REVIEW

Cardiovascular protection effect of chlorogenic acid: focus on the molecular mechanism [version 1; peer review: 1 approved, 2 approved with reservations]

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Abstract

Vascular endothelial cells have a variety of functions such as the control of blood coagulation, vascular permeability, and tone regulation, as well as quiescence of immune cells. Endothelial dysfunction is a cardiovascular events predictor, which is considered the initial stage in atherosclerosis development. It is characterized by alterations in endothelium functions due to imbalanced vasodilators and vasoconstrictors, procoagulant and anticoagulant mediators, as well as growth inhibitor and promotor substances. Chlorogenic acid (CGA) is the primary polyphenol in coffee and some fruits. It has many health-promoting properties, especially in the cardiovascular system. Many studies investigated the efficacy and mechanism of this compound in vascular health. CGA has several vascular benefits such as anti-atherosclerosis, anti-thrombosis, and anti-hypertensive. This review focuses on the molecular mechanism of CGA in vascular health.

Keywords

Chlorogenic acid, polyphenol, endothelial dysfunction, vascular health

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Introduction

Vascular endothelial cells have a variety of functions, such as the control of blood coagulation, vascular permeability, and tone regulation, as well as quiescence of immune cells¹. Endothelial dysfunction (ED) is considered as a cardiovascular events predictor, and it is characterized by alterations in endothelium functions that tend to be vasoconstricted, procoagulant, and prothrombotic². Chlorogenic acid (CGA) is a compound of phenol that consists of a caffeic and quinic acid moiety; therefore, it is also called 5-O-caffeoylquinic acid (5-CQA), although many authors refer to it as 3-CQA. A cup of coffee (200 ml) consists of 20–350 mg CGA, which contains 35–175 mg of caffeic acid. Therefore, an average coffee drinker consumes 0.5–1 g of CGA daily³. Moreover, this compound is found in fruits, such as pears, strawberries, eggplant, apples, blueberries, and tomatoes⁴. CGA is widely studied because of its health properties, such as anticancer, antineurodegenerative, antidiabetic, anti-inflammatory, antilipidemic, and antioxidant. This review discusses CGA's effects on vascular health, focussing on its molecular mechanism.

Endothelial dysfunction (ED)

The functions of vascular endothelial cells include vascular permeability, and tone regulation, as well as quiescence of immune cells. Vascular tone is mainly regulated by nitric oxide (NO). Healthy endothelium is protected from adhesion and aggregation through the release of NO, prostacyclin, and platelet ADP degradation⁵. As long as the endothelial layer is healthy and intact, platelets in circulation remain in an inactive state. ED is a cardiovascular events predictor and considered as the initial stage of atherosclerosis development. It is characterized by alterations in endothelium functions due to imbalanced vasodilators and vasoconstrictors, procoagulant and anticoagulant mediators, as well as growth inhibitor and promoter substances⁶.

Adiponectin is the biomarker of some cardiovascular disease risk factors such as diabetes, metabolic syndrome, atherosclerosis, or obesity. This adipokine has antioxidant, insulin-sensitizing, and anti-inflammatory properties⁷. Both of its receptors, AdipoR2 and AdipoR1 have anti-atherogenic activity through the improvement of PPAR and AMPK ligand activity⁸. In endothelial cells, this substance may downregulate adhesion molecules expression such as ICAM-1, which facilitates monocyte attachment to the endothelium by inhibiting TNF- α -mediated activation of NF- κ B. The activity of endothelial nitric oxide synthase (eNOS) can also be increased by adiponectin by facilitating its phosphorylation at Ser1177 via AMPK. It also inhibits reactive oxygen species (ROS) production by oxidized low-density lipoprotein (oxLDL) in cultured endothelial cells. These effects show that high adiponectin levels may prevent atherosclerosis^{9–11}.

