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Review Article   **Open Access**

Neuroprotective effects of green coffee bean extract against Alzheimer's and Parkinson's disease: a mini review

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Abstract

Green coffee bean extract (GCBE) is known as an anti-obesity dietary supplement, but its neuroprotective effects have been recently reported. Since GCBE and its main phenolic acids, chlorogenic acids (CGA), share similar physiological effects, this mini review summarizes the most current research of the neurobiological effects of GCBE and CGA. GCBE and/or CGA act on acetylcholine, glutamate, and insulin signaling pathways to reduce the risk of Alzheimer's disease by reducing amyloid-β proteins (Aβ) and tau proteins in the brain of rodents. Clinical trials, although limited, further suggest that CGA improves cognition, which was associated with changes in blood Aβ levels. In addition, CGA modulates the dopamine metabolism to reduce neurotoxicity in animal models of Parkinson's disease, although there is no direct association between GCBE and Parkinson's disease in humans. The antioxidant and anti-inflammatory effects of GCBE and CGA are suggested to be the underlying mechanisms that help to protect from the development of these diseases. GCBE and CGA have potential benefits to prevent the development of neurodegenerative diseases, but there is still a great need to further investigate their effects on Alzheimer's and Parkinson's disease.

Keywords: Alzheimer's disease, brain disorders, chlorogenic acid, coffee, Parkinson's disease.

Introduction

Nutraceuticals are defined as foods, or parts of foods, that provide health benefits beyond basic nutrition. The nutraceutical market is growing continuously to reflect consumers' interest in enhancing general health with natural alternatives (Hys, 2020). Along with an increasingly aged population, aging-associated neurological diseases are on the rise (Feigin et al., 2020), and the need for nutraceuticals targeting brain health is growing to provide an alternative approach that satisfies the demand for natural treatments.

Coffee, one of the most widely consumed beverages in the world, is typically brewed from the dried and roasted coffee seeds of *Coffea arabica* (Arabica) or *C. canephora* (Robusta) (Farah, 2012). However, it is known that the typical method of preparing coffee for consumption by roasting beans at high temperature causes heat degradation of beneficial polyphenolic compounds (Şemen et al., 2017). Therefore, much attention has been brought to green (unroasted) coffee beans, because they may serve a better source of polyphenols and have better bio-

activities (Perrone et al., 2012). Previously, green coffee bean extract (GCBE) has been reported to have potential activity to mitigate neurological dysfunctions, such as Alzheimer's disease (Ho et al., 2012; Ishida et al., 2020b; Mohamed et al., 2020). Moreover, the intake of the GCBE's main active compound, chlorogenic acids (CGA), for 3–6 months improved cognitive function in humans with no or mild cognitive impairment (Kato et al., 2018; Ochiai et al., 2019; Saitou et al., 2018). The neuroprotective effects of GCBE and CGA together with their antioxidant, anti-inflammatory and anti-diabetes properties may help to prevent the development of Alzheimer's and Parkinson's disease. Thus, the objective of this mini review is to summarize the current knowledge on the neurobiological effects of GCBE and CGA that may help to prevent Alzheimer's and Parkinson's disease (Table 1).

Green coffee bean extract

GCBE is prepared from the unroasted seeds of the coffee plant. Without heat processing, GCBE retains a higher content

Table 1. Summary of studies of the neurobiological effects of green coffee bean extract (GCBE), chlorogenic acids (CGA)[1], and 5-*O*-caffeoylquinic acid (5-CQA) *in vivo*

