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REVIEW

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The neuroprotective effects of Robusta coffee (*Coffea canephora*) on neurodegenerative diseases

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Abstract: Neurodegenerative diseases represent a growing global health challenge, particularly in aging populations. This review examines the neuroprotective potential of Robusta coffee (*Coffea canephora*) and its bioactive compounds in neurodegenerative conditions. Robusta coffee contains a rich profile of bioactive compounds, including caffeine, chlorogenic acids, and other polyphenols, which demonstrate significant antioxidant, anti-inflammatory, and neuroprotective properties. Evidence from preclinical and epidemiological studies suggests that these compounds can modulate multiple pathways involved in neurodegenerative processes, including oxidative stress, neuroinflammation, and protein aggregation. This review synthesizes current findings on the molecular mechanisms underlying the neuroprotective effects of Robusta coffee components in conditions such as Alzheimer's disease, Parkinson's disease, and other neurodegenerative disorders. Recent advances in delivery systems, such as nanoparticle formulations, are also discussed as potential approaches to enhance the bioavailability and efficacy of coffee bioactives. By identifying the therapeutic potential of Robusta coffee components and highlighting gaps in current knowledge, this review provides a foundation for developing novel preventive and therapeutic interventions for neurodegenerative diseases based on these naturally occurring compounds.

Keywords: Robusta coffee, Coffea canephora, neurodegenerative diseases, caffeine, chlorogenic acid, neuroprotection

Introduction

Neurological disorders represent the leading cause of physical and cognitive disability worldwide, currently affecting approximately 15% of the global population. The absolute number of patients has increased considerably over the past three decades, with the burden of chronic neurodegenerative conditions expected to at least double in the next two decades [1]. Neurodegenerative diseases are characterized by progressive damage or death of nerve cells, affecting sensory processing, motor, and cognitive functions. Common examples include Alzheimer's disease, Parkinson's disease, Amyotrophic Lateral Sclerosis (ALS), multiple sclerosis, Huntington's disease, and stroke [2].

The prevalence of neurodegenerative disorders continues to rise alongside global aging populations. Since 2022, Indonesia has been classified as a country with an aging population, with one in ten residents being elderly citizens aged over 60 years. Based on data from the Ministry of Health, Indonesia had 27 million elderly people in 2020, projected to increase to 40 million by 2035 [3]. This demographic shift is expected to significantly increase the prevalence of neurodegenerative diseases. In Indonesia, approximately 876,665 people were affected by Parkinson's disease in 2010, with a prevalence ranging from 0.5-1% at ages 65-79 years, increasing to 1-3% at age 80 years or older [4]. Similarly, the prevalence of Alzheimer's dementia in Indonesia is approximately 27.9%, with more than 4.2 million residents suffering from dementia [5].

Current pharmacological approaches for treating neurodegenerative diseases primarily focus on symptom management rather than addressing the underlying pathological mechanisms. These treatments often have limited efficacy, significant side effects, and do not halt disease progression [2]. This therapeutic gap has prompted extensive research into alternative approaches, including natural compounds with potential neuroprotective properties.

Coffee, one of the most widely consumed beverages globally, contains numerous bioactive components that have shown promising neuroprotective effects [6]. Robusta coffee (*Coffea canephora*) is the most widely cultivated coffee variety in Indonesia due to its superior adaptability to various climatic conditions compared to Arabica coffee [7]. Robusta coffee beans

contain approximately 2.2-2.4% caffeine by dry weight, significantly higher than the 1.2% found in Arabica coffee [8,9]. This higher caffeine content, along with other bioactive compounds, presents unique potential for neuroprotection.

Despite growing evidence supporting the neuroprotective effects of coffee consumption, several critical gaps remain in our understanding. First, most studies have focused on caffeine, overlooking the potential contributions of other bioactive compounds in coffee. Second, the mechanisms underlying the neuroprotective effects of coffee components are not fully elucidated. Third, the specific effects of Robusta coffee, with its unique phytochemical profile, remain inadequately explored compared to other coffee varieties. Fourth, novel delivery systems for coffee bioactives, which could enhance their therapeutic potential, have received limited attention in the context of neurodegenerative diseases.

