) significantly increase mRNA levels of PPAR γ , LXR α , ABCA1 and ABCG1, as well as the transcriptional activity of PPAR γ , and inhibit atherosclerosis; 2) increase the activation of PKA or cAMP levels, reduce platelet inflammatory mediators (sP-selectin, CCL5, sCD40L and IL-1 β), inhibit TXA₂ secretion, inhibit platelet activity; 3) modulate the renin-angiotensin-aldosterone system (RAAS) and increase NO levels, as well as attenuate pro-inflammatory cells factors (IL-1 β and TNF- α) and other inflammation-related markers (such as IL-6), thereby lowering blood pressure; 4) inhibit ACE activity and smooth muscle cell proliferation, and block HIF-1 α /AKT signaling pathway, with remodeling of blood vessels.²¹

Antioxidant and anti-inflammatory properties

Various studies shown that CGA has antioxidant and anti-inflammatory properties. CGA (mainly 5-CQA) has antioxidant effects by way of mechanisms such as PI3K/AKT, ERK1/2 and JNK signaling pathways and regulation of FOXO gene activation, preventing apoptosis, and antagonizing potential damage to vascular endothelia, brain, nerves, liver, and lung. As an anti-inflammatory vehicle, it inhibits the TLR4, TNF-A, NF- κ B and JNK pathways and decreases the expression of matrix metalloproteinases (MMP-1, MMP-3 and MMP-13).

HAZARDS AND TOXICITY WITH OVERDOSE

A cross-control study showed that 20 healthy men and women took 2 g (5.5 mmol) /d of CGA for 7 consecutive days. Compared with the placebo group, plasma homocysteine in the CGA group increased by 12% (1.2 mmol/L, 95% CI: 0.6-1.7) at 4-5h after the last administration,

and the fasting plasma homocysteine increased by 4% (0.4 mmol/L, 95% CI: 0.6-1.7) after 20h.²² This suggests that chronic excessive intake may cause transient acute elevation of plasma homocysteine. Significantly, elevated plasma homocysteine is associated with CVD.

CGA has been reported to be allergenic. However, recent studies show that CGA itself is not allergenic, but that large molecular impurities in the low-purity CGA are responsible for the observed allergic reactions.

Animal experiments show that high dose (7 mg/kg) intravenous CGA increases the number of adherent leukocytes in rats, resulting in the generation of peroxides in the venule wall and the leakage of albumin in mesenteric venules. In addition, it also induces increases in malondialdehyde, myeloperoxidase, inflammatory cytokines, and NADPH oxidase activities, as well as decreased superoxide dismutase and catalase activities,²³ that is, an oxidative stress response.

No death occurs in rats when intraperitoneal injection of CGA is 2437 mg/kg or less. The mortality rate is 4 out of 6 when injection dose is 4000 mg/kg (National Toxicology Program of NIEHS in NIH, USA, 2005). The oral lethal dose 50 (LD50) in the red-winged blackbird is greater than 100mg/kg (National Toxicology Program of NIEHS in NIH, USA, 2005).

Experiments to date on sub-chronic toxicity, chronic toxicity and genotoxicity (National Toxicology Program of NIEHS in NIH, USA, 2005) have not observed any toxic or side effects.^{24, 25}

DIETARY INTAKE AND EVALUATION

CGA has a wide range of food sources, and dietary intake greatly affected by dietary habits and pattern. A cohort study of 36,037 people from 10 European countries showed that the average intake of CGA was 450 mg/d.²⁶ Clifford et al assessed the intake of CGA in British people according to their eating habits of usual breakfast, lunch, and dinner and whether they drank coffee regularly.²⁷ The intake of CGA could easily reach 500 to 1000 mg/d in those who habitually drank several cups of coffee per day, while in infrequent coffee drinkers and those who seldom ate fresh fruits and vegetables, it was less than 25mg/d.²⁷ According to the national food consumption survey, Radtke et al estimated the intake of CGA in Germans to be 5 to 983 mg/d for men and 6 to 787 mg/d for women,²⁸ consistent with the estimates for British people by Clifford et al. Brazilian survey data show that the daily intake of CGA is about 260 mg.²⁹ According to the Japan functional food factor database, Japanese consume more than 10 μ mol (> 4 mg/d) of CGA per day, a likely reflection of preferred beverage intake from tea.

