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Gallic Acid: A Natural Compound with Multi-dimensional Potential for Repairing Neurodegenerative Diseases

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Abstract: Neurodegenerative diseases (NDs) encompass a spectrum of chronic, progressive disorders defined by the insidious loss of neuronal structure and function, the multifactorial etiologies of which remain incompletely understood. To date, clinical interventions for NDs have primarily targeted four domains: neuroprotection, the clearance of aberrant protein aggregates, restoration of neurotransmitter homeostasis, and suppression of neuroinflammation. However, most conventional pharmacotherapies provide only palliative symptomatic relief rather than addressing the fundamental etiological drivers of NDs. Furthermore, their clinical utility is often hampered by off-target effects and a mono-targeted approach, which fails to counteract the multifaceted nature of disease progression. Conversely, natural products derived from traditional Chinese medicine (TCM) offer unique advantages, characterized by high biocompatibility, minimal toxicity, and the capacity for pleiotropic regulation through multi-target synergistic mechanisms, ranging from the preservation of cellular homeostasis to the modulation of the neuro-microenvironment and the promotion of neuroplasticity and regeneration. Focusing on gallic acid (GA) as a prototypical bioactive polyphenolic compound, this review provides a comprehensive synthesis of recent advances and the molecular underpinnings of its neuroprotective and neurorestorative effects, offering critical insights and a theoretical framework for the development of TCM-derived candidates as novel neurotherapeutics.

Keywords: Gallic acid; Alzheimer's disease; Neuroprotection; Natural products

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1. Introduction

1.1. Global burden of neurodegenerative diseases and unmet clinical needs

Neurodegenerative diseases (NDs) comprise a spectrum of chronic, progressive pathologies characterized by the selective attrition and functional loss of neurons, predominantly affecting the central nervous system (CNS). Representative disorders within this category include Alzheimer's disease (AD), Parkinson's disease (PD), and amyotrophic lateral sclerosis (ALS) [1]. The etiology of NDs is multifactorial, arising from a complex interplay between

genetic predispositions, environmental stressors, aging, and lifestyle influences [2]. Among these, AD represents the most prevalent ND, clinically manifested by progressive cognitive decline, memory impairment, aphasia, and behavioral disturbances, ultimately necessitating protracted long-term care. Consequently, these conditions impose substantial socioeconomic and psychological burdens on caregivers and exert significant pressure on global healthcare systems.

According to the World Alzheimer Report, the global prevalence of AD currently exceeds 55 million, a figure projected to escalate to 78 million by 2030 and 152 million by 2050 [3]. Similarly, PD constitutes the second most frequent and most rapidly expanding ND worldwide, with a prevalence exceeding 6 million—a 2.5-fold increase over the previous generation—and is forecasted to double to over 12 million by 2040 [4]. Driven by the global demographic shift toward an aging population, the rising incidence of NDs continues to exert an unprecedented strain on public health resources.

To date, no curative therapies exist for NDs, including AD. Current pharmacological interventions remain largely symptomatic and single-target oriented. For instance, Donepezil enhances cognitive function through the inhibition of acetylcholinesterase (AChE) activity and the subsequent augmentation of acetylcholine concentrations in the synaptic cleft [5]. Nevertheless, such agents offer only palliative benefits without modulating the underlying disease progression, and chronic administration is frequently associated with adverse effects, including nausea, emesis, and diarrhea [6]. Similarly, Memantine, an N-methyl-D-aspartate (NMDA) receptor antagonist, mitigates glutamate-induced excitotoxicity and demonstrates clinical efficacy in moderate-to-severe AD cases, yet fails to arrest the underlying pathology [7–9]. Furthermore, its long-term use is often complicated by adverse reactions such as vertigo, somnolence, and constipation [10]. Consequently, there is an imperative need to identify novel, multi-target therapeutic candidates capable of providing more effective, disease-modifying interventions.

1.2. Gallic acid: A natural compound with multitarget therapeutic potential

Gallic acid (GA, C7H6O5C7), systematically designated as 3,4,5-trihydroxybenzoic acid, is a low-molecular-weight triphenolic compound that constitutes a primary bioactive constituent in various botanical sources, including *Galla chinensis*, *Cornus officinalis*, *Punica granatum*, and *Rheum palmatum*. Structure-activity relationship (SAR) studies indicate a positive correlation between the degree of phenolic hydroxylation and its potent antioxidant capacity [11]. The specific trihydroxyl arrangement in GA confers exceptional free radical scavenging efficacy, primarily through a hydrogen atom transfer (HAT) mechanism that neutralizes peroxyl radicals (ROO·ROO·, RO·RO·, and R·R·) into stable molecular species (ROOHROOH, ROHROH, and RHRH) (**Figure 1**) [12]. Beyond its antioxidant properties, GA exhibits significant antimicrobial potential by partitioning into bacterial lipid bilayers via hydrogen bonding, thereby compromising membrane integrity and inducing the leakage of essential intracellular constituents [13].