These knowledge gaps are particularly significant given the increasing coffee consumption trends globally, especially among younger generations. Coffee has become an integral part of contemporary lifestyle, particularly among Generation Z (those born between 1997-2012), with coffee shops becoming social hubs that facilitate social interaction and networking [10]. This cultural shift presents an opportunity to leverage a widely accepted beverage as a potential preventive or adjunct therapeutic approach for neurodegenerative disorders.

Therefore, this review aims to address these critical gaps by comprehensively evaluating the neuroprotective effects of Robusta coffee and its bioactive components on neurodegenerative diseases. We examine the molecular mechanisms underlying these effects, with particular focus on antioxidant, anti-inflammatory, and neurotrophic pathways. Additionally, we discuss recent developments in delivery systems for coffee bioactives and their potential clinical applications in neurodegenerative disorders.

Bioactive compounds in Robusta coffee

Chemical composition of Robusta coffee

Robusta coffee contains a complex mixture of bioactive compounds that contribute to its potential health benefits. The primary components include caffeine, chlorogenic acids (CGAs), caffeic acid, trigonelline, diterpenes (cafestol and kahweol), and various flavonoids [6]. The composition of these compounds varies depending on factors such as growing conditions, processing methods, and roasting levels.

Caffeine is one of the most studied components of coffee, and Robusta coffee typically contains approximately 2.2% caffeine by dry weight, which is significantly higher than the 1.2% found in Arabica coffee [8]. Caffeine acts primarily as an adenosine receptor antagonist in the central nervous system, which explains its psychostimulant effects [2].

Chlorogenic acids are a family of esters formed between quinic acid and trans-cinnamic acids, primarily caffeic acid. The main CGAs in coffee include 5-O-caffeoylquinic acid (5-CQA), 4-O-caffeoylquinic acid (4-CQA), and 3-O-caffeoylquinic acid (3-CQA) [11]. These compounds are known for their strong antioxidant and anti-inflammatory properties, which may contribute to their neuroprotective effects [12].

Tandi et al. (2023) conducted a qualitative and quantitative analysis of secondary metabolites in Robusta coffee bean ethanol extract using UV-Vis spectrophotometry [13]. They found that the extract contained alkaloids, flavonoids, saponins, and tannins but not steroid compounds. The quantitative test revealed total alkaloid content of 0.1973% w/w (caffeine equivalent), flavonoids at 1.2106% w/w (quercetin equivalent), saponins at 0.536% w/w (sapogenin equivalent), and tannins at 9.7103% w/w (tannic acid equivalent).

Similarly, Walid (2023) [14] conducted phytochemical screening and total phenol determination of Robusta coffee grown in the Petungkriyono region of Pekalongan, Indonesia. The study found that Robusta coffee beans contained secondary metabolites including alkaloids, flavonoids, saponins, tannins, triterpenoids, and phenols, with a total phenol content of 565.5 GAE/g.

Effects of processing on bioactive content

The processing of coffee beans, particularly roasting, significantly affects the content and bioavailability of bioactive compounds. For instance, roasting decreases the content of chlorogenic acids while increasing the levels of melanoidins and other products of the Maillard reaction [6]. The degree of roasting also influences caffeine levels, with higher temperatures resulting in decreased caffeine content. According to Ihsan et al. (2023), the highest caffeine content is found in light roast profiles (up to 8%) [15].

Suci et al. (2024) [16] investigated the effect of roasting duration on caffeine content in Robusta coffee beans using UV-Vis spectrophotometry and found that longer roasting times resulted in lower caffeine content. The caffeine content in raw Robusta coffee beans averaged 1.77%, while beans roasted for 10, 15, and 21 minutes had average caffeine contents of 1.62%, 1.31%, and 1.10%, respectively.

Neuroprotective effects of Robusta coffee components

Antioxidant activity

Oxidative stress plays a critical role in the pathogenesis of neurodegenerative diseases, and the antioxidant properties of coffee components may contribute to their neuroprotective effects. Both caffeine and chlorogenic acids in Robusta coffee exhibit significant antioxidant activity through various mechanisms.

Chlorogenic acid (CGA) provides neuroprotection against oxidative damage through multiple mechanisms. It can directly scavenge free radicals and exhibits metal-chelating properties [12]. Additionally, CGA activates the Nrf2 pathway, a master regulator of antioxidant responses, leading to the upregulation of antioxidant enzymes such as heme oxygenase-1 (HO-1), NAD(P)H: quinone oxidoreductase 1 (NQO1), glutathione, thioredoxin reductase 1, and thioredoxin 1 [17]. This dual mechanism of direct free radical scavenging and indirect antioxidant enzyme induction makes CGA a potent neuroprotective agent against oxidative stress-induced neuronal damage.

