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Review article

Neuroprotective effects of baicalin and baicalein on the central nervous system and the underlying mechanisms

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ABSTRACT

Baicalin and baicalein are the primary flavonoids derived from the desiccated root of *Scutellaria baicalensis*, which is a member of the Lamiaceae family; these flavonoids have diverse pharmacological properties and show significant potential for the management of central nervous system disorders. Multiple studies have indicated that these substances effectively reduce the severity of illnesses such as depression, stroke, and degenerative disorders of the central nervous system by exerting antioxidant and anti-inflammatory effects, regulating programmed cell death, and reducing mitochondrial malfunction. Recent studies have highlighted the connection between the accumulation of iron and the ability of baicalein to protect the nervous system. Given the diverse therapeutic effects of baicalein, this review aims to thoroughly investigate the regulatory pharmacological mechanisms through which baicalein influences the development of central nervous system disorders. By elucidating these mechanisms, this review contributes to the development of therapeutic approaches that target disorders of the central nervous system.

1. Introduction

Neurological disorders (NSDs) are a leading cause of disability and mortality in humans. Stroke and neurodegenerative diseases of the central nervous system (CNS) are the most common NSDs and have received the most attention. Nerve cells are the fundamental components of the CNS, and many CNS illnesses are caused by nerve cell injury or death. Stroke, which is the main cause of death in the population [1], damages the CNS by causing direct or indirect damage to brain tissue and nerve cells through various mechanisms. In 2019, the global prevalence of stroke was 101.5 million individuals [2]. Approximately 2.4 million individuals in China experience new strokes each year, resulting in approximately 1.1 million stroke-related deaths [3]. Given the large numbers of affected individuals and related deaths, stroke will undoubtedly impose an even greater burden with the increasing aging of society. Degenerative diseases of the CNS include a range of disorders that are characterized by neurodegeneration, which impairs the function and structure of the nervous system and affects neuronal activity. Examples of such diseases include Parkinson's disease (PD), amyotrophic lateral sclerosis, Alzheimer's disease (AD), and frontotemporal lobe dementia [4]. Despite extensive research on NSDs, still some of the underlying mechanisms are still incompletely understood [5]. The majority of therapeutic regimens for PD and AD focus on slowing disease progression. Therefore, how to avoid the risk of CNS diseases and improve the health of people has become one of the most urgent issues. Due to the development of resistance during long-term treatment as well as treatment side effects, more effective therapeutic

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drugs that can be used in combination to alleviate patient discomfort are needed.

Chinese medicine is a valuable repository for advances in traditional Chinese medical research. Many of the concepts that are used in the development of contemporary medicine are the result of thousands of years of experience with the use of medications. An herbaceous perennial plant in the Lamiaceae family, *Scutellaria baicalensis* Georgi, is widely distributed throughout Shanxi, Liaoning, Inner Mongolia, Hebei, Heilongjiang, Gansu, Henan, Shandong, and Sichuan [6,7]. The ancient Pharmacopeia "Compendium of Materia Medica" indicates that this substance has the ability to alleviate heat and eliminate moisture, treat diarrhea, detoxify the body, control bleeding, and calm fetuses. Currently, this substance is frequently used in clinical settings to treat cardiovascular disorders [8], cancer [9], liver injury [10], and inflammatory diseases [11].

Baicalin (baicalein-7-O-glucuronide) and its aglycone baicalein (5,6,7-trihydroxyflavone) are major flavonoids that are found in the roots of *S. baicalensis*, which is a legume that belongs to the Lamiaceae family [12]. Its effects on inflammation, oxidative stress, and apoptosis have been shown to be effective in regulating tumor progression [13]. Recent studies have shown its good protective effect on neurons and brain tissues [14]. Due to the diverse activities of baicalin and baicalein in the treatment of NSDs, the main mechanisms of action of baicalin and baicalein in NSDs are summarized in this paper, with the goal of providing more comprehensive evidence for future studies and promoting the clinical application of baicalin and baicalein.

2. Methodology

In this study, information was obtained from PubMed and the Web of Science using “baicalin” and “baicalein” as the search terms. The most recent data were collected from studies published up to May 2024. A total of 158 publications mentioning these terms were identified, 45 of which were clinical studies related to baicalin or baicalein. The inclusion criterion for the literature was that the study focused on the pharmacologic effects of baicalin or baicalein on central nervous system disorders and their underlying mechanisms. Studies that included compounds with baicalin or baicalein were excluded. The aim of this review is to provide a useful reference for the development of clinical applications of baicalin and baicalein by comprehensively analyzing the included literature for future studies.

3. Structure and pharmacokinetics of baicalin and baicalein

Baicalin (baicalein-7-O-glucuronide) is a glycoside flavonoid that is obtained from the dried root of *S. baicalensis*, which belongs to the Labiatae family [15] (Fig. 1A). Baicalin is a glucurinated form of baicalein, and its chemical formula is $C_{21}H_{18}O_{11}$ [16]. The multiple phenolic hydroxyl groups in a molecule are important for its antioxidant function. Baicalein is an aglycone of baicalin and is chemically known as 5,6,7-trihydroxyflavone (Fig. 1B). Its benzene and epoxy rings give it strong anti-inflammatory and antioxidant properties.

The different structures of these compounds result in different bioavailabilities. Baicalin has limited permeability because of its relative hydrophilicity and high molecular weight. In contrast, baicalein, because of its low molecular weight, high lipophilicity, and absence of transporter proteins, may easily pass from the apical surface to the extracellular substrate [17]. The primary route of baicalein metabolism is through glucuronidation. When taken orally, baicalin is converted to baicalein via β-glucuronidase (GUS), which is produced by the intestinal flora. In the intestine, baicalein is absorbed and then metabolized to baicalein-7-glucuronide, baicalein 6-O-glucuronide, and trace amounts of baicalein-6,7-diglucuronide by UDP glucuronosyltransferase (UGT) [18]. Following the process of glucuronidation, baicalin is transported to different tissues through the enterohepatic circulation. Pharmacokinetics indicate that baicalein has a higher absorption rate than baicalein [19], but once it is absorbed, baicalein is quickly degraded in the bloodstream, yielding baicalein and baicalein 6-O-sulfate [20]. Research has shown that approximately 90 % of baicalein is metabolized in the body, resulting in the production of baicalin [21]. Hence, this study primarily investigated the distribution of the drug baicalin within the body (Fig. 2). After intravenous injection, baicalein is distributed throughout the lungs, liver, heart, brain, and kidneys in a pathophysiologically distinct manner, according to an in vivo study that measured the levels of the drug in the blood of rats. Physiologically, baicalin is primarily distributed in lung tissue, whereas after brain Ischemia/Reperfution (I/R) injury, its distribution in brain tissue increases significantly. Approximately half an hour after the intravenous injection of 24 mg/kg baicalin, the maximum concentration of baicalin in the cerebrospinal fluid (CSF) is 344 g/L. The distribution half-life and elimination half-life of