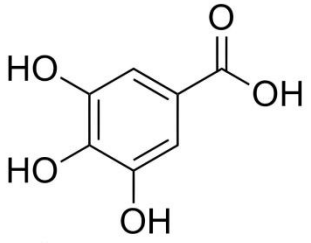

Figure 1. Molecular structure of gallic acid

The therapeutic application of GA-rich matrices can be traced to the historical tenets of Traditional Chinese Medicine (TCM). While "gallic acid" as a discrete chemical entity was not identified in antiquity, the clinical utility of its primary botanical vehicle, *Galla chinensis* (Wu Bei Zi), has been documented and exploited for centuries. In TCM theory, *Galla chinensis* is characterized by its bitter and astringent nature, with meridian tropism toward the lung, spleen, and kidney. Its pharmacological profile emphasizes "astringent and consolidating" properties, which are traditionally employed to secure the essence, arrest protracted diarrhea, and stabilize lung function. These therapeutic claims are corroborated by canonical pharmacopoeias; for instance, the Xinxiu Bencao (Newly Revised Materia Medica) highlights its efficacy in managing chronic dysentery and accelerating tissue regeneration (myogenesis), while the Yaoxing Lun (Treatise on Medicinal Properties) underscores its role in alleviating infantile abdominal cold and refractory diarrhea. This historical foundation underscores the multifaceted role of GA-rich materials in managing gastrointestinal and metabolic imbalances, providing a precedent for its modern pharmacological investigation.

With the advancement of modern pharmacological research techniques, the biological activities of GA have been gradually revealed. Its diverse pharmacological effects have made it a research hotspot in the field of natural drugs. Modern studies have confirmed that gallic acid possesses significant biological activities such as anti-inflammatory, antioxidant, antiviral, and antibacterial properties, and the underlying mechanisms have been initially elucidated. In terms of anti-inflammatory effects, gallic acid can effectively attenuate inflammatory responses in the body by inhibiting the release of inflammatory cytokines, chemokines, and adhesion molecules, and reducing inflammatory cell infiltration [14]. In the fields of antioxidation and antibacterial activity, structural modification strategies can further enhance their efficacy—for instance, grafting gallic acid onto pectin molecules for structural improvement results in products with significantly superior antioxidant and antibacterial activities compared to natural pectin [15]. Additionally, composite biomaterials constructed with gallic acid as the core component have demonstrated excellent biological properties: for example, the gallic acid-containing composite hydrogel (RHCMA-CSGA) not only exhibits good biocompatibility but also possesses potent antibacterial activity, opening up new directions for its application in the biomedical field [16].

In recent years, with the increasing incidence of neurodegenerative diseases, the search for safe and effective therapeutic drugs has become a major focus and challenge in the global biomedical field. Against this backdrop, the potential value of gallic acid in the treatment of neurodegenerative diseases has been gradually explored, showing tremendous research potential and application prospects. Existing studies have indicated that gallic acid can exert neuroprotective effects through multiple pathways, including scavenging excessive reactive oxygen species (ROS) in the body, inhibiting the activation of neuroinflammatory pathways, and reducing neuronal apoptosis, thereby alleviating the pathological damage of major neurodegenerative diseases such as AD and PD. These findings provide important candidate directions and solid research bases for the development of novel natural anti-neurodegenerative drugs, and also promote the in-depth exploration of the mechanisms underlying gallic acid's neuroprotective effects.

Based on the above research background, this review systematically summarizes the main molecular mechanisms of gallic acid's neuroprotective effects, comprehensively elaborates on its regulatory roles in key pathways such as oxidative stress, inflammatory response, and neuronal apoptosis, aiming to provide a more comprehensive theoretical basis for subsequent drug development and clinical applications.

2. Core neuroprotective mechanisms of gallic acid

2.1. Resistance to oxidative stress

Oxidative stress (OS) represents a pivotal pathological hallmark of neuronal injury, characterized by a fundamental disruption of redox homeostasis. This state arises from the aberrant accumulation of reactive oxygen species (ROS) and reactive nitrogen species (RNS), driven by either accelerated pro-oxidant production or the impaired sequestration of free radicals by cellular antioxidant defense systems. Gallic acid (GA) mitigates oxidative damage through dual mechanisms: the direct neutralization of free radicals via its potent hydrogen-donating and electron-scavenging capacities, and the indirect enhancement of the intracellular antioxidant status.

