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Therapeutic Potential of Hydroxycinnamic Acid in Neurological Disorders: Mechanisms, Pharmacological Activities, and Clinical Perspectives

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Abstract

Background: Modern lifestyle, environment, and dietary patterns are heavily misaligned with our body's actual needs, leading to a widespread global increase in severe mental health issues. According to the WHO, 1 in 7 people worldwide (over one billion as of 2021) live with a mental disorder, which significantly reduces life expectancy; for example, individuals with bipolar disorder die 13 years earlier on average. Improving dietary practices by including grains, fruits, vegetables, nuts, and seeds is imperative. These foods are rich in dietary fibre and polyphenols. Hydroxycinnamic acids (HCAs), a subclass of phenolic acids, offer wide-ranging pharmacological and therapeutic effects. However, compared with other polyphenols such as anthocyanins, there is a distinct gap in knowledge regarding the bioavailability and bioefficacy of HCAs. **Aim:** To examine how hydroxycinnamic acids (HCAs) affect neuroprotection and various aspects of therapeutic applications. **Methods:** A comprehensive review was conducted focusing on the bioavailability, mechanisms of action, and biological activities of the dominant HCAs, including caffeic, ferulic, and sinapic acids. **Results:** HCAs have several pharmacological and therapeutic effects. They mitigate neurodegeneration by regulating neuroinflammation, maintaining redox homeostasis, and preventing amyloid plaque aggregation. **Conclusion:** HCAs hold significant therapeutic promise for neurological disorders, though understanding of their bioavailability remains limited.

Major Findings: HCAs exhibit significant neuroprotective effects through modulation of neuro-inflammatory signalling, maintenance of mitochondrial function, and prevention of protein aggregation. However, poor bioavailability and rapid metabolism remain major barriers to their clinical translation.

Keywords: Caffeic Acid, Hydroxycinnamic Acids, Neurodegenerative Disorders, p-Coumaric Acid, Sinapic Acid

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1. Introduction

Neurodegenerative disorders, including Alzheimer's disease, Parkinson's disease, and related dementias, are characterised by progressive neuronal loss and cognitive impairment, with memory decline being a central clinical feature. Increasing evidence suggests that neuropsychiatric symptoms such as anxiety and depression frequently accompany these disorders and may serve as early indicators, contributing factors, or consequences of the underlying neurodegenerative process[1]. Anxiety is particularly prevalent during both

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the early and advanced stages of neurodegenerative diseases and has been associated with accelerated cognitive decline and an increased risk of progression to dementia[2]. The relationship between anxiety, memory dysfunction, and neurodegeneration is complex and involves overlapping biological pathways, genetic susceptibility, and psychosocial influences[3]. Natural products have attracted considerable attention as potential therapeutic agents for neurodegenerative disorders. Among them, polyphenols represent one of the most abundant and biologically important classes of phytochemicals. In plants, phenolic compounds function as protective metabolites that contribute to defence against microbial pathogens, ultraviolet radiation, and environmental stressors[4,5]. Based on their chemical structure, polyphenols are broadly classified into flavonoids, phenolic acids, stilbenes, and lignans. Phenolic acids are further divided into hydroxybenzoic acids and HCAs, both of which contain a carboxylic acid moiety and exhibit diverse biological activities[6]. Hydroxycinnamic acids constitute one of the most extensively investigated subclasses of phenolic acids. They are widely distributed in fruits, vegetables, cereals, coffee, tea, seeds, and medicinal plants. The principal members of this group include caffeic acid, ferulic acid, p-coumaric acid, and sinapic acid, all of which have demonstrated significant antioxidant, anti-inflammatory, antimicrobial, cardioprotective, and neuroprotective properties[7]. Structurally, HCAs are phenylpropanoid derivatives characterised by a C6-C3 carbon skeleton. Their concentration and composition vary considerably among plant species, with members of the Solanaceae family often accumulating substantial amounts of chlorogenic acid and free HCAs. In some fruits, these compounds are concentrated in the outer layers and may account for up to 75% of total phenolic acids[8]. Dietary studies conducted in different populations highlight the substantial contribution of phenolic acids, particularly HCAs, to total polyphenol intake. In European adolescents, flavonoids account for approximately 75-76% of total polyphenol consumption, whereas phenolic acids contribute around 17-19%[9]. In elderly Brazilian populations, hydroxycinnamic acids, primarily derived from coffee, represent nearly 61% of total polyphenol intake[10]. Similarly, phenolic acids constitute the major dietary polyphenol class among Mexican women, accounting for 56-69% of total intake[11]. In Danish adults, phenolic acids, predominantly HCAs, contribute approximately 56-79% of total dietary polyphenol consumption[12]. These findings emphasise the widespread dietary exposure to HCAs and their potential relevance to human health. Owing to their potent antioxidant, anti-inflammatory, and neuroprotective properties, HCAs have emerged as promising candidates for the prevention and management of neurodegenerative disorders. Recent studies suggest that these compounds can modulate oxidative stress, neuroinflammation, mitochondrial dysfunction, protein aggregation, and neuronal signalling pathways implicated in the pathogenesis of Alzheimer's disease, Parkinson's disease, and related neurological conditions. Therefore, this review aims to comprehensively summarise the sources, pharmacological activities, neuroprotective mechanisms, and therapeutic potential of hydroxycinnamic acids, with particular emphasis on their role in neurological disorders and future clinical applications.