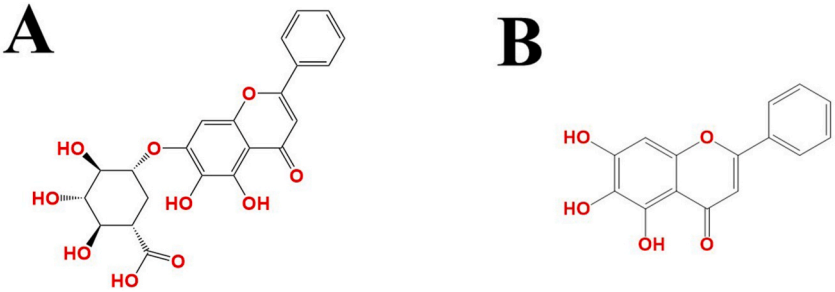

Fig. 1. Chemical structures of baicalin (A) and baicalein (B).

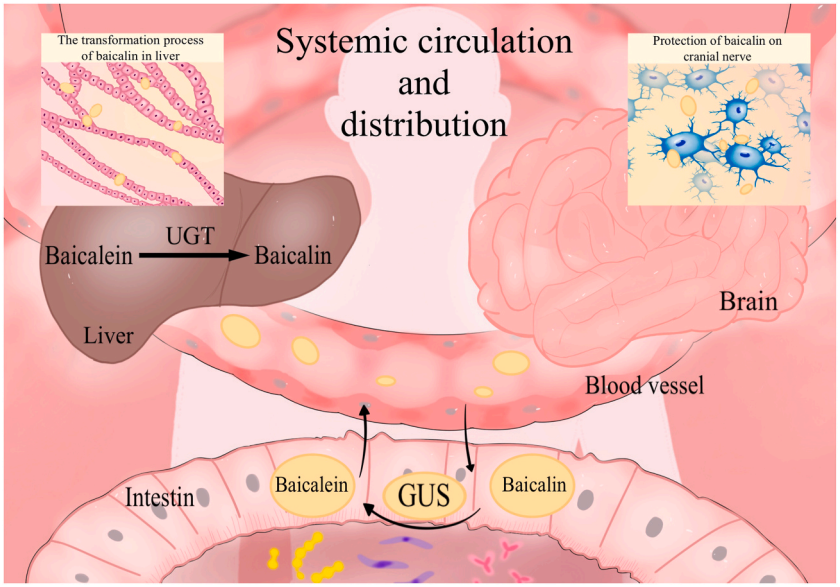

Fig. 2. Metabolism and distribution of baicalin and baicalein in the body. Baicalin, which is transported to the intestine after oral administration, is converted into baicalein by GUS. The absorbed baicalein is converted into baicalin by UGT in the liver and then enters the enterohepatic circulation. During this process, baicalin can be distributed to the brain, lung, heart and other organs. Abbreviations: β-glucuronidase (GUS), UDP-glucuronosyltransferase (UGT).

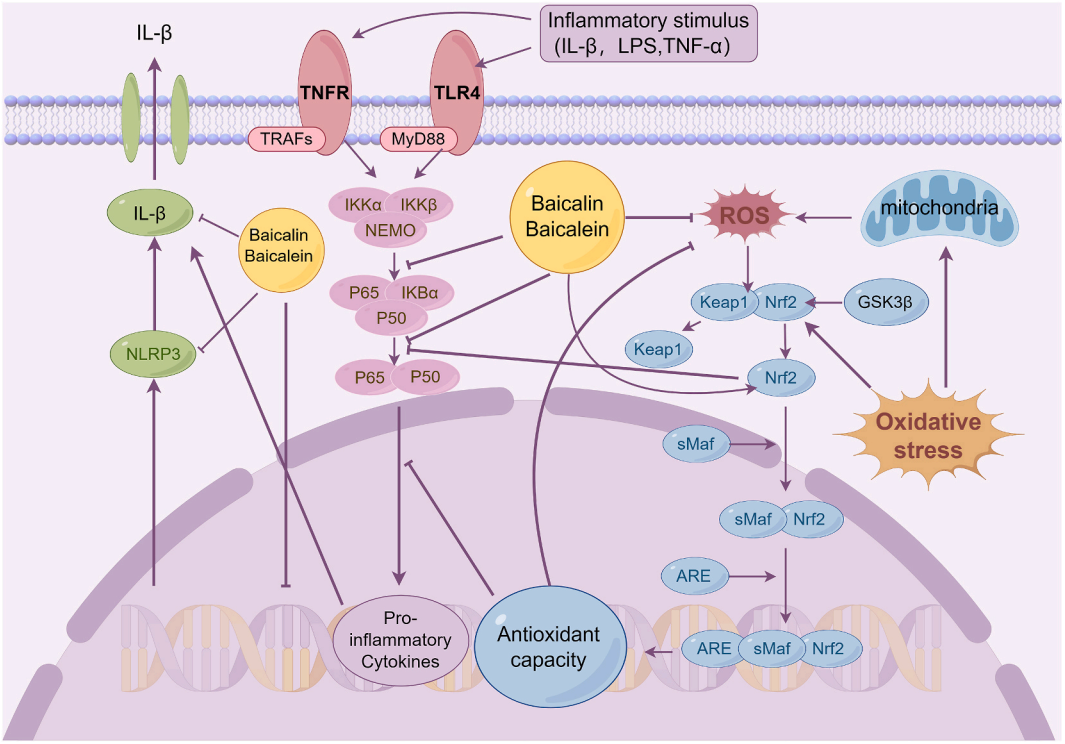

Fig. 3. Main mechanisms underlying the anti-inflammatory and antioxidant effects of baicalin and baicalein. Abbreviations: reactive oxygen species (ROS), tumor necrosis factor receptor (TNFR), tumor necrosis factor receptor-associated factors (TRAFs), IL-1β (interleukin-1β), toll-like receptor 4 (TLR4), myeloid differentiation primary response protein 88 (MyD88), tumor necrosis factor-α (TNF-α), lipopolysaccharide (LPS), NLR family pyrin domain containing 3 (NLRP3), glycogen synthase kinase 3 β (GSK3β), antioxidant response elements (AREs), nuclear factor erythroid 2-related factor 2 (Nrf2), kelch-like ECH-associated protein 1 (Keap1), small Maf transcription factor (sMaf), inhibitory kappa B kinase α (IKKα), inhibitory kappa B kinase β (IKKβ), nuclear factor κB essential modulator (NEMO), and inhibitor kappa B α (IKBα).

baicalin in the CSF of normal rats are 0.8868 and 26.0968 min, respectively. In contrast, the distribution and elimination half-lives in the brains of I/R model rats are 2.084 min and 34.4998 min, respectively [22]. In addition, data from another study suggested that the absorption of baicalin in rats with middle cerebral artery occlusion is superior to that in sham-operated rats [23]. These findings suggest that baicalin possesses superior therapeutic qualities in brain tissues under pathological conditions, and its extended half-life must be considered when this medicine is administered.