Recent studies have elucidated the molecular pathways through which GA orchestrates these effects. Garg et al. demonstrated that mitochondria-targeted antioxidants incorporating GA moieties activate the Nrf2/Keap1 signaling axis, thereby bolstering cellular resistance to lipopolysaccharide (LPS)-induced oxidative stress and ameliorating neuroinflammation-associated cognitive and affective deficits in rats [17]. Similarly, Huang et al. engineered iron-gallic acid coordination polymer nanoparticles (Fe-GA CPNs), showcasing synergistic antioxidant and anti-inflammatory properties that effectively sequester ROS to prevent oxidative damage [18]. In rodent models, Dastan et al. observed that GA (100 mg/kg) reversed memory decline, concurrently suppressing lipid peroxidation and replenishing the total thiol pool [19]. Furthermore, Ojo et al. reported that GA treatment significantly improved the antioxidant profile in cadmium-intoxicated Wistar rats by upregulating the activities of superoxide dismutase (SOD) and catalase (CAT), and increasing glutathione (GSH) concentrations within the brain [20].

The neuroprotective efficacy of GA has also been validated in alternative models. In zebrafish, Agostini et al. demonstrated that GA (5–10 mg/L) restored ethanol-induced impairment of choline acetyltransferase (ChAT) activity while reducing levels of thiobarbituric acid reactive substances (TBA-RS) and 2',7'-dichlorodihydrofluorescein diacetate (DCFH-DA) oxidation [21]. In stressed rat models, GA-mediated attenuation of oxidative damage significantly mitigated neuronal attrition within the hippocampus and prefrontal cortex (PFC) [22]. Consistently, GA has been shown to protect the cerebral cortex, hippocampus, and striatum of LPS-challenged mice by reducing ROS and nitrite levels while enhancing the activity of endogenous antioxidant enzymes [23]. To improve delivery, Abbasalipour et al. developed GA-loaded sumac nano-liposomes, which were shown to regulate the Keap1/Nrf2 gene expression profile [24]. This intervention enhanced antioxidant enzyme activities and effectively alleviated learning and memory impairments induced by valproic acid (VPA).

In summary, GA reinforces cellular antioxidant defenses and mitigates neuronal damage by modulating the Nrf2/Keap1 signaling axis, augmenting the enzymatic activities of SOD, CAT, and GSH, and providing direct scavenging of excessive ROS.

2.2. Regulation of apoptosis: Maintaining neuronal survival

Apoptosis, a highly regulated form of programmed cell death, serves as a fundamental driver of neuronal loss following central nervous system (CNS) insults. The induction of the apoptotic cascade leads to a progressive attrition of functional neurons and the exacerbation of neurological deficits, while simultaneously triggering secondary neuroinflammatory responses that expand the area of lesion. Emerging evidence highlights the potent anti-apoptotic properties of gallic acid (GA) in various pathological contexts.

In in vitro models of ischemic stroke, GA intervention has been shown to effectively counteract the detrimental effects of oxygen-glucose deprivation/reoxygenation (OGD/R), which typically triggers massive apoptosis and intracellular calcium overload [25]. Similarly, in in vivo models of Parkinson's disease (PD), Jiang et

al. reported that GA administration significantly inhibits neuronal apoptosis within the substantia nigra of MPTP-induced mice [26]. Beyond classical apoptotic pathways, GA has been found to modulate endoplasmic reticulum (ER) stress, a critical mediator of cellular dysfunction. Specifically, GA treatment markedly downregulates Caspase-12 expression across neurons, glial cells, and vascular endothelial cells, thereby mitigating ER stress-induced cell death and reinforcing its role in immune-related signaling crosstalk [27].

Furthermore, the anti-apoptotic efficacy of GA extends to Alzheimer's disease (AD) models. Chen et al. demonstrated that GA conjugates significantly enhance neuronal survival in the hippocampus and substantia nigra of APP/PS1 transgenic mice [28]. This neuroprotective effect is primarily mediated through the activation of the PI3K/Akt signaling axis, which subsequently modulates downstream apoptotic effectors. Pretreatment with GA led to a marked reduction in amyloid-beta (Aβ) deposition and a decreased proportion of apoptotic cells, characterized by the upregulation of PI3K and the concomitant suppression of pro-apoptotic markers, including Bax, cytochrome c (Cyt C), and Caspase-3 [28].

