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Therapeutic potential of chlorogenic acid in age-associated metabolic and neurodegenerative disorders

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Chlorogenic acid (CGA), a polyphenolic compound abundant in coffee and various plants, exhibits broad therapeutic potential in age-related metabolic and neurodegenerative disorders.
CGA exerts potent antioxidant, anti-inflammatory, and metabolic regulatory effects by modulating key signaling pathways such as AMPK, SIRT1, mTOR, FOXO, and Nrf2. Preclinical studies demonstrate its ability to mitigate oxidative stress, regulate autophagy, improve lipid and glucose metabolism, and protect against neurodegeneration. Moreover, CGA enhances mitochondrial function and preserves cellular homeostasis. However, emerging evidence suggests that under conditions of low folate or B-vitamin availability, CGA may increase plasma homocysteine levels, raising concerns about its effects on methylation and vascular health.
This review provides a comprehensive analysis of CGA's molecular targets and mechanisms of action, with particular emphasis on its implications in redox regulation, autophagy, metabolic homeostasis, and neurodegeneration. Collectively, current evidence positions CGA as a promising nutraceutical candidate for integrative strategies aimed at preventing or mitigating chronic degenerative diseases and promoting healthy aging.

KEY WORDS: chlorogenic acid / aging / metabolic disorders / oxidative stress / autophagy / neurodegeneration

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Aging and the progression of chronic diseases such as type 2 diabetes, cardiovascular disorders, neurodegeneration, and non-alcoholic fatty liver disease (NAFLD) are strongly associated with oxidative stress, low-grade systemic inflammation, and disruption of metabolic and catabolic homeostasis [Kitada *et al.* 2021, Leyane *et a*l. 2022]. There is growing scientific interest in phytochemicals with pleiotropic bioactivities, especially polyphenols [Lu *et al.* 2020]. Among these, chlorogenic acid (CGA), a naturally occurring ester of caffeic acid and quinic acid, has emerged as a promising nutraceutical due to its broad pharmacological profile [Nguyen *et al.* 2024].

CGA is abundant in green coffee beans and is also found in significant quantities in fruits, vegetables, and herbs [Holowinski *et al*. 2022, Lu *et al*. 2020]. It exhibits potent antioxidant, anti-inflammatory, anti-apoptotic, and metabolic regulatory effects, and has been shown to influence key molecular pathways associated with aging and cellular homeostasis, including AMPK[1], SIRT1[2], mTOR[3], and FOXO[4] signaling [Chen *et al*. 2020, Kitada *et al.* 2021, Siswanto *et al*. 2022]. Experimental studies have demonstrated that CGA modulates redox balance by enhancing endogenous antioxidant enzyme activity, suppresses inflammatory cytokine production via inhibition of the NF-κB[5] and TLR4[6] pathways, and promotes autophagic and mitochondrial function in various diseases [Hada *et al*. 2020, Nguyen *et al*. 2024, Liang Wang *et al*. 2022].

Furthermore, CGA plays an important role in the regulation of lipid and glucose metabolism, including favorable modulation of apolipoproteins, improvement in insulin sensitivity, and attenuation of hepatic steatosis [Meng *et al*. 2013, Nguyen *et al.* 2024, Tajik *et al*. 2017]. Its neuroprotective properties have also been substantiated by preclinical models of Alzheimer's and Parkinson's diseases, in which CGA preserved neuronal viability, attenuated oxidative damage, and restored neurotrophic signaling [Bezerra *et al*. 2025, Gao *et al.* 2023, Zheng *et al.* 2021] – Figure 1.

Despite its beneficial effects, CGA also exhibits context-dependent effects on metabolism, particularly with regard to homocysteine metabolism and the methylation cycle. Some research suggests that under conditions of inadequate folate or vitamin B cofactor availability, CGA may elevate plasma homocysteine levels, potentially increasing the risk of endothelial dysfunction and nitrosative stress [Atazadegan *et al.* 2021, Olthof *et al*. 2001]. These dual effects underscore the need for a nuanced assessment of its therapeutic applications.

This review aims to provide a comprehensive overview of the antioxidant, anti-inflammatory, anti-apoptotic, and autophagy-modulating properties of CGA, with a

[1]AMPK - AMP-activated protein kinase.
[2]SIRT1 - Sirtuin1.
[3]mTOR - Mammalian target of rapamycin kinase.
[4]FOXO - forkhead box O.
[5]NF-κB - nuclear factor kappa-light-chain-enhancer of activated B cells.
[6]TLR4 - toll-like receptor 4.

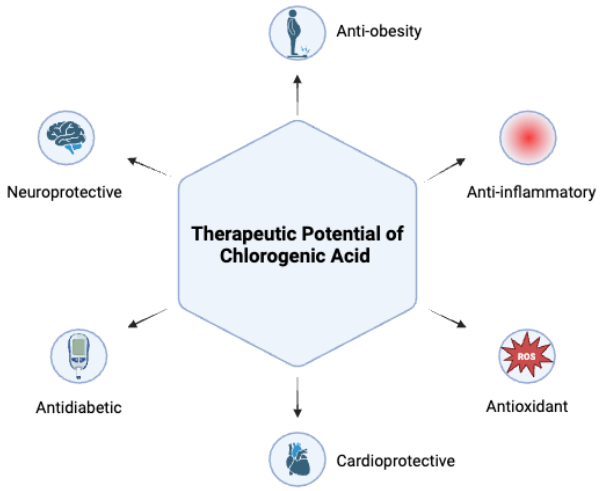

Fig. 1. Potential health effects of chlorogenic acid.

particular focus on its molecular mechanisms of action and potential implications in the prevention and management of age-related and degenerative diseases. Additionally, this work will address the paradoxical aspects of CGA's influence on homocysteine metabolism, highlighting its benefits and limitations as a dietary supplement.

Chlorogenic acid - biological and pharmacological characteristics

CGA, chemically known as 5-O-caffeoylquinic acid (5-CQA) – Figur 2, is one of the most abundant polyphenolic compounds in the human diet. It naturally occurs in high concentrations in coffee, fruits (e.g., apples, pears, plums), vegetables (e.g., artichokes, tomatoes), herbs, and various medicinal plants [Lu *et al*. 2020, Santana-Gálvez *et al*. 2017]. Belonging to the class of hydroxycinnamic acid derivatives, CGA represents the esterification product of caffeic acid and quinic acid and is the predominant member of chlorogenic acids [Clifford *et al.* 2017, Li *et al*. 2020]. The broader group of these compounds includes isomeric forms such as caffeoylquinic acids (CQA), feruloylquinic acids (FQA), and dicaffeoylquinic acids (diCQA) [Abrankó *et al.* 2017].

