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Pharmacological Activities and Molecular Mechanisms of Sinapic Acid in Neurological Disorders

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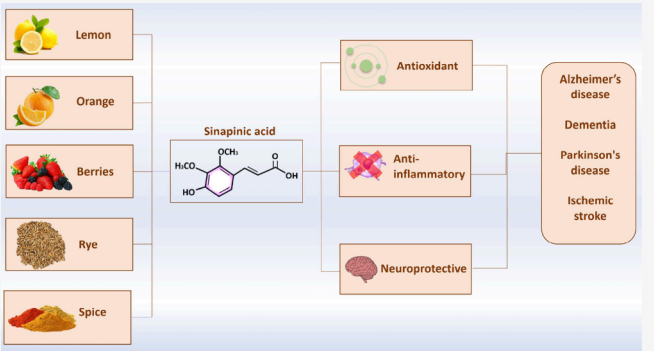
ABSTRACT: Sinapic acid (SA) is a phenylpropanoid derivative found in various natural sources that exhibits remarkable versatile properties, including antioxidant, anti-inflammatory, and metal-chelating capabilities, establishing itself as a promising candidate for the prevention and treatment of conditions affecting the central nervous system, such as Alzheimer's disease (AD), Parkinson's disease (PD), ischemic stroke, and other neurological disorders. These effects also include neuroprotection in epilepsy models, as evidenced by a reduction in seizure-like behavior, cell death in specific hippocampal regions, and lowered neuroinflammatory markers. In AD, SA treatment enhances memory, reverses cognitive deficits, and attenuates astrocyte activation. SA also has positive effects on cognition by improving memory and lowering oxidative stress. This is shown by lower levels of oxidative stress markers, higher levels of antioxidant enzyme activity, and better memory retention. Additionally, in ischemic stroke and PD models, SA provides microglial protection and exerts anti-inflammatory effects. This review emphasizes SA's multifaceted neuroprotective properties and its potential role in the prevention and treatment of various brain disorders. Despite the need for further research to fully understand its mechanisms of action and clinical applicability, SA stands out as a valuable bioactive compound in the ongoing quest to combat neurodegenerative diseases and enhance the quality of life for affected individuals.



KEYWORDS: *Sinapic acid, neurological disorder, hydroxycinnamic acids, Alzheimer's disease, herbal medicine, Parkinson's disease*

1. INTRODUCTION

Neurodegenerative disorders (NDs) are the leading causes of disability and also account for the second-leading cause of mortality worldwide.[1] NDs are a heterogeneous group of complex human health issues that affect millions of people, mostly the elderly, globally, and they represent various patterns of neuron loss in the motor, sensory, or cognitive systems, contributing to various movement, cognition, memory, and psychosocial functioning problems.[2−4] NDs stem from various causes, most of which are genetic predisposition, misfolded protein accumulation, mitochondrial dysfunction, oxidative stress, neuroinflammation, ion channels' function changes, and excitotoxicity. Oxidative stress represents an imbalance between oxidants and antioxidants in a biological system, because of either the enhancement of reactive oxygen species (ROS) or a deficient function of the antioxidant system, which results in lipid peroxidation, DNA damage, and neuroinflammation. The cellular antioxidant system, composed of superoxide dismutase (SOD), catalase (CAT), peroxidase, and reduced glutathione (GSH), acts as a free radical scavenger, and neurodegeneration is promoted due to an imbalance in the defensive actions of antioxidants and overproduction of ROS.[5,6] Moreover, neuroinflammation, which is initially crucial for stimulating tissue repair and removing the brain's cellular waste, could be a significant key factor in the pathogenesis and progression of various NDs in cases of persistence due to genetic mutations, trauma, and infection, which play their roles via proinflammatory agent release, including interleukin-6 (IL-6) and immune cell activation, leading to neuronal dysfunction and destruction. In fact, the engagement and overactivity of microglia and astrocytes in neuroinflammatory responses might be responsible for the pathogenesis of neurodegenerative diseases, especially Alzheimer's disease, in which microglia play a vital role in responding to Aβ aggregation.[7−10] The major NDs include Alzheimer's disease (AD), Parkinson's

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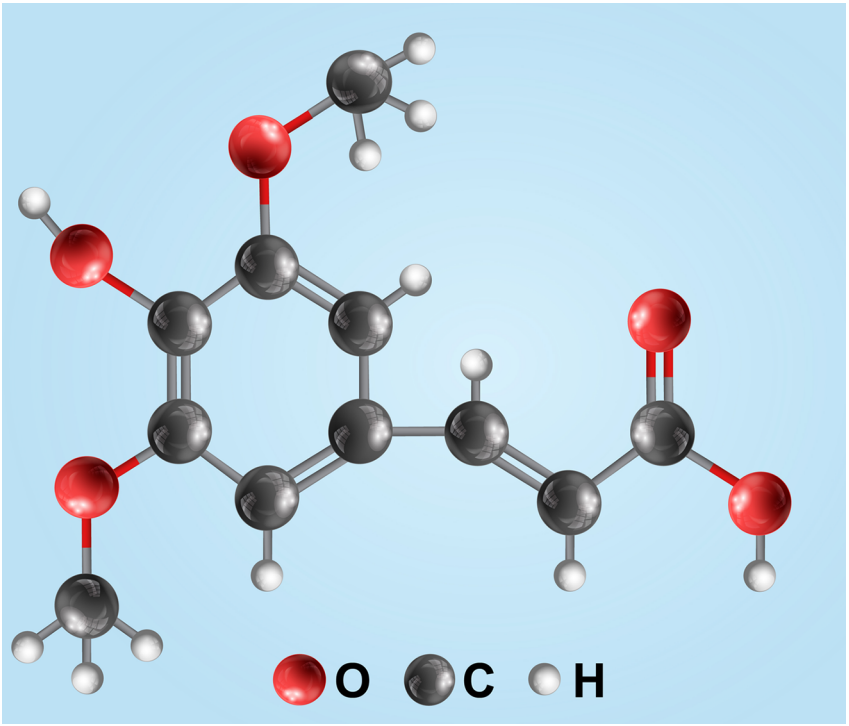

Figure 1. Chemical structure of sinapic acid: gray spheres, carbon atoms; red spheres, oxygen atoms; white spheres, hydrogen atoms.

disease (PD), ataxia, Huntington's disease (HD), motor neuron disease, multiple system atrophy, and progressive supranuclear palsy, in which the main causes are reported to be the accumulation of amyloid β (Aβ), Tau, and α-synuclein in the form of insoluble fibrillary deposits with β-sheet structure in the brain of patients.[11,12] According to the Global Burden of Disease (GBD) study, a variety of conditions, including AD, PD, multiple sclerosis (MS), and epilepsy, as well as headache disorders such as migraine, tension-type headache, and medication-overuse headache, collectively contribute to 3% of the GBD. The top 50 causes of disability-adjusted life years (DALYs) include dementia, epilepsy, migraine, and stroke.[13]

Migraine and epilepsy have significantly contributed to the overall disease burden in the past decade, representing roughly one-third and one-quarter of this burden, respectively. Additionally, dementia and PD have emerged as notable contributors to the disease burden, ranking among the top 15 conditions with the most substantial increase in burden over the same period.[13−15]

Specifically, when considering the impact on years lived with disability (YLDs), NDs accounted for approximately 5.5% of the total YLDs, equivalent to a staggering 42.9 million YLDs. Notably, conditions such as migraine, epilepsy, and dementia were among the top 25 causes of YLDs in 2010. The number of individuals affected by migraines alone represents over 50% of those experiencing neurological YLDs, or approximately 2.9% of the global YLDs. In contrast, epilepsy accounts for approximately 1.1% of the global YLDs.[13] Despite extensive research, effective and targeted treatments for these disorders remain elusive.