Material	Doses[2]	Duration (d)	Model[3]	Subject[4] (sex)	Effects	Targets[5]	References
Clinical trials							
CGA	1 g (p.o.)	84	Mild cognitive impairment	Human (♂♀)	↑Cognition		(Ochiai et al., 2019)
	300 mg (p.o.)	112	Healthy, middle and elderly population	Human (♂)	↑Cognition	↑ApoA1 ↑TTR	(Saitou et al., 2018)
	330 mg (p.o.)	168	Healthy elderly population	Human (♂♀)	↑Cognition	↓Aβ42/Aβ40	(Kato et al., 2018)
Pre-clinical trials							
GCBE	100 mg/kg b.w. (p.o.) (67% CGA)	28	Cortical injury induced by high-fat diet and streptozotocin	Wistar rats (♂)	↑Neurotransmitters ↓Apoptosis ↓Inflammation ↓Oxidative stress	↑Bcl2 ↑Cat ↑GPx ↑GSH ↑SOD ↓Bax ↓Caspase 3 ↓IL-1β ↓iNOS ↓TNF-α	(Al-Brakati et al., 2020)
	1% diet (48% CGA)	126	Alzheimer's disease	APP/PS2 mice (♂)	↑Cognition	↑TTR ↓APP ↓Aβ plaques	(Ishida et al., 2020b)
	40 mg/kg b.w. (p.o.) (50% CGA)	154	Fructose-induced Alzheimer's disease	Wistar rats (♂)	↑Cognition	↑Akt ↑PI3K ↓GSK3β ↓p-IRS Ser307 ↓p-Tau	(Mohamed et al., 2020)
	80 mg/kg b.w. (p.o.) (45% CGA)	140	Brain insulin resistance induced by high-fat diet	C57B6SJL mice (♀)	Gene expression changes in the brain	604 genes, which some are involved in glucose, lipid, insulin and redox signaling pathways	(Ho et al., 2012)
5-CQA	0.8% diet	147	Alzheimer's disease	APP/PS2 mice (♂)	↑Cognition ↓Aβ plaques	↑AQP4 ↑LRP-1	(Ishida et al., 2020a)
	100 mg/kg b.w. (p.o.)	24	MPTP-induced Parkinson's disease	Swiss mice (♂)	↑Locomotor behavior ↓Apoptosis ↓Neurodegeneration ↓Oxidative stress ↓Inflammation	↑Bcl-2 ↑Cat ↑IL-10 ↑p-Akt ↑p-ERK1/2 ↑p-GSK3β ↑SOD ↓Bax ↓IL-1β ↓iNOS ↓NF-κB ↓TNFα	(Singh et al., 2018, 2020)
	60 mg/kg b.w. (i.p.)	7	6-OHDA-induced Parkinson's disease	Sprague-Dawley rats (♂)	↑Locomotor behavior ↓Oxidative stress	↑Bcl-2 ↑GPx ↑SOD ↓Bax	(Shan et al., 2019)

[1] CGA extracted from green coffee beans.
[2] b.w., body weight; i.p., intraperitoneally; p.o., per oral.
[3] 6-OHDA, 6-hydroxydopamine; MPTP,1-methyl-4-phenyl-1,2,3,6-tetrahydopyridine.
[4] APP, amyloid-β precursor protein; PS2, presenilin 2.
[5] Aβ, amyloid-β proteins; Akt, protein kinase B; Apo, apolipoprotein; AQP, aquaporin; Bax, Bcl-2-associated X; Bcl, B-cell lymphoma; BDNF, brain derived natriuretic factor; Cat, catalase; ERK, extracellular signal-regulated kinase; GSK3β, glycogen synthase kinase-3β; GPx, glutathione peroxidase; GSH, reduced glutathione; IL, interleukin; iNOS, inducible nitric oxide synthase; IRS, insulin receptor substrate; LPR, low-density lipoprotein receptor; NF-κB, nuclear factor kappa B; p, phosphorylated; PI3K, phosphoinositol-3 kinase; Ser, serine; SOD, superoxide dismutase; TNF, tumor necrosis factor; TTR, transthyretin.

of polyphenols compared to roasted coffee beans that are typically used to make brewed coffee drink (Jeszka-Skowron et al., 2016; Perrone et al., 2012). Therefore, there has been great interest in assessing the beneficial biological properties of GCBE and its bioactives, including neurological benefits.GCBE composition varies according to type of extraction methods. One extraction method to produce GCBE is first softening raw green coffee beans, extracting with edible oil derived from petroleum (i.e., solvent oil number 6), ethanol, and water, followed by filtration and drying to yield an extract powder with approximately 50% CGA and 12% caffeine content (Cheng et al., 2014). Commercially available GCBE are standardized to contain 50% CGA, but GCBE also contains other bioactive compounds, such as theophylline, theobromine, cafestol, kahweol, tocopherols, choline and trigonelline (Ciaramelli et al., 2018; Farias-Pereira et al., 2018; Jeszka-Skowron et al., 2016).