4. Physiological functions of baicalin and baicalein and the underlying mechanisms

4.1. Anti-inflammatory activity

Organisms use inflammation in the CNS for two purposes. Appropriate inflammation is necessary for the repair of tissues. However, excessive inflammation not only exacerbates tissue damage but also induces an accelerated process of oxidative stress. The relevant mechanism can be seen in Fig. 3. This is also is an important cause of secondary brain damage. The activation of glial cells is one of the hallmarks of CNS inflammation. Microglia are endogenous immune cells of the CNS and can regulate the immunological balance within the CNS [24,25]. Upon the occurrence of a stroke, microglia are promptly activated in response to cell death or blood leakage. The differentiation of activated microglia leads to their polarization toward two phenotypes: proinflammatory M1 microglia and anti-inflammatory M2 microglia. Microglia with the proinflammatory phenotype secrete neurotoxic chemicals such as proteases, nitric oxide (NO), and proinflammatory factors, causing the adherence and accumulation of neutrophils and macrophages [26]. Inflammatory factors stimulate the activation of microglia and increase the synthesis of additional inflammatory factors through the generation of reactive oxygen species (ROS) and reactive nitrogen species (RNS) [27].

Astrocytes and microglia play overlapping roles in the release of chemokines, cytokines, and inflammatory substances. Both cell types participate in the production of brain-derived neurotrophic factor (BDNF). BDNF is crucial for the development and maintenance of the CNS. BDNF is extensively involved in the development of synapses, the expansion of synapses and dendrites, and the preservation of normal cognitive function [28]. BDNF also coordinates neurorehabilitation and neuroplasticity after the onset of various neurological disorders. BDNF has been extensively studied in rodent models and has been demonstrated to have significant efficacy in the treatment of stroke [29]. The mechanism underlying the anti-inflammatory effects of baicalin is shown in Table 1.

4.1.1. Stroke

Inflammation plays an essential role in the progression of stroke [30]. The inflammatory cytokines IL-1, IL-6, and TNF-α have the

Table 1
Anti-inflammatory mechanisms of baicalin and baicalein.

Disease	Compound	Concentrations	Model	Molecular mechanisms	References
Stroke	Baicalin	2.5, 7.5, and 22.5 μM	BV-2 cells	Inhibition of the TLR4/MyD88/NF-κB signal transduction pathway mediated by TLR4	[41]
	Baicalin	100 mg/kg	Sprague–Dawley rats	Suppression of TLR2/4 and NF-κB expression, hence decreasing the synthesis of iNOS, COX2, and TNF-α	[43]
	Baicalin	25 μg/mL	I/R model rats	Reductions in TNF-α, IL-6, iNOS, TLR2, TLR4 and NF-κB expression	[44]
	Baicalein	5, 10, and 20 μM	C57BL/6 mice	Inhibition of LPS-mediated $sPLA_2$-IIA expression via the suppression of cPLA2 and ERK 1/2	[48]
	Baicalein	30 mg/kg	Sprague–Dawley rats	Upregulation of p38 MAPK, cPLA2 and downregulation of 12/15-LOX after cerebral ischemia	[50]
	Baicalin	10 μg/mL 50 mg/kg	Wistar rats PC12 cells	Effective downregulation of the expression of NOD2 and TNFα	[52]
	Baicalin	100 mg/kg	Sprague–Dawley rats	Reduced blood concentrations of TNF-α and IL-1β, decreased expression of TLR4 and NF-κB, and decreased activities of iNOS and COX2	[53]
	Baicalin	4, 8, and 16 μM	HT-22 cells	Inhibition of the expression of NLRP3	[55]
	Baicalein	50 mg/kg	Sprague–Dawley rats	Decrease in the ROS levels in the ICH, thus inhibiting high NLRP3 inflammasome expression	[56]
	Baicalin	100 and 200 mg/kg	Sprague–Dawley rats	Decrease in NLRP3 inflammasome activity to trigger the AMPK signaling pathway	[57]
Alzheimer's disease	Baicalin	1 mg/mL	BV2 cells, SH-SY5Y cells	Suppression of activation of the NLRP3 inflammasome and the TLR4/NF-κB signaling pathway	[58]
	Baicalein	50 and 100 mg/kg/	VD rats	Attenuated hippocampal inflammatory responses by inhibiting the activation of the TLR4/MyD88/NF-κB signaling pathway.	[59]
	Baicalin	5, 10, and 20 μmol/L	BV2 cells	Promotion of the polarization of microglia from a proinflammatory phenotype to an anti-inflammatory phenotype and inhibition of the activation of downstream NF-κB	[60]
Depression	Baicalin	20 and 40 mg/kg	Sprague–Dawley rats	Reduced the amounts of IL-1β and IL-6 and inhibited the activation of the NLRP3 inflammasome	[64]
	Baicalin	20 and 40 mg/kg	Sprague–Dawley rats	Inhibiting the activation of the GSK3β/NF-κB/NLRP3 signaling pathway	[67]
	Baicalin	25 and 50 mg/kg	ICR mice	Suppressed the expression of HMGB1, TLR4, p-NF-κBp65, IL-1β, IL-6, and TNF-α	[68]

potential to disrupt the blood–brain barrier, impair neuronal function and neuroplasticity, and exacerbate neurological impairments [31]. Inflammatory markers in the serum have become important indicators for predicting the prognosis of stroke [32]. The causal relationship between nuclear factor-kappa B (NF-κB) and inflammatory factors has been clearly established. Cytokines such as TNF-α and IL-1 can stimulate NF-κB. Under typical physiological conditions, NF-κB signaling in neurons can increase synaptic development and activity, which is advantageous for the survival of neurons [33,34]. Conversely, in the context of neurodegenerative diseases and traumatic injuries, the activation of NF-κB signaling in microglia and astrocytes facilitates proinflammatory reactions and the release of inflammatory substances. Inhibiting NF-κB in cells is beneficial for the restoration of neurological function [35].