In recent years, there has been a growing interest in neuropharmacology to discover new therapeutic agents that can improve the underlying mechanisms of NDs.[16] One promising field is the utilization of natural products containing secondary metabolites found in plants, which play a crucial role in drug discovery since the synthetic drugs could damage neurons due to their toxicity and might contribute to brain disorders because they modulate the activity of multiple brain circuits controlling decision-making power, memory, learning, and other functions.[17,18] To date, several plant-derived compounds, including polyphenols and mostly flavonoids like myricetin, naringenin, curcumin, luteolin, fisetin, cornin, hesperidin, apigenin, and quercetin, have proved to be promising neuroprotective agents due to their antioxidant, free radical clearance, anti-inflammatory, and antimutative properties.[5,6,19−22] Studies have shown that flavonoids play a key role as antioxidants by activating SOD, CAT, and GPx, lowering GSH, and stopping lipid peroxidation. They also have anti-inflammatory properties that come from their ability to control tyrosine and serine−threonine kinases, cyclooxygenase (COX) and lipoxygenase suppression, and the production of

Table 1. Amounts of Sinapic Acid Content in Natural Sources[32]

source	product	sinapic acid (μg/g)
Fruits	Lemon (*Citrus limon* (L.) Burm. f.)	72.1
	Orange (*Citrus sinensis*)	9.67; 17.28
	Strawberries (*Fragaria ananassa* L.)	450.30
	Raspberries (*Rubus idaeus* L.)	36.89
	Mango (*Mangifera indica* L.)	7.55
	Apples (*Malus domestica* L.)	13.42
Vegetables	Garlic (Allium sativum L.)	0.5
	White cabbage (*Brassica oleracea* var. *capitata*)	1.80
	Red onion (*Allium cepa* L.)	2.0
Cereal grains	Rice	1.05
Herbs and Spices	Basil (*Ocimum basilicum* L.)	150
	Rosemary (*Rosmarinus officinalis* L.)	690
	Chillies (*Capsicum*)	100

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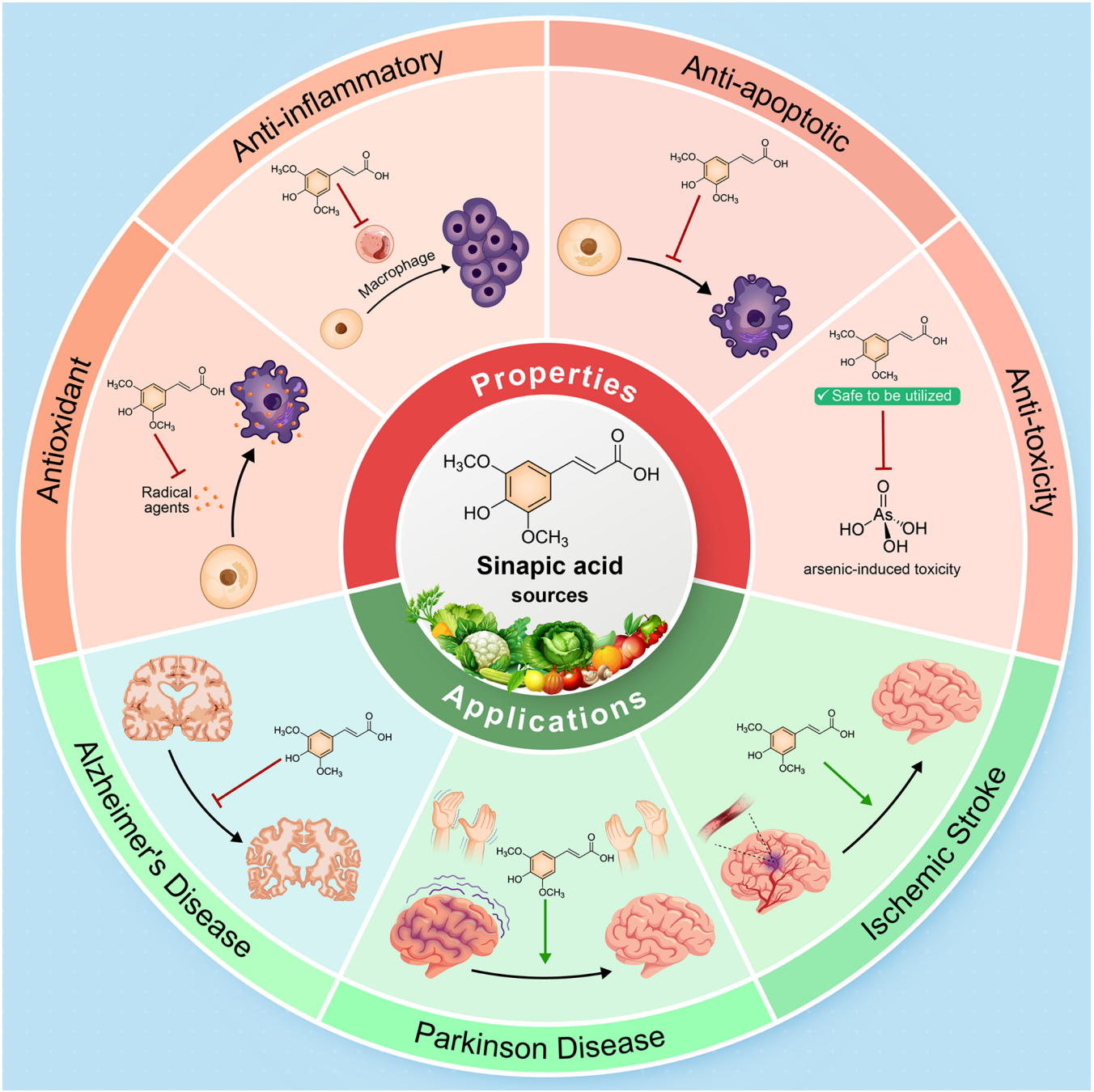

Figure 2. Neuroprotective properties of sinapic acid in neurological disorders through its anti-inflammatory, antioxidant, antiapoptotic, and antitoxicity activities, which enable it to remove free radicals and cellular toxins while blocking inflammatory and apoptosis pathways.

proinflammatory molecules such as nitric oxide, prostaglandins, and leukotrienes. They do this while also controlling cytokine and chemokine levels and stopping leukocyte adhesion at the site of inflammation.[5]