CGA exhibits structural diversity, which has necessitated the development of a standardized nomenclature to ensure clarity in scientific communication [Abrankó et al. 2017]. The molecule contains key functional groups responsible for its chemical reactivity, including ester bonds, hydroxyl groups, and conjugated double bonds [Huang *et al*. 2023]. In plants, CGA is biosynthesized via the phenylpropanoid pathway, involving key enzymes such as phenylalanine ammonia-lyase (PAL), hydroxycinnamoyl-CoA: quinate hydroxycinnamoyl transferase (HQT), and

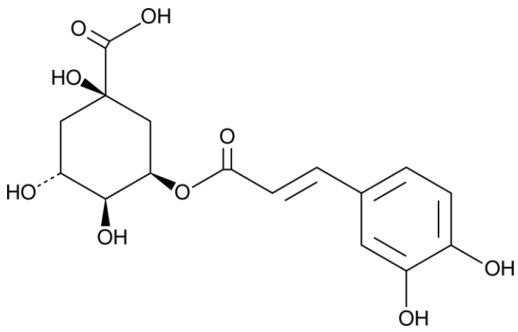

Fig 2. 5-Caffeoylquinic acid structure.

hydroxycinnamoyl-CoA shikimate/quinate hydroxycinnamoyl transferase (HCT) [Liang Wang *et al.* 2022].

Despite its widespread presence in the diet, CGA displays relatively low bioavailability. After oral ingestion, only a minor portion of the intact molecule is absorbed in the small intestine. The majority undergoes hydrolysis by microbial esterases in the colon to produce caffeic and quinic acids, which are subsequently absorbed and further metabolized in the liver [Clifford *et al*. 2020, Liu *et al*. 2022]. These metabolites, including ferulic acid and dihydrocaffeic acid, are bioactive and detectable in systemic circulation. Metabolic transformations include hydrolysis, sulfation, glucuronidation, and oxidative modifications, with interindividual differences in gut microbiota significantly influencing CGA metabolism and systemic effects [Liu *et al*. 2022, Lu *et al.* 2020].

CGA exhibits a broad spectrum of pharmacological properties, including antioxidant, anti-inflammatory, hepatoprotective, antidiabetic, neuroprotective, cardioprotective, antimicrobial, anti-obesity, anticarcinogenic, and osteogenic effects [Naveed *et al*. 2018, Nguyen *et al.* 2024, Shen *et al*. 2024, Xue *et al*. 2023]. These diverse actions are mediated through the modulation of key cellular signaling pathways, including Nrf2/Keap1[7], NF-κB, AMPK, TLR4, SIRT1, and ERK1/2[8] [Huang *et al.* 2023, Li *et al*. 2020, Ziółkiewicz *et al.* 2024].

Chlorogenic acid and aging processes

Aging is a complex, multifactorial biological process characterized by a progressive decline in physiological integrity, increased vulnerability to chronic diseases, and eventual loss of organismal viability [Frenk *et al*. 2018, Zia *et al.* 2021]. At the molecular level, aging involves cumulative cellular damage, oxidative stress, mitochondrial dysfunction, impaired degradation of protein, and dysregulated

[7]Nrf2/Keap1 - nuclear factor erythroid 2-related factor 2/ kelch-like ECH-associated protein 1.
[8]ERK1/2 - extracellular signal–regulated kinases 1 and 2.

nutrient-sensing pathways such as AMPK, SIRT1, and mTOR [Kitada *et al*. 2021, Sadria *et al*. 2021, Zheng *et al*. 2021]. Redox imbalance and chronic low-grade inflammation are considered key mechanisms in the pathogenesis of age-associated degenerative diseases, particularly in the nervous and cardiovascular systems [Leyane *et al.* 2022, Patel 2016]. Among the key regulators of cellular homeostasis is SIRT1, a nicotinamide adenine dinucleotide (NAD^+) - dependent deacetylase that modulates a wide range of processes, including DNA repair, apoptosis, chromatin remodeling, and transcription of stress-responsive genes [Chen *et al*. 2020, Hori *et al*. 2013, Ong *et al.* 2018]. SIRT1 deacetylates p53 in a NAD^+-dependent manner, thereby inhibiting its transcriptional activity, reducing cellular senescence, and modulating pathways involved in tissue homeostasis. Although SIRT1 expression declines with age, potentially as a protective mechanism against oncogenesis, its activation in aging cells may protect against p53-dependent apoptosis or senescence, while predisposing cells to malignant transformation [Ong *et al*. 2018].

Recent attention has turned to CGA for its potential to modulate aging-related pathways. CGA exerts a wide range of biological effects, including antioxidant, anti-inflammatory, neuroprotective, anti-apoptotic, and metabolic benefits [Feng *et al*. 2016, Ontawong *et al.* 2023, Siswanto *et al*. 2022]. At the molecular level, CGA modulates signaling networks related to insulin/IGF-1, FOXO, AMPK, and mTOR, and improves cellular stress resistance. In the Caenorhabditis elegans (C. elegans) model, CGA extends lifespan and enhances stress tolerance by activating FOXO homolog DAF-16 and transcriptional regulators such as SKN-1 (a Nrf2 homolog) and HSF-1 [Siswanto *et al*. 2022, Zheng *et al.* 2017]. CGA also influences the alternative FOXO3-DDB1-WDR23 axis, which leads to the stabilization of SKN-1, resulting in enhanced transcription of antioxidant enzymes and increased organismal longevity [Siswanto *et al.* 2022]. Furthermore, CGA affects NAD^+ metabolism and enhances SIRT1 activity, integrating metabolic and caloric stress responses [Zia *et al*. 2021]. Its ability to upregulate genes such as superoxide dismutase 2 (SOD2) and catalase (CAT) underscores its role in maintaining redox balance [Chen *et al*. 2020, Hori *et al.* 2013].

Experimental studies provide further support for CGA's geroprotective properties. Rodent models of D-galactose-induced aging demonstrate that CGA supplementation reduced liver and kidney damage and improved blood biochemical markers, pointing to systemic anti-aging effects [Feng *et al.* 2016]. In models of sporadic Alzheimer's disease, CGA improved memory, protected hippocampal neurons, and mitigated neuroinflammation by preventing a decline in brain-derived neurotrophic factor (BDNF) expression [Bezerra *et al.* 2025]. In gut aging models, CGA, especially in combination with epigallocatechin gallate (EGCG) restored intestinal barrier integrity, modulated the Firmicutes/Bacteroidetes ratio, and reduced oxidative stress and inflammation [Di Salvo *et al*. 2023, Wei *et al*. 2023]. Importantly, CGA suppresses age-associated expression of inflammatory cytokines, promotes mitochondrial biogenesis, and stabilizes genome integrity. These effects align with several established hallmarks of aging [Frenk *et al.* 2018]. In C. elegans, CGA inhibits DAF-16a, thereby decreasing

DDB-1 expression and limiting CRL4WDR23[9] ligase activity, leading to SKN-1 accumulation and life extension [Siswanto *et al*. 2022].