Intakes of CGA in Chinese residents appear not to have been reported. In a cross-sectional study of dietary phenolic compound intakes among 413 college students in Ning Xia, total food phenolic acid intake was about 525 mg per day.³⁰ Based on these Ning Xia college data, the daily intake of CGA was estimated to be 50 to 70 mg with the main contribution from food (as calculated by the present authors).

GUIDANCE ON BENEFICIAL AND SAFE INTAKES

Health benefit considerations

Based on assessments of dietary habits and food consumption in Europe, the United Kingdom, Germany, Brazil and Japan, the estimated dietary intake of CGA is 5 to 1000 mg/d, while that of regular coffee drinkers (2 cups of espresso/d) and of those who regularly consume fresh vegetables and fruits is 500 to 1000 mg/d.

Regulation of glucose and lipid metabolism

A systematic review and dose-response meta-analysis including 14 RCTs (published between 2004 and 2019) evaluated the role of green coffee bean extract supplements in regulating glycolipid metabolism.⁹ The sample size was 766 (including 380 in the CGA group and 386 in the control group), the dose of CGA was 13.5 to 1200 mg/d, and the intervention period was 2 to 16 weeks. CGA significantly reduced FBG (WMD: -2.35 , 95% CI: -3.78 , -0.92 mg/dL, $p=0.001$), serum insulin (WMD: -0.63 , 95% CI: -1.11 , -0.15 $\mu\text{U/L}$, $p=0.01$) and serum total cholesterol (TC) (WMD: -4.51 , 95% CI: -8.39 , -0.64 mg/dL $p=0.02$), especially in individuals with a high cholesterol. Further, subgroup analyses, including men and women, showed that CGA could significantly reduce serum triglyceride (TG); studies with an intervention duration of ≥ 8 weeks showed that CGA significantly reduced serum low density lipoprotein cholesterol (LDL-C) and increased high density lipoprotein cholesterol (HDL-C) in women. There was a nonlinear dose-response relationship between CGA and FBG, TG and HDL-C. At a dose ≥ 200 mg/d, the FBG was more significantly reduced and an obvious dose-response relationship from 13.5 to 500 mg/d (Figure 3) as evident.

Another meta-analysis of 14 high-quality RCTs (published in 2015-2020) evaluated the effects of coffee and GCE on indicators of the metabolic syndrome (MetS) in healthy individuals, overweight and obese, and hypertension, dyslipidemia, and insulin resistant participants.³¹ Its sample size was 821, and the intervention period 60 minutes to 24 weeks. Supplementation with GCE containing 180 to 376 mg/d of CGA for 4 weeks or more effectively reduced waist circumference, FBG, TG, systolic blood pressure (SBP) and

diastolic blood pressure (DBP) and improved HDL-C. Supplementation of decaffeinated coffee containing 510.6 mg/d of CGA for 4 weeks or more effectively reduced waist circumference, FBG, TG, SBP and DBP. GCE combined with resistance exercise further enhanced the improvement of MetS-related indicators.

Weight management

A systematic review and meta-analysis of 15 RCTs (published from 2005 to 2019) evaluated the effect of GCE and coffee drinks on body weight, with a sample size of 897 participants, 30 to 1200 mg/d of CGA, 1 to 12 weeks of intervention period.¹⁵ The findings demonstrated a beneficial effect of GCE supplementation in reducing body weight (WMD: -1.23 , 95% CI: -1.64 , -0.82 kg, $p < 0.001$), BMI (WMD: -0.48 , 95% CI: -0.78 , -0.18 kg/m², $p = 0.001$), and WC (WMD: -1.00 , 95 % CI: -1.70 , -0.29 cm, $p = 0.006$). However, there was no significant dose-response relationship between CGA dosage and changes in anthropometric measurements. Low dosage GCE (< 400 mg/d) in the long-term use (≥ 8 weeks) is more effective than the high dosage short-term use insofar as body composition outcomes are concerned. There are no detectable or recognized side effects with consumption of high dosage GCE, but underlying food and beverage culture may substantially change the risk profile.