Collectively, these findings indicate that GA preserves neuronal integrity by orchestrating a multifaceted anti-apoptotic response, primarily through the activation of the PI3K/Akt survival pathway and the systemic inhibition of the mitochondrial and ER-mediated apoptotic cascades (e.g., Bax, Cyt C, and Caspase-12/3).

2.3. Protection of mitochondrial function

As the primary bioenergetic hubs of the cell, mitochondria are indispensable for maintaining neuronal health and function. Through oxidative phosphorylation, these organelles generate adenosine triphosphate (ATP) to meet the high metabolic demands of neurons. However, mitochondrial dysfunction precipitates bioenergetic failure, intracellular calcium dyshomeostasis, and excessive oxidative stress, which collectively exacerbate the proteotoxicity of Aβ and hyperphosphorylated tau, ultimately triggering synaptic failure and cognitive decline [29].

Recent investigations have highlighted the mitoprotective potential of GA and its derivatives. Lin et al. engineered calcium-gallic acid nanozymes (CaGA) that exhibited exceptional biocompatibility and significantly stabilized the mitochondrial membrane potential (ΔΨm) under pathological stress [30]. Beyond structural stability, GA also modulates mitochondrial quality control; for instance, Chen et al. elucidated that GA induces mitophagy via the activation of Transient Receptor Potential Vanilloid 4 (TRPV4) [31]. In models of systemic inflammation, Diao et al. utilized JC-1 fluorescence signaling to demonstrate that GA intervention effectively counteracts LPS-induced mitochondrial depolarization in macrophages [32]. Similarly, in 6-OHDA-induced PD rat models, GA administration significantly lowered lactate dehydrogenase (LDH) leakage and improved motor performance, indicating the preservation of cellular integrity [33].

Furthermore, Ma et al. evidenced that GA restores mitochondrial metabolic flux and ΔΨm in primary microglia, leading to a marked reduction in mitochondrial-derived ROS (mtROS) and the subsequent attenuation of neuroinflammation [34]. The neuroprotective scope of GA-related compounds also includes heavy metal detoxification; Wang et al. demonstrated that epigallocatechin gallate (EGCG), a prominent GA derivative, alleviates lead-induced neuronal damage by regulating mitochondrial redox homeostasis [35]. Mechanistically, Sun et al. established that GA exerts a direct protective effect on mitochondria by inhibiting the opening of the mitochondrial permeability transition pore (mPTP) [36]. This is achieved not only by blocking the binding of cyclophilin D (CypD) to the adenine nucleotide translocator (ANT) but also by promoting the phosphorylation of extracellular signal-regulated kinase (ERK). The resulting downregulation of CypD expression desensitizes neurons to MPTP-mediated neurotoxicity, inhibits downstream caspase activation, and ultimately promotes

neuronal survival.

In summary, GA safeguards mitochondrial integrity by preventing the CypD-ANT association, enhancing ERK-mediated signaling, and suppressing mPTP opening. These actions maintain bioenergetic stability and provide a robust defense against mitochondrial-driven neurodegeneration.

2.4. Regulation of autophagy: restoration of intracellular homeostasis

Autophagy represents a fundamental, conserved catabolic process essential for maintaining cellular proteostasis. It facilitates the sequestration and degradation of aberrant protein aggregates and dysfunctional organelles, which are hallmark features of neurodegeneration. In the context of the nervous system, autophagy serves as a critical defense mechanism by eliminating misfolded proteins and regulating cell death pathways and neuroinflammatory responses [37].

Emerging evidence underscores the role of GA and its derivatives in modulating autophagic activity. Lin et al. elucidated that epigallocatechin gallate (EGCG), a prominent GA derivative, triggers microglial autophagy to facilitate Aβ clearance by antagonizing the HDAC6-PI3K/AKT/mTOR signaling axis [38]. Mechanistically, EGCG was found to suppress HDAC6 expression, inhibit the phosphorylation of PI3K, AKT, and mTOR, and elevate the LC3-II/LC3-I ratio, thereby enhancing the phagocytic and degradative capacity of microglia. Consistently, Sun et al. reported that EGCG ameliorates spatial learning and memory deficits in APP/PS1 mice, a benefit potentially derived from the augmentation of hippocampal autophagic flux and the subsequent reduction in cerebral Aβ deposition [39].