Given its pleiotropic effects and ability to modulate conserved longevity pathways, CGA represents a promising candidate for interventions targeting aging and associated pathologies.

Effects of chlorogenic acid on oxidative stress and degradation processes

Oxidative stress is defined as an imbalance between oxidants and antioxidants, accompanied by disruption of the redox cycle and damage to macromolecules [Patel 2016]. This imbalance leads to excessive accumulation of reactive oxygen species (ROS) and reactive nitrogen species (RONS) in cells and tissues. According to the "free radical theory of aging", ROS play a central role in causing structural and functional damage through cumulative oxidative modifications of cellular and extracellular matrix components. This aging process may result from both intrinsic and extrinsic factors, including dietary habits, smoking, physical inactivity, environmental toxins, and radiation. Accumulated oxidative stress and chronic inflammation are key contributors to the progression of aging and chronic degenerative diseases. Overproduction of ROS/RONS induces deleterious modifications to DNA, proteins, and lipids, exacerbating cellular dysfunction [Leyane *et al*. 2022, Yeung *et al*. 2024].

Mitochondria are the primary site of ROS generation during cellular respiration, primarily due to electron leakage from the mitochondrial respiratory chain [Moloudizargari *et al.* 2017]. To combat oxidative stress, cells are equipped with a multilayered antioxidant defense system. The first line includes enzymatic antioxidants such as superoxide dismutase (SOD), CAT, and glutathione peroxidase (GPx), along with non-enzymatic low-molecular-weight antioxidants such as glutathione (GSH) and thioredoxin (Trx), which serve as essential cofactors. The second line encompasses diet-derived antioxidants, including vitamins C and E, carotenoids, and polyphenols. The third line involves enzymes that repair or remove oxidized biomolecules, thereby maintaining redox homeostasis [Bartel *et al*. 2025, Jomova *et al*. 2024].

CGA stands out due to its potent antioxidative, anti-inflammatory, and cytoprotective properties [Bagdas *et al*. 2020, Liang Wang *et al*. 2022]. CGA exhibits strong antioxidant capacity via both direct free radical scavenging and indirect upregulation of endogenous antioxidant systems. It scavenges ROS and enhances the activity of endogenous antioxidant enzymes such as SOD, CAT, and GPx, while reducing levels of malondialdehyde (MDA), a marker of lipid peroxidation [Chen *et al*. 2025, Ontawong *et al*. 2023, Liang Wang *et al*. 2022]. In various models, CGA activates the KEAP1/Nrf2/ARE[10] signaling pathway, leading to transcriptional

[9]CRL4WDR23 - Cullin-RING E3 ubiquitin ligase 4 complex with WD repeat-containing protein 23.
[10] KEAP1/Nrf2/ARE - Kelch-like ECH-associated protein 1/nuclear factor erythroid 2–related factor 2/ antioxidant response element.

activation of antioxidative enzymes, including HO-1[11] [Dai et al. 2024, Nguyen *et al.* 2024].

In cellular models, CGA activated Nrf2 signaling, restored redox balance, and reduced oxidative damage and apoptosis [Zada *et al*. 2021]. In endothelial cells, CGA promoted Nrf2 nuclear translocation and increased HO-1 expression, leading to a reduction in oxidative DNA damage, particularly in the form of 8-hydroxy-2'-deoxyguanosine (8-OHdG), a key biomarker of oxidative injury [Di Minno *et al.* 2016, 2017, Hada *et al*. 2020]. Furthermore, CGA decreases lipid peroxidation and protein carbonylation, preserving the structural and functional integrity of vital tissues, including the liver, kidneys, and brain. In a D-galactose-induced aging model, CGA significantly improved renal and hepatic function, attenuated histological damage, and normalized oxidative biomarkers [Feng *et al*. 2016].

In addition to its antioxidant role, CGA demonstrates potent anti-inflammatory effects. It inhibits the expression of pro-inflammatory cytokines such as tumor necrosis factor α (TNF-α), interleukin-1β (IL-1β), and interleukin-6 (IL-6) by suppressing the NF-κB and TLR4 signaling pathways [Bagdas *et al.* 2020, Ontawong *et al.* 2023, Ye *et al.* 2017]. In models of lipopolysaccharide (LPS)-induced acute kidney injury, CGA attenuated renal damage by inhibiting TLR4/NF-κB signaling and reducing inflammatory cytokine production [Dai *et al*. 2024]. CGA also modulates apoptotic signaling. It downregulates pro-apoptotic proteins including Bax, cleaved caspase-3, and caspase-9, while upregulating the anti-apoptotic protein Bcl-2, thereby promoting cell survival [Metwally *et al*. 2020]. In dry eye disease models, CGA suppressed autophagy and apoptosis by regulating the AMPK/ ULK1[12] axis [Chen *et al*. 2025], which is critical for cellular energy homeostasis and degradation control. CGA has shown efficacy in preventing oxidative stress-induced cellular senescence. In angiotensin II-treated aged mice, CGA significantly reduced senescence-associated β-galactosidase activity and decreased the expression of senescence markers such as p53, p21, and PAI-1. Simultaneously, it upregulated the expression of SIRT1 and endothelial nitric oxide synthase (eNOS), which are important regulators of vascular function and longevity [Hada *et al.* 2020]. CGA also demonstrates protective effects in gastrointestinal and neurological models. In dextran sulfate sodium (DSS)-induced colitis, CGA reduced IL-8 expression, improved mucosal integrity, and alleviated inflammation [Shin *et al.* 2015]. In arsenic-induced neurotoxicity, CGA restored neurotransmitter balance, enhanced BDNF, and reduced neuroinflammation and apoptosis [Metwally *et al*. 2020]. In cardiovascular studies, CGA protected against endothelial dysfunction, improved lipid metabolism, and prevented vascular injury caused by oxidized LDL [Nguyen *et al*. 2024], highlighting its systemic relevance.

Chlorogenic acid exerts multidimensional protective effects by modulating oxidative stress, suppressing inflammation, regulating apoptosis, and preserving redox

[11]HO-1 - heme oxygenase-1.
[12]ULK1 - Unc-51 like autophagy activating kinase 1.

equilibrium. Through the activation of pathways such as Nrf2/HO-1 and AMPK/ULK1, and inhibition of NF-κB and TLR4, CGA demonstrates strong potential in preventing and managing oxidative stress-associated degenerative diseases. Its therapeutic versatility supports its inclusion in strategies aimed at mitigating age-related cellular dysfunction and chronic inflammation.