Chlorogenic acid (CGA)

CGA is a compound of phenol that consists of caffeic and quinic acid moiety. It is also called 5-O-caffeoylquinic acid (5-CQA), although some authors refer to it as 3-CQA. This compound is the primary polyphenol in coffee. A cup of coffee (200 ml) consists of 20–350 mg CGA, which contains 35–175 mg of caffeic acid¹². Therefore, an average coffee drinker consumes 0.5–1 g of CGA daily. In addition, this compound is found in

some fruits, such as pears, blueberries, eggplant, strawberries, apples, and tomatoes. It is widely studied since it has several healthy properties, such as antioxidant, anti-inflammatory, anticancer, antilipidemic, antidiabetic, anti-hypertensive, and anti-neurodegenerative.

Mechanism of CGA in inhibiting atherosclerosis

Atherosclerosis is a multifactorial inflammatory disease initiated by oxidative stress and foam cell formation. Foam cell formation can be inhibited by inducing cholesterol efflux to lipid-poor apolipoprotein such as ApoA1. ABCG1 and ABCA1 are cholesterol transporters that play a significant role in mediating cholesterol efflux to high-density lipoprotein. These molecules are regulated by nuclear transcriptional factors LXR α and PPAR γ ¹³. CGA has been shown to significantly increase mRNA levels of PPAR γ , LXR α , ABCA1 and ABCG1, as well as the transcriptional activity of PPAR γ . In addition, a cholesterol efflux assay showed that three major metabolites, caffeic, ferulic and gallic acids, significantly stimulated cholesterol efflux from RAW264.7 cells. These results suggest that CGA potentially reduces atherosclerosis development in ApoE^{-/-} mice and promotes cholesterol efflux from RAW264.7 macrophages¹⁴.

CGA also has a dual PPAR α/γ agonist. Previous studies revealed that its administration enhanced AMPK phosphorylation, adiponectin, and its receptors¹⁵. These mechanisms indirectly have a beneficial effect on preventing ED, and AMPK activation has been shown to inhibit protein kinase C as a potent atherogenic substance¹⁶. Several studies have revealed the effect of PPAR γ agonists on improving ED. PPAR γ agonist reverses oxLDL-induced ED through AMPK activation, which consequently enhances eNOS activity. Also, it increased adiponectin levels as a potent anti-inflammatory agent^{17–19}. CGA and its major metabolite, caffeic acid, have antioxidant effects *in vitro* that alter LDL oxidation. The antioxidant effect of this compound increases LDL resistance to *ex vivo* oxidation¹⁴.

Lysophosphatidylcholine (LPC) is the primary atherogenic compound of oxLDL. It increases intracellular calcium through store-operated channels (SOCs). Moreover, it decreases cell viability and increases ROS generation. The expression of transient receptor potential canonical (TRPC) channel is significantly increased by LPC treatment^{20,21}. Previous studies showed that CGA inhibited ROS production by reducing TRPC1 expression, and therefore restored cell viability. Meanwhile, it inhibits LPC-induced Ca²⁺ influx through SOC. Thus, CGA protects endothelial cells from LPC injury and consequently inhibits atherosclerosis²².

Hemeoxygenase-1 is induced in response to ROS in endothelial cells, which plays a role in preventing damage. CGA reduces xanthine oxidase-1 and ROS, as well as enhances hemeoxygenase-1 and superoxide dismutase levels in endothelial cells. Its effects were described on endothelial function in an isolated aortic ring from mice. It was also shown in this study to decrease HOCl-induced oxidative damage in endothelial cells, and this mechanism is related to the induction of hemeoxygenase-1 and NO production²³. Consuming coffee high

cytochrome c reductase activity. Furthermore, CGA increases cAMP, cGMP, and intracellular Ca²⁺-antagonists formation^{31,32}. These results suggest that CGA has antiplatelet activity through the increase of cAMP, cGMP and reduction of thromboxane A₂ levels. Meanwhile, CGA shows an antiplatelet activity *in vitro* at a 50 nM concentration in mice. The same result was obtained *in vivo* after orally administering 400 mg per 30 g body weight to mice. In humans, this dose will be achieved after consuming about three cups of coffee rich in CGA, which will result in a low nM concentrations in the bloodstream³³.