2. Sources and Occurrence of HCAs

Hydroxycinnamic Acids (HCAs) are widely distributed in plants and usually occur in conjugated forms. They commonly exist as esters of quinic, shikimic, and tartaric acids and may also be linked to sugars, flavonoids, cellulose, lignin, and proteins[13]. Their levels vary from one food to another, and some genotype-specific compounds dominate others within their respective plant groups. The common food sources and quantities of dominant HCAs are shown in Table 1.

Apples are exceptionally rich in chlorogenic acid, which makes up nearly 87% of their total HCA content. These acids make important contributions to our overall diet. Berries, grapes, and a variety of vegetables, including spinach, garlic, and artichokes, are good sources of caffeic, ferulic, chlorogenic, p-coumaric, and sinapic acids[8]. Cereal grains, especially barley, oats, and wheat, are major reservoirs of HCAs, with ferulic acid predominating and normally bound to cell wall components. Beverages make a valuable contribution, especially coffee, with 50-200 mg/mL of chlorogenic acids, providing an estimated daily intake of 120-594 mg[14]. The high levels of caffeoyl further increase the typical daily intake of hydroxycinnamic compounds and p-coumaroyl-quinic acids found in

Table 1. Sources and occurrence of hydroxycinnamic acid

Food sources	Dominant HCAs	Quantity	References
Coffee	Chlorogenic acids	50-200 mg/mL brew	[14]
Apples	Chlorogenic acid	Up to 87% HCA	[8]
Garlic	Caffeic acid	1.7-28 mg/kg	[8]
Cereals	Ferulic acid (cell wall-bound)	--	[15]
Blueberries	Caffeic acid	0.5-2 g per fruit	[8]
Artichokes	Chlorogenic acid	37.8-734.7 mg/kg dry weight	[16,17]