Chlorogenic acid vs autophagy and the mTOR pathway

Autophagy is a crucial catabolic process through which cells maintain homeostasis by degrading misfolded proteins and damaged organelles via lysosomal pathways. Autophagy comprises three primary forms: microautophagy, chaperone-mediated autophagy (CMA), and macroautophagy. Among these, macroautophagy is the most extensively studied in relation to aging and metabolic disorders [Park *et al.* 2020]. Macroautophagy involves sequential steps: initiation, phagophore formation, elongation, and fusion with lysosomes, where cargo degradation occurs [Rana *et al.* 2021]. Its efficiency diminishes with age and nutrient overload, contributing to the development of metabolic pathologies such as insulin resistance, type 2 diabetes, and sarcopenic obesity. The dysregulation of autophagy leads to the accumulation of damaged cellular components, aggravating oxidative stress and promoting senescence or cell death [Kitada *et al*. 2021]. Autophagy is tightly regulated by nutrient-sensing signaling pathways including mTORC1, AMPK, and SIRT1. Starvation activates AMPK and SIRT1, suppressing mTORC1 and thus promoting autophagy. In contrast nutrient abundance has the opposite effect, enhancing mTORC1 activity and inhibiting autophagic processes [Kitada *et al*. 2021, Park *et al*. 2020]. The mTOR pathway functions as a central inhibitor of autophagy by phosphorylating ULK1, whereas AMPK stimulates autophagy through phosphorylation of ULK1 at alternative sites [Rana *et al*. 2021].

CGA exhibits robust antioxidant and anti-inflammatory activities. Recent scientific reports suggest that CGA may modulate autophagy through both mTOR and AMPK signaling axes, offering therapeutic potential in diseases characterized by autophagic dysfunction [Gonzalez *et al*. 2020, Rahman *et al*. 2017]. Studies have demonstrated that CGA can restore impaired autophagic flux, particularly under oxidative stress or protein aggregation conditions, leading to either cytoprotective or cytotoxic outcomes depending on the cellular context and disease state.

In Alzheimer's disease models, CGA mitigated Aβ25-35-induced neurotoxicity via modulation of the mTOR/TFEB pathway. Specifically, CGA suppressed autophagosome accumulation, enhanced lysosomal degradation, and upregulated cathepsin D expression, reflecting improved autophagic flux and lysosomal function [Gao *et al.* 2020]. CGA also promoted TFEB nuclear translocation, counteracting mTOR inhibition and activating lysosomal and autophagy-related gene transcription [Gao *et al*., 2020, Rana *et al*. 2021].

Similarly, in oxidative stress-induced dry eye models, CGA downregulated AMPK/ULK1 signaling, reduced ROS and MDA levels, restored SOD1 activity, and inhibited apoptosis, indicating suppression of excessive autophagy [Chen *et al*. 2025]. CGA also enhances autophagy in Parkinson's disease models. Zebrafish studies have shown that CGA alleviates Parkinsonian symptoms, including dopaminergic neuron loss and motor dysfunction, by upregulating genes such as lc3b, atg5, atg7, and ulk1b, and reducing the expression of α-synuclein and p62, suggesting restoration of functional autophagy. In vitro studies using 6-hydroxydopamine (6-OHDA)-treated SH-SY5Y cells confirmed that CGA reduced LC3B accumulation and cellular apoptosis. These results implicate CGA in the reactivation of impaired autophagy during neurodegeneration [Gao *et al*. 2023].

Further, CGA may influence secretory autophagy (SA) - a non-canonical pathway involved in the unconventional secretion of aggregation-prone proteins such as Aβ and α-synuclein. By upregulating ATG5 and ATG7, CGA potentially facilitates SA-mediated clearance of neurotoxic aggregates, thus reducing oxidative stress and proteotoxicity [Gonzalez *et al*. 2020, Rahman *et al.* 2017]. The mTORC1 complex also plays a role in suppressing lysosomal biogenesis by phosphorylating transcription factors like TFEB and repressing genes containing CLEAR motifs [Deleyto-Seldas *et al.* 2021]. CGA's ability to reverse these effects through indirect mTOR inhibition or AMPK activation further supports its role in autophagy regulation [Yao *et al*. 2025]. Importantly, unlike pharmacologic mTOR inhibitors such as rapamycin, which may induce immunosuppression, CGA represents a safer, naturally occurring compound capable of fine-tuned, context-dependent autophagy modulation [Deleyto-Seldas *et al*. 2021].

Its broad cytoprotective effects ranging from ROS scavenging and apoptosis inhibition to behavioral improvement in disease models position CGA as a compelling therapeutic agent for managing conditions involving autophagic imbalance. Despite these promising findings, further research is required to delineate tissue-specific responses to CGA, optimize dosing strategies, and evaluate long-term safety and efficacy in chronic diseases where dysregulated autophagy is a contributing factor.

Chlorogenic acid vs homocysteine - effects on methylation cycle and nitrosative e stress

Homocysteine (Hcy) is a sulfur-containing non-proteinogenic amino acid produced during the demethylation of methionine. Under physiological conditions, Hcy participates in vital transmethylation reactions via the methionine cycle. It is either remethylated to methionine or catabolized through the transsulfuration pathway. These reactions are critically dependent on the availability of methyl donors and vitamin cofactors - namely folate, vitamin B12, and vitamin B6 [Moretti *et al.* 2021]. Disruption of this homeostasis leads to the accumulation of Hcy in plasma, a condition termed hyperhomocysteinemia (HHcy), clinically defined by serum levels

exceeding 15 μmol/L. Elevated Hcy is an established risk factor for cardiovascular, cerebrovascular, and neurodegenerative disorders, and has been strongly associated with oxidative stress, endothelial dysfunction, DNA hypomethylation, and neuronal apoptosis [Moretti *et al*. 2021, Yuan *et al.* 2021]. Hcy metabolism proceeds along two main routes: remethylation and transsulfuration. In the remethylation pathway, methionine synthase (MS) and betaine-homocysteine methyltransferase (BHMT) catalyze the reconversion of Hcy into methionine, requiring folate and vitamin B12 as cofactors. Methylenetetrahydrofolate reductase (MTHFR) plays a pivotal role in this process by generating 5-methyltetrahydrofolate, the methyl donor for Hcy remethylation. In parallel, the transsulfuration pathway, catalyzed by the vitamin B6-dependent enzymes cystathionine β-synthase (CBS) and γ-cystathionase (CSE), converts Hcy to cysteine [Atazadegan *et al.* 2021, Moretti *et al*. 2021]. Any impairment in these enzymatic pathways due to genetic polymorphisms (e.g., MTHFR C677T), vitamin deficiencies, or oxidative insults results in reduced methylation potential and an increase in plasma Hcy. The accumulation of S-adenosylhomocysteine (SAH), a byproduct of methylation reactions and potent inhibitor of methyltransferases, further compromises DNA and protein methylation, promoting genomic instability and transcriptional dysregulation [Moretti *et al*. 2021, Yuan *et al*. 2021].