Mechanism of CGA in inhibiting hypertension

The evidence of CGA as a hypotensive agent has been suggested by many studies, for example in spontaneously hypertensive rats and mild essential hypertensive patients³⁴. CGA controls hypertension by reducing ROS through the attenuation of NAD(P)H-dependent superoxide. This effect inhibits the proliferation of smooth muscle cells *in vitro*, as well as *in vivo* by decreasing angiotensin-converting enzyme activity³⁴. Thus, CGA modulates the renin-angiotensin-aldosterone system. Ferulic acid, the CGA metabolite, has a considerable effect on blood pressure reduction. Its administration enhances acetylcholine-induced vasodilation and increases the bioavailability of NO in the arterial vasculature³⁵.

In addition, CGA extracted from green coffee was tested for its efficacy in lowering the blood pressure (BP) of hypertensive patients. A double-blind and randomized clinical trial on 117 subjects, where the intervention group received different quantities of the CGA extract for 28 days compared to a placebo group, showed that the extract markedly reduced BP without any adverse effects. Meanwhile, a meta-analysis showed that CGA reduced both systolic and diastolic BP³⁶.

Previous studies showed that CGA modulates NO levels in rat vessels³⁷, and therefore has a vasodilation effect. In addition, a study in humans investigated its acute effect on BP, NO status, and endothelial function; administration of 400 mg resulted in lower systolic and diastolic BP (−2.41 and −1.53 mmHg respectively; $p < 0.05$) compared to the control group. However, endothelial function and NO status were not significantly influenced. Ward *et al.* also investigated the acute effect of 900 mg of CGA on BP and endothelial function, and found that there was no marked effect on peak flow-mediated dilation. Meanwhile, there was continuous dilation improvement. Both 900 and 450 mg of CGA resulted in a high ($p < 0.05$) continuous flow-mediated dilation at 1 h, and higher at 4 h (0.44%)³⁸.

CGA has been shown to induce the production of NO and enhance antioxidant activity. For instance, caffeoylquinic consumption for eight weeks significantly enhanced NO production and reduced NADPH-dependent ROS in the aorta of hypertensive rats³⁹. Also, CGA has been shown to block the expression of the NADPH-oxidase gene, which helps to control vascular tone³⁵. These results indicate that CGA might induce NO production, decrease oxidative stress, and prevent some conditions, such as hypertension and vascular hypertrophy.

Mechanism of CGA in inhibiting trans-endothelial migration

Atherosclerosis is a complex process that is initiated by inflammation and leukocyte migration to the inflamed area. Expression of cell adhesion molecules (CAM) on the endothelium and the attachment of monocytes to endothelium may play a major role in the early atherogenic process. During this process, adhesion molecules play a pivotal role in leukocyte cells recruitment and cellular matrix protein development. Ninjurin is a crucial molecule that increases the recruitment and activity of leukocytes during inflammation phase. A previous study showed the dose dependent manner inhibitory effect of CGA in mRNA Ninj1 gene expression that induced by LPS. Moreover, CGA significantly inhibited not only NO production but also the expression of COX-2 and iNOS, without any cytotoxicity. CGA also attenuated pro-inflammatory cytokines (including IL-1b and TNF-a) and other inflammation-related markers such as IL-6 in a dose-dependent manner⁴⁰. Moreover, CGA inhibited the nuclear translocation of NF-kB and blocked LPS-induced $\beta 2$ integrin expression and L-selectin shedding. Meanwhile, it inhibited LECAM-1 expression on neutrophil membranes. CGA was also shown to inhibit immunoglobulin molecules by decreasing vascular CAM-1 expressions on the endothelium of human umbilical venule. However, another study suggested that its effects on the expression of PECAM-1 does not involve genetic synthesis^{25,41}.