4.1.1.1. NF-κB. The NF-κB signaling pathway is a well-established pathway that is involved in the inflammatory response. Stimuli such as TNF-α and LPS in the blood can activate NF-κB. The degradation and phosphorylation of IκB family members drive the translocation of the NF-κB p65-p50 dimer into the nucleus, where it interacts with target genes and performs its transcriptional function. Toll-like receptor 4 (TLR4) is an upstream protein that activates the inflammatory response. It initiates signaling that mediates the phosphorylation and degradation of IκB. Moreover, TLR4 stimulates and supports the NF-κB complex, as well as NF-κB p65, which translocates into the nucleus [36]. At this time, microglia polarize toward the M1 phenotype and secrete inflammatory factors, contributing to the development of neuroinflammation.

In innate immunity, TLRs are a classical family of molecules that are intimately associated with the inflammatory response in CNS disorders. TLRs are widely expressed in microglia and astrocytes [37,38]. TLRs activate the NF-κB pathway, ultimately leading to the translocation of the NF-κB complex to the nucleus, where it binds to DNA, promoting gene transcription and the release of chemokines, cytokines, and other cytotoxic chemicals that regulate inflammation [39]. Research indicates that inhibiting TLR4 can reduce MyD88 and NF-κB expression in microglia, thereby suppressing M1 polarization and alleviating inflammation [40]. A docking analysis revealed that baicalin could bind to and interact robustly and stably with the TLR4-MD2 active site [41]. The synthesis of IL-1β by microglia is the initial event that triggers neuroinflammation, leading to the amplification of the cascade inflammatory response and the development of neurodegenerative disorders. PGE2, which is an important biomarker of inflammatory conditions, is a byproduct of arachidonic acid that is synthesized by the enzyme cyclooxygenase-2 (COX-2), which controls the rate of its production [42]. In a lipopolysaccharide (LPS)-induced BV-2 microglial model, PGE2 attenuated the production of the inflammatory mediators NO, iNOS, IL-1β, PGE2, and COX-2. Baicalin suppressed the activities of TLR4, MyD88, and IRAK1 in LPS-induced microglia and decreased the production of NF-κB P65 and p-IκBα while increasing the levels of IκBα. Researchers have determined that the antineuroinflammatory effect of baicalein is strongly associated with the suppression of the TLR4/MyD88/NF-κB pathway [41]. Elevated levels of the NF-κB p65, iNOS, and COX-2 proteins were observed in rats with permanent middle cerebral artery occlusion (MCAO), along with the production of TNF-α and IL-1β in brain tissues, which coincided with cerebral infarction. This effect was reversed when the mice were administered 100 g/kg baicalin via intraperitoneal injection. By decreasing the expression of TLR2/4, NF-κB p65 was inhibited. The enzyme activities of iNOS and COX-2 and the serum levels of TNF-α and IL-1β also appeared to be reduced. These findings suggest that the ability of baicalin to attenuate the inflammatory response to cerebral infarction is correlated with its ability to inhibit TLR2/4 and NF-κB [43]. Baicalin has neuroprotective effects by reducing neurological function scores, decreasing the volume of tissue damage caused by stroke, and decreasing the amount of water in the brain, thus ameliorating aberrant brain structures and preventing the infiltration of immune cells in living organisms. The mechanism also involves the suppression of TLR2, TLR4, and NF-κB expression and decreasing the levels of TNF-α, iNOS, and IL-6 in tissues [44].

4.1.1.2. CPLA2. Increased concentrations of fatty acids and PLA2 derivatives, such as arachidonic acid-like substances and PAF, are characteristic indicators of cerebral ischemia and reperfusion. These substances can cause cell damage and death [45]. Cytoplasmic phospholipase A2 (CPLA2) is a member of the PLA2 family. CPLA2 functions by breaking down phosphatidic acid, resulting in the release of arachidonic acid (AA). The release of AA then triggers the inflammatory cascade. Astrocytes are the main source of cPLA2 in the CNS [46]. As an enzyme that regulates the process of forming biologically active molecules, such as AA, prostaglandins, and platelet-activating factor (PAF) [47], it has been associated with neurological diseases, acute inflammatory responses and oxidative stress. Baicalein exerts a favorable inhibitory effect on cPLA2, and it can attenuate the inflammatory response of cells by inhibiting cPLA2 [48]. Previous research has shown that the secretion of IL-1β and IL-6 can be diminished by blocking the p38 MAPK/cPLA2 pathway [49]. Baicalein, a lipoxygenase inhibitor, attenuates the inflammatory response in brain tissues, reduces the brain water content and infarct area, and relieves neurological deficit symptoms by downregulating the levels of 12/15-lipoxygenase (12/15-LOX), p38 mitogen-activated protein kinase (p38 MAPK), and cPLA2 in the ischemic cortex [50].

4.1.1.3. NLRs. Nod-like receptors (NLRs) are sensors that participate in intracellular pattern recognition and perform important functions in host innate immune responses and immunological homeostasis preservation. NOD-like receptor protein 1 (NOD1), NOD-like receptor protein 2 (NOD2), and NOD-like receptor protein 3 (NLRP3) belong to the NLR family, and members of this family are essential for the body's inherent immunity. NOD1 and NOD2 activate the NF-κB and MAPK pathways to initiate the inflammatory response. NLRP3, on the other hand, can be triggered by pathogen-associated molecular patterns and damage-associated molecular patterns. Then, NLRP3 interacts with associated proteins and enzymes to produce the NLRP3 inflammasome [51]. The impact of baicalin on NOD2/TNFα signaling was investigated by Li et al. both in vitro in cells exposed to hypoxic glucose deprivation (OGD) and in vivo in animals subjected to cerebral I/R injury. These findings indicated that the expression of NOD2 and TNFα was increased in cells subjected to OGD. Nevertheless, the administration of baicalin reversed this effect, thereby mitigating the inflammatory response associated with brain injury [52]. Another study suggested that baicalein exerts neuroprotective effects by inhibiting TLR2/4-NOD2

expression in neurons, preventing NF-κB translocation to the nucleus and consequently inhibiting the production of TNF-α, IL-6, and IL-1β to prevent inflammatory reactions [53].