Sinapic acid (SA), 3,5-dimethoxy-4-hydroxycinnamic acid, belongs to the phenylpropanoid family and is commonly found in the human diet[23] (Figure 1). It is present in various plant sources such as cereals, nuts like hazelnuts, seed oils, mustard, and rapeseeds, as well as in fruits like oranges, grapefruits, and berries, exhibiting antioxidant properties (Table 1).[24,25] Additionally, SA is found in wine and vinegar and is notably abundant in cereal bran along with ferulic acid.[26,27] SA is capable of either scavenging excessive free radicals or mitigating the effects of oxidants.[28] In addition to its antioxidant properties, SA demonstrates metal-chelating potential, anti-inflammatory effects, antiapoptotic properties, and neuroprotective qualities, with the last attributed to the inhibition of inducible nitric oxide synthase (iNOS) expression and nitric oxide blockade. Moreover, SA demonstrates promise in safeguarding against lysosomal dysfunction and mitigating carbon tetrachloride-induced inflammation in rats, potentially via nuclear factor κ light chain enhancement of activated B cells (NF-kB) activation and the modulation of proinflammatory cytokines.[24,29,30]

Neuroinflammation, oxidative stress, and programmed cell death are central features of many neurological disorders. SA's

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ability to modulate these pathways suggests a potential therapeutic role in mitigating the underlying causes of neuronal damage. Understanding the mechanistic insights of SA at the molecular and cellular levels is pivotal in unraveling its pharmacological potential.[31] Therefore, the focus of this current review is to investigate the protective effects of SA in the context of neurodegenerative diseases. Our investigation encompasses an examination of its chemical properties, pharmacokinetics, toxicity, mechanism of action, and demonstrated efficacy in various neurological disorders.

2. SEARCH STRATEGY

In this literature review, we conducted searches using specific keywords, including sinapinic acid, sinapic acid, neurodegeneration, neurotoxicity, neuroinflammation, Alzheimer's disease, Parkinson's disease, epilepsy, seizure, multiple sclerosis, neuroprotection, oxidative stress, and brain ischemia. We conducted these searches across various databases, including PubMed, Google Scholar, Web of Science, ResearchGate, and Science Direct, specifically targeting English-language papers. As a result, we thoroughly reviewed the articles extracted from these searches.

3. NATURAL SOURCES

Hydroxycinnamic acids (HCAs) are an important group of phenolic compounds. SA, cinnamic acid, caffeic acid, *p*-coumaric acid, and ferulic acid are some of the most well-known HCAs.[25] Particularly, SA is highly prevalent and found in various vegetables, fruits, oilseed crops, certain spices, medicinal plants, and cereal grains. Among fruits, strawberries (*Fragaria ananassa* L.) contain the highest amount of SA, at 450.3 μg/g. For vegetables, broccoli (*Brassica oleracea* L. var. *italica*) contains 25−82 μg/g of SA. Oats (*Avena sativa* L.) top the list among cereal grains, with 56.05 μg/g, and borage (*Borago officinalis* L.) is the leading herb and spice, containing 1210 μg/g of SA.[33]

4. CHEMICAL PROPERTIES

HCAs exist in free form and as ester compounds, such as sugar esters (glycosides). Within the cell walls of cereals, ferulic acid and SA can combine to form dimers. SA is a crystalline powder with a molecular weight of 224.21 g/mol and a melting point in the range of 203−205 °C that exhibits incompatibility with strong oxidizing agents and strong base chemicals, plus low solubility in water.[34] Antioxidant, anticancer, and neuroprotective activities have been observed in SA as a natural HCA.[26] SA has also shown metal chelating potential, anti-inflammatory, antibacterial, antihyperglycemic, antimicrobial, anxiolytic, and tumor-fighting activities, peroxynitrite and free-radical scavenging, plus antihypertensive and cardiovascular remodeling[11,35] (Figure 2). It is shown that SA's poor solubility, hydrophobic nature, low in vitro dissolution rate, reduced oral bioavailability, and enhanced lipophilicity due to the esterification are responsible for its limited therapeutic potential whereas the increased lipophilicity results in higher affinity for the lipophilic phase of certain drug delivery systems and the cell membrane.[36−38] In this regard, several studies have been performed to investigate the possible strategies for a more effective delivery of SA for therapeutic purposes. SA encapsulation in various nano delivery systems including solid lipid nanoparticles, glucosamine nanoparticles, ethosomes, transferosomes, and liposomes has been shown to be a promising technique to overcome SA's lack of solubility and bioavailability contributing to their interesting properties like high biocompatibility, protected drug release, and cross-skin permeability which lead to efficient penetration of the embedded molecule into the target site and a better therapeutic result.[36,37,39,40]

5. PHARMACOKINETICS

Upon ingestion, SA undergoes metabolic processes within the epithelial cells of the small intestine, yielding metabolites like methyl sinapate sulfate and 3-hydroxy-5-methoxyphenyl-propionic acid. Consequently, the small intestine serves as the primary absorption site for orally administered SA, facilitated by active Na^+ gradient-driven transport.[41] Serum albumin assists in distributing SA throughout the body by binding to it through hydrophobic interactions and hydrogen bonding, aiding its transport to various tissues. Distribution is influenced by SA's lipophilicity and the presence of transport proteins in the bloodstream, determining its ability to traverse cell membranes and reach target tissues. The accumulation of SA in specific tissues depends on their affinity for phenolic acids and the presence of metabolizing enzymes.[42]

SA and its metabolites are mainly eliminated from the body through urine and bile. After absorption and metabolism in the small intestine, including phase I and II reactions producing metabolites like 3-hydroxy-5-methoxyphenylpropionic acid and methyl sinapate sulfate, they enter the bloodstream. From there, these compounds are likely filtered by the kidneys and excreted in urine. Biliary excretion into the intestine is another route for their elimination. The exact pathways and rates of excretion may vary due to individual metabolism and dosage levels, but renal and biliary excretion are the primary routes for eliminating SA from the body.[43] Specific data on the half-life of SA in humans are limited. Various studies have shown that SA and its metabolites have different elimination rates, indicating varying half-lives. These studies underscore the variability in SA's half-life across different species and highlight the need for further research to understand its persistence and effects in humans.[44]

6. TOXICITY

Although SA possesses several beneficial pharmacological characteristics, it is important to note that its cytotoxic reaction can vary among different cell types depending on the dosage. However, studies have shown that, except for extremely high concentrations, SA does not induce cytotoxicity in the investigated cell lines. This is evidenced by the absence of any symptoms of toxicity or mortality at doses up to 2000 mg/kg when administered orally, since 40 mg/kg of SA has been shown to be capable of ameliorating ethanol-induced gastric ulcers in rats through modulating vital signaling pathways, leading to cell viability increase.[45,46] Moreover, following 24 h exposure of SH-SY5Y cells to SA at various concentrations, no toxic effects were observed (maximum safe concentration: 800 μM), leading to the conclusion that it is safe to be utilized in different settings.[47] In an in vitro PD study on these cell lines also, 30 μg/mL of SA was announced as the highest dose for optimal cell viability.[48]

The ability of SA to chelate metals plays a crucial role in protection against arsenic-induced toxicity in vivo studies, in one of which 40 mg/kg bw/day oral administration of SA in rats revealed vital hepatic protective properties without any