Caffeine also demonstrates antioxidant effects through different pathways. It can directly neutralize reactive oxygen species (ROS) and indirectly enhance antioxidant defense mechanisms [18]. Studies have shown that caffeine reduces oxidative stress markers, such as malondialdehyde (MDA), and increases the activities of antioxidant enzymes, including superoxide dismutase (SOD) and glutathione peroxidase (GSH-Px) in brain tissues [2].

Anti-inflammatory effects

Neuroinflammation is a common feature of many neurodegenerative diseases, and compounds that can modulate inflammatory responses may offer neuroprotection. Coffee contains several bioactive compounds with anti-inflammatory properties, including caffeine and chlorogenic acids.

Caffeine exerts anti-inflammatory effects in the central nervous system primarily through antagonism of adenosine A2A receptors (A2AR) on microglia, the resident immune cells of the brain [19]. Microglia activation is a key component of neuroinflammation, and excessive or prolonged activation can lead to neuronal damage. By blocking A2AR, caffeine can modulate microglial activation and reduce the production of pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), interleukin-1 beta (IL-1β), and interleukin-6 (IL-6) [20].

Chlorogenic acid also exhibits potent anti-inflammatory effects through multiple mechanisms. It can inhibit the nuclear factor-kappa B (NF-κB) signaling pathway, a key regulator of inflammatory responses, leading to reduced expression of pro-inflammatory genes [21]. Additionally, CGA can suppress the activation of inflammatory cells, including microglia and astrocytes, in the brain, which contributes to its neuroprotective effects in neurodegenerative diseases [22].

A systematic review of clinical trials assessing the effects of coffee or coffee components on inflammatory markers found that coffee consumption predominantly has anti-inflammatory effects [23]. These effects were observed with low, medium, and high coffee intake, suggesting that regular coffee consumption may help reduce low-grade inflammation associated with neurodegenerative diseases.

Effects on neurotransmitter systems

Coffee components, particularly caffeine, can modulate various neurotransmitter systems in the brain, which may contribute to their neuroprotective effects in neurodegenerative diseases. Caffeine is well-known for its effects on the adenosine system, acting as a competitive antagonist at adenosine A1 and A2A receptors (A1R and A2AR). By blocking these receptors, caffeine can enhance dopaminergic neurotransmission, which is particularly relevant for Parkinson's disease (PD), a condition characterized by dopaminergic neuron degeneration [24]. Studies have shown that caffeine increases dopamine release in the striatum and enhances dopamine receptor signaling, which may explain its protective effects against PD [2].

In addition to dopaminergic effects, caffeine can also influence other neurotransmitter systems. It modulates cholinergic signaling by inhibiting acetylcholinesterase (AChE), the enzyme that breaks down acetylcholine, a neurotransmitter critical for

cognitive function and memory. This inhibition leads to increased acetylcholine levels, which may benefit patients with Alzheimer's disease (AD), as this condition is associated with cholinergic deficits [2].

Chlorogenic acid also affects neurotransmitter systems. It can inhibit AChE activity, potentially enhancing cholinergic neurotransmission [25]. Furthermore, CGA has been shown to modulate glutamatergic signaling by protecting neurons against glutamate-induced excitotoxicity, a process implicated in various neurodegenerative conditions [26].

Protection against protein aggregation

Protein aggregation is a hallmark of many neurodegenerative diseases, including the accumulation of amyloid-beta (Aβ) and tau in AD, alpha-synuclein in PD, and mutant huntingtin in Huntington's disease. Coffee components have been shown to inhibit or modulate these protein aggregation processes.

Chlorogenic acid exhibits anti-amyloidogenic properties by directly interacting with Aβ peptides and preventing their aggregation [2]. It can also reduce the production of Aβ by modulating the activity of enzymes involved in amyloid precursor protein (APP) processing. Additionally, CGA can decrease tau hyperphosphorylation, which is responsible for the formation of neurofibrillary tangles in AD [27].

Caffeine also demonstrates the ability to reduce protein aggregation in neurodegenerative diseases. It can decrease Aβ production and accumulation in the brain through multiple mechanisms, including the modulation of β- and γ-secretase activities, enzymes involved in APP processing [24]. In PD models, caffeine has been shown to reduce alpha-synuclein aggregation and protect against the neurotoxicity associated with these aggregates [28].