CGA is widely studied for its antioxidant, anti-inflammatory, and antidiabetic properties. However, its impact on homocysteine metabolism presents a paradox. Although CGA is considered a beneficial nutraceutical, emerging evidence suggests it may disrupt the methylation cycle under certain conditions. In a controlled crossover study involving healthy adults, Olthof *et al*. [2001] demonstrated that daily supplementation with 2 g of CGA over seven days led to a significant increase in total plasma homocysteine – 12% in postprandial samples (1.2 μmol/L) and 4% in fasting samples (0.4 μmol/L) – compared to placebo. Notably, this homocysteine-raising effect was accompanied by an 8% reduction in plasma folate concentrations, suggesting interference with folate-mediated remethylation pathways. The methylation of CGA and other polyphenols is believed to compete with endogenous transmethylation reactions, as O-methylation reactions require S-adenosylmethionine (SAM) as a methyl donor. Increased polyphenol metabolism could therefore divert SAM away from essential methylation pathways, resulting in elevated Hcy production [Atazadegan *et al*. 2021, Olthof *et al.* 2001]. It has been speculated that CGA metabolism may also involve hepatic and microbial pathways overlapping with those of Hcy, further complicating its net biological impact, depending on nutritional status, gut microbiota composition, and genetic background.

HHcy contributes to oxidative and nitrosative stress by increasing the formation of peroxynitrite ($ONOO^-$), a highly reactive molecule generated from the interaction of nitric oxide (NO) and superoxide (O_2^-). This cascade leads to nitration of tyrosine residues in proteins, DNA damage, and mitochondrial dysfunction. Endothelial nitric oxide synthase (eNOS) is inhibited by HHcy, while the Rho-associated protein kinase (ROCK) pathway is upregulated, exacerbating endothelial injury and reducing NO

bioavailability [Moretti *et al*. 2021]. These mechanisms are central to the pathogenesis of cerebral small vessel disease (SVD), a neurovascular condition characterized by perivascular inflammation, impaired autoregulation, astrocyte dysfunction, and blood-brain barrier breakdown. HHcy upregulates NMDA receptor subunits, induces matrix metalloproteinase-2 (MMP-2), and downregulates astrocytic aquaporin-4 channels, molecular hallmarks of SVD and vascular cognitive impairment [Moretti *et al*. 2021].

Paradoxically, CGA also exhibits well-documented antioxidant properties in preclinical models. It has been shown to reduce lipid peroxidation (as measured by malondialdehyde), increase the activity of superoxide dismutase and glutathione peroxidase, and decrease pro-inflammatory cytokines like TNF-α [Atazadegan *et al.* 2021]. These effects underscore the compound's potential for mitigating oxidative stress. However, in the context of insufficient methyl donor availability (e.g., folate or B-vitamin deficiency), CGA-induced elevations in homocysteine may outweigh its antioxidant benefits. This shift from protective to detrimental is particularly concerning in populations with poor nutritional status, subclinical B-vitamin deficiencies, or genetic polymorphisms affecting one-carbon metabolism. While other polyphenols such as epigallocatechin-3-gallate (EGCG), curcumin, and resveratrol have demonstrated protective effects against homocysteine-induced neurotoxicity in experimental models, similar benefits of CGA in HHcy conditions remain unproven. For instance, curcumin has shown efficacy in preventing homocysteine-induced apoptosis in neuronal cultures, and EGCG has been reported to ameliorate cerebrovascular injury caused by HHcy [Atazadegan *et al*. 2021]. Conversely, no robust data exist indicating that CGA can attenuate homocysteine-related toxicity or reverse its molecular consequences.

CGA represents a compelling example of a bioactive compound with context-dependent physiological effects. Its pro-antioxidant properties are well-documented, yet its impact on homocysteine metabolism suggests caution, particularly in individuals with inadequate methylation capacity. The observed increase in plasma Hcy following CGA intake, especially in the absence of sufficient folate, vitamin B6, and B12, may exacerbate nitrosative stress, DNA hypomethylation, and endothelial dysfunction.

CGA and lipid and apolipoprotein metabolism

CGA demonstrates significant therapeutic potential in modulating lipid metabolism. A wide array of *in vitro*, *in vivo*, and clinical studies indicates that CGA can positively influence plasma lipoprotein levels, apolipoprotein expression, and fatty acid profiles [Meng *et al*. 2013, Tajik *et al*. 2017]. Supplementation with CGA has been associated with reductions in low-density lipoprotein cholesterol (LDL-C) and apolipoprotein B (ApoB) – a primary constituent of atherogenic lipoproteins, alongside increases in high-density lipoprotein cholesterol (HDL-C) and apolipoprotein A1 (ApoA1), contributing to its anti-atherosclerotic properties [Tajik *et al*. 2017]. Several animal studies have also reported decreased levels of triglycerides (TG) and very low-density

lipoproteins (VLDL), potentially through modulation of hepatic gene expression related to lipid metabolism, including SREBP-1c and PPARα. In high-fat diet-fed rodents and ApoE$^{-/-}$ mice, CGA significantly reduced serum total cholesterol (TC), TG, and LDL-C while increasing HDL-C levels [Nguyen *et al*. 2024, Wu *et al*. 2014]. These effects are mediated by enhanced fatty acid β-oxidation via upregulation of genes such as CPT1a and ACOX1, suppression of lipogenesis through downregulation of DGAT1/2 and MGAT1, and inhibition of intestinal lipid absorption. Moreover, CGA influences fatty acid composition in plasma and cellular membranes by increasing the proportion of polyunsaturated fatty acids (PUFAs), such as omega-3, and reducing saturated fatty acids (SFAs) [Meng *et al*. 2013]. Additionally, CGA activates AMPK, promoting lipid catabolism, reducing hepatic steatosis, and lowering plasma lipid levels [Nguyen *et al*. 2024, Yan *et al*. 2022].

Among apolipoproteins, ApoA1 and ApoA5 play protective roles in lipid metabolism by promoting cholesterol efflux and triglyceride hydrolysis, respectively [Su et al. 2020]. Although direct studies are scarce, CGA's beneficial effects on lipid metabolism and oxidative stress likely support favorable modulation of apolipoprotein profiles. Through PPAR activation, CGA may enhance ApoA5 expression and lipoprotein lipase (LPL)-mediated TG clearance, while reducing the expression of pro-atherogenic ApoC3, which inhibits lipolysis [Su *et al*. 2020]. Apolipoproteins, key regulators of lipid transport and metabolism, are also modulated by CGA. While direct evidence on apolipoprotein gene expression remains limited, CGA has been shown to influence transcriptional regulators such as PPARα and PPARγ, which are central to apolipoprotein biosynthesis [Fuior *et al*. 2019]. Specifically, CGA upregulates ApoA1 in liver tissues of aquatic organisms and enhances cholesterol efflux via the PPARγ-LXRα-ABCA1/ABCG1 pathway in macrophages, a crucial mechanism in reverse cholesterol transport [Wu *et al*. 2014, Yin *et al*. 2021].