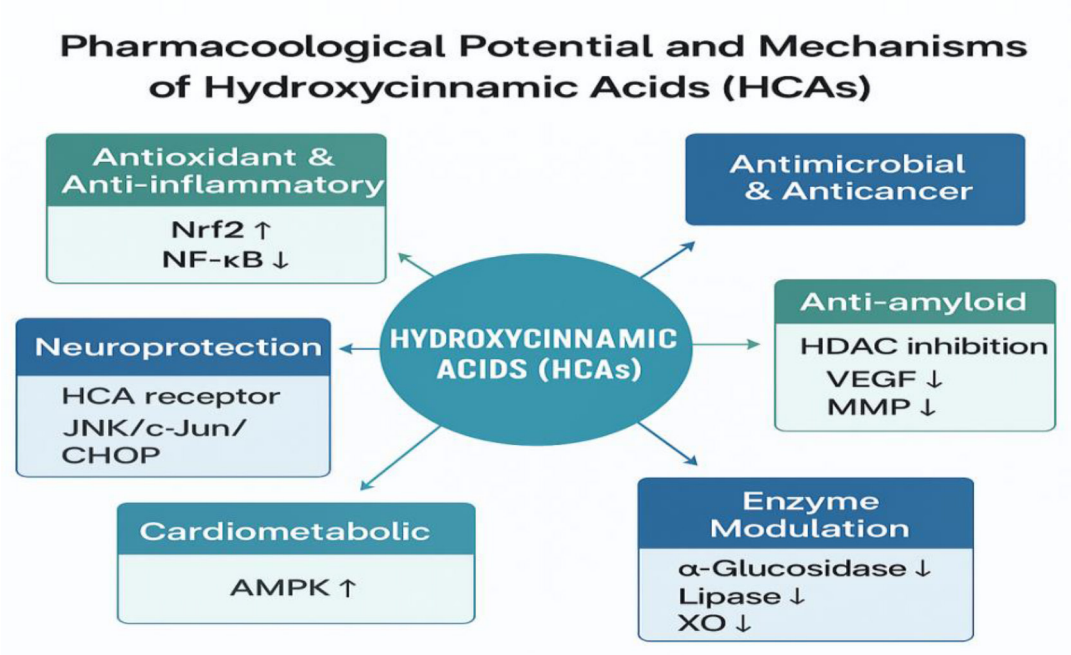


Figure 1. The effect of hydroxycinnamic acid in different systems of the body.

tea leaves, as well as the abundance of rosmarinic and caffeic acids found in herbs and spices like basil, oregano, rosemary, and parsley[19]. The broad pharmacological potentials and various therapeutic mechanisms of HCAs are shown in Figure 1.

3. Dominant HCAs and their Pharmacological Aspects

3.1 Caffeic Acid (CA)

3.1.1 Sources

Caffeic acid (CA) is a naturally occurring hydroxycinnamic acid widely distributed in plant-based foods. It is abundant in dietary sources such as yerba mate (1.5 g/kg), thyme (1.7 g/kg), apples, pears, berries, coffee, and several medicinal herbs[20]. Owing to its widespread occurrence and potent biological activities, CA has attracted considerable attention as a promising therapeutic phytochemical.

3.1.2 Pharmacological Activities

CA exhibits diverse pharmacological properties (Table 2), including antioxidant, anti-inflammatory, anticancer, hepatoprotective, and renoprotective effects. Its anti-inflammatory activity is primarily mediated through inhibition of aconitate decarboxylase 1 (ACOD1), a key regulator of neuroinflammatory signalling. By suppressing the ACOD1-PERK-NF-κB pathway, CA reduces the production of inflammatory mediators and attenuates inflammatory responses[21].

In addition, CA demonstrates significant anticancer activity by inhibiting cellular proliferation, inducing

apoptosis, and suppressing signalling pathways such as PI3K/Akt, MAPK, and NF-κB. It also downregulates Vascular Endothelial Growth Factor (VEGF), thereby limiting tumour growth and angiogenesis[22]. Furthermore, CA exhibits hepatoprotective and renoprotective properties by improving antioxidant status, reducing oxidative stress, and inhibiting NF-κB-mediated inflammatory pathways[22].

3.1.3 Neuroprotective Effects

CA exerts significant neuroprotective effects through multiple mechanisms. It activates the Nrf2/HO-1 signalling pathway, leading to enhanced expression of endogenous antioxidant enzymes and strengthening cellular antioxidant defences[26]. In experimental models of traumatic brain injury, ischemic stroke, and Alzheimer's disease, CA increased superoxide dismutase activity while reducing malondialdehyde levels, thereby protecting neurons against oxidative damage and improving neuronal survival[27].

Moreover, CA inhibits 5-lipoxygenase, an enzyme involved in leukotriene synthesis, thereby reducing neuroinflammation and protecting against cerebral ischemic injury[27]. It also prevents excessive microglial activation and limits the release of pro-inflammatory mediators, thereby mitigating neuroinflammatory responses associated with diabetic neuropathy and Alzheimer's disease[28]. Additionally, CA modulates insulin-like growth factor-1 (IGF-1) signalling, which activates antioxidant and anti-inflammatory pathways that contribute to neuroprotection in diabetic neuropathy[29].

3.2 Ferulic Acid (FA)

3.2.1 Sources

Ferulic acid (FA) is a naturally occurring phenolic compound belonging to the hydroxycinnamic acid family. It is widely distributed in plant-based foods, including rice bran, wheat bran, oats, barley, maize, coffee, oranges, tomatoes, and several medicinal plants. FA is commonly present in plant cell walls, where it is esterified to polysaccharides and lignin.