NLRP3-coupled proteins and enzymes can regulate the secretion and maturation of IL-1β and IL-18 precursors and induce inflammation after the formation of the NLRP3 inflammasome [51]. Both glial cells and neurons frequently contain NLRP3 inflammatory cysts. The activation of the NLRP3 inflammasome can promote the polarization of microglia toward the M1 phenotype, which in turn exacerbates neuroinflammation [54]. Baicalin suppresses the activation of the NLRP3 inflammasome, leading to a decrease in inflammation and the preservation of nerve cells [55]. As a result of NLRP3 inflammasome inhibition, baicalin reduces inflammation and protects neuronal cells. In a rat intracerebral hemorrhage (ICH) model, baicalein reduces brain damage caused by ICH by suppressing the accumulation of the NLRP3 inflammasome [56]. Furthermore, regarding cerebral ischemia–reperfusion injury, the activation of the NLRP3 inflammasome leads to notable increases in the production of NLRP3, ASC, IL-1β, IL-18, and cleaved caspase-1. In contrast, baicalin decreases NLRP3 inflammasome activation and suppresses cerebral ischemia–reperfusion damage [57]. The regulation of NOD-like receptor proteins has clearly emerged as an effective mechanism by which baicalin alleviates secondary brain damage caused by inflammation.

4.1.2. Alzheimer's disease

The transcription factor NF-κB plays a pivotal role in intracellular signaling, exerting effects on both apoptotic and inflammatory responses. The specific and major function of this protein has attracted substantial attention within the context of AD. Researchers have reported an increase in the expression of TLR4 and an increase in the phosphorylation of IκBα and NF-κB p65 in AD model animals and in LPS/Aβ-treated BV2 cells. Additionally, increased neuronal death was observed, leading to learning and memory impairments in the mice. In contrast to the findings mentioned earlier, baicalein reduces the expression of TLR4, hinders the phosphorylation and degradation of IκBα, and suppresses the subsequent translocation of NF-κB p65 to the nucleus. These findings indicate that baicalin reduces neuroinflammation in microglia and ameliorates cognitive impairment by blocking the TLR4/NF-κB signaling pathway [58]. Another study revealed that baicalein inhibits the progression of AD by modulating the phosphorylation of NF-κB pathway components. In microglia, p-IκBα and p-NF-κB p65 are inhibited by baicalein, which effectively reduces the production of NO, iNOS, COX-2, IL-1β and PGE2 [41]. In recent studies, baicalein was shown to reduce glial cell activation and proinflammatory factor release by modulating the TLR4/MyD88/NF-κB signaling pathway. This activity effectively attenuated the cognitive dysfunction caused by neuronal damage in the CA1 region of the hippocampus [59]. Furthermore, baicalin not only suppresses the phosphorylation of NF-κB pathway components and their nuclear translocation but also mitigates the neurodegenerative damage induced by inflammation by regulating the transformation of neuronal cells to an anti-inflammatory state. Treatment with baicalin decreases the number of M1-type BV2 cells, increases the number of M2-type BV2 cells, and restores the semiadherent round or spindle cell morphology of some cells [60].

4.1.3. Depression

Although the exact cause of depression remains uncertain, a significant amount of clinical evidence indicates that inflammatory conditions play an integral role in its development. Research has indicated that individuals who suffer from depression frequently experience inflammatory problems or heightened levels of inflammatory markers. Moreover, depressive symptoms are effectively relieved by the suppression of inflammation [61]. Due to the favorable anti-inflammatory properties of baicalin and baicalein, their ability to treat depression has been well explored.

The activation of the innate immune system in the nervous system is initiated by chronic stress, leading to the formation of NLRP3 inflammasome complexes with ASC and the transformation of procaspase-1 into active caspase-1. This process is considered one of the causes of depression. Activated caspase-1 can cleave pro-IL-1β to produce IL-1β, which leads to the development of neuroinflammation. An essential part of the innate immune system in the CNS is the NOD-like receptor protein 3 (NLRP3) inflammasome. In fact, this inflammasome is the link between chronic stress, proinflammatory cytokines and depression [62]. The brains of mice with LPS-induced depression exhibit elevated expression of IL-1β and the NLRP3 inflammasome, indicating that the NLRP3 inflammasome represents a crucial intermediate between chronic stress and neuroinflammation [63]. The prefrontal cortex (PFC) of the brain was found to have elevated levels of proinflammatory cytokines, such as IL-1β and IL-6, as well as increased expression of proteins in the NLRP3 inflammasome pathway, including NLRP3, ASC, and cleaved caspase-1, in a rat chronic unpredictable mild stress (CUMS) model of depression. In contrast, the levels of NLRP3 inflammasome pathway proteins are notably decreased, and the levels of IL-1β and IL-6 in the blood are decreased following the administration of baicalin. Moreover, the locomotor activity of rats was markedly increased, and their stationary behavior decreased. This finding indicates a significant association between the positive impact of baicalin on depressive symptoms and its capacity to inhibit NLRP3 inflammasome activation, hence decreasing neuroinflammation [64].

NF-κB serves as the upstream signaling molecule of the NLRP3 inflammasome. The suppression of NF-κB results in reduced expression of NLRP3 [65]. Glycogen synthase kinase-3 (GSK3) is a kinase that participates in the TLR4 signaling pathway connected to depression in the nervous system [66]. Activation of this process stimulates the generation of cytokines, but the function of GSK3 is inhibited when it is phosphorylated. In their constructed model, Zhang et al. showed that rats exposed to CUMS had decreased levels of p-GSK3β and significantly increased levels of NF-κB, NLRP3, ASC, and caspase-1 in the hippocampus. Conversely, baicalein administration increased the phosphorylation of GSK3β, hence inhibiting the activation of the NF-κB and the NLRP3 inflammasome. Consequently, neuroinflammation was decreased due to a reduction in the levels of the inflammatory markers caspase-1 and IL-1β. Therefore, the primary characteristic of depression, namely, weight loss, was reduced compared with that in the control group. Additionally, these rats exhibited increased levels of activity. This study proposed that baicalin improves depression-like behavior

through the control of the GSK3/NF-B/NLRP3 signaling pathway [67]. Moreover, another study showed that the expression of HMGB1, TLR4, and p-NF-κBp65 was reduced by baicalin, leading to a significant reduction in the levels of the proinflammatory cytokines IL-1β, IL-6, and TNF-α in PC12 cells. Thus, through the suppression of the corticosterone-induced HMGB1/TLR4/NF-κB pathway in PC12 cells, baicalein effectively decreases symptoms associated with depression [68].

Overall, baicalin regulates inflammation and may alleviate depression through the upstream and downstream regulation of NF-κB.