CGA and its metabolites, including caffeic, ferulic, and gallic acids, stimulate PPARγ activation, leading to increased expression of LXRα and ATP-binding cassette transporters ABCA1 and ABCG1. This promotes cholesterol efflux from macrophages, thereby inhibiting foam cell formation and attenuating atherosclerotic plaque development. In ApoE$^{-/-}$ mice, dietary CGA supplementation (400 mg/kg) reduced plaque size in the aortic root and improved vascular integrity, demonstrating an effect comparable to atorvastatin [Wu *et al*. 2014]. Furthermore, CGA exhibits dual agonist activity for PPARα and PPARγ, enhancing lipid oxidation and improving insulin sensitivity. In vitro studies have shown increased expression of these nuclear receptors and downstream targets such as GLUT4 and FATP in both adipocytes and hepatocytes [Sanchez *et al*. 2017], suggesting coordinated regulation of lipid uptake, transport, and clearance.

Clinical evidence supports these findings. Administration of CGA-rich extracts in humans resulted in significant reductions in serum TG, LDL-C, and inflammatory markers such as TNF-α and C-reactive protein (CRP), with concurrent increases in HDL-C [Nguyen *et al*. 2024]. Habitual consumption of CGA-enriched coffee has also

been associated with reduced visceral adiposity and improved lipid profiles [Watanabe *et al.* 2019].

CGA modulates lipid pathways at multiple regulatory points, including TG synthesis, fatty acid oxidation, lipoprotein remodeling, and apolipoprotein expression. Several in vivo and clinical investigations have confirmed its hypolipidemic effects. For example, in a randomized clinical trial among women with polycystic ovary syndrome (PCOS), six-week supplementation with green coffee extract containing CGA significantly decreased serum cholesterol and TG levels [Meshkani *et al*. 2022], indicating direct involvement in lipid regulation through suppression of hepatic lipogenesis and enhancement of β-oxidation. These findings are further supported by preclinical studies. Tajik *et al*. [2017] reviewed multiple experimental models demonstrating CGA's ability to reduce hepatic lipid accumulation and improve plasma lipid parameters. CGA inhibits the expression of key lipogenic enzymes such as fatty acid synthase (FAS) and acetyl-CoA carboxylase (ACC), while upregulating genes involved in fatty acid β-oxidation, including PPARα.

The liver plays a pivotal role in TG synthesis, storage, and export. Under physiological conditions, TGs synthesized from fatty acids and glycerol are stored or secreted as VLDL. However, excessive fatty acid influx or deregulated lipogenesis contributes to hepatic steatosis [Alves-Bezerra *et al*. 2017]. CGA may counteract these processes by attenuating hepatic TG accumulation through downregulation of transcription factors such as SREBP-1c and ChREBP, thereby reducing ACC and FAS activity and limiting palmitate synthesis and lipid droplet formation [Meshkani *et al*. 2022, Tajik *et al*. 2017]. Simultaneously, CGA enhances mitochondrial and peroxisomal β-oxidation, sustaining hepatocyte energy homeostasis.

Finally, a recent study identified a novel interface between lipid metabolism and inflammation involving the liver X receptor (LXR) and the enzyme SMPDL3A. Upon lipid stimulus, LXR induces SMPDL3A, which degrades cGAMP and suppresses STING-mediated inflammatory signaling. Although primarily related to immunometabolic responses, this pathway highlights the intricate relationship between lipid regulation and innate immunity, an axis that CGA may influence through its anti-inflammatory and lipid-modulating actions [Hou *et al.* 2023].

Importance of CGA in metabolic and neurodegenerative diseases

Metabolic diseases

Diabetes. Chlorogenic acid has been extensively studied for its potential to prevent and manage type 2 diabetes mellitus (T2DM). Regular consumption of CGA-rich foods has been associated with a reduced risk of T2DM in epidemiological and interventional studies [Meng *et al*. 2013]. Accumulating experimental and clinical data suggest that CGA contributes to glycemic control through its multifaceted effects on glucose metabolism, insulin sensitivity, intestinal absorption, and inflammation. CGA plays a pivotal role in glucose homeostasis by modulating key molecular and

physiological pathways. Both animal and clinical studies consistently demonstrate its hypoglycemic activity. In rodent models of insulin resistance and diet-induced diabetes, CGA supplementation significantly reduced fasting blood glucose levels and improved glucose tolerance [Ong *et al*. 2013, Rodriguez de Sotillo *et al*. 2002, Santana-Gálvez *et al*. 2017]. Similarly, clinical trials in patients with metabolic syndrome have shown that supplementation with CGA-containing green coffee extracts lowers fasting plasma glucose and improves insulin sensitivity [Nguyen *et al*. 2024]. In human observational studies, plasma concentrations of CGA were inversely correlated with fasting glucose, glycated hemoglobin (HbA1c), and CRP, suggesting both glycemic and anti-inflammatory effects [Lee *et al*. 2016]. These findings are corroborated by randomized controlled trials in individuals with impaired glucose tolerance, where CGA supplementation (400 mg, three times daily) resulted in significant reductions in fasting glucose, insulin levels, BMI, and triglycerides [Nguyen *et al.* 2024].

CGA exerts its effects on glucose metabolism at multiple levels. It inhibits the activity of key intestinal enzymes α-glucosidase and α-amylase, thereby delaying carbohydrate digestion and glucose absorption [Meng *et al*. 2013, Santana-Gálvez *et al*. 2017]. Moreover, CGA may antagonize glucose transporters in the intestinal epithelium, further limiting postprandial glucose spikes. In the liver, CGA suppresses gluconeogenesis by downregulating glucose-6-phosphatase (G6Pase), contributing to decreased hepatic glucose output [Meng *et al.* 2013]. A crucial component of CGA's antidiabetic mechanism is its ability to activate AMPK, a cellular energy sensor. AMPK activation enhances the translocation of GLUT4 glucose transporters to the cell membrane, thereby increasing glucose uptake in peripheral tissues such as skeletal muscle and adipose tissue [Nguyen *et al.* 2024]. Additionally, CGA modulates the expression of transcription factors such as peroxisome proliferator-activated receptor alpha (PPARα), which are involved in fatty acid and glucose metabolism [Santana-Gálvez *et al*. 2017]. CGA also influences enteroendocrine responses. It has been shown to modulate gut hormones such as glucose-dependent insulinotropic peptide (GIP) and glucagon-like peptide-1 (GLP-1), which contribute to glucose regulation through insulin-dependent and independent mechanisms [Meng *et al*. 2013, Shi *et al*. 2021]. Notably, CGA-enriched beverages reduce postprandial glucose levels without increasing insulin secretion, indicating alternative pathways of action [Meng *et al.* 2013].