Regulating blood pressure

In a systematic review of 8 clinical trials evaluating the antihypertensive effects of CGA, 4 in normal blood pressure population and another 4 in hypertension population with total sample size of 522 participants,³² 3 out of 8 trials showed that CGA could significantly reduce SBP, and in another 5 trials CGA had no significant effect on SBP. In 2 out of 8 trials CGA significantly reduced DBP, and in 6 out of 8 trials it had no recognizable effect. The antihypertensive effect of CGA seems only to be apparent in hypertensive populations, but, even then, with no detectable dose-response effect. An antihypertensive effect of high doses (more than 300 mg/d) may peak after 4 weeks, then return to baseline, suggesting adaptation to long-term CGA use. Long-term use of low doses of CGA (140 mg/d) may be more effective in BP modulation, but the case is out.

Based on the available findings, an intake of 13.5 mg to 1200 mg/d CGA can reduce FBG, improve glucose tolerance, reduce excess weight, and may improve blood pressure in hypertensive individuals. An intake of 200 mg or more may be more effective in reducing FBG with a dose-response effect. Allowing for evidence from the available population

intervention studies, an SPL of CGA might permit an improvement in FBG where it is ≥ 200 mg/d (11mmol).

Clinical studies on the regulation of glycolipid metabolism and blood pressure by CGA are shown in Table 1.

Tolerable upper intake level (TUIL)

Studies on the risks of excessive and large dose CGA on population intervention trials have found no apparent adverse effect of CGA intake. Toxicity and side effects have not been observed in sub-chronic toxicity, chronic toxicity, and genotoxicity studies. To date, no international organization or other jurisdiction has recommended an intake (DRI) or TUIL for CGA.

The data available are not sufficient to formulate a TUIL so this is not proposed for the time being. In the meantime, an appreciation of known benefits and risk may be useful in food and beverage policy development.

PRIMARY FOOD SOURCES

CGA is widely found in natural plant foods, and its content is affected by food type. These differ by the entire food system which generates the ingestible commodity. Of particular relevance will be place of origin, variety, maturity, plant anatomy, seasonality, preparation, infusion technique, each of which may affect the content of CGA. For example, the content of CGA in Western pears and Oriental pears are 309 mg/kg (fresh weight) and 163 mg/kg (fresh weight) respectively. It is 5.1 mg/kg (fresh weight) in cherry tomato, which may be reduced to 0.6 mg/kg (fresh weight) after over ripening. Clearly, food storage and processing can affect the amount of CGA. It can be increased when potatoes are exposed to light during storage. During the roasting of coffee bean, CGA can release the quinic acid radical, which can theoretically be converted into quinic acid and its glycoside products, resulting in a decrease of CGA. With longer baking times, more CGA is lost. Coffee beans and coffee products are the most available and major sources of CGA for many people. CGA is also high in foods such as chicory, blueberries, sunflower seeds, cherries, eggplants, potatoes, apples, pears, and hawthorn berries. The content of CGA in food is shown in Table 2.^{1,33,34}

In summary, CGA can play an important role in regulating glycolipids metabolism. However, since it is not an essential, or even conditionally essential, nutrient or food and beverage component, a recommended intake is not appropriate. In population-based studies, daily oral doses of CGA at 13.5 to 1200 mg can reduce FBG, improve glucose tolerance, lead

to weight loss and/or prevent weight gain, and improve blood pressure in hypertensive patients. Additionally, taking CGA ≥ 200 mg per day may reduce FBG with a dose response effect. Therefore, an SPL of CGA to improve FBG would be ≥ 200 mg/d for the population with impairment of FBG. However, data availability for CGA are not sufficient to formulate an TUIL. Meanwhile, food and nutrition policy could reflect the apparently safe and desirable levels of CGA intakes and sources, emphasizing that these depend on the food and beverage culture and background diet in question. More specifically, any impairment of FBG (exceeding 5.8 mmol/L or 100 mg /dL) could encourage a safe level of CGA intake on the basis of the evidence available. As with all nutritional policy, food cultural context and commodity usage close to its origin provides for greater awareness of risk. Thus beverages consumed as traditional infusions like tea, consumed with meals, snacks or other episodes of eating have a safety margin conferred by the company of others and co-ingestion. Isolated extracts may provide for an enhanced action of interest in therapeutics, but not for advancement of the public health where the risk-benefit ratio must be negligible.