Direct evidence regarding GA's modulation of autophagy has also begun to emerge. Hua et al. demonstrated that pure GA enhances microglial autophagy via the mTOR signaling pathway, which provides a neuroprotective effect against cerebral ischemia-reperfusion injury in mice [40]. Furthermore, in models of Parkinson's disease, EGCG has been shown to alleviate α-synuclein accumulation via the autophagy-lysosome pathway [41]. In these MPTP-induced PD models, GA derivative treatment significantly upregulated the expression of Beclin 1 and the LC3-II/I ratio while concurrently reducing p62 levels—a classic indicator of successful autophagic degradation.

Based on the synthesis of these findings, it is postulated that GA preserves intracellular homeostasis by orchestrating autophagic activities, potentially through the HDAC6-PI3K/AKT/mTOR regulatory network. However, while the autophagic-inductive effects of GA-related compounds like EGCG are well-documented, direct empirical studies specifically focusing on pure GA remain relatively nascent, necessitating further rigorous investigation to fully consolidate its therapeutic potential.

2.5. Inhibition of neuroinflammation

Chronic neuroinflammation serves as a fundamental driver in the pathogenesis and progression of diverse neurological disorders. The aberrant activation of microglia and astrocytes triggers the secretion of a myriad of pro-inflammatory cytokines, culminating in synaptic dysfunction, neuronal degeneration, and eventual attrition, thereby exacerbating neural damage. Substantial evidence underscores the potent anti-neuroinflammatory properties of gallic acid (GA), primarily mediated by the downregulation of inflammatory mediators and the suppression of glial overactivation. For instance, Dong et al. demonstrated that GA attenuates neuronal apoptosis and inhibits microglial overactivation in neonatal rats following hypoxic-ischemic (HI) insult [25]. Mechanistically, Chen et al. elucidated that GA alleviates paclitaxel-induced neuroinflammation and diminishes IL-1β release by modulating the NLRP3 inflammasome signaling axis, a mechanism further supported by Hua et al. in cerebral

ischemia-reperfusion models [40, 42].

The scope of GA's anti-inflammatory action extends to the regulation of specific phosphorylation events and structural preservation. Xia et al. evidenced that GA suppresses the phosphorylation of IKK (p-IKK) and p65 (p-p65) in astrocytes, while concurrently reducing the transcriptional levels of IL-1β, IL-6, and TNF-α [43]. Furthermore, Qu et al. reported that GA treatment preserves blood-brain barrier (BBB) integrity, mitigates cerebral edema, and dampens systemic microglial activation in mice subjected to ischemia/reperfusion injury [44]. Consistently, previous research by Huang et al. established that iron-GA coordination polymer nanoparticles (Fe-GA CPNs) antagonize neuroinflammation via the TLR4/NF-κB cascade while curtailing aberrant tau hyperphosphorylation, significantly improving cognitive outcomes in AD rats [18]. Beyond the inhibition of pro-inflammatory signals, GA also preserves anti-inflammatory homeostasis, as demonstrated by Adedara et al., who observed that GA restores the levels of the potent anti-inflammatory cytokine IL-10 following aflatoxin B1 exposure. Collectively, these findings highlight that GA confers neuroprotection by orchestrating a multifaceted anti-inflammatory response, primarily through the antagonism of the TLR4/NF-κB and NLRP3 inflammasome signaling networks and the subsequent downregulation of cytokines such as IL-1β, TNF-α, and IL-6 [45].

Among these mediators, Nuclear Factor-kappa B (NF-κB) stands as a pivotal nuclear transcription factor that orchestrates cellular immune responses, inflammatory cascades, and apoptotic pathways in response to diverse stimuli. Its aberrant activation is intricately linked to the pathogenesis of malignancies, chronic inflammatory conditions, and neurodegenerative diseases. In the context of Alzheimer's Disease (AD), hyperactivation of the NF-κB signaling axis triggers a robust secretion of pro-inflammatory mediators, such as IL-1β and TNF-α, from microglia and astrocytes, thereby exacerbating inflammation-mediated neuronal insult.

Investigating the regulatory mechanisms of GA, Xia et al. demonstrated that GA targets β-arrestin2 to suppress astrocytic inflammation; specifically, GA treatment at high dosages significantly attenuated the phosphorylation of IKK and p65, while concomitantly impeding the nuclear translocation of the p65 subunit [43]. This suggests that GA effectively suppresses astrocytic NF-κB signaling by blocking the nuclear recruitment of key transactivators. Furthermore, Kim et al. evidenced that GA inhibits the post-translational acetylation of NF-κB, thereby neutralizing Aβ-induced neurotoxicity and preventing neuronal attrition [43]. Beyond direct pathway inhibition, GA has been shown to mitigate cognitive deficits in LPS-challenged rats by downregulating the transcriptional levels of NF-κB, TNF-α, and Caspase-3, while reducing lipid peroxidation and restoring thiol homeostasis [19]. Notably, Ma et al. reported that GA can counteract Aβ42-induced microglial dysfunction by facilitating a phenotypic shift from the pro-inflammatory M1 state toward the neuroprotective M2 phenotype, which consequently favors the expression of anti-inflammatory cytokines over pro-inflammatory factors [35]. In summary, GA exerts potent neuroprotective effects by antagonizing the NF-κB signaling cascade across various glial populations, thereby mitigating neurotoxicity and fostering a neurosupportive environment.