3.2.2 Pharmacological Activities

Ferulic acid exhibits diverse pharmacological properties, including antioxidant, anti-inflammatory,

Table 2. Biological activities of caffeic acid

Disease/Condition	Biological Effect	Mechanism of Action	References
Alzheimer's disease	Cognitive improvement, anti-amyloid activity	Modulation of BAX, CASP3, CASP8, MMPs, β-catenin, PRKCA, SIRT1, and cytochrome signaling pathways	22-24
Cancer	Anti-proliferative, pro-apoptotic	Inhibition of PI3K/Akt, MAPK, NF-κB pathways; downregulation of VEGF	25
Liver disorders	Hepatoprotective, antioxidant, anti-inflammatory	Restoration of hepatic enzyme levels, redox balance, and inflammatory status	22
Kidney disorders	Renoprotective	Reduction of NF-κB signalling, oxidative stress, and apoptosis	22

Table 3. Biological activities of ferulic acid

Disease/Condition	Biological Effect	Mechanism of Action	References
Alzheimer's disease	Anti-amyloidogenic, antioxidant, anti-inflammatory, synaptic protection	Inhibits β-secretase (BACE1), reduces amyloid-β production and plaque formation, and destabilises preformed amyloid fibrils	30,31
Cancer	Anti-tumour activity	Induces apoptosis and inhibits proliferation, invasion, metastasis, and angiogenesis in various cancers	32,33
Liver disorders	Hepatoprotective	Modulates TLR4/NF-κB, Keap1/Nrf2, SIRT1/autophagy, Akt/FoxO1, AMPK, PPARγ, and Smad2/3 signaling pathways	34
Kidney disorders	Nephroprotective	Regulates AGEs, MAPKs, NF-κB signalling, and mitochondrial function	33,35

anticancer, hepatoprotective, nephroprotective, and cardioprotective activities. Both *in vitro* and *in vivo* studies have demonstrated that FA suppresses the production of inflammatory mediators, modulates cytokine expression, and attenuates oxidative stress-induced cellular damage. Its antioxidant activity is primarily attributed to its ability to scavenge free radicals and enhance endogenous antioxidant defences. The biological activities of ferulic acid, including its therapeutic effects and proposed mechanisms of action in different disease conditions, are summarised in Table 3.

In addition to these effects, ferulic acid improves lipid metabolism by reducing total cholesterol and low-density lipoprotein cholesterol levels through inhibition of HMG-CoA reductase. It also suppresses inflammatory signalling pathways by inhibiting NF-κB activation and reducing the production of TNF-α and hs-CRP, thereby contributing to cardiometabolic protection.

3.2.3 Neuroprotective Effects

Ferulic acid exerts significant neuroprotective effects through multiple complementary mechanisms. It enhances endogenous antioxidant defences by increasing the activities of Superoxide Dismutase (SOD), catalase, and glutathione peroxidase while reducing oxidative stress markers such as Reactive Oxygen Species (ROS) and Malondialdehyde (MDA). These effects protect neurons from oxidative injury associated with neurodegenerative disorders, including Alzheimer's disease and Parkinson's disease.

FA also suppresses excessive activation of microglia and astrocytes, thereby reducing the expression of cyclooxygenase-2 (COX-2), inducible nitric oxide synthase (iNOS), and pro-inflammatory cytokines. Furthermore, it exhibits anti-amyloidogenic activity by reducing amyloid-β aggregation and tau hyperphosphorylation while preserving mitochondrial integrity and function. Ferulic acid additionally modulates neurotransmitter homeostasis by increasing serotonin and norepinephrine levels and inhibiting monoamine oxidase A activity, thereby producing antidepressant-like effects. Moreover, it promotes hippocampal neurogenesis and upregulates Brain-Derived Neurotrophic Factor (BDNF), supporting neuronal survival, synaptic plasticity, and cognitive function[27,29].

3.3 Sinapic Acid (SinA)

3.3.1 Sources

Sinapic acid (SinA) is one of the most abundant hydroxycinnamic acids. It is widely distributed in fruits, vegetables, cereals, oilseeds, spices, and medicinal plants, particularly those belonging to the Brassicaceae family. It is an important dietary polyphenol that contributes substantially to total phenolic intake. SinA and its derivatives are recognised for their antioxidant, antimicrobial, anti-inflammatory, anticancer, and anxiolytic properties. The decarboxylation product of SinA, 4-vinylsyringol, exhibits potent antioxidative, antimutagenic, and anti-inflammatory activities. Another important derivative, sinapine (sinapoyl choline), functions as an acetylcholinesterase inhibitor and has been proposed as a promising lead compound for the management of neurological disorders[36].