CONFLICT OF INTEREST AND FUNDING DISCLOSURE

The authors have no conflicting interests.

The support of the DRIs Revision Special Fund of Chinese Nutrition Society is acknowledged with appreciation.

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Table 1. Summary of clinical studies on chlorogenic acid and disease

	Asbaghi O,2020 ⁹	Asbaghi O, 2020 ¹⁵	Loader,2017 ³²
Study type	Meta-analysis containing 14 RCT	Meta-analysis containing 15 RCT	Systemic review containing 8 RCT
Sample size	Total: 766; Int: 380; Con: 386	Total: 897; Int: 489; Con: 408	Total: 522; Int: 354 (different dose group); Con: 168
Source of study population	5 of Iran, 4 of Japan, 2 of South Korea, 2 of Spain and 1 of Mexico.	6 of Iran, 2 of Japan, 2 of South Korea, 2 of Spain, 1 of France, 1 of Jordan and 1 of Mexico.	5 of Japan, 2 of Australia and 1 of Colombia.
Characteristics of study subjects	Including 2 studies in healthy people, 5 in obesity, 2 in hypertension, 2 in normal/hypercholesterolemia, 1 in impaired glucose tolerance, 1 in metabolic syndrome, 1 in nonalcoholic fatty liver disease and obesity, and 1 in mildly xerotic skin.	Including 2 studies in normal weight, 13 in overweight or obese. Accompanied by dyslipidemia, metabolic syndrome, nonalcoholic fatty liver disease, and hypertension.	Including 4 in normal blood pressure, 4 in mild hypertension
Age of study subjects	20-60 yrs	18-75 yrs	18-70 yrs
Source of chlorogenic acid	GCE, pure CGA. 6 of dietary supplements and 8 of drinks.	GCE, coffee drinks. 10 of dietary supplements and 5 of drink powder.	GCE
Dosage of chlorogenic acid	GCE: 90-6000 mg/d; CGA:13.5-1200 mg/d	GCE: 90-6000 mg/d; CGA: 30-1200 mg/d	CGA: 25-900 mg
Intervention duration	2-16 weeks	1-12 weeks	Once to 16weeks
Results	CGA can significantly reduce FBG, serum insulin and cholesterol levels. The effect of reducing FBG showed a nonlinear dose-effect relationship, and the effect was more obvious when ≥ 200 mg/d.	CGA can significantly reduce body weight, BMI and waist circumference, and there is no significant dose-effect relationship. The effect of low dose (less than 400 mg/d) and long-term (≥ 8 weeks) intervention on BMI was better than that of high dose short-term intervention. The Cost-effective of CGA was better than Orlistat (weight-loss drug). No side effects were found in high-dose and long-term intervention.	3 of 8 trials showed that CGA could significantly reduce systolic blood pressure, and 2 of 8 trials showed that CGA could significantly reduce diastolic blood pressure. Low dose (140 mg/d, 12W) and long-term oral administration can reduce blood pressure in patients with mild hypertension.

[†]RCT: randomized controlled trial; Int: intervention group; Con: control group; GCE: green coffee bean extract; CGA: chlorogenic acid; FBG: fasting blood-glucose; BMI: body mass index.

Table 2. Content of chlorogenic acid in common foods and beverages (mg/100mL or mg/100g of edible part)

Food or beverage	Chlorogenic acid content
Green Coffee Bean (dry)	6000-10000
Coffee (very strong)	337.5
Espresso Coffee;	150-175
Arabica coffee	35-100
Kuding tea (dry)	2564
Acer truncatum tea (dry)	2387
Lonicera japonica (dry)	2256
Unfermented green tea (dry)	1-40
Semi-fermented tea (dry)	1-21
Fermented tea (dry)	1-3
Chicory	260
Blueberry	50-200
Sunflower seed	63.0-97.1
Cherry	15-60
Eggplant	60
Batatas	10-50
Globe artichoke	45
Apple	6.2-38.5
Occidental pears	30.9
Hawthorn berries	23.4
Potato	26.7
Chinese anise	10-20
Oriental pears	16.3
Peach	15.5
Blackcurrant	14
Curly kale/cabbage/Brussels Sprout	0.6-12
Carrot	12
Chinese yam	6.2-10.3
Solanum tuberosum	9.1
Tangerine	8.6
Tomato	1-8
Blackberry	7
Celery	0.2-6.5
Calabrese	6
Chocho	2.0-4.2
Lettuce	3.8
Strawberry	2.9
Broccoli and radishes	2.0
Walnut	1.8
Red raspberry	1.5
Kiwi fruit	1.1
Cherry tomato	0.5