4.2. Antioxidant activity

OS is a condition in which the body's oxidation process is out of sync with antioxidant action. OS damages tissues and results in excessive levels of free radicals. ROS and RNS are two common types of free radicals. The significant ROS that are involved in OS are the hydroxyl radical (OH), superoxide radical anion (O2-), nitric oxide (NO), and peroxyl radical (ROO) [69]. Because of its high oxygen consumption, the brain is prone to an oxidative imbalance, which leads to the generation of more ROS. Conversely, the limited function of antioxidant enzymes in neurons in the brain hinders the efficient and rapid elimination of free radical-induced damage under oxidative stress conditions. Hence, OS is crucial for the progression of NSDs. The antioxidant mechanism of baicalin is illustrated in Table 2.

4.2.1. Stroke

4.2.1.1. Nrf2. The Nrf2 signaling pathway is the major antioxidative stress mechanism in organisms, and Nrf2 serves as a key regulator of this process. The Nrf2 signaling pathway is activated in response to ROS exposure, and Keap1 dissociates from Nrf2. Superoxide dismutase (SOD), heme oxygenase (HO-1), glutathione S-transferase (GST), and NAD(P)H are among the antioxidant-related genes that are transcriptionally activated when Nrf2 migrates to the nucleus and binds to AREs. The substantial levels of ROS that are present during the occurrence of ischemic stroke result in oxidative stress. Apoptosis and brain tissue damage are reduced by quickly attenuating the injury caused by OS through the activation of the Nrf2 signaling pathway. Scientific research has substantiated this fact. By stimulating the Nrf2 signaling pathway and increasing Nrf2 nuclear translocation, atorvastatin effectively decreases OS in ischemic cerebral infarction and enhances neurological recovery in stroke model mice [70]. Nrf2 also represents a potential therapeutic target for cerebral hemorrhage [71]. These findings indicate a significant association between the Nrf2 pathway and the process of recovery from stroke.

Antioxidant enzymes in the body, including SOD and GST, protect the organism from OS-mediated damage caused by ROS. Baicalin (when administered at 4 μg/mL and 8 μg/mL) strongly reduced ROS generation and supported an increase in SOD secretion from

Table 2
Antioxidant mechanisms of baicalin and baicalein.

Disease	Compound	Concentrations	Model	Molecular mechanisms	References
Stroke	Baicalin	60 mg/kg	bEnd.3 cells	Activation of the Nrf2 pathway, leading to increased expression of Nrf2, HO-1, and NQO1	[72]
	Baicalin	50, 100, and 150 mg/kg	TBI model mice	Increases in the GSH-Px and SOD levels and decreases in the levels of Bax and caspase3 by activating the Akt/Nrf2 pathway	[74]
	Baicalin	3 and 8 mg/mL	RAW264.7 cells	Activation of the Nrf2/HO-1 pathway and reduction in ROS production	[75]
	Baicalin	15 mg/kg	Sprague–Dawley rats	Scavenging of hydroxyl radicals, superoxide anion, and DPPH radicals	[77]
	Baicalin	5, 20, and 50 μM	SH-SY5Y cells, MCAO model rats	Direct scavenging of superoxide and peroxynitrite	[78]
	Baicalin	50, 100, and 150 mg/kg	MCAO model rats	Inhibition of peroxynitrite-mediated MMP-9 activation	[80]
Parkinson's disease	Baicalin	50, 100, and 150 mg/kg	PD model mice	Increases in the SOD, CAT, and GSH-Px contents in the striatum	[82]
	Baicalin Baicalein	10, 25, 50, and 100 μM	SH-SY5Y cells	Reductions in Bax expression and caspase-3 cleavage by promoting ERK1/2 phosphorylation and inhibiting ROS production and ΔΨm loss	[83]
	Baicalin	100 mg/kg	PD model mice	Increase in the brain GSH and GSH-Px contents and reduction in MDA levels	[84]
	Baicalin	1, 10, and 100 μM	*C. elegans*	Decrease in MDA production and increases in GSH and GSH-PX expression by modulating the p38 MAPK signaling pathway	[85]
	Baicalin	12.5, 25, and 50 μM 50, 100, and 200 mg/kg	BV2 cells PD model mice	Upregulation of the Nrf2 pathway and inhibition of NLRP3 inflammasome activation	[86]
	Baicalin	10, 50, 100, and 400 μg/mL	PD model rats	Reduction in iron accumulation in the substantia nigra by decreasing the iron concentration, positive regulation of divalent metal transporter protein 1 expression, and negative regulation of iron transporter protein 1 expression	[89]
	Baicalin	78 mg/kg	Wistar rats	Decreased accumulation of iron in the brain through the regulation of DMT1 and FP1 expression	[90]

bEnd.3 cells in which OS was triggered by LPS. Baicalin has also been shown to exert antioxidant effects by inhibiting Nrf2, HO-1, and NQO1 and stimulating the intracellular Nrf2 pathway to protect the blood–brain barrier [72]. AKT is a cellular signaling protein. The translocation of activated AKT to the nucleus results in the phosphorylation of Nrf2 [73]. Fang et al. reported that the activation of the Akt pathway resulted in increased Nrf2 nuclear translocation and immunoreactivity in a group treated with baicalin. The expression of the downstream antioxidant genes HO-1 and NQO-1 increased as a result. Additionally, the high levels of MDA and low expression of the antioxidant enzymes SOD and GSH-Px were reversed. Thus, baicalin is thought to reduce TBI-induced neurological impairments and cerebral edema by stimulating the Akt/Nrf2 pathway [74]. Furthermore, baicalein effectively crosses the blood–brain barrier (BBB) and stimulates the Nrf2/HO-1 pathway via specialized brain-targeted exosomes derived from macrophages loaded with baicalein. In ischemia-damaged brain tissues, ROS levels decrease, and OGD-induced neuronal damage is reversed. According to the results, specific targeting of the brain by Exos-BA resulted in stronger cerebral protective effects than baicalin [75]. Another study on baicalein revealed that baicalein activated the Nrf2/ARE pathway by decreasing the expression of miR-106a-5p, which targets PHLPP2, in rats with cerebral hemorrhage, resulting in increased serum levels of SOD and GSH-Px. Moreover, baicalein inhibited the development of OS after cerebral hemorrhage and attenuated brain tissue damage and neuronal apoptosis [76].

Baicalin is a potent free radical scavenger. Researchers discovered that baicalin inhibited the ROS production and reduced MDA levels in brain tissues from a rat model of cerebral I/R injury induced by middle cerebral artery occlusion (MCAO). Both NADPH oxidase activity and SOD activity increased concurrently. Baicalin also exerted direct antioxidant effects by scavenging superoxide anions, hydroxyl radicals, and DPPH radicals [77]. Superoxide anions were eliminated from brain tissues following baicalein treatment, according to the findings of electron paramagnetic resonance (EPR) spin-trapping investigations. Although baicalin was used only at a concentration of 5 nM, it inhibited the superoxide signal intensity by 26.687 ± 5.37 % [78].