3.3.2 Pharmacological Activities

Sinapic acid possesses diverse pharmacological activities, including antioxidant, anti-inflammatory, anticancer, hepatoprotective, and renoprotective effects. Its therapeutic potential has been demonstrated in

Table 4. Biological activities of sinapic acid

Disease/Condition	Biological Effect	Mechanism of Action	References
Alzheimer's disease	Neuroprotective, anti-inflammatory	Inhibits acetylcholinesterase (AChE), restores BDNF/TrkB signalling, and suppresses COX-2 and IL-1β expression	37-39
Cancer	Anti-proliferative, pro-apoptotic, anti-metastatic	Modulates BAX, CASP3, CASP8, and matrix metallo-proteinases (MMPs)	40,41
Liver disorders	Hepatoprotective, antioxidant, anti-inflammatory	Reduces oxidative stress and inflammation through Nrf2/HO-1 and SIRT1 activation and NF-κB inhibition	42,43
Kidney disorders	Renoprotective	Attenuates oxidative stress and inflammatory responses through activation of the Nrf2/HO-1 pathway	42,44

several experimental models by modulating oxidative stress, inflammatory signalling, apoptosis, and cellular survival pathways. The biological activities of sinapic acid, including its therapeutic effects and proposed mechanisms of action in different disease conditions, are summarised in Table 4.

3.3.3 Neuroprotective Effects

Sinapic acid exerts significant neuroprotective effects through antioxidant, anti-inflammatory, cholinergic, and mitochondrial regulatory mechanisms. It enhances endogenous antioxidant defences by increasing glutathione, catalase, and Superoxide Dismutase (SOD) activities while reducing Reactive Oxygen Species (ROS) and nitrite levels, thereby protecting neurons from oxidative damage[45].

SinA also attenuates neuro-inflammation by suppressing cyclooxygenase-2 (COX-2) expression and reducing pro-inflammatory cytokines, including TNF-α and IL-1β[37]. Furthermore, it improves cognitive function by inhibiting acetylcholinesterase, thereby increasing acetylcholine availability and enhancing cholinergic neurotransmission. Regulation of monoamine oxidase A (MAO-A) and B (MAO-B) activities further contributes to neurotransmitter homeostasis and mood stabilisation.

In addition, SinA protects neuronal cells against mitochondrial dysfunction and endoplasmic reticulum stress, mechanisms that are particularly relevant in Parkinson's disease. It also inhibits ferroptosis by regulating antioxidant enzymes, including heme oxygenase-1 (HO-1) and glutathione peroxidase-4 (GPX4), thereby maintaining redox balance and neuronal viability[37,46].

3.4 p-Coumaric Acid

3.4.1 Sources

p-Coumaric acid (p-CA) is one of the major hydroxycinnamic acids and occurs in both free and bound forms in numerous plants and fungi. It is widely distributed in fruits such as apples, pears, grapes, berries, and oranges; vegetables including potatoes, onions, broad beans, and soybeans; and cereals, particularly maize and oats. Tea is also an important dietary source of p-coumaric acid[47].

3.4.2 Pharmacological Activities

p-Coumaric acid exhibits a broad spectrum of biological activities, including antioxidant, anti-inflammatory, antimicrobial, metabolic regulatory, and dermatological effects. It enhances cellular antioxidant defences by activating the nuclear factor erythroid 2-related factor 2 (Nrf2) pathway, thereby increasing the expression of endogenous antioxidant enzymes. In addition, p-CA suppresses inflammatory responses by inhibiting the production of pro-inflammatory cytokines and mediators[48].

The compound also contributes to metabolic health by supporting glucose and lipid homeostasis. Furthermore,