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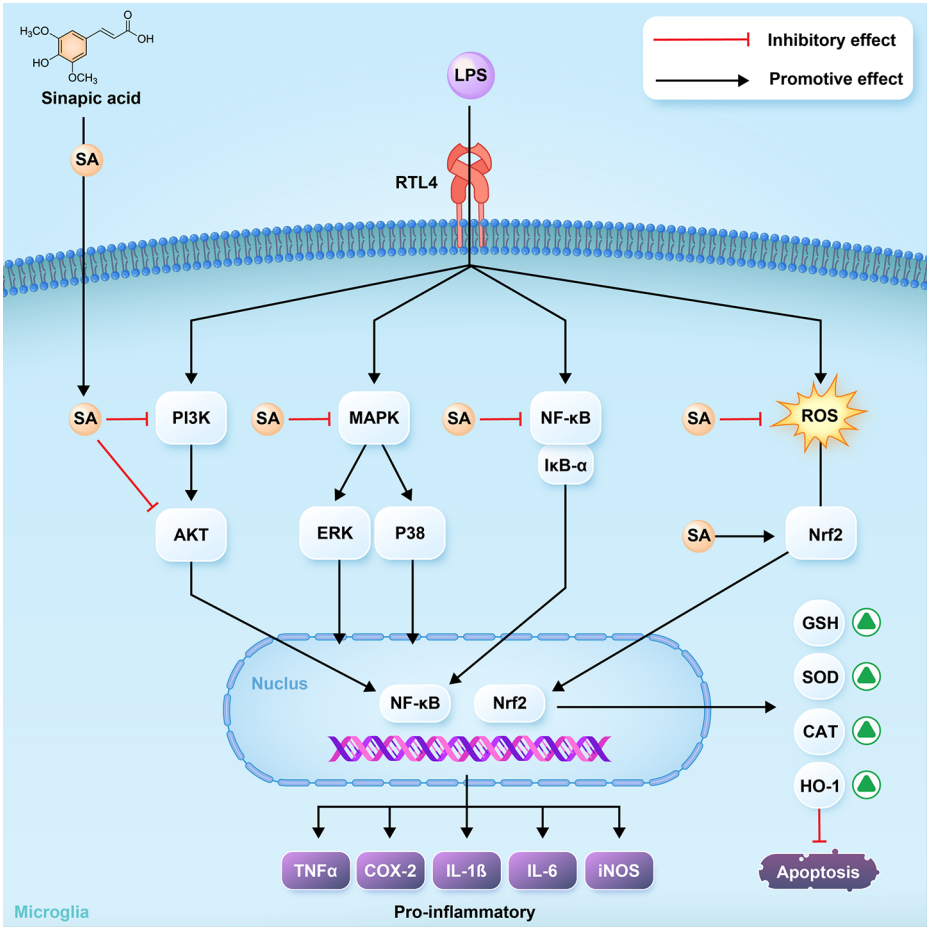

Figure 3. Schematic illustration of the mechanisms by which sinapic acid performs its neuroprotective actions. It demonstrates that sinapic acid is capable of modulating essential signaling pathways involved in the pathophysiology of neurological diseases, including the inhibition of MAPK, PI3K, and NF-κB pathways, as well as ROS generation and apoptotic cascades' blockade. Abbreviations: AKT, protein kinase B; CAT, catalase; ERK, extracellular signal-regulated kinase; COX-2, cyclooxygenase-2; GSH, glutathione; HO-1, heme oxygenase; IκB-α, nuclear factor of κ light polypeptide gene enhancer in B-cells inhibitor α; IL, interleukin; iNOS, inducible nitric oxide synthase; LPS, lipopolysaccharide; MAPK, mitogen-activated protein kinases; NF-kB, nuclear factor κ-light-chain-enhancer of activated B cells; Nrf2, nuclear factor erythroid-2 related factor 2; p38, mitogen-activated protein kinases; PI3K, phosphoinositide 3-kinase; ROS, reactive oxygen species; SA, sinapic acid; SOD, superoxide dismutase; TLR4, Toll-like receptor 4; TNF-α, tumor necrosis factor-α.

further toxicity induction.[49] SA (0.1% and 0.2%) has demonstrated a remarkably low toxicity profile in broiler chickens, as reported in the absence of any alterations in serum lactate dehydrogenase (LDH) and creatine kinase (CK) activity, considering SA safe for being used in various physiological aspects of animals.[41,50]

7. PROPERTIES

7.1. Antioxidant. As previously mentioned, the antioxidant profile of SA and its derivatives, maintained through free radical scavenging, plays a crucial role in neuroprotection against lysosomal dysfunction.[13] SA's ability to donate hydrogen atoms and use the conjugated system to stabilize the resultant phenoxyl radicals is critical to its antioxidant action.[34] SA is known to scavenge various radicals such as 2,2-diphenyl-1-picrylhydrazyl (DPPH$^{\bullet}$), superoxide anion radical ($O_2^{\bullet-}$), highly reactive hydroxyl radicals ($^{\bullet}OH$), hydroperoxyl radical ($^{\bullet}OOH$), nitric oxide radical ($^{\bullet}NO$), and peroxynitrite ($ONOO^-$). It effectively scavenges both naturally occurring $ONOO^-$ and $ONOO^-$ generated from the peroxynitrite donor 3-morpholinosydnonimine hydrochloride (SIN-1).[41] At a dosage of 20 μM, SA was reported to inhibit 33.2% of the DPPH radical. Furthermore, studies noted that SA demonstrated stronger antiradical activity than its alkyl esters.[34,51] SA's ability to inhibit lipid oxidation is another property, although it exhibits concentration-dependent inhibition in hydroperoxide formations. It efficiently blocks lipid peroxidation caused by peroxyl radicals generated during Cu^{2+}-induced oxidation of human low-density lipoproteins (LDL).[41,52] SA demonstrates the most potent inhibition, followed by caffeic acid and ferulic acid.[41] High concentrations of tocopherol (vitamin E) have been shown to reduce SA's antioxidant effects on lipids.[53]

7.2. Anti-Inflammatory. The anti-inflammatory and anticarcinogenic properties of SA and its derivatives are well-established.[33] The cancer-killing potential of SA was evaluated, and a minimal impact on breast carcinoma was found, whereas its inhibitory effects on colon cancer cells, capable of tumorigenesis, were obvious.[54] Conversely, SA demonstrated an antiproliferative effect on the human breast T47D cancer cell line. However, the effects of SA vary depending on the duration of exposure and the dosage administered.[33,55] Available data demonstrate a significant reduction in experimental colitis symptoms in a mouse model induced by

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2,4,6-trinitrobenzenesulfonic acid (TNBS), exerting strong anti-inflammatory actions. Here, SA's protective effects were primarily attributed to its inhibitory properties on inflammatory cytokine generation, such as myeloperoxidase (MPO) and tumor necrosis factor-α (TNF-α), which contribute to tissue damage and severe inflammation.[56] Similarly, in RAW264.7 macrophages, the anti-inflammatory effects of SA were found to be due to the suppression of COX-2, TNF-α, and IL-1β expression.[24] Multiple studies have linked SA's anti-inflammatory effect to NF-κB modulation and the expression of pro-inflammatory cytokines, which play a crucial role in safeguarding the mouse liver against inflammation induced by carbon tetrachloride.[13,57,58]