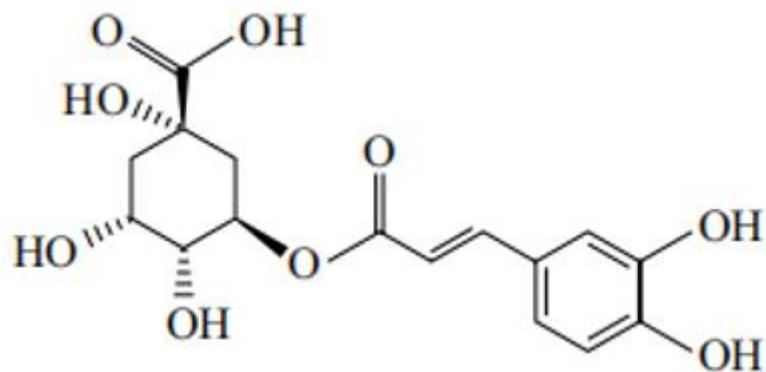


Figure 1. Chemical structure of chlorogenic acid (Fischer, 1932).

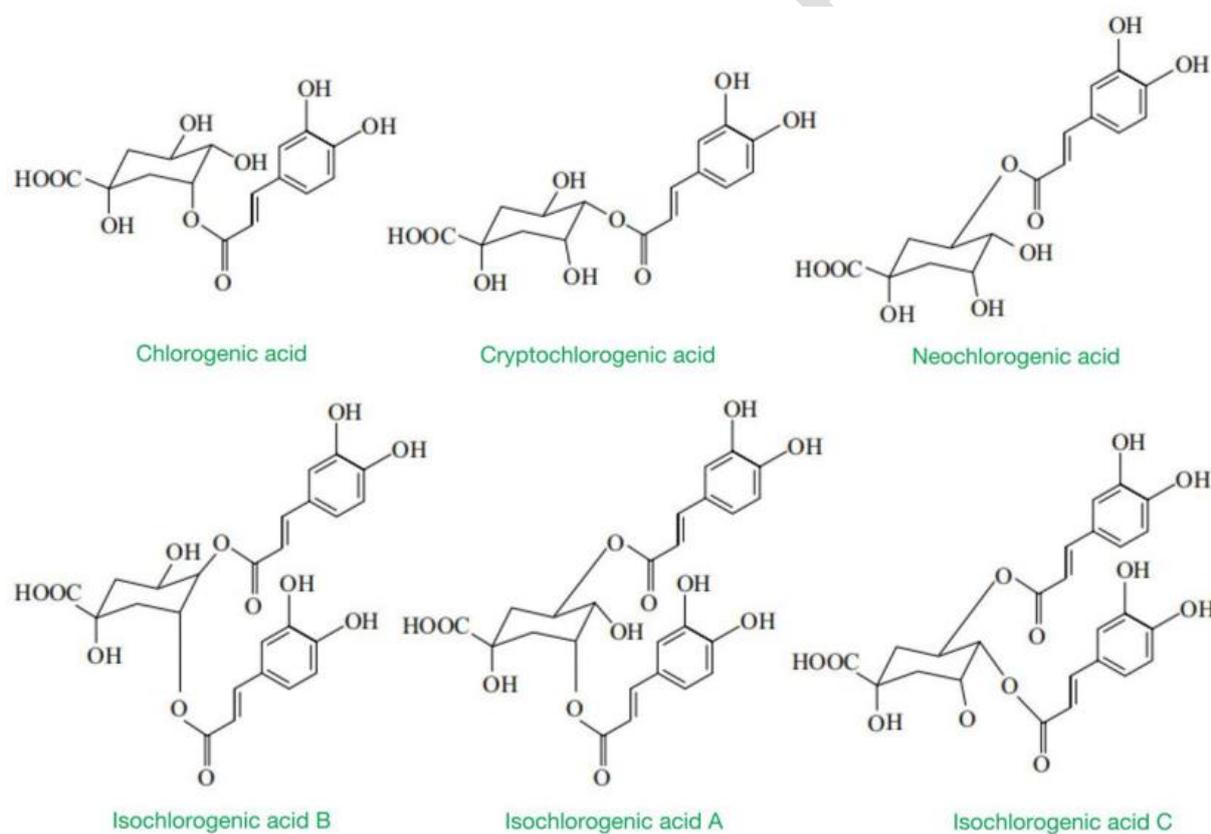


Figure 2. Chlorogenic acid isomers

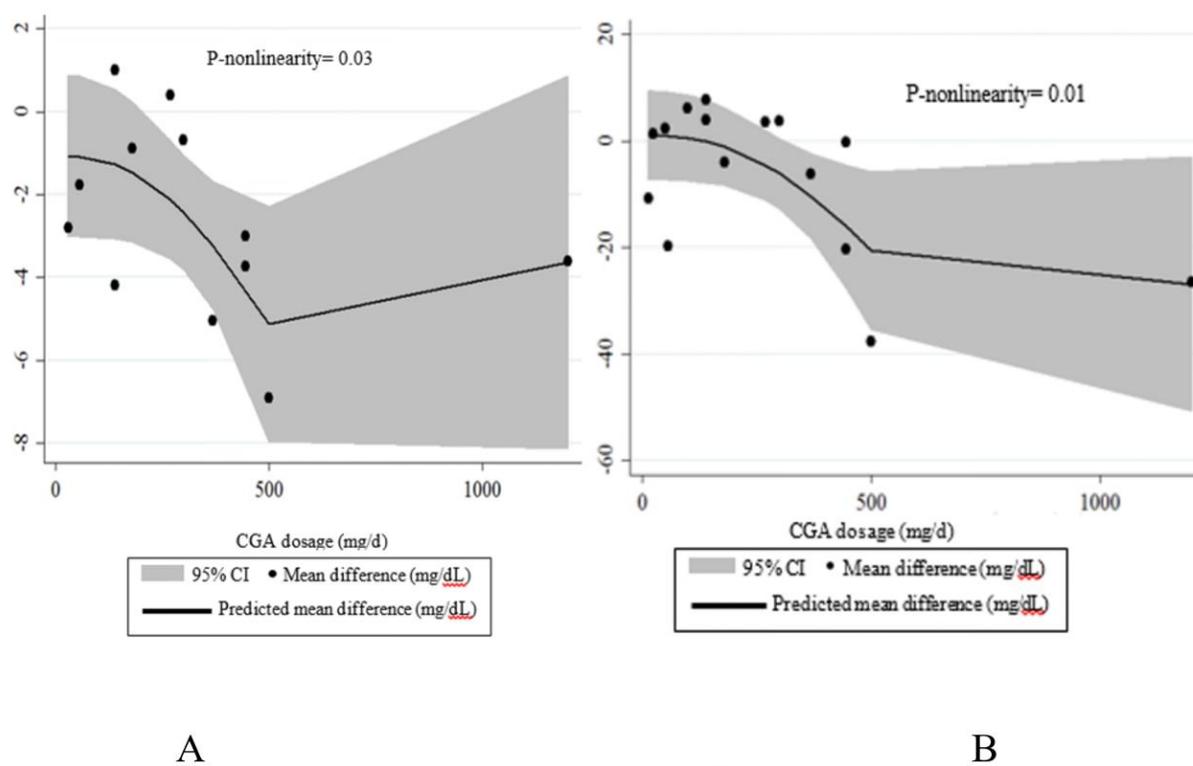


Figure 3. Non-linear dose-response effects of CGA dosage (mg/d) on (A) FBG and (B) serum concentrations of TG. The 95% CI is demonstrated in the shaded regions. CGA: chlorogenic acid, FBG: fasting blood glucose, TG: triglycerides.⁹