2.6. Neural plasticity and regeneration

Impairment of synaptic plasticity constitutes a crucial early hallmark of neurodegenerative diseases, directly exacerbating the trajectory of neuronal attrition. Consequently, preserving the structural and functional integrity of synapses represents a primary therapeutic objective for neuroprotection. Gallic acid (GA) facilitates the establishment of a conducive cellular microenvironment via multifaceted mechanisms, thereby indirectly sustaining synaptic homeostasis. Specifically, by effectively mitigating oxidative damage and inflammatory stress,

GA ensures the proteostatic stability of essential synaptic markers, such as PSD-95 and synaptophysin, preventing these key structural proteins from functional compromise under pathological conditions.

Substantial evidence underscores the neuroprotective efficacy of GA and its potentiation of synaptic plasticity. Jiang et al. demonstrated that GA selectively steers the differentiation of neural stem cells (NSCs) toward an immature neuronal lineage and augments NSC proliferation through the activation of the mitogen-activated protein kinase/extracellular regulated kinase (MAPK/ERK) pathway [47]. Furthermore, in APP/PS1 transgenic models, Ding et al. evidenced that GA stimulates hippocampal neurogenesis via the GSK-3β-Nrf2 signaling axis, which not only rescues spatial memory deficits but also enhances synaptic plasticity, concurrently attenuating tau hyperphosphorylation and Aβ burden [48]. Regarding the protection against neuroexcitotoxicity, Maya et al. revealed that GA significantly mitigates glutamate-induced neurotoxicity, shielding neurons from the multifaceted pathophysiological insults characteristic of neurodegenerative cascades, while Chandrasekhar et al. confirmed its capacity to antagonize 6-hydroxydopamine (6-OHDA)-induced toxicity in SH-SY5Y cells [49–50]. Additionally, GA has been implicated in antidepressant-like activities by activating the hippocampal BDNF-Akt-mTOR signaling cascade and restoring BDNF and p-TrkB levels following chronic mild stress (CMS) [51]. In summary, GA promotes neural regeneration through pivotal signaling pathways, including MAPK/ERK and GSK-3β-Nrf2, effectively bolstering synaptic plasticity and conferring broad neuroprotective effects. These properties position GA as a promising therapeutic agent for the prophylaxis and management of neurodegenerative disorders and associated neurological pathologies.

3. Multidimensional synergistic reparative effects of GA on neural cells

In summary, the neuroprotective efficacy of GA is fundamentally rooted in its multifaceted synergistic regulatory network, which can be categorized into three interconnected dimensions: first, the preservation of basal cellular physiological processes, encompassing antioxidant defense, anti-apoptotic signaling, and mitochondrial homeostasis; second, the modulation of the intracellular microenvironment through anti-inflammatory responses and the induction of autophagy; and third, the structural and functional remodeling dimension involving the promotion of neural plasticity and regeneration (**Figure 2**). These dimensions are not mutually exclusive but function as a highly integrated system, collectively establishing the pharmacological foundation of GA-mediated neuroprotection.

Specifically, the preservation of basal cellular functions represents an intrinsic cytoprotective program activated in response to endogenous and exogenous stressors. The tripartite axis of antioxidant, anti-apoptotic, and mitochondrial stability serves as the critical threshold for transitioning from neurodegenerative containment to active regenerative intervention. At the antioxidant level, GA significantly augments the activity of key enzymes, including SOD, CAT, and GSH, by upregulating the Nrf2/Keap1 signaling axis and directly neutralizing reactive oxygen species (ROS), thereby exerting dual-action protection against oxidative stress-induced neurotoxicity. Regarding mitochondrial integrity, GA hinders the interaction between Cyclophilin D (CypD) and Adenine Nucleotide Translocase (ANT) while enhancing ERK phosphorylation, which effectively desensitizes neurons to mitochondrial permeability transition pore (mPTP)-mediated injury and maintains mitochondrial structural stability. Concurrently, GA precisely modulates apoptosis via the PI3K/Akt pathway, downregulating pro-apoptotic markers such as Bax, Cytochrome C, and Caspase-3. Simultaneously, it reduces HDAC6 levels and inhibits the overactivation of the PI3K/Akt/mTOR axis, resulting in an increased LC3-II/LC3-I ratio, which