Beyond its peripheral effects, CGA positively impacts pancreatic β-cell function. In vitro studies using INS-1E insulinoma cells and isolated rat islets revealed that CGA stimulates insulin secretion under both basal and glucose-stimulated conditions [Tousch *et al*. 2008]. It also protects β-cells from oxidative damage by scavenging ROS and enhancing the activity of endogenous antioxidant enzymes such as SOD, CAT, and GPx [Meng et al. 2013; Nguyen et al. 2024]. Insulin resistance in T2DM is often exacerbated by chronic low-grade inflammation. CGA ameliorates this condition by downregulating pro-inflammatory cytokines such as TNF-α, IL-6, and IL-1β. These anti-inflammatory effects are mediated through inhibition of the NF-κB

signaling cascade and Toll-like receptor 4 (TLR4)/MyD88 pathway [Nguyen *et al.* 2024]. Concurrently, CGA activates the Nrf2 pathway, enhancing antioxidant defenses and preserving insulin receptor function. Preclinical studies in high-fat diet-induced obese models showed that CGA not only improved fasting glucose and HOMA-IR values but also corrected dyslipidemia without causing adverse effects such as weight gain, a common side effect of thiazolidinediones [Meng *et al*. 2013, Ong *et al.* 2013].

Obesity. Obesity is a complex metabolic disorder characterized by excessive accumulation of body fat and chronic low-grade inflammation, which predisposes individuals to numerous comorbidities, including type 2 diabetes, cardiovascular disease, and non-alcoholic fatty liver disease (NAFLD). As the prevalence of obesity continues to rise globally, the search for effective and safe therapeutic agents has intensified. Among various bioactive compounds of plant origin, chlorogenic acid has gained considerable interest due to its broad spectrum of biological activities, including anti-obesity, antioxidant, and anti-inflammatory effects [Liang Wang *et al*. 2022]. CGA, found predominantly in green coffee beans in the form of 3-caffeoylquinic and 5-caffeoylquinic acid, has demonstrated significant anti-obesity effects in both animal and human studies. It modulates several key pathways involved in lipid metabolism, adipogenesis, and energy balance. Specifically, CGA suppresses lipogenesis by downregulating the expression of enzymes such as fatty acid synthase (FAS), acetyl-CoA carboxylase (ACC), and sterol regulatory element-binding protein-1c (SREBP-1c), while simultaneously enhancing fatty acid β-oxidation through upregulation of carnitine palmitoyltransferase-1 (CPT-1) [Choi *et al*. 2016, Pimpley *et al.* 2023, Liang Wang *et al.* 2022]. Preclinical studies using high-fat diet (HFD)-induced obese mouse models have consistently demonstrated that CGA or green coffee extract (GCE) supplementation leads to reductions in body weight gain, liver and adipose tissue mass, and visceral fat deposition [Pimpley *et al.* 2020, 2023]. These effects were achieved without altering physical activity levels and were partly mediated by enhanced thermogenesis. Notably, CGA increased body temperature, thermal dissipation, and brown adipose tissue (BAT) activity, a key site of non-shivering thermogenesis [He *et al.* 2021]. CGA also affects lipid homeostasis and lipolysis. Animal studies have revealed a reduction in triglyceride and cholesterol concentrations in plasma, liver, and adipose tissue following CGA administration. These effects are thought to result from inhibition of fatty acid and cholesterol synthesis, as well as increased mitochondrial fatty acid oxidation in hepatic tissues [Meng *et al*. 2013]. Moreover, CGA has been shown to modulate adipokine signaling by decreasing circulating levels of leptin and insulin, and by enhancing the expression of adiponectin and its receptors, which contribute to improved insulin sensitivity and metabolic homeostasis [Pimpley *et al.* 2020].

In terms of glucose metabolism, CGA enhances insulin sensitivity by activating and upregulating glucose transporter type 4 (GLUT4). This results in decreased fasting plasma glucose levels and improved glucose tolerance in HFD-fed mice [He *et al.* 2021]. Furthermore, CGA supplementation has been associated with favorable

changes in lipid profiles, although clinical data show variability in effects on LDL and HDL cholesterol [He *et al*. 2021, Pimpley *et al.* 2023]. Clinical evidence supports the anti-obesity potential of CGA in humans. In a randomized, double-blind, placebo-controlled study, daily supplementation with 500 mg of CGA-7™ for 12 weeks led to significant reductions in body weight, body mass index (BMI), fat mass, and waist circumference and increased lean body mass in overweight individuals. Importantly, the intervention was well tolerated and did not produce adverse effects or significant alterations in hematological or biochemical markers [Sudeep *et al*. 2021]. Recent innovations in green extraction technology have further enhanced the potential of GCE as a functional supplement. GCE produced via enzymatic hydrolysis and steam-assisted methods yielded extracts with higher CGA content and bioactivity. In mice, these preparations significantly attenuated HFD-induced weight gain, improved fecal fat excretion, modulated gene expression related to lipid biosynthesis (e.g., SREBP-1c, FAS, ACC) and upregulated hepatic antioxidant defenses including superoxide dismutase and catalase [Pimpley *et al.* 2023].

Collectively, the available preclinical and clinical data strongly suggest that CGA exerts multifaceted anti-obesity effects through modulation of energy metabolism, adipocyte function, lipid and glucose homeostasis, and hormonal regulation.

Neurodegenerative diseases (NDDs). Neurodegenerative diseases are a group of over a dozen diseases characterized by diverse pathogenesis, hallmarks and symptoms [Wilson *et al*. 2023]. Different NDDs may affect particular brain structures (e.g. amyotrophic lateral sclerosis) or the whole brain (e.g. Creutzfeldt-Jakob disease) [Wilson *et al*. 2023]. Although not all NDDs are related with aging, two of the most prevalent – Alzheimer's disease (AD) and Parkinson's disease (PD) – are strongly connected with age [Boyd *et al*. 2022]. Both above-mentioned diseases belong to the most numerous groups of NDDs related to abnormal protein plaque aggregation (amyloid-β in AD and α-synuclein in PD) in the central nervous system (CNS). During progression of both diseases, microglia and astrocytes become activated and release pro-inflammatory cytokines along with subsequent release of ROS and nitric oxide (NO), leading to neuroinflammation and further neurodegeneration [Boyd *et al.* 2022].

Despite pathological protein plaque aggregation and further consequences, NDDs such as multiple sclerosis (MS) lead to degradation of the myelin sheath enwrapping axons along with development of neuroinflammatory state [Montani 2021, Dobson *et al*. 2019]. Myelin, synthesized by oligodendrocytes in CNS and Schwann cells in peripheral nervous system, is one of the most lipid-rich membranes in the body, consisting of approximately 70-80% lipids by dry weight. Among these, cholesterol accounts for ~40% of the molar lipid fraction, while glycosphingolipids constitute ~20%. These lipids contribute not only to the compact structure of myelin but also to its stability, phase behavior, and protein distribution [Montani 2021]. Formed myelin sheaths guarantee rapid and efficient nerve conduction through saltatory propagation [Stadelmann *et al*. 2019]. It is important to note that during aging myelin sheaths degrade, which in combination with lipid metabolism dysregulation or impaired lipid

clearance may lead to accumulation of cholesterol-rich debris. In this situation, if lingering debris is not properly scavenged by microglia, it may lead to low-grade inflammation in *CNS, further causing development of NDDs* [Graciani *et al.* 2023, Stadelmann *et al*. 2019].