7.3. Antiapoptotic. The antiapoptotic property of SA has also been proven by several investigations. In rat liver lesions induced by methotrexate (MTX), SA exhibited the ability to restore antioxidant defenses, reduce oxidative stress and levels of inflammatory cytokines (TNF-α and IL-1), and prevent apoptosis. These effects appear to be the result of NF-κB blockade, leading to the activation of the nuclear factor erythroid-2-related factor 2 (Nrf2)/heme oxygenase (HO-1) pathway, which prevents apoptosis and stimulates antioxidant enzymes. Treatment with SA significantly ameliorated the severity of MTX-induced liver damage.[59] Furthermore, immediate administration of SA has been shown to have protective effects against KA-mediated hippocampal neuronal cell death, attributed to the anticonvulsant activity mediated by γ-aminobutyric acid (GABA) receptor activation and SA's free radical inhibitory activity.[60]

8. SINAPIC ACID'S MECHANISMS OF ACTION

Neuroinflammation happens when cells in the central nervous system, mainly microglia, recognize pathogen endotoxins through Toll-like receptors (TLRs) and start the inflammatory process. They then release cytokines and proinflammatory agents, such as nitric oxide, prostaglandin E2, and ROS.[61,62] Moreover, these cells activate downstream proteins, including protein kinase B (AKT) and mitogen-activated protein kinases (MAPKs), by triggering antigen-induced signal transduction pathways. Stimulation by lipopolysaccharide (LPS) leads to the activation of MAPK cascades, with AKT serving as an essential effector kinase downstream of phosphoinositide 3-kinases (PI3K).[63] In terms of SA's anti-inflammatory properties, studies done in vitro and in vivo showed that it could work as an active substance by blocking the MAPK and AKT signaling pathways to stop LPS-induced inflammation and could be a possible therapeutic choice for treating NDs that are connected to inflammation.[61] The mechanism of SA's neuroprotective activity has also been investigated in connection with GABA, which is the primary inhibitory neurotransmitter for the adult central nervous system, generated by the GABAergic neurons in the hippocampus, thalamus, basal ganglia, hypothalamus, and brainstem, and it reduces neuronal excitability through nerve transmission blockade. For a proper neurologic function, there must be a balance between inhibitory neuronal transmission via GABA and excitatory transmission via glutamate. GABA receptors, GABAa and GABAb (GABARs), respond when GABA is released into the postsynaptic nerve terminal, and mutations of their genes are seen in most NDs.[64−66] Normally, dopaminergic neurons of the nigro-striatal pathway which are responsible for the cerebral cortex's motor activity, facilitate the GABAergic pathway. Loss of dopaminergic neurons in this pathway, which happens in PD, reduces the inhibitory effects of GABAergic neurons and results in motor activity deficiencies.[5] In this regard, it is suggested that SA might act as a potential agonist for GABA receptors since 1 μM of SA enhanced GABA currents, and reactive I_{GABA} rose to 1.8 times.[60] Additionally, the potential of trans-SA as a neuromodulator and its impact on the release of monoamine oxidase (MAO-A and MAO-B), TNF-α, and acetylcholinesterase (AchE) enzymes were observed (Figure 3).[28]

8.1. Alzheimer's Disease and Memory Impairment. AD is acknowledged as the most common type of NDS, affecting more than 50 million people worldwide, and is characterized by the brain accumulation of extracellular Aβ aggregates (plaques) and intraneuronal Tau deposits (neurofibrillary tangles).[67] As an incurable and advancing condition, AD is distinguished by two principal molecular processes: the cholinergic hypothesis, which is associated with the degeneration of cholinergic neurons in the frontal region of the brain, and the amyloid β protein hypothesis, which is linked to the deposition of this protein and the resultant oxidative stress.[68,69] AD is also strongly associated with dementia and is caused by various mechanisms, including mitochondrial dysfunction, apoptosis, endoplasmic reticulum stress, genetic factors, oxidative stress, neuroinflammation, microRNA signaling dysregulation, and cholinergic dysfunction, which collectively contribute to the progression of the disease, leading to NDs and cell death as they mutually influence one another.[60,70−73] Current treatments, including medications such as tacrine, rivastigmine, galantamine, donepezil, and memantine, aim to alleviate symptoms but do not effectively delay the progression of the disease.[74−77] Given the substantial social and economic impact of this disease, it is imperative to redirect treatment efforts toward addressing the diverse mechanisms of neuronal degeneration implicated in its development.

Plant-derived compounds, specifically flavonoids like limonene, curcumin, naringin, resveratrol, crocin, and naringenin, have gained significant attention for AD treatment during the past decades due to their promising neuroprotective effects via binding to toxicity, ansferrin, downregulating TNF-α, nitric oxide, and oxidative stress, reducing Aβ protein generation and ROS clearance, hindering proinflammatory cytokines' production, plus mitochondrial toxicity and cholinergic dysfunction reduction.[78−85] In this context, multiple studies have investigated the therapeutic potency of SA in AD models. SA administration in AD in vivo models, induced by $A\beta_{(1-42)}$, $AlCl_3$, and streptozotocin, demonstrated neuronal cell death reduction, glial cell activation, iNOS expression enhancement, and increased antioxidant enzyme levels leading to memory loss prevention and MAO-A and MAO-B blockade, in addition to an appropriate response to chemical and pathological changes in induced memory and learning impairment.[86−88] In scopolamine-induced AD models, Lee et al. demonstrated SA's potency to ameliorate both long- and short-term spatial memory deficits as well as avoid memory loss through upregulation of hippocampus synaptic activity and the stimulation of brain-derived neurotrophic factor (BDNF) and tropomyosin receptor kinase B (TrkB) expression. SA also hindered inflammation by lowering the levels of prostaglandin-endoperoxide synthase 2 (COX-2) and IL-1β; plus it was capable of reversing cognitive decline brought on by cholinergic receptor blockage and long-term potentiation (LTP) impairment.[89] Another study aimed to investigate the influence of SA on the equilibrium of TNF-α, malondialdehyde

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Table 2. Preclinical Studies Investigating the Neuroprotective Effects of Sinapic Acid in Different Neurological Conditions[a]