A study by Chang *et al.*²¹ showed that CGA treatment significantly reduced the concentration of proinflammatory cytokines that play an important role in the progression and development of atherosclerosis (Figure 2). Its anti-inflammatory properties explained its inhibitory effects on CAM expression, as it suppressed ICAM-1, VCAM-1, and E-selectin expression, which is induced by IL-1 β ²⁵. However, it should be noted that consuming a high dose coffee might increase the concentration of homocysteine in human plasma that will consequently lead to ED⁴². A previous study by Chang *et al.*, showed that CGA suppressed cytokine-induced CAM expression and inhibited p50 and p65 nuclear translocation in endothelial cells²⁵. Therefore, this study also showed that it reduced IL-1 β -induced ROS production in human umbilical vein endothelial cells (HUVECs). Furthermore, CGA removed RO• and ROO•, as well as DPPH radicals, which are produced from LDL oxidation^{43–45}. Finally, a previous study also showed that CGA at 50 and 25mmol/L inhibited U937 monocyte-like adhesion, expression of adhesion molecules, NF-KB translocation, and ROS production in HUVECs²⁵.

Anti-angiogenic mechanism of CGA

Hypoxia-induced angiogenesis plays a pivotal role in the development of atherosclerotic lesions. It enhances endothelial cell and vascular smooth muscle cell proliferation through the HIF-1a–VEGF pathway, and contributes to vulnerable plaque progression leading to destabilization. During atherogenesis, the tunica intima is thickened due to cell and matrix accumulation, thus impairing oxygen diffusion. The microenvironment within the plaque is hypothesized to be an essential determinant of plaque

Figure 2. The mechanism of CGA in inhibiting atherosclerosis and hypertension. PPAR, peroxisome proliferator activated receptor; HIF-1 α , hypoxia inducible factor1- α ; VEGF, vascular endothelial growth factor; COX-2, cyclooxygenase-2; PGI, prostacyclin; TXA₂, thromboxane A₂; MMP9, matrix metalloproteinase 9; NADPH, Nicotinamide adenine dinucleotide phosphate; ROS, reactive oxygen species; CRP, C-reactive protein; TNF α , tumor necrosis factor α ; IL6, interleukine 6; MAPK, mitogen-activated protein kinase; NF- κ B, nuclear factor kappa-B; V-CAM, vascular cell adhesion molecule-1, I-CAM, intercellular adhesion molecule; MCP-1, monocyte chemoattractant protein-1, ET-1, endothelin-1; ENOS, endothelial nitric oxide; NO, nitric oxide, ETA, endothelin A.

progression. During hypoxic condition, several HIF-responsive genes are shown to be upregulated in atherosclerosis such as VEGF, endothelin-1, and matrix metalloproteinase-2⁴⁶. Some studies suggest that CGA ameliorates hypoxia induced atherosclerosis via modulation of HIF-1 α -VEGF pathway. A study in A549 cells, as well as in DU145 cells, showed that CGA treatment significantly decreased hypoxia-induced HIF-1 α protein that consequently reduced the expression of VEGF. Moreover, during hyperglycemia CGA suppressed serum VEGF and HIF-1 alpha translocation. It was also suggested that CGA blocks *in vivo* and *in vitro* angiogenesis of HUVEC cells⁴⁷. In addition, CGA has been shown to phosphorylates VEGFR2, ERK 1/2 and AKT in order to inhibit VEGF-induced proliferation, migration, and invasion of HUVEC cells⁴⁸.

CGA and vascular health in human studies

From various human studies (Table 1), it can be seen that CGA administration in various doses resulted in favourable effect in improvement of cardiovascular function, through amelioration of flow mediated dilatation (FMD) after either acute or chronic administration of CGA. A single intake of

CGA with the dose of 400 mg improved FMD and lowered BP. Moreover, it has been suggested that administration of low hydroxyhydroquinone CGA results in better improvement of FMD compared to that of high hydroxyhydroquinone³⁶.