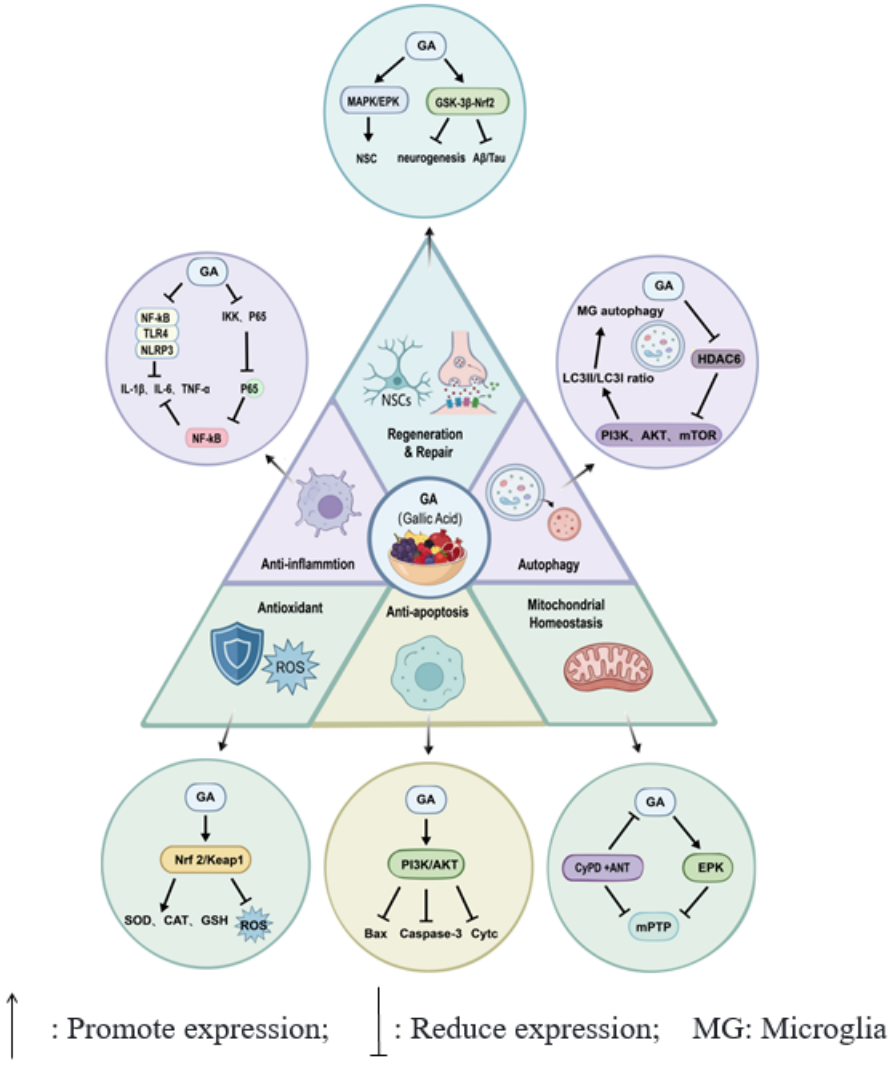

Figure 2. Schematic diagram of GA exerting neuroprotective effects through multiple dimensions

stimulates microglial autophagy to facilitate the clearance of aberrant intracellular components. Collectively, these mechanisms constitute the primary defense system and the requisite foundation for cellular repair.

Furthermore, the regulation of the intracellular microenvironment is essential for sustaining life-sustaining cellular activities. While the induction of autophagy degrades pathological protein aggregates for metabolic recycling, the anti-inflammatory action reprograms the "chronic neuroinflammatory milieu" into a "pro-repair microenvironment." The orchestration of these two processes constitutes a sophisticated bidirectional regulatory network that maintains cellular homeostasis. At the anti-inflammatory level, GA precisely antagonizes the TLR4/NF-κB and NLRP3 inflammasome cascades, thereby suppressing the secretion of pro-inflammatory cytokines such as IL-1β, TNF-α, and IL-6. This comprehensive blockade of neuroinflammation is further supported by the reduction of p-IKK and p-p65 levels and the inhibition of p65 nuclear recruitment in astrocytes. This phase of "environmental detoxification" is a prerequisite for the subsequent replenishment of neuronal populations (neurogenesis) and the reconstruction of neural circuits (synaptic remodeling).