neurological disorder	animal model	induction model	sinapic acid dose	route of sinapic acid administration	effective dose	findings	ref
Alzheimer's disease	Male Wistar rats	Intracerebroventricular streptozotocin injection	10, 20 mg/kg; once daily for 3 weeks	Intragastrical	20 mg/kg	• Improved performance in the MWM test after STZ-induced challenges • Restored normal behavior in the fourth quadrant of the MWM test on day 21 • Enhanced retention in the passive avoidance test following STZ treatment • Reversed STZ-induced decreases in GSH levels at 20 mg/kg in both cortex and hippocampus • Prevented increased MDA levels in the cortex and hippocampus caused by STZ • Reduced TNF-α and IL-1β levels in both cortex and hippocampus • Reestablished normal ChAT expression in the hippocampus after STZ treatment • Diminished neural loss in the CA1 region of the hippocampus due to STZ	90
	Male ICR mice	Hippocampus bilateral injection of Aβ1−42 protein	1, 3,10 mg/5 mL/kg, once daily for 7 days	Oral	10 mg/kg	• Reversed Aβ1−42 protein-induced step-through latency reduction in passive avoidance task • Increased Nissl-positive cells in CA1 • Reduced TUNEL-positive cells in hippocampal CA1 • Lowered caspase-3-positive cell count in hippocampal CA1 • Decreased OX-42-positive cell presence • Attenuated astrocyte activation by reducing GFAP-positive cells • Diminished anti-NT immunoreactivity post Aβ1−42 treatment • Lowered NT expression in hippocampal CA1	86
	Wistar rats	Administration of 175 mg/kg AlCl3 for 25 days	30, 60 mg/kg	Oral		• Improved memory deficits caused by AlCl3 • Positive effects on biochemical and pathological changes	114
	Sprague-Dawley rats	Hippocampus injection of scopolamine	10 mg/kg, for 14 days	Oral		• Improved avoidance memory and spatial recognition learning, both short and long-term • Reduced inhibition of BDNF and TrkB, and dampened activation of COX-2 and IL-1β induced by scopolamine in the hippocampus	89
	Male & female Wistar albino rats	Oral administration of 175 mg/kg AlCl3 for 25 days	20, 40 mg/kg	Oral	40 mg/kg	• MAO-A/B blockade • Increased levels of CAT, SOD, GSH • Reduced levels of TNF-α in a dose-dependent manner	88
	Male Wistar rats	Intracerebroventricular streptozotocin injection	2.5, 5, 10, and 20 mg/kg bw, daily for 28 days	Intragastric	10 and 20 mg/kg	• Enhanced memory by extending retention • Reduced dark compartment time in avoidance test • Suppressed hippocampus TNF-α levels • Boosted antioxidant enzyme activity (CAT, SOD, GPX) • Lowered brain MDA levels, and minimized neural damage in cortex and hippocampus	87
Parkinson's disease	Male Wistar rats	Unilateral intrastriatal 6-hydroxydopamine injection	10 and 20 mg/kg	Oral		• Reduced rotations in response to apomorphine • Enhanced Nissl-stained neuron count in the SNC • Elevated TH-positive neuron count on the left side of SNC	101

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Table 2. continued

neurological disorder	animal model	induction model	sinapic acid dose	route of sinapic acid administration	effective dose	findings	ref
						• Lowered iron reactivity in the left midbrain (iron-staining assay) • Decreased MDA and nitrite levels, with no notable improvement in SOD activity	
	Male C57BL/6 mice	30 mg/kg MPTP injection, on 5 consecutive days	10, 20 mg/kg		20 mg/kg	• Improved behavior and prevented dopaminergic neuron loss in PD models • Enhanced mitochondrial function, countering the effects of MPTP treatment • MPTP treatment increased Drp1 and phospho-Drp1 Ser616 levels • Reversed phospho-Drp1 Ser616 and REV-ERB α protein expression in MPTP-treated mice	102
	Sprague-Dawley male rats	Intrastriatal and intrategmental rotenone (5 μg/μL) injection	30 mg/kg, for 28 days after PD model induction	Oral		• Enhanced movement and reduced stillness in the open field test • Alleviated rotenone-induced uneven forelimb usage • Lowered serum iron levels and restrained transferrin increase • Elevated serum HO-1 and brain GPx-4 levels • Safeguarded against rotenone-induced CAT and SOD reduction in the brain • Prevented rotenone-induced decline in brain CAT and SOD levels • Curbed lipid peroxidation by reducing brain MDA levels • Augmented TH activity in dopaminergic SNC neurons	103
Hippocampal Neuronal damage	Male ICR mice	Injection of 0.2 μg/5 μL kainic acid into the right-lateral ventricles	1, 3, and 10 mg/kg	Oral	10 mg/kg	• Reduced seizure-like behavior and cell death in the CA1 and CA3 regions of the hippocampus • Reduced nitrotyrosine formation and boosted iNOS expression caused by KA • Diminished activation of microglia and astrocytes in the hippocampus due to KA • Improved memory in the passive avoidance task and reversed reduced step-through latency caused by KA	113
Ischemia and cognitive impairments	Male Wistar rats	1.5% isofluorane in N_2O:O_2 (70:30) mixture injection, both common carotid arteries occlusion	1, 3, and 10 mg/kg	Intraperitoneal	10 mg/kg	• Rescued ischemic neurons. Decreased prolongation of latency in MWM	110
Neuroinflammation	Male ICR mice, BV-2 cells	2.5 mg/kg/day intraperitoneal LPS injection, 30 min after SA oral gavage, 3 days before sampling the models	10 and 20 mg/kg/day for 8 days	Oral	20 μM	• Reduced iNOS expression in BV-2 cells • Lowered IL-6 levels in BV-2 microglia and serum • Enhanced IL-10 production in serum • Diminished JNK, p38, and ERK phosphorylation in BV-2 cells, mitigating LPS-induced activation • Reduced AKT phosphorylation during LPS stimulation • Potential safeguarding of microglia from LPS-triggered inflammation via AKT inhibition • Inhibited MAPK and AKT signaling pathways in LPS-induced mouse cerebral cortex, suggesting protective effects	61

[a]Abbreviations: Aβ1, amyloid β; AchE, acetylcholinesterase; AKT, protein kinase B; CAT, catalase; ChAT, choline acetyltransferase; Drp1, dynamin-related protein 1; ERK, extracellular signal-regulated kinase; GFAP, glial fibrillary acidic protein; GPX, glutathione peroxidase, GSH, glutathione; HO-1, heme oxygenase-1; IL-1β, interleukin-1β; iNOS, inducible nitric oxide synthase; JNK, Jun N-terminal kinase; KA, kainic acid; LPS, lipopolysaccharide; MAO, monoamine oxidase; MAPK, mitogen-activated protein kinase; MDA, malondialdehyde; MPTP, neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; MWM, Morris water maze; NT, nitrotyrosine; OX-42, anti-CD11b; p38, p38 mitogen-activated protein kinases; PD, Parkinson's disease; REV-ERB, nuclear receptor subfamily 1

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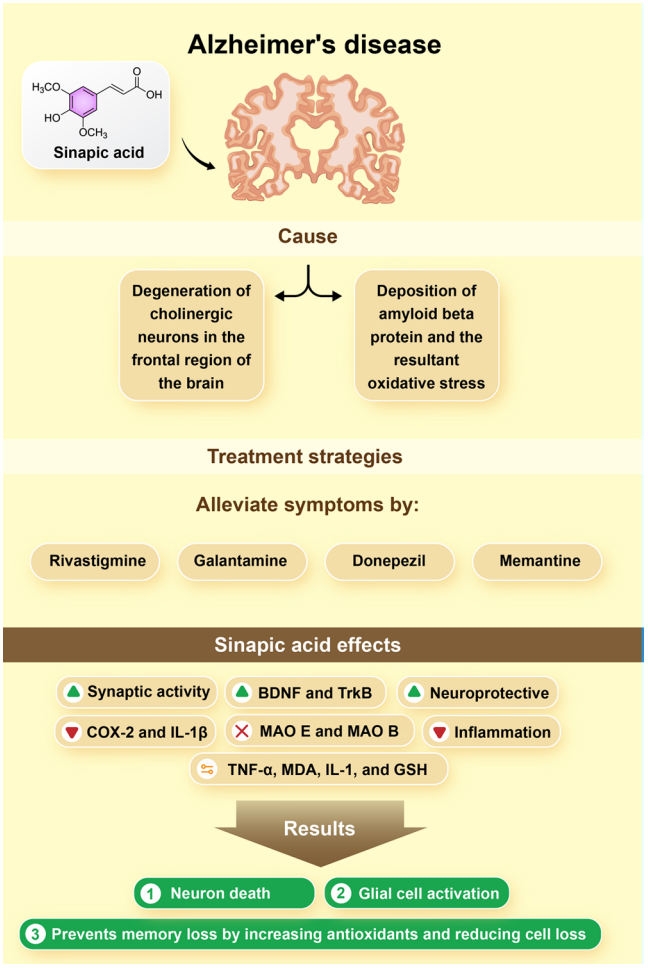