4.2.1.2. RNS. In brain I/R injury, RNS are important neurotoxins that increase the vulnerability of brain tissues to ischemic injury. Peroxynitrite (ONOO-), which is generated when superoxide radicals and nitric oxide (NO) combine, is a typical RNS [79]. ONOO- has been shown to be involved in the development of neurodegenerative disorders, vascular illnesses, and I/R trauma. Xu et al.'s mass spectrometry (MS) studies revealed that baicalin can directly interact with ONOO- and decrease the neurotoxicity of both naturally occurring and externally introduced ONOO- in SH-SY5Y cells [78]. Other studies using the MCAO rat model confirmed this finding. In the baicalin-treated group, ONOO- was effectively removed, and the mortality rate was significantly reduced, ameliorating the t-PA-mediated hemorrhagic transformation and disruption of the blood–brain barrier. Inhibiting activation of MMP-9 by ONOO- may minimize neurological damage [80]. The strong antioxidant potential of baicalein may be attributed largely to its direct scavenging of peroxynitrite.

4.2.2. Parkinson's disease

One of the pathological pathways that leads to PD is OS. Patients with PD are at risk of neurodegenerative diseases because of the susceptibility of the substantia nigra to OS. Antioxidant enzymes, including SOD, GSH-Px, GSH and catalase (CAT), are thought to become less active as we age. Therefore, the antioxidant system cannot reduce the levels of free radicals [81]. Therefore, older people are more frequently diagnosed with PD in the clinic. MDA levels are increased, but SOD, CAT, and GSH-Px activities are decreased in PD model rats in the OS state. By protecting the rats from the oxidative damage caused by 6-OHDA and reducing apoptosis, baicalin reversed these effects. Moreover, after the administration of baicalin, monoamine neurotransmitter release was increased, and abnormal behavioral symptoms, such as rigidity and body tremors, were ameliorated in PD model rats [82]. In a study on the neuroprotective effects of baicalein on rotenone-induced cytotoxicity, rotenone-treated cells displayed nuclear condensation and fragmentation along with widespread death. In addition, the ROS levels increased 2.19 ± 0.36-fold. Baicalein effectively decreased apoptosis, decreased ROS generation, and ameliorated PD symptoms to attenuate OS [83]. Another study investigating the impact of baicalin on MPTP-induced PD in mice revealed that baicalin diminished MDA levels and elevated GSH and GSH-Px levels in brain tissues [84]. In a 6-hydroxydopamine (6-OHDA)-treated model of *Cryptococcus hippocastanum* infection, baicalein decreased cleaved caspase-3 protein levels and attenuated OS in vivo by decreasing MDA levels and increasing SOD, CAT, GSH, and GR levels [85]. Recent studies have shown that the neuroprotective mechanism of baicalin in PD models is related to the Nrf2 pathway. By significantly upregulating the expression of Nrf2 and its downstream antioxidant enzymes, as well as inhibiting the activation of NLRP3 inflammatory vesicles, baicalin alleviated oxidative stress, microglial activation, and inflammatory responses [86].

Furthermore, an irregular distribution of Fe2+ has been observed in the brain. Fe2+ levels are relatively high in the substantia nigra and are localized in the dense zone of the substantia nigra [87]. Thus, DA neurons are susceptible to Fenton or Haber–Weiss reactions. These processes change H_2O_2 to OH, which results in elevated OS, DNA damage, and autophagic cell death [88]. Research suggests that brain tissues often exhibit increased levels of OS indicators and iron accumulation in PD patients. Previous research revealed that baicalein negatively affects the expression of iron transporter protein 1 (FP1) and positively regulates the expression of divalent metal transporter protein 1 (DMT1), lowering the concentration of iron in the substantia nigra [89]. According to another PD study, baicalin suppresses iron accumulation and OS levels by controlling the expression of DMT1 and FP1, increasing GSH levels, and decreasing MDA levels [90]. Several investigations have established a correlation between the accumulation of iron and the manifestation of symptoms associated with PD. The ability of baicalin to alleviate oxidative stress and ameliorate PD symptoms may be mediated by reducing iron accumulation in the substantia nigra.

4.3. Resistance to cell death

External factors or intracellular disorders usually cause regulated cell death (RCD). Necroptosis, pyroptosis, ferroptosis, alkaliptosis, and oxeiptosis are among the RCD pathways [91]. Among these processes, we investigated the associations among necroptosis, iron shortage, and the development of brain illnesses.

Apoptosis is a genetically controlled form of programmed cell death that maintains the intracellular environment. It consists of two main forms: endogenous apoptosis and exogenous apoptosis. Exogenous apoptosis is mediated by membrane receptors, including the cell surface death receptor FAS and TNF receptor superfamily member 1A (TNFRSF1A), and is driven by caspase 9 or caspase 8 [92]. The BCL2 family governs mitochondrial outer membrane permeabilization (MOMP), which triggers endogenous apoptosis. Caspases 3 and 6 ultimately trigger substrate cleavage and disruption of the subcellular structure, which ultimately results in apoptosis [93].

Ferroptosis is a form of iron-dependent programmed cell death. Its primary mechanism is the induction of cell death through ester oxygenase or divalent iron-catalyzed lipid peroxidation of unsaturated fatty acids in the cell membrane [91]. Recent research has confirmed its importance in neurological conditions [94,95]. Table 3 displays the mechanisms by which baicalin and baicalein impact programmed cell death.

4.3.1. Stroke

4.3.1.1. Ferroptosis. System Xc-/GSH/GPX4 is the classical pathway of ferroptosis. SLC7A11 and SLC3A2 comprise System Xc-, which is a cystine/glutamate reverse transporter on the plasma membrane [96]. System Xc-transfers extracellular cystine to the nucleus for GSH synthesis. GSH is an important substrate for the generation of GPX4. GPX4 is a lipid peroxide scavenger and a downstream regulator of ferroptosis. When GPX4 is inactivated, the accumulation of lipid peroxides triggers ferroptosis [97]. The toxic effects of iron overload are among the factors that contribute to secondary damage in hemorrhagic stroke patients. Heme is released in large quantities after the lysis of red blood cells in hematomas. Iron, biliverdin, and carbon monoxide are produced following heme degradation [98]. Concomitantly, the amounts of the iron-binding proteins ferritin and transferrin (TF) are increased. Cell death results from the oxidation of lipids through OS and cell membranes caused by excessive iron accumulation [99]. Because of the deterioration of the BBB during ischemic stroke, large amounts of unbound iron and ferritin can reach the brain tissue [100]. On the other hand, the acidic environment induces the dissociation of Fe from TF [101], increases intracellular iron absorption, and promotes increased extracellular levels of iron and its transmission to neurons [102]. The excessive accumulation of iron triggers the Fenton reaction, leading to the generation of ROS, which in turn initiate the ferroptosis process and ultimately cause cell death [100]. Eliminating iron accumulation has been documented to be a successful therapeutic strategy for ischemic stroke [103]. Research indicates that the gradual exacerbation of iron-induced cell death in brain tissues can be reduced by the ferroptosis inhibitors ferrostatin-1 (Fer-1) and liproxstatin-1 (Lip-1) [104].