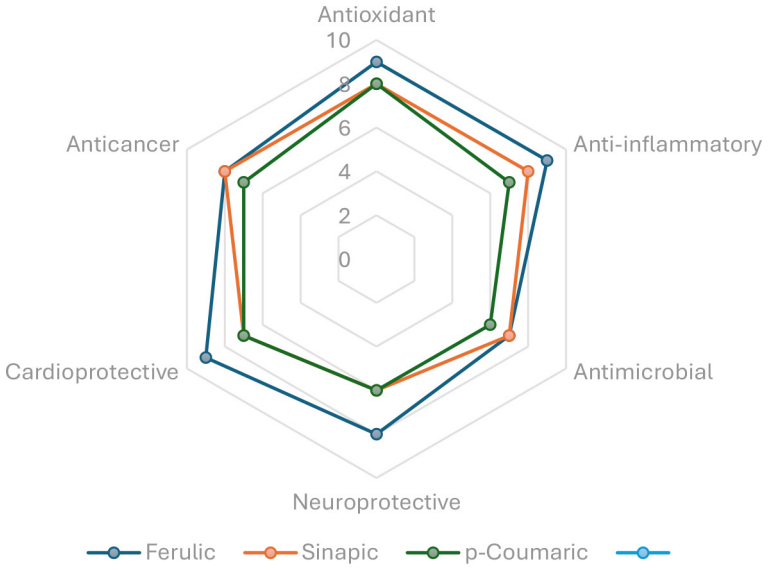


Figure 2. Comparative biological effects of major HCAs.

p-CA demonstrates antimicrobial activity by disrupting bacterial cell membrane integrity and impairing DNA stability, thereby inhibiting microbial growth[49]. Owing to its ability to inhibit tyrosinase activity and reduce melanin synthesis, p-coumaric acid has attracted considerable interest in dermatological and cosmetic applications, particularly in skin-lightening formulations[50].

3.4.3 Therapeutic Applications

The diverse pharmacological properties of p-coumaric acid support its potential therapeutic applications in various disease conditions. Its antioxidant and anti-inflammatory activities may help protect against oxidative stress-related disorders, while its metabolic regulatory effects suggest potential benefits in managing metabolic syndrome and associated complications. The antimicrobial activity of p-CA underscores its potential as a natural agent against pathogenic microorganisms.

In addition, inhibition of tyrosinase and melanin production has encouraged its application in the treatment of hyperpigmentation disorders and cosmetic skin-care products. Collectively, these findings indicate that p-coumaric acid is a multifunctional bioactive compound with promising pharmaceutical, nutraceutical, and industrial applications (Figure 2).

4. Pharmacokinetics and Metabolism of HCAs

Following oral administration, hydroxycinnamic acids (HCAs)—including caffeic, ferulic, chlorogenic, and sinapic acids—exhibit complex pharmacokinetic behaviour. While they are moderately absorbed in the small intestine, a considerable fraction reaches the colon, where gut microbiota biotransform them into smaller phenolic metabolites such as dihydroferulic and phenylpropionic acids[51-54]. These microbial metabolites often achieve higher systemic concentrations than their parent compounds and play a substantial role in mediating the overall biological effects of HCAs.

After absorption, HCAs undergo extensive phase II biotransformation, mainly through glucuronidation, sulfation and O-methylation, resulting in the formation of water-soluble conjugates that predominate in systemic circulation[55,56]. The parent compounds generally display low plasma concentrations in the nanomolar to micromolar range, have short half-lives of approximately 1- 3 hours, and are poorly distributed to tissues[57]. As a consequence, low oral bioavailability and fast clearance constitute important drawbacks for therapeutic use[58].

5. Neuroprotective Effects of HCAs

5.1 HCAs (GPR109A) Receptor Activation

Hydroxycinnamic acids (HCAs), together with structurally related compounds such as nicotinic acid, can activate the HCA_2 receptor (GPR109A) expressed on microglial cells. Activation of this receptor regulates microglial responses to neuronal stress and injury, contributing to the maintenance of central nervous system homeostasis[59]. HCA_2 receptor stimulation