Achieving high CGA benefit from coffee manufacturing process

Many procedures have been introduced in the coffee manufacturing process to achieve more benefits during coffee consumption. Previous studies have shown that roasting levels alter CGA content and antioxidant activity; lightly roasted coffee had more of this compound compared to other groups, and has a higher antioxidant activity based on 2,2-diphenyl-1-picrylhydrazyl (DPPH) assay^{44,49}. The most abundant CGA isomer was 5-CQA with an estimate of 69–74% in the extracts, especially those from green beans⁵⁰. The 5-CQA content decreased to less than 85% in brews from non-roasted green beans obtained from the same location, and the total CGA content in the extracts of dark-, medium-, and light-roasted beans decreased to 80.60%, 62.91%, and 35.60% respectively⁵¹. In addition, 4-CQA and 3-CQA were found at higher percentages in the light-roasted

Table 1. Effect of chlorogenic acid consumption on vascular health: evidence from human studies.

Design	Sample characteristics	Primary end points	Intervention	Results	References
Double-blind, randomized controlled crossover study	23 healthy men and women. All participants were regular tea (mean $\pm$ SD, 1.7 ± 1.5 cups/day) and coffee (mean $\pm$ SD, 1.7 ± 1.6 cups/day) consumers	Plasma RXNO, nitrite, and NOx Blood pressure FMD of the brachial artery	Single intake of 400 mg of chlorogenic acid (3-O-caffeoylquinic acid).	Lower mean SBP and DBP compared to those of control group. The markers of nitric oxide status and endothelial functions were not significantly affected.	36
Single-blind, randomized, placebo-controlled, crossover-within-subject	37 men and women with borderline or stage 1 hypertension	FMD	Single intake of beverage A that contained chlorogenic acids: 412 mg, hydroxyhydroquinone: 0.11 mg, and caffeine: 69 mg) or beverage B that contained chlorogenic acids: 373 mg, hydroxyhydroquinone: 0.76 mg, and caffeine: 75 mg	The intake of coffee with high chlorogenic acid and low hydroxyhydroquinone improved post prandial FMD vasodilatation and reduced circulating 8-isoprostane levels	52
Single blind, randomized, controlled clinical trial	38 healthy men and 37 healthy women	Lipid profile and vascular function based on FMD, BP, NO metabolites.	8 week consumption of a medium CGA content (MCCGA; 420 mg) or high CGA content (HCCGA; 780 mg)	No significant differences in the lipid, FMD, BP, or NO plasma metabolite values were observed between the groups.	53
A double-blind, randomised, placebo controlled cross-over trial	17 healthy men and women. The participants consumed coffee regularly	FMD, BP, plasma nitrite concentrations	Single intake of 450 mg purified 5-CGA or 900 mg purified 5-CGA	No significant effect of 5-CGA, at 450 and 900 mg, on peak FMD response. However, there were significant improvements in mean post-ischaemic FMD response, particularly at the 1 h time point in this group of healthy individuals	38
Single-blind, randomized, controlled, crossover trial	20 healthy males	Reactive hyperemia ratio	CQA 140 mg/day for 4 months	Higher RHR compared to that of placebo group	54
Double-blind, placebo controlled, pilot study	16 healthy men	Cardio-ankle vascular index (CAVI), FMD, sympathetic nervous activity (SNA)	2 weeks consumption of a beverage contained 300 mg CGA	The CAVI change was significantly greater in the cGCE group than in the placebo group. In addition, FMD increased and SNA decreased in the cGCE group.	55
Double-blinded, randomized crossover trial	13 healthy men aged 30–60 years old	FMD	Single intake of a beverage contained 600 mg of CGA	The postprandial impairment of FMD was significantly improved compared to the placebo group.	56
Two randomized, controlled, crossover clinical trial	Study 1: 15 healthy males Study 2: 24 males	FMD	Study 1: single intake of a beverage containing 89 mg CGA or 310 mg CGA. Study 2: single intake of purified 5-CQA at a dose of 450 mg or 900 mg	CGA intake with low and high polyphenol acutely improved FMD	41
randomized acute clinical intervention study with crossover design	15 healthy men aged 20–60 years old	Reactive hyperemia index (RHI)	600 mg CQA	Higher RHI at 1.5 hours after ingestion significantly increased from the baseline value and was significantly different from that in the Glu group.	57