Chlorogenic acids

The main polyphenolic compound in GCBE is CGA, which refers to a family of compounds that are esters of cinnamic and quinic acids, including subgroups of mono-, di-, tri-, and tetra-esters of caffeic acid, coumaroylquinic acids and feruloylquinic acids, and mixed di-esters of caffeic and ferulic acid (Abrankó and Clifford, 2017; Farah, 2012). In addition, every CGA ester contains several isomeric forms, like 5-*O*-caffeoylquinic acid (5-CQA), 4-CQA, 3-CQA, and varying residues of caffeic acid or quinic acids generating molecules like caffeoylferuloylquinic acids and caffeoylsinapoylquinic acids (Clifford et al., 2017). Thus, a sample of GCBE can contain many CGA esters and their isomers. However, the most common and commercially available isomer of CGA is 5-CQA (Farias-Pereira et al., 2018). It should be noted that after the identity of CGA was determined, the International Union of Pure and Applied Chemistry (IUPAC) reversed the order of numbering of atoms on the quinic acid ring, so that what is 5-CQA now, was formerly known as 3-CQA (Abrankó and Clifford, 2017). Though some literature and chemical suppliers still use the old convention, this review will refer to the most abundant isomer of CGA as 5-CQA to stay consistent with current IUPAC nomenclature and more recent publications.

Alzheimer's disease

Alzheimer's disease, which is the most common neuro-

degenerative disease, is characterized by protein and filaments accumulation in the brain. Epidemiological studies, although limited, suggest that coffee consumption is associated with a reduced risk of Alzheimer's disease (Grosso et al., 2017). Previously it was reported that GCBE and 5-CQA reduced amyloid-β proteins (Aβ) accumulation in the brain of APP/PS2 mice used as Alzheimer's disease model (Ishida et al., 2020b, 2020a). This effect was suggested to be due to direct interaction between 5-CQA and Aβ by binding Aβ oligomers (Ciaramelli et al., 2018; Ishida et al., 2020b). Moreover, 5-CQA can reduce Aβ accumulation via transthyretin (TTR) and low-density lipoprotein receptor 1 (LRP1), both of which are involved in the transport of Aβ (Ishida et al., 2020b, 2020a). Consistently, the daily intake of 300–330 mg CGA extracted from green coffee beans for 4–6 months improved cognitive function in healthy humans, which was associated with reduced Aβ42/Aβ40 levels and an increased TTR and apolipoprotein A1 (ApoA1), also involved in Aβ transport (Kato et al., 2018; Saitou et al., 2018).

Others reported that GCBE inhibits acetylcholinesterase and butyrylcholinesterase, which would increase acetylcholine in the brain (Budryn et al., 2018; Dhakal et al., 2019; Sekeroglu et al., 2012). GCBE inhibited acetylcholinesterase and butyrylcholinesterase by 53% and 20%, respectively, *in vitro* studies (Sekeroglu et al., 2012). Caffeine may be the most likely coffee bioactive responsible to inhibit acetylcholinesterase, while the inhibitory effects of GCBE on butyrylcholinesterase were associated with its phenolics acids, particularly ferulic acid, 3-CQA, 4-CQA and 4,5-di-*O*-dicaffeoylquinic acid (Budryn et al., 2018).

Another target for Alzheimer's disease treatment is glutamate signaling pathway, resulting in reduced neuronal cell death via N-methyl-D-aspartate (NMDA) receptor (Dhakal et al., 2019). CGA, caffeic acid and ferulic acid have all been shown to reduce glutamate-induced neurotoxicity by inhibiting glutamate-induced Ca^{2+} entry via NDMA receptor (Colombo and Papetti, 2020; Mikami and Yamazawa, 2015; Rebai et al., 2017; Taram et al., 2016). In particular, 5-CQA and caffeic acid's effects on glutamate-induced neurotoxicity were dependent on the caspases (1, 8 and 9) and the Ca^{2+}-dependent protease calpain, both are known to be involved in the apoptotic effects of glutamate in rodent cortical neurons (Rebai et al., 2017). In addition, the antioxidant property of 5-CQA further helps to protect neurons by reducing the production of reactive oxygen species (ROS) and reducing depolarization of mitochondrial membrane (Rebai

et al., 2017).

The improvement of insulin resistance by GCBE was suggested to contribute to the neuroprotective effects against the development of Alzheimer's disease in rodents (Ho et al., 2012; Mohamed et al., 2020). GCBE suppressed the expression of the glycogen synthase kinase 3β (GSK3β), a major tau kinase that leads for the aggregation of tau proteins in fructose-drinking rats (Mohamed et al., 2020). Taken together, GCBE and CGA may protect the nervous system from the development of Alzheimer's disease by modulating acetylcholine, glutamate and insulin signaling pathways, and preventing Aβ accumulation in the brain.