Within this complex biological context, chlorogenic acid (CGA) has emerged as a promising neuroprotective agent. Its multifactorial bioactivity, including antioxidant, anti-inflammatory, anti-apoptotic, and metabolic regulatory effects, renders CGA particularly suitable for addressing the pathophysiological mechanisms common to abovementioned NDDs and aging [Heitman *et al.* 2017, Fukutomi *et al*. 2021]. CGA's neuroprotective mechanisms are primarily mediated through modulation of oxidative stress and inflammation. It scavenges reactive oxygen species (ROS), reduces lipid peroxidation, and enhances endogenous antioxidant defenses, including superoxide dismutase (SOD) and catalase [Heitman *et al.* 2017]. Concurrently, CGA suppresses pro-inflammatory signaling cascades by activating the SIRT1/Nrf2 axis and inhibiting NF-κB-mediated transcription of cytokines such as IL-6 and TNF-α [Y. Zheng *et al*. 2021]. Indeed, treatment of human neuroblastoma line SH-SY5Y with CGA-rich coffee extracts resulted in a reduction of oxidative stress and lesser aggregation of amyloid-β peptide (present in AD), ultimately leading to better survival of cells [Ciaramelli *et al*. 2018]. Research on an animal model of AD showed that CGA administration caused alleviation of neuroinflammation and cognitive processing improvement via SIRT1/PGC-1α/PPARɣ pathway [Shi *et al*. 2023]. More detailed analysis indicated that CGA treatment results in higher survival rate of neural cells in hippocampus and prefrontal cortex, reduced activation of microglia and astrocytes and thus diminished inflammatory response in mice with streptozotocin-induced AD [Bezerra, de Souza Nascimento *et al.* 2025]. Interestingly, CGA presence also had a beneficial effect on brain-derived neurotrophic factor (BDNF) level in selected brain structures, which further enhanced its neuroprotective actions [Bezerra *et al*. 2025]. One of the most recent research indicated that CGA may exert its anti-inflammatory and procognitive actions through the Wnt signaling pathway, however it needs to be furtherly explored [Lei Wang *et al*. 2025]. In in vitro and in vivo models of PD, treatment with CGA intercepted overproduction of ROS by modulation of Akt/ERK1/2 pathway, thus producing neuroprotective effects against 6-hydroxydopamine (6-OHDA) toxicity [He *et al*. 2024]. Further, behavioral studies in which administration of CGA diminished locomotor dysfunction of mice with PD indicated great therapeutic potential of this polyphenol [He *et al*. 2024].

Due to its high anti-inflammatory potential and high effectiveness in the treatment of NDDs related to protein plaque aggregation, CGA has been recently explored in MS [Kang *et al*. 2023, 2024]. Indeed, administration of this compound in experimental autoimmune encephalomyelitis (EAE) model resulted in diminished neuroinflammatory response in CNS, expressed by reduced astrogliosis and microglia activation as well as downregulation of IL-1β, IL-6, TNFα and IFNɣ in spinal cord [Kang *et al.* 2023, 2024]. Spectacularly, treatment reduced the severity of the disease

manifested by lowered clinical score of EAE and body weight loss in animals, which indicates that CGA may be a promising target in further trials with MS patients [Kang *et al.* 2023, 2024].

Beyond direct neuronal protection, CGA may exert indirect benefits on CNS homeostasis by preserving oligodendrocyte viability and supporting myelin integrity. Although the role of CGA in myelinogenesis remains underexplored, its robust antioxidant and anti-inflammatory properties are likely to reduce oxidative insults to oligodendrocytes, which are particularly vulnerable to ROS due to their high metabolic demands during myelination [Montani 2021]. Emerging evidence also highlights the importance of non-vesicular lipid transfer from the endoplasmic reticulum in myelin biosynthesis, a process potentially sensitive, to redox and metabolic disturbances [Wu *et al*. 2024].

Given its favorable pharmacokinetic properties, including the ability to cross the blood-brain barrier [Heitman *et al.* 2017], CGA is a compelling candidate for nutritional and therapeutic strategies aimed at slowing CNS degeneration. Recent research indicates that the therapeutic potential of CGA may be increased by regular physical exercises [Shi *et al.* 2023] or by conjugation with nanocarriers [Wang *et al*. 2025]. Moreover, epidemiological data support a protective association between regular coffee consumption and reduced incidence of AD and PD, possibly due in part to CGA and related polyphenols [Fukutomi *et al*. 2021].

Nonetheless, despite encouraging preclinical results, there is a critical need for well-controlled clinical trials to evaluate CGA's efficacy, optimal dosage, and long-term safety in human populations at risk for neurodegeneration. Furthermore, integrative studies focusing on CGA's impact on oligodendrocyte function and remyelination could broaden our understanding of its full therapeutic potential in neurodegenerative and demyelinating diseases.

Conclusion

Chlorogenic acid exerts a wide spectrum of biological activities with strong relevance to the prevention and management of chronic degenerative diseases. Through its potent antioxidant, anti-inflammatory, anti-apoptotic, and metabolic regulatory effects, CGA modulates key molecular pathways implicated in aging, oxidative stress, autophagy, mitochondrial function, and energy metabolism. By influencing signaling networks such as AMPK, SIRT1, mTOR, FOXO, and Nrf2, CGA contributes to cellular homeostasis and promotes resilience against age-related cellular dysfunction. Experimental and preclinical studies consistently demonstrate CGA's capacity to ameliorate metabolic syndrome components, support neuroprotection, and preserve vascular integrity. Additionally, its role in regulating lipid profiles, apolipoprotein expression, and glucose metabolism further supports its therapeutic potential in cardiometabolic disorders. Importantly, CGA also engages in the regulation of autophagy and lysosomal function, which are critical to ensuring

effective protein degradation and combating neurodegeneration. However, despite its generally favorable safety and efficacy profile, CGA's context-dependent effects, particularly its potential to interfere with the methylation cycle and elevate plasma homocysteine levels under suboptimal nutritional conditions, warrant caution. These findings emphasize the need for personalized strategies when considering CGA as a dietary supplement or therapeutic adjunct, especially in populations at risk for one-carbon metabolism disturbances.

In summary, CGA represents a promising candidate for integrative strategies aimed at mitigating oxidative damage, chronic inflammation, and age-associated metabolic and neurodegenerative diseases. Nonetheless, further clinical studies are needed to clarify its long-term safety, optimal dosage, bioavailability, and interactions with genetic and nutritional factors in order to fully harness its therapeutic potential.

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