Figure 4. Pathophysiological mechanisms involved in Alzheimer's disease, primarily amyloid-β aggregation and cholinergic neurons degeneration. Sinapic acid's potential as a promising therapeutic molecule for Alzheimer's disease is shown, as it can modulate various inflammatory, apoptotic, and oxidative stress-inducing agents, contributing to memory loss prevention and neural cell damage reduction. Abbreviations: BDNF, brain-derived neurotrophic factor; COX-2, cyclooxygenase-2; GSH, glutathione; IL, interleukin; MAO, monoamine oxidase; MDA, malondialdehyde; TNF-α, tumor necrosis factor-α; TrkB, tropomyosin receptor kinase B.

(MDA), IL-1, and GSH levels, which exhibited alterations and a noticeable decrease in choline acetyltransferase (ChAT) expression. SA's neuroprotective effect on oxidative stress, neuroinflammation, cholinergic dysfunction, and neuron loss led to an improvement in AD patients.[90] According to the results of experiments in this field, SA could be a promising therapeutic agent for AD due to its effects on both molecular pathways assumed for AD, delaying effects and preventing the progression of the disease, in addition to alleviating the symptoms currently available in the therapeutic pathways (Table 2, Figure 4).[41]

8.2. Parkinson's Disease. PD is the second most common neurodegenerative disease, characterized by dopaminergic neuronal degeneration in the mesencephalic substantia nigra pars compacta (SNC) and the accumulation of α-synuclein-rich clumps called Lewy bodies and Lewy neurites. In fact, PD is a movement disorder characterized by gradual motor function reduction, which results in tremors, bradykinesia, muscle stiffness, balance, and walking difficulty, in addition to

Table 2. continued

group D; SA, sinapic acid; SNC, substantia nigra pars compacta; SOD, superoxide dismutase; STZ, streptozotocin; TBARS, thiobarbituric acid reactive substance; TH, tyrosine hydroxylase; TNF-α, tumor necrosis factor-α.

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cognitive impairment, anxiety, and sleep disruption.[91,92] The most effective drug for managing the motor symptoms of PD is L-DOPA, whose chronic use is associated with side effects, including motor response fluctuations and dyskinesia, and its effectiveness diminishes as the disease progresses.[93−96] To address this, strategies involving neuroprotective agents are recommended to slow down the progression of PD.[24] Possible therapeutic strategies for managing PD involve diminishing oxidative stress through the elimination of free radicals and addressing glutamate receptors, which are generated because of heightened levels of reactive oxygen species.[24,60]

Furthermore, iron accumulation plays a significant role in PD pathophysiology, and increased iron levels in the SNC contribute to oxidative stress and the accumulation of α-synuclein, leading to oxidative damage to dopaminergic neurons.[24]

Natural products and phytochemicals for PD therapy have garnered significant attention due to their potential to reduce the side effects of chemical medications. Naringenin, curcumin, saffron, and crocin are herbal compounds that have shown neuroprotective profiles in PD models via their antioxidant, antidepressant, and anti-inflammatory properties, hindering α-synuclein fibrillation.[97−100] The potential neuroprotective activities of SA have also been observed in PD models. Administration of SA in rat models induced by 6-hydroxydopamine (OHDA-6) led to improved turning behavior, prevented SNC dopaminergic neuron destruction, reduced iron reactions, and increased levels of MDA and nitrites when compared to the effects of apomorphine after surgery.[101] Moreover, through the control of nuclear receptor subfamily 1 group D (REV-ERB) protein production, SA was pharmacologically triggered in a PD model induced by neurotoxin, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), revealing a unique function of REV-ERB in maintaining the equilibrium between two forms of dynamin-related protein 1 (Drp1) phosphorylation. Although it remains uncertain whether SA directly affects mitochondria and the expression of the REV-ERB protein, it may play a role in restoring abnormal mitochondrial conditions and regulating REV-ERB expression.[102] In a rotenone-induced PD model, SA also exhibited neuroprotective properties, with a focus on the connection between iron and ferroptosis. Treatment with SA significantly reduced the loss of tyrosine hydroxylase (TH)-positive neurons in the striatum, improved motor symptoms, and lowered indicators of lipid peroxidation, oxidative stress, as well as serum iron and transferrin levels.[103] As a result, the usage of SA in the treatment of PD, due to its neuroprotective potential and other mentioned properties, could become more effective and overstep just relieving the symptoms of the disease (Table 2, Figure 5).[104]

8.3. Ischemic Stroke. Ischemic stroke involves a period of reduced blood flow to the brain before restoring blood flow through medical intervention. This often leads to ischemia/reperfusion injury, which is now widely recognized for its detrimental effects on cognitive function.[105,106] These effects manifest as various neurological and behavioral abnormalities, including vertigo, disorientation, and cognitive decline.[107−109] Regarding the neuroprotective properties of phytochemicals for alleviating cerebral ischemia's complications, SA has revealed promising capabilities for preventing nerve damage and memory impairment due to its agonistic properties on the GABA receptor and inhibitory effect on free radicals.[110]

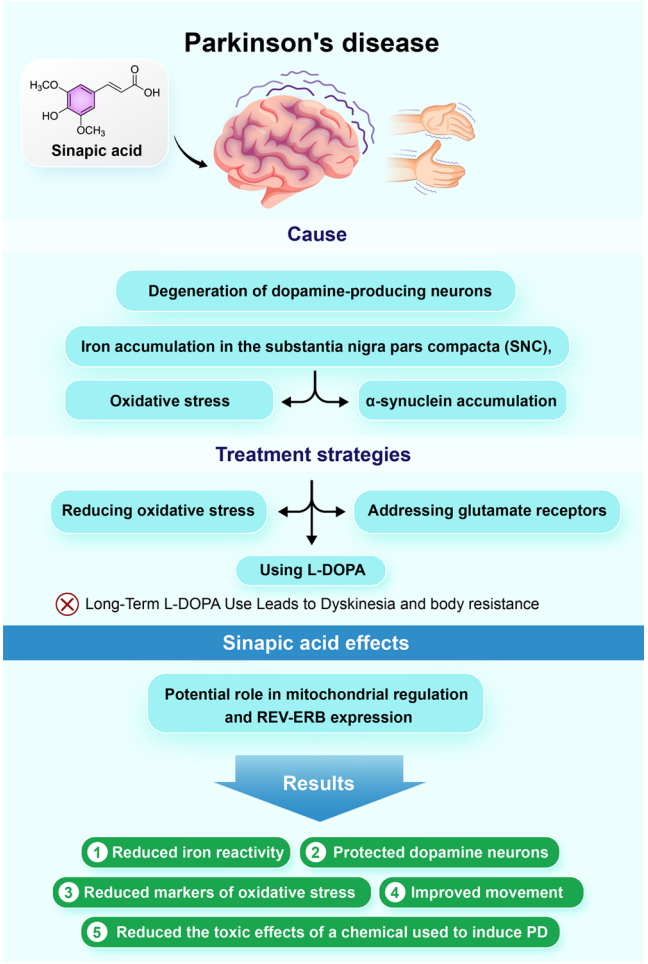

Figure 5. Pathophysiological changes involved in Parkinson's disease, including dopaminergic neurons' degeneration and α-synuclein accumulation in SNc, are shown. It is also proven that sinapic acid, as an alternative treatment for L-DOPA, can represent neuroprotective profiles in this disease via mitochondrial regulation, as well as the reduction of oxidative stress and iron reactivity, leading to improved movement and protection of dopaminergic neurons. Abbreviations: PD, Parkinson's disease; REV-ERB, nuclear receptor subfamily 1 group D.