Parkinson's disease

Coffee consumption is associated with reduced risk of Parkinson's disease, which is characterized by the degeneration of dopaminergic neurons in the substantia nigra (Grosso et al., 2017; Ludwig et al., 2014). Although there is currently no direct evidence that GCBE ameliorates Parkinson's disease in humans, limited studies suggest that both caffeine and CGA within coffee products contribute to a reduced risk of Parkinson's disease (Colombo and Papetti, 2020; Heitman and Ingram, 2017; Ludwig et al., 2014). The stimulation of dopamine release by caffeine by antagonizing A2 adenosine receptor may lead to reduced symptoms of Parkinson's disease (Ludwig et al., 2014). Others reported that CGA protected dopamine neurons from death induced by 6-hydroxydopamine (6-OHDA) and 1-methyl-4-phenyl-1,2,3,6-tetrahydopyridine (MPTP) in rodent models for Parkinson's disease (Shan et al., 2019; Singh et al., 2018, 2020). This was due to CGA's antioxidant effects by scavenging ROS and increasing superoxide dismutase (SOD) activity that protected against death of the dopamine neurons in rodent Parkinson's disease models and nerve growth factor-differentiated PC12 cells (Lin et al., 2020; Shan et al., 2019; Singh et al., 2020).

Others suggested that CGA is an inhibitor of the catechol-*O*-methyltransferase (COMT) in rat liver, which metabolizes levodopa (L-dopa) to 3-*O*-methyldopa (Engelbrecht et al., 2019). This suggests that CGA could increase L-dopa uptake in the brain, thus, reducing symptoms of Parkinson's disease (Engelbrecht et al., 2019). However, it is not yet clear if CGA inhibits COMT to assist L-dopa therapy in Parkinson's disease in humans. Even though GCBE, shares similar biological properties with CGA, due to its composition, future studies are needed to determine if GCBE supplementation would have similar effects on development of Parkinson's disease as CGA.

Oxidative stress and inflammation

GCBE and CGA's antioxidant and anti-inflammatory properties can help to protect neurons from oxidative stress and inflammation (Al-Brakati et al., 2020; Lee et al., 2020; Rebai et al., 2017). It was previously reported that GCBE reduced chemically-induced oxidative stress in human and murine neurons (Chu et al., 2009; Ciaramelli et al., 2018). The antioxidant effects of GCBE on neurons were in part by reducing generation of free radicals by directly chelating transition metals and scavenging free radicals (Cheng et al., 2020; Lee et al., 2020; Rebai et al., 2017; Wang et al., 2017; Zang et al., 2003). In addition, GCBE and CGA modulated antioxidant transcription factors, such as extracellular signal-regulated protein kinases 1/2 (ERK1/2) and nuclear factor erythroid 2-related factor 2 (Nrf2), to enhance the antioxidant response in the neurons (Chu et al., 2009; Gong et al., 2019; Singh et al., 2018, 2020; Yao et al., 2019). Consistently, GCBE and CGA increased the expression of antioxidant enzymes, such as SOD, catalase (CAT), glutathione peroxidase (GPx), and glutathione reductase (GR) in rodent brain tissues (Al-Brakati et al., 2020; Lee et al., 2020; Metwally et al., 2020; Singh et al., 2018). Moreover, it has been reported that CGA reduced the expression of pro-inflammatory cytokines (e.g. tumor necrosis factor alpha (TNF-α), interleukin (IL)-1 beta and IL-6) and increases anti-inflammatory cytokines (e.g. IL-4 and IL-13) in brain tissue of rodents (de Lima et al., 2019; Lee et al., 2020; Metwally et al., 2020; Singh et al., 2018). Shen et al. (2012) suggested that CGA regulates inflammation by modulating the nuclear factor kappa B (NF-κB) signaling pathway as observed by suppressed I kappa B (IκB) phosphorylation and degradation in lipopolysaccharide-stimulated rodent glial cells. Consistently, 5-CQA inhibited the NF-κB activation followed by the reduced inflammation markers, including inducible nitric oxide synthase (iNOS) in the brain of MPTP-treated mice (Parkinson's disease model) (Singh et al., 2018). Although only limited studies have investigated the antioxidant and anti-inflammatory properties of GCBE and CGA in neurons *in vivo*, these effects of GCBE and CGA are suggested to contribute significantly to their preventive roles in neurodegenerative diseases, including Alzheimer's and Parkinson's disease. Further studies are needed to determine whether GCBE and CGA are

more effective against oxidative stress and inflammatory conditions than other nutraceuticals and bioactives in the nervous system.

Conclusion

The consumption of GCBE and its main component CGA may have the potential to improve human health, including brain health. However, future clinical studies with GCBE are needed to validate the current knowledge.

Conflicts of Interest

The authors declare no potential conflict of interest.

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Ethics Approval

This article does not require IRB/IACUC approval because there are no human and animal participants

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