Design	Sample characteristics	Primary end points	Intervention	Results	References
Randomized, placebo, controlled cross over design	7 healthy men and 5 healthy women	FMD	Ground caffeinated coffee contained 95 mg CGA and decaffeinated coffee contained 132 mg CGA	Higher FMD response in caffeinated coffee group	58
Single blind, randomized, placebo-controlled crossover trial	19 healthy males	FMD	Coffee polyphenol extract contained 355 mg CQA	Higher postprandial FMD	24

FMD, flow mediated dilatation; RHI, reactive hyperemia index; CAVI, cardio-ankle vascular index; SNA, sympathetic nervous activity; NO, nitric oxide; RXNO, S-nitrosothiols and other nitrosylated species; NOx, nitric oxides comprising nitros(yl)ated species + nitrite; BP, blood pressure; SBP, systolic blood pressure; DBP, diastolic blood pressure; CQA, caffeoylquinic acid.

brew compared to green beans. Another study using ABTS and Folin-Ciocalteu assays showed that there is high antioxidant activity in medium and light-roasted brews⁵⁰.

High CGA also can be achieved through fermentation process. Some fermentation procedures had been proposed such as using *Saccharomyces cerevisiae* and *Bacillus subtilis* strains. A fermentation procedure of coffee pulp using *Saccharomyces cerevisiae* resulted in 400% richer CGA content. Interestingly, the addition of ultrasound treatment did not increase the yield from the extracted coffee pulp. Moreover, the use of *Bacillus subtilis* strains during fermentation process lead to 20% greater CGA content from green coffee bean extract^{59,60}.

Conclusion

CGA protects vascular health by inhibiting ED. Several mechanisms explain its effects on LPC injury and atherosclerosis, modulation of dual PPAR α/γ agonist, AMPK phosphorylation, adiponectin, and adiponectin receptors. It plays a role in reducing proinflammatory cytokine concentration

that contribute to atherosclerosis development and progression. Furthermore, it suppresses the expression of E-selectin, VCAM-1, and ICAM-1, as well as decreases HOCl-induced oxidative damage in endothelial cells. In addition, CGA induces hemeoxygenase-1 and antiplatelet activity through thromboxane A2 (TXA2) reduction, and attenuates ROS by decreasing the production of NAD(P)H-dependent superoxide. Furthermore, it inhibits the activity of ACE and the proliferation of smooth muscle cells. Finally, it has been shown to block the HIF-1 α /AKT signalling pathway, which plays a crucial role in the activation of VEGF and angiogenesis.

Data availability

No data are associated with this article.

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Version 1

Reviewer Report 02 March 2021

<https://doi.org/10.5256/f1000research.28955.r79914>

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Suowen Xu

Department of Endocrinology, University of Science and Technology of China (USTC), Hefei, 230037, China

This is a very comprehensive review of CGA in cardiovascular health and diseases. By reading through the whole manuscript, the message conveyed is scattered and not focused. For example, the authors can divide the Atherosclerosis related mechanisms into sub-sections: endothelial dysfunction, macrophage inflammation and foam cell formation, VSMC dysfunction, platelet activation etc. How other CVD protective actions, the authors can talk about cardiac hypertrophy and heart failure, as CVD is very broad, it is hard to give concise review and discussion on all forms of CVD. I would suggest to focus on hypertension and atherosclerosis in particular. The detailed molecular targets of CGA can be given in a pictorial way as new figures which is very important.