Given SA's promising impact on mitigating nerve damage and memory impairment caused by ischemia, it appears to be an effective neuroprotective agent. This suggests that SA could play a significant role in therapeutic approaches targeting ischemia-related delayed neuronal death in the hippocampus as well as processes associated with hippocampal learning and memory (Table 2).[111]

8.4. Hippocampal Neural Damage and Neuroinflammation. Two primary factors trigger the initiation of neuronal cell death: an excess of calcium and the production of free radicals due to the heightened activation of excitatory amino acid receptors.[112] When neurons experience cell death due to free radicals induced by kainic acid (KA), it can lead to severe outcomes such as epilepsy, neurodegeneration, memory loss, or nerve cell demise.[60] Administration of natural compounds, SA in this context, has shown promising therapeutic properties for KA-induced hippocampal neural damage and neuroinflammation via cell death and iNOS expression reduction, MAPK and AKT signaling pathway hindrance, in addition to decreasing the levels of IL-6 (Table 2).[61,113]

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9. DISCUSSION

NDs are severely disabling conditions that result from the gradual deterioration of the central nervous system's neurons, leading to changes in the neurons' structure and eventual death. After neural deterioration or severe damage, neurons are unable to regenerate on their own. Among different human NDs, AD has the highest rate of incidence, with approximately 5 million, followed by PD (1 million), MS (400 000), amyotrophic lateral sclerosis (ALS) (30 000), and HD (3000), according to the fact that the incidence of these diseases is expected to rise as the population ages.[115,116] Due to their remarkable biological characteristics, numerous studies have so far assessed the therapeutic effectiveness of diverse plant-derived compounds in treating neurodegenerative diseases.[117] SA is an interesting phenylpropanoid derivative, having multiple biological properties which have made it a potential therapeutic molecule via revealing antioxidant, anti-inflammatory, cancer-fighting, and antimicrobial activities, among which its antioxidant function has gained significant attention due to the oxidation-mediated mechanisms involved in neurodegenerative diseases' pathology.[118] Different plants containing SA have demonstrated promising therapeutic effects on neurological issues. For instance, *Polygala tenuifolia*, which contains a great amount of SA, has shown potency to improve scopolamine-induced memory impairment. Additionally, SA and related compounds such as tenuifoliside B and 3,6′-disinapolysucrose can show pharmacological effects, as well as protecting the brain and improving cognitive function. In cereal bran, SA is also found alongside ferulic acid (more prevalent), playing a vital role in neuroprotection against diseases related to peroxy nitrite, exhibiting antineoplastic effects, and suppressing inflammatory markers in macrophages.[111]

Anxiolytic effects have been highlighted as another amazing property of SA, which is performed through the GABAergic system, potentially acting on GABARs, in which the GABAR activation reduces neurotoxicity induced by certain substances. SA's ability to decrease Aβ levels, prevent neuronal cell death, inhibit antioxidant enzymes' activation, and modulate neurotransmitter systems underscores its anti-inflammatory and neuroprotective properties. Together, SA's antioxidant and anti-inflammatory activities are important properties that make it a promising candidate for mitigating pathogenic changes associated with NDs.[60]

10. CONCLUSION

Several studies on SA's biological properties in NDs show that it is a useful natural molecule with important therapeutic properties, such as anti-inflammatory, antiapoptotic, and antioxidant properties. Before sinapic acid can be clinically applied, its pharmacokinetics and safety profile must be thoroughly examined in vitro and in vivo. Understanding its absorption, metabolism, and excretion is crucial for designing effective therapeutic interventions. These considerations pave the way for sinapic acid to move from experimental settings to clinical trials and therapeutic development. However, to validate and expand upon these findings, further research is necessary. Collaborative efforts among researchers, clinicians, and pharmaceutical developers are essential for advancing our understanding of sinapic acid's potential and translating it into effective treatments for individuals with NDs.

■ ASSOCIATED CONTENT

Data Availability Statement

The authors confirm that the data supporting the findings of this study are available within the article.

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Notes

Declaration of Generative AI and AI-Assisted Technologies in the Writing Process. During the preparation of this work the authors used chat.openai in order to detect grammar errors. After using this tool/service, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

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■ ABBREVIATIONS

Aβ: amyloid β
AchE: acetylcholinesterase

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AD: Alzheimer's disease
AKT: protein kinase B
ALS: amyotrophic lateral sclerosis
BDNF: brain-derived neurotrophic factor
CAT: catalase
ChAT: choline acetyl transferase
CK: creatine kinase
COX-2: cyclooxygenase-2
DALYs: disability-adjusted life years
DPPH: 2,2-diphenyl-1-picrylhydrazyl
Drp1: dynamin-related protein 1
GABA: γ-aminobutyric acid
GABARs: GABA receptors
GBD: Global Burden of Disease
GFAP: glial fibrillary acidic protein
GPX: glutathione peroxidase
GSH: glutathione
HCA: hydroxycinnamic acid
HD: Huntington's disease
IL: interleukin
iNOS: inducible nitric oxide synthase
KA: kainic acid
LDH: lactate dehydrogenase
LDL: low-density lipoprotein
LPS: lipopolysaccharide
LTP: long-term potentiation
MAO: monoamine oxidase
MAPKs: mitogen-activated protein kinases
MDA: malondialdehyde
MPO: myeloperoxidase
MPTP: 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine
MS: multiple sclerosis
MTX: methotrexate
NDs: neurodegenerative disorders
NF-kB: nuclear factor κ-light-chain-enhancer of activated B cells
Nrf2/HO-1: nuclear factor erythroid-2 related factor 2/ heme oxygenase-1
OHDA-6: 6-hydroxydopamine
PD: Parkinson's disease
PI3K: phosphoinositide 3-kinase
REV-ERB: nuclear receptor subfamily 1 group D
ROS: reactive oxygen species
RSN: reactive nitrogen species
SA: sinapic acid
SIN-1: 3-morpholinosydnonimine hydrochloride
SNC: substantia nigra pars compacta
SOD: superoxide dismutase
TBARS: thiobarbituric acid reactive substance
TH: tyrosine hydroxylase
TLRs: Toll-like receptors
TNBS: 2,4,6-trinitrobenzenesulfonic acid
TNF-α: tumor necrosis factor-α
TrkB: tropomyosin receptor kinase B
YLDs: years lived with disability
DALYs: disability-adjusted life years

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