In the dimension of neural remodeling and regeneration, GA promotes the proliferation of neural stem cells

(NSCs) via the MAPK/ERK pathway and accelerates neurogenesis through the GSK-3β-Nrf2 signaling axis. These effects, combined with the attenuation of tau hyperphosphorylation and Aβ burden, significantly upregulate synapse-associated proteins and bolster synaptic plasticity. Enhancing neural plasticity and regeneration constitutes the definitive stage of neurorestoration. In conclusion, the neuroprotective profile of GA does not rely on an isolated mechanism but emerges from a synergistic network. The hierarchical progression—from basal cellular preservation to microenvironmental modulation and, ultimately, structural remodeling—underscores the core advantage of GA as a potent therapeutic agent for the management of neurodegenerative diseases and associated neurological pathologies.

4. Acquisition and nutritional significance of gallic acid

Gallic acid (GA) is ubiquitously distributed across the plant kingdom, occurring prominently in medicinal plants such as *Galla chinensis*, *Rheum palmatum*, *Eucalyptus robusta*, and *Cornus officinalis*, as well as in various fruits, including apples, lemons, grapes, pomegranates, and persimmons. Notably, immature persimmons exhibit high GA concentrations (3–4g/100g), while significant quantities are also detected in dietary staples like green and black tea.

As a bioactive phytochemical, GA holds substantial potential in the development of functional foods, nutraceutical formulations, and clinical adjuvant therapies. Specifically, a CA-GA@ZIF-8 composite film—engineered by encapsulating GA within ZIF-8 frameworks embedded in a carrageenan (CA) matrix—effectively retards proteolysis in stored beef, minimizes the accumulation of total volatile basic nitrogen (TVB-N), and preserves the post-harvest quality of green grapes [52]. Additionally, a chitosan-GA composite solution exerts potent antimicrobial and antioxidant activities, extending the shelf-life of *Larimichthys crocea* while preserving its volatile flavor profiles [53]. Furthermore, composite masks formulated with collagen peptides and GA-modified chitosan exhibit superior hygroscopic and moisture-retention properties, characterized by a moisture absorption rate of 50.33% and a retention rate of 12.14% [54]. Compared to conventional cotton fiber substrates, the integration of micro-nanofiber membranes facilitates a 160.85% augmentation in epidermal hydration after 20 minutes of application, demonstrating profound moisturizing efficacy and sustained radical scavenging capacity.

Beyond industrial and cosmetic applications, GA demonstrates significant therapeutic potential across various pathological conditions. In oncology, the synergistic administration of GA and cisplatin (DDP) suppresses esophageal carcinoma progression via the downregulation of cyclooxygenase-2 (COX-2) [55]. In inflammatory models, GA attenuates gouty arthritis by activating the Nrf2 signaling pathway and subsequently inhibiting NLRP3 inflammasome-mediated pyroptosis [56]. Furthermore, GA promotes oral wound healing by upregulating the activity of fibroblast growth factor (FGF) and epidermal growth factor (EGF) in burn injury models [57]. As a promising adjunct to metformin, GA potentiates the therapeutic efficacy of metformin against murine diabetic kidney disease [58]. Simultaneously, it mitigates diet-induced metabolic dysregulation in skeletal muscle and enhances metabolic flexibility by modulating lactate metabolism and optimizing mitochondrial function [59].

In conclusion, GA is a ubiquitous natural compound with multifaceted utility in food preservation, cosmeceuticals, and adjuvant clinical therapies, representing immense potential for industrial exploitation. Its integration into broader interdisciplinary frameworks warrants further rigorous investigation.

5. Conclusion

Gallic acid (GA) emerges as a significant multi-target therapeutic candidate for neurodegenerative diseases, addressing the limitations of conventional pharmacotherapies, which often offer only palliative relief and carry adverse side effects. This review establishes that GA provides robust neuroprotection through the pleiotropic regulation of oxidative stress, neuronal apoptosis, and inflammatory pathways, including the modulation of β-arrestin2 and microglial polarization. Characterized by high biocompatibility and low toxicity, GA effectively counteracts the multifaceted etiology of neuronal loss compared to traditional mono-targeted approaches. Furthermore, the compound's versatility extends beyond clinical applications to food preservation and cosmeceuticals, highlighting its substantial potential for industrial exploitation. Rigorous investigation within broader interdisciplinary frameworks is essential to further elucidate these molecular mechanisms and facilitate the development of GA-based disease-modifying interventions and adjuvant clinical therapies.

Disclosure statement

The authors declare no conflict of interest.

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