It is also good to include are there any clinical trials of CGA in Clinicaltrial.gov? What are unexplored and important in CGA research? In particular, CGA functions as more than antioxidant, which failed in most clinical trials.

Is the topic of the review discussed comprehensively in the context of the current literature?

Yes

Are all factual statements correct and adequately supported by citations?

Yes

Is the review written in accessible language?

Yes

Are the conclusions drawn appropriate in the context of the current research literature?

Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: natural product pharmacology, atherosclerosis, endothelial cell biology

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Reviewer Report 24 February 2021

<https://doi.org/10.5256/f1000research.28955.r77826>

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Arrigo F. G. Cicero

Hypertension Research Unit, University of Bologna, Bologna, Italy

I've read with attention the narrative review by Lukitasari et al. on the pharmacological activities of chlorogenic acid on vascular health. The review is interesting, well-organized, overall well-written and updated. My only suggestion is to report quantitative results when speaking about human studies. The conclusion should also include 1-2 sentences on the perspective of research in this field.

Is the topic of the review discussed comprehensively in the context of the current literature?

Yes

Are all factual statements correct and adequately supported by citations?

Yes

Is the review written in accessible language?

Yes

Are the conclusions drawn appropriate in the context of the current research literature?

Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Cardiovascular disease prevention in clinical settings

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Reviewer Report 01 February 2021

<https://doi.org/10.5256/f1000research.28955.r76178>

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Katalina Muñoz-Durango

Nutresa Business Group, Vidarium - Nutrition, Health and Wellness Research Center, Medellín, Colombia

I consider that the topic is of great interest. Chlorogenic acids are important bioactive compounds that have been a matter of extensive research in the last decades. Therefore, a review related to the cardiovascular protective effect of chlorogenic acid: focus on the molecular mechanism, is convenient and necessary. Nevertheless, some important aspects should take into account.

INTRODUCTION

- Instead of "Chlorogenic acid (CGA) is the primary polyphenol" I suggest "Chlorogenic acid (CGA) is the primary phenolic compound"
- Change "compound of phenol" by "phenolic compound"
- Please, verify the sentence "Chlorogenic acid (CGA) is a compound of phenol that consists of a caffeic and quinic acid moiety; therefore, it is also called 5-O-caffeoylquinic acid (5-CQA), although many authors refer to it as 3-CQA"

It is well known that the major CGAs isomers in coffee include chlorogenic (3-CQA), cryptochlorogenic (4-CQA) and neochlorogenic (5-CQA) acids, as well the dimers 3,4-diCQA, 3,5-diCQA and 4,5-diCQA [1,2].

- Add the reference: A cup of coffee (200 ml) consists of 20–350 mg CGA, which contains 35–175 mg of caffeic acid.
- Ref 3 is used to indicate the average of CGA consumed by coffee drinkers, please do not use a reference related to green coffee extract, and be sure that you are talking about chlorogenic acid and not chlorogenic acids (CGAs), that is, in my opinion, the right on in this case. Authors should clarify when they refer to chlorogenic acid as the chemical entity (the ester of caffeic acid and (–)-quinic acid) or when they want to talk about chlorogenic acids (CGAs) as the group of phenolic compounds formed by a hydroxycinnamic acid and quinic acid classified by the number, position and type of hydroxycinnamic acid. The most common groups of CGAs are *p*-coumaroylquinic acids, feruloylquinic acids, caffeoylquinic acids (CQAs) and dicaffeoylquinic acids (diCQAs). As I mentioned before, to date, the major CGAs isomers in coffee include chlorogenic (3-CQA), cryptochlorogenic (4-CQA) and neochlorogenic (5-CQA) acids, as well the dimers 3,4-diCQA, 3,5-diCQA and 4,5-diCQA.