Modulation of cellular signaling pathways

Coffee bioactive compounds can influence various cellular signaling pathways relevant to neurodegeneration and neuroprotection. Understanding these molecular mechanisms is crucial for elucidating the neuroprotective effects of coffee components.

Caffeine activates the cAMP/PKA/CREB pathway, which is involved in synaptic plasticity, memory formation, and neuroprotection. By increasing cAMP levels through adenosine receptor antagonism, caffeine enhances the activity of PKA, leading to CREB phosphorylation and the subsequent expression of neuroprotective genes, such as brain-derived neurotrophic factor (BDNF) [24].

Chlorogenic acid modulates several signaling pathways involved in neuroprotection. It activates the PI3K/Akt pathway, which promotes neuronal survival by inhibiting apoptotic processes and enhancing the expression of anti-apoptotic proteins like Bcl-2 [18]. CGA also activates the AMPK pathway, a key regulator of cellular energy homeostasis that plays a crucial role in preventing neurodegeneration [12].

Both caffeine and CGA can influence the Nrf2/ARE pathway, a master regulator of antioxidant responses. By activating this pathway, these compounds increase the expression of various antioxidant enzymes, enhancing the brain's defense against oxidative stress, a significant contributor to neurodegeneration [27].

Robusta coffee and specific neurodegenerative diseases

Alzheimer's disease

Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by memory loss, cognitive decline, and behavioral changes. Pathologically, it is defined by the accumulation of extracellular amyloid-beta (Aβ) plaques and intracellular neurofibrillary tangles composed of hyperphosphorylated tau protein.

Epidemiological studies have consistently shown an inverse relationship between coffee consumption and the risk of developing AD. A study by Cornelis et al. (2022) [29] found that caffeine intake is inversely correlated with the risk of AD, with increased caffeine consumption associated with a reduced risk of developing the disease. This protective effect is thought to be mediated by caffeine's antagonism of adenosine A2A receptors, which modulates the neuroinflammatory response and reduces Aβ production and accumulation.

Chlorogenic acid also contributes to the neuroprotective effects against AD. It has been shown to inhibit Aβ aggregation and reduce tau hyperphosphorylation, two key pathological processes in AD [2]. Additionally, CGA improves cognitive function by enhancing cholinergic neurotransmission through inhibition of acetylcholinesterase (AChE) activity.

In vivo studies using animal models of AD have provided further evidence for the neuroprotective

effects of coffee components. Stazi et al. (2021) demonstrated that long-term caffeine treatment ameliorated behavioral deficits and neuron loss in transgenic mouse models of AD [30]. The treatment also promoted neurogenesis and synaptic plasticity, crucial processes for cognitive function that are impaired in AD.

Recent research has also explored the effects of combined coffee compounds on AD pathology. Tira et al. (2023) found that espresso coffee extract, particularly its components caffeine and genistein, prevented the aggregation, condensation, and seeding activity of tau protein in vitro [31], suggesting a potential mechanism for coffee's protective effects in AD.

Parkinson's disease

Parkinson's disease (PD) is a progressive neurodegenerative disorder characterized by the loss of dopaminergic neurons in the substantia nigra pars compacta, leading to motor symptoms such as tremor, rigidity, and bradykinesia. The hallmark pathological feature is the presence of Lewy bodies, which are intracellular inclusions containing aggregated alpha-synuclein.

Multiple epidemiological studies have demonstrated an inverse association between coffee consumption and the risk of developing PD. A case-control study by Medeiros et al. (2021) found that coffee intake was inversely associated with PD, even after adjusting for other factors like smoking history and age [34]. This protective effect appears to be more pronounced in men than in women, suggesting a possible interaction with hormonal factors.

The neuroprotective effects of caffeine in PD are primarily attributed to its antagonism of adenosine A2A receptors, which are highly expressed in the basal ganglia. By blocking these receptors, caffeine enhances dopaminergic neurotransmission and protects dopaminergic neurons from degeneration [24]. Takeshige-Amano et al. (2020) identified a shared metabolic profile of caffeine in parkinsonian disorders, including PD, progressive supranuclear palsy, and multiple system atrophy [32], suggesting common mechanisms of neuroprotection.