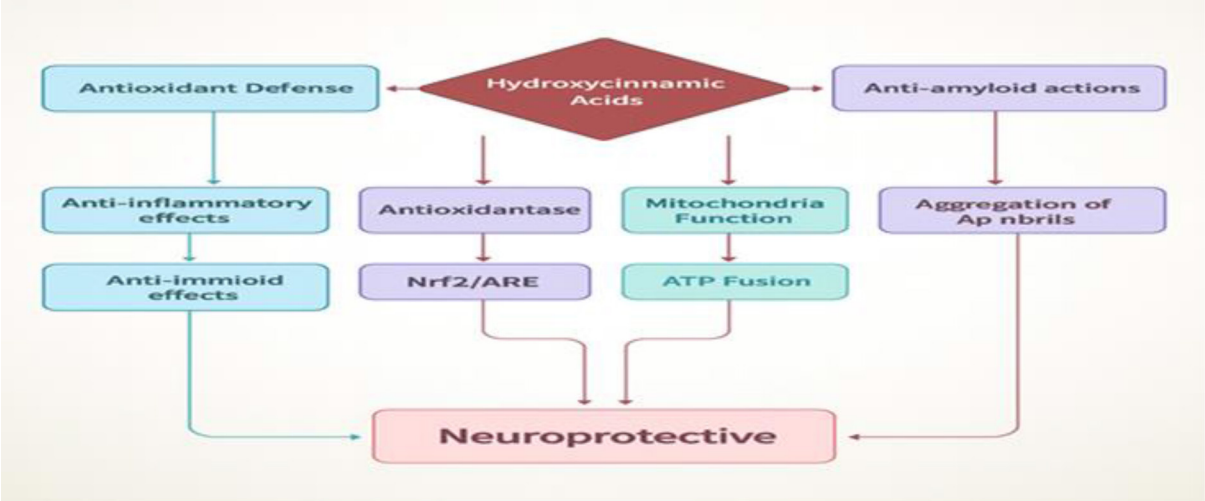


Figure 3. Neuroprotective effects of HCAs.

promotes a shift in microglial phenotype toward a neuroprotective state through modulation of the AKT/PPARγ signalling pathway and suppression of NF-κB activity. This phenotypic transition supports tissue repair, neuronal survival, and the resolution of neuroinflammatory insults, thereby preserving neural integrity and function (Figure 3)[60].

5.2 Mitochondrial and Cellular Energy Homeostasis

HCAs contribute to neuronal viability by maintaining mitochondrial function and cellular bioenergetics. 4-Hydroxycinnamic acid enhances the activity of plasma membrane-associated redox enzymes, increasing the NAD^+/NADH ratio and supporting efficient cellular metabolism. Furthermore, HCAs stimulate mitochondrial respiratory chain complexes I and II, improve ATP production, promote mitochondrial fusion, and limit excessive mitochondrial fission. These effects help preserve neuronal energy balance, maintain mitochondrial integrity, and reduce susceptibility to apoptosis under pathological conditions[61].

5.3 Anti-amyloid and Proteostais Regulating Activity

Several HCA derivatives interact directly with aggregation-prone proteins, including α-synuclein and prion proteins, preventing their conformational misfolding and subsequent aggregation into toxic species. By interfering with protein aggregation pathways, HCAs may reduce proteotoxic stress and slow the progression of neurodegenerative disorders characterised by abnormal protein deposition[62].

In addition, certain HCA derivatives influence cellular protein quality-control mechanisms by modulating Endoplasmic Reticulum (ER) stress responses and autophagy-related pathways. Activation of the JNK/c-Jun/CHOP/BiP signalling cascade promotes the clearance of damaged proteins and cellular components, highlighting the role of HCAs in maintaining proteostasis and cellular survival[63].

5.4 Neuronal Network Modulation

Hydroxycarboxylic acid receptors, particularly HCAR1, influence neuronal communication through Gi-protein-coupled signalling. Receptor activation reduces intracellular cAMP levels and modulates protein kinase A (PKA)-dependent pathways, thereby affecting neuronal excitability and synaptic transmission. Interactions with neurotransmitter systems further contribute to the regulation of neural network activity and signal processing within the brain[64].

6. Antimicrobial and Antiviral Activities of HCAs

Hydroxycinnamic Acids (HCAs) exhibit broad-spectrum antibacterial, antifungal, and antiviral activities, underscoring their potential to address the growing challenge of antimicrobial resistance.

6.1 Antibacterial

Ferulic acid-chitosan conjugates have been shown to effectively inhibit the formation of *Listeria monocytogenes* and *Staphylococcus aureus* biofilms[65]. Ferulic acid also suppresses the expression of fimbriae and curli fibres in *Escherichia coli* and exhibits synergistic activity when combined with conventional antibiotics[66].

6.2 Antifungal

Caffeic and ferulic acids disrupt fungal cell membrane integrity and inhibit ergosterol biosynthesis, while ethyl ferulate demonstrates strong antifungal activity against various pathogenic fungi[67].

6.3 Antiviral

Ferulic and caffeic acid derivatives have been reported to inhibit viral replication in Porcine Reproductive and Respiratory Syndrome Virus (PRRSV), Herpes Simplex Virus (HSV), and adenoviruses. Sinapic acid exhibits inhibitory activity against the MERS-CoV main protease. However, quercetin and cinnamic acid esters work well together to prevent HCoV-OC43 infection[68].