ENDOTHELIAL DYSFUNCTION (ED)

- Taking into account that the paper is related to molecular mechanism, I suggest the author consider go further back "ED is a cardiovascular events predictor and considered as the initial stage of atherosclerosis development". Please, consider in this section to mention the

key atherogenic process related to ED. Macrophage foam cells and their role in atherosclerosis. Oxygen species (ROS) production, inflammatory responses and accumulation of lipids, which lead to fatty streak formation in the vascular wall. The massive uptake of oxLDL by macrophages via scavenger receptors (SR-A and CD36) and lectin-like oxLDL receptor-1 (LOX-1), etc. Oxylipins and prostaglandins, among others.

CHLOROGENIC ACID

- This section is extremely general, in my opinion, it could be added in any other section.
- Idem previous sections. Please be clear with the chemistry, avoid sentences like “It is also called 5-O-caffeoylquinic acid (5-CQA), although some authors refer to it as 3-CQA”, it is not important if other authors confuse the nomenclature, do it right is enough, in my opinion. But, it is a matter of discussion in this paper, please reference the wrong ones, and discuss. Please, check: “A cup of coffee (200 ml) consists of 20–350 mg CGA” You should make the difference between the chemical compound (CGA) and the group of the isomers named CGAs (I already mentioned it before).

MECHANISM OF CGA IN INHIBITING ATHEROSCLEROSIS

- Add reference: CGA has been shown to significantly increase mRNA levels of PPAR γ , LXR α , ABCA1 and ABCG1, as well as the transcriptional activity of PPAR γ .
- The next section is not adequately referenced. The only bibliography added does not correspond to the effect of chlorogenic acids.

“CGA has been shown to significantly increase mRNA levels of PPAR γ , LXR α , ABCA1 and ABCG1, as well as the transcriptional activity of PPAR γ . In addition, a cholesterol efflux assay showed that three major metabolites, caffeic, ferulic and gallic acids, significantly stimulated cholesterol efflux from RAW264.7 cells. These results suggest that CGA potently reduces atherosclerosis development in ApoE^{-/-} mice and promotes cholesterol efflux from RAW264.7 macrophages (14)”

- Related to CGAs in inhibiting atherosclerosis, authors should consider literature that mentioned their in vitro and in vivo (clinical studies) effects on oxylipins, isoprostanes, and prostaglandins.

MECHANISM OF CGA IN INHIBITING HYPERTENSION

I suggest the authors consider the expression “inhibiting hypertension”, for this section. In my opinion, it exceeds what the studies have found. There are conflicting results related to this topic.

- Ref 38: important to mention that There was no significant effect of any of the treatments on BP.
- In the last paragraph on the action add caffeoylquinic “acid”

In this section, the authors analyzed FMD, BP, and NO, nevertheless, in the section “CGA and vascular health in human studies”, they go back to the same topics. I would like to see more linkage among the topics, and more discussion related to table 1. In this table, you include 11 references, but in the section authors only discusses ref 36.

ACHIEVING HIGH CGA BENEFIT FROM COFFEE MANUFACTURING PROCESS

This section is extremely general. I don't see the point to have an independent section. This information could be added to the introduction, in a general manner. The paper is not about coffee, is about CGAs. Coffee is a very important source, but the focus of the paper is more

oriented to the molecule 5-CQA, and sometimes to the group of isomers (CGAs). Authors must clarify it, as well as when use references related to coffee.

CONCLUSION

The conclusion leaves out many of the aspects mentioned and discussed.

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Is the topic of the review discussed comprehensively in the context of the current literature?

Partly

Are all factual statements correct and adequately supported by citations?

Partly

Is the review written in accessible language?

Yes

Are the conclusions drawn appropriate in the context of the current research literature?

Partly

Competing Interests: I am a researcher at Vidarium, Nutrition, Health, and Wellness Research Center. Grupo Nutresa.

Reviewer Expertise: Antioxidants, mass spectrometry, biomarkers, bioavailability, clinical studies, obesity, cardiovascular health, chronic non-communicable diseases

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

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