Chlorogenic acid also contributes to the neuroprotective effects in PD through its antioxidant and anti-inflammatory properties. Singh et al. (2022) demonstrated that CGA treatment mitigated neuroinflammation, oxidative stress, and dopaminergic neuron loss in an MPTP-induced mouse model of PD [33]. The protective effect was associated with improved mitochondrial function and reduced apoptosis.

Recent research has explored the molecular mechanisms underlying the protective effects of coffee components in PD. Jakova et al. (2024) [28] found that caffeine and its related compounds attenuated alpha-synuclein misfolding, neurodegeneration, and behavioral deficits in a rodent model of PD through modulation of adenosine A1 receptors.

Other neurodegenerative conditions

Beyond AD and PD, coffee components have shown potential neuroprotective effects in various other neurodegenerative conditions, including amyotrophic lateral sclerosis (ALS), multiple sclerosis (MS), and Huntington's disease (HD).

In ALS, caffeine appears to modulate glutamate-mediated excitotoxicity, a key mechanism in the disease's pathogenesis. Chronic neuroinflammation in ALS is associated with increased extracellular glutamate levels, and caffeine can weaken microglial activation in the hippocampus, potentially reducing neuroinflammation and glutamate release [35].

For MS, studies have shown that caffeine can reduce the activation of the NLRP3 inflammasome, providing neuroprotective effects by inducing autophagy and reducing inflammatory cell infiltration and demyelination [35]. Clinical studies have revealed a significant association between high coffee consumption and a decreased risk of MS, with positive effects on disease progression and course when comparing daily coffee drinkers to non-daily coffee drinkers.

In HD, caffeine treatment for varying durations (7, 14, and 21 days) has been shown to completely restore motor function in rat models treated with quinolinic acid (QA). Additionally, caffeine administration significantly reduced oxidative stress in QA-treated mice, increasing endogenous antioxidant capacity and reducing oxidative damage in a dose- and time-dependent manner [35].

Chlorogenic acid has also demonstrated neuroprotective effects in various neurodegenerative conditions. In a model of intracerebral hemorrhage, CGA treatment attenuated neuroinflammation, blood-brain barrier disruption, and neuronal death by inhibiting the expression of extracellular matrix

metalloproteinase inducer (EMMPRIN) and matrix metalloproteinases (MMPs) [36].

Novel delivery systems for coffee bioactives

The bioavailability of coffee bioactive compounds, particularly polyphenols like chlorogenic acid, is often limited by their poor solubility, low absorption, and rapid metabolism. Nanoparticle formulations offer an innovative approach to overcome these limitations and enhance the therapeutic potential of these compounds for neurodegenerative diseases.

Yunida et al. (2021) developed caffeine nanoparticles from Robusta coffee beans using PLGA (Poly lactic-co-glycolic acid) and PVA (poly-(vinyl alcohol)) as polymers [37]. PLGA is a biodegradable polymer approved by the FDA for drug delivery applications due to its ability to be hydrolyzed into monomeric metabolites (lactic acid and glycolic acid) that are easily metabolized by the body. This reduces systemic toxicity when used as drug carriers. The nanoparticles had submicron sizes (200-600 nm), making them suitable for various pharmaceutical applications.

Mangunsong et al. (2022) further characterized these caffeine nanoparticles and found that they had an average diameter of 173.8 nm, a zeta potential of -16.2 mV, and a polydispersity index (PDI) of 0.148 [38]. The morphology showed a spherical surface shape, which is ideal for drug delivery systems. Pharmacokinetic parameters revealed a volume of distribution (Vd) of 1954.159 ml, an elimination rate constant (ke) of 0.00119 min^{-1}, a half-life ($t_1/_2$) of 580.979 min^{-1}, and a clearance (Cl) of 2.331 mg/min at a maximum concentration time (Tmax) of 30 minutes. These properties make the nanoparticles suitable for topical pharmaceutical and cosmetic applications.

Conclusion

Robusta coffee and its bioactive compounds show promising potential as preventive and therapeutic agents for neurodegenerative diseases. By addressing the identified research gaps and advancing our understanding of the molecular mechanisms underlying these effects, we can work toward developing evidence-based interventions that harness the neuroprotective properties of these naturally occurring compounds. As the global burden of neurodegenerative diseases continues to rise, particularly in aging populations, such natural approaches represent an important avenue for improving health outcomes and quality of life for affected individuals.

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Declaration of interest

None.

Author contributors

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