7. Cardioprotective and Metabolic Effects of HCAs

Hydroxycinnamic Acids (HCAs) support cardiovascular and metabolic health by enhancing antioxidant defences, regulating lipid metabolism, exerting antihypertensive effects, and modulating glucose homeostasis. Vascular effects: Ferulic acid restores nitric oxide (NO)-mediated vasodilation,

while chlorogenic acid improves endothelial function by promoting vascular relaxation and reducing oxidative stress[69]. Lipid/glucose regulation: Chlorogenic acid activates AMP-activated Protein Kinase (AMPK), thereby enhancing lipid utilisation and improving glucose metabolism[70]. Ferulic acid decreases atherosclerotic lesions and cholesterol[71]. BP/antiplatelet activity: Ferulic acid lowers blood pressure and suppresses ACE. Ferulic and caffeic acids both lessen platelet aggregation[72]. Anti-obesity: HCAs inhibit PPARγ and activate AMPK, thereby reducing adipogenesis[73]

8. Anti-cancer and Chemopreventive Effects of HCAs

HCAs act at multiple stages of carcinogenesis—initiation, promotion, and progression. Ferulic acid reduces oxidative DNA lesions in colon cells; chlorogenic acid upregulates detox enzymes. Inflammation suppression: CAPE inhibits NF-κB in breast cancer 4; ferulic acid suppresses COX-2 in colon cancer[74]. Apoptosis and cell cycle: p-Coumaric acid induces G0/G1 arrest; sinapic acid activates caspase-3 and p53[75]. Metastasis/angiogenesis inhibition: Ferulic and caffeic acids downregulate VEGF and MMP pathways[76].

9. Antioxidant and Anti-inflammatory Actions of HCAs

Antioxidants: They scavenge free radicals, chelate metals, and activate Nrf2, increasing antioxidant enzyme activity. Anti-inflammatory: They inhibit NF-κB and suppress COX-2, iNOS, and pro- inflammatory cytokines. These dual activities support their protective role in arthritis, colitis, metabolic syndrome, and other chronic conditions.

10. Enzyme Modulation and Molecular Targets of HCAs

HCAs influence multiple enzymes beyond antioxidant and inflammatory pathways: XO inhibition (reducing uric acid)[70,77], Inhibition of α-glucosidase (improving glycemia)[78], Inhibition of cholinesterase (improving neurotransmission)[79], MMP suppression, which prevents invasion and metastasis[80], Inhibition of tyrosinase (lightening of the skin)[75]. Inhibition of pancreatic lipase (anti-obesity)[73], Modulation of histone deacetylases (HDACs) (anticancer epigenetics).

11. Safety and Toxicology of HCAs

Pharmacokinetics: Poor systemic absorption and rapid metabolism reduce the risk of toxicity. [51]. *In vitro*/animal studies: Largely non-genotoxic; low acute toxicity observed, though high or parenteral doses may induce organ-specific effects[81-85].

12. Current Scenario: Research, Applications, and Market of HCAs

Focus on nano formulations, microbiome interactions, and synthetic derivatives. Limitations and Research Gaps: Major barriers include. Few clinical trials, Poor bioavailability, Variability in research methodology, Insufficient analytical uniformity, and inadequate long-term safety information.

13. Conclusion

Hydroxycinnamic Acids (HCAs) represent a promising class of naturally occurring phenolic compounds with diverse pharmacological activities. Through antioxidant, anti-inflammatory, anti-amyloidogenic, antimicrobial, cardioprotective, and neuroprotective mechanisms, HCAs demonstrate significant therapeutic potential in the prevention and management of neurological and other chronic disorders. Despite encouraging preclinical evidence, their clinical application remains limited because of poor bioavailability, rapid metabolism, and insufficient large-scale clinical studies. Future research should focus on advanced delivery systems, optimisation of pharmacokinetic properties, and well-designed clinical trials to establish the efficacy and safety of HCAs in human populations.

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Author Contribution

Shoyab Ali: Manuscript preparation, data collection and original writing. Pooja Negi and Dr. Rekha Chauhan: Guidance throughout the preparation of the manuscript. Digvijay Singh: Data curation, formal analysis, and reference management. Rishav Raj and Jyoti Sharma helped compile the data. All authors have read and agreed to the published version of the manuscript.