Baicalin, which is a potent antioxidant, has been proven to mitigate iron-induced cell death by regulating molecules both upstream and downstream of GPX4 [105]. Lipid peroxidation and the accumulation of oxidation products serve as indicators of iron-induced cell death [106]. By establishing a model of early brain injury following subarachnoid hemorrhage, Zheng et al. studied the link between baicalein and iron mortality. Baicalin increased the GSH and GPX4 protein levels while decreasing the Fe2+, MDA, and lipid ROS levels. Moreover, the beclin1 protein level was reduced in brain tissues, indicating that cellular autophagy was inhibited. By modulating the GSH/GPX4 pathway, baicalein attenuated the damage caused by ferroptosis in the brain tissues of SAH model rats [107]. The

Table 3
Mechanisms by which baicalin and baicalein prevent cell death.

Disease	Compound	Concentrations	Model	Molecular mechanisms	References
Stroke	Baicalin	4 mL/kg	SAH model rats	Decreases in the Fe^{2+}, malondialdehyde, and ROS levels and downregulation of the protein expression of beclin1, LC3-II, and LC3-I	[107]
	Baicalin	5, 10, and 20 μM	ICH model mice PC12 cells	Increases in GPX4 production and System Xc- activity, reductions in ROS generation and inhibition of ferroptosis	[109]
	Baicalein	50 mg/kg	Sprague–Dawley rats	Inhibition of ferroptosis by targeting ALOX15	[110]
	Baicalin	50, 100, and 200 mg/kg	Mongolian gerbils	Promotion of BDNF expression, increase in the antioxidant enzyme content in brain tissue, and inhibition of caspase-3 expression	[122]
	Baicalin	40 μM	SCI model rats	Stimulation of the PI3K/Akt signaling pathway, leading to a decrease in the expression of Bax and Caspase-3	[118]
	Baicalein	3.5 μM	Sprague–Dawley rats	Increased GSK3β gene expression by stimulating the PI3K/Akt signaling pathway	[119]
	Baicalein	200 mg/kg	Sprague–Dawley rats	Increase in the Bcl-2/Bax ratio and reduction in caspase-3 production by activation of the PI3K/Akt/mTOR pathway	[120]
	Baicalin	120 mg/kg	HIE rats	Upregulation of p-Akt and glutamate transporter protein 1 expression	[131]
	Baicalin	25, 50, and 100 mg/kg	Wistar rats	Inhibition of PAR-1 and Caspase-3 expression	[124]
Alzheimer's disease	Baicalin	5, 10, 20, 30, and 40 μM	SH-SY5Y cells	Regulation of the level of the CyclinD1 protein by inhibiting the Ras-ERK signaling pathway	[130]

TFRC and solute carrier family 11 membrane 2 (SLC11A2) genes regulate intracellular iron transport and deposition [108]. By inhibiting ROS production and suppressing the iron transport gene SLC11A2, baicalin inhibited ROS production. The levels of GPX4 and SLC7A11 expression were markedly increased, as was the activity of System Xc-. This treatment alleviated motor deficits in ICH model mice, which inhibited neuronal ferroptosis [109]. Furthermore, in a brain I/R injury model, baicalein reversed the brain damage caused by ferroptosis by regulating the GPX4/ACSL4/ACSL3 axis. In contrast to the model group, baicalein-treated mice presented decreased ACSL4 activity and increased levels of GPX4, ACSL3, and SLC7A11 in their brains [109]. Another study revealed that baicalein decreased ROS and iron accumulation and increased GPX4 levels in organisms suffering from traumatic brain injury due to cardiac arrest [110]. These findings indicate that baicalein is critical for inhibiting the progression of stroke by inhibiting lipid peroxidation and iron accumulation.

4.3.1.2. Apoptosis

4.3.1.2.1. PI3K/AKT. Apoptosis is characterized by the degradation of cellular components and the shrinking of a cell. In response to cerebral ischemia, decreased levels of Bcl-2 and increased levels of Bax activate caspases to initiate apoptosis-related cascades [111]. Caspase 3 mediates apoptosis, exacerbating DNA damage and fragmentation. Both Bcl-2 and Bax belong to the Bcl-2 family. Bcl-2 opposes apoptosis, whereas Bax promotes it. Astrocytic dysfunction can be effectively alleviated by increasing Bcl-2 expression in neurons [112,113]. For this reason, Bcl-2, Caspase-3, and Bax are important indicators of apoptosis. Several studies have shown that inhibiting apoptosis reduces ischemic damage in the brain [114].

As one of the irreplaceable signaling pathways in organisms, the phosphatidylinositol 3-kinase (PI3K)/protein kinase B (AKT) pathway plays vital roles in cell survival, apoptosis, and proliferation. Studies of stroke have shown that the PI3K/AKT pathway attenuates brain tissue damage through several mechanisms [115,116]. Zhao et al. investigated the effects of baicalein on spinal cord injury using a modified Allen shock model. In an excitotoxic model in SH-SY5Y cells, p-PI3K, p-Akt, and Bcl-2 were downregulated, whereas Bax and Caspase-3 were upregulated. These results are consistent with those of previous studies [117]. The phosphorylation of PI3K and AKT by baicalin leads to an increase in Bcl-2 levels and decreases in Bax and Caspase-3 levels. Furthermore, the disruption of the BBB and neuronal apoptosis are attenuated. Moreover, baicalin also reverses the expression of NF-κB and attenuates neuroinflammation [118]. PTEN is a negatively regulated phosphatase of AKT that causes cells to cease division and undergo apoptosis. Neuronal cells that were treated with baicalin were less likely to undergo OGD/R-induced apoptosis. Due to the ability of baicalin to block PTEN phosphorylation in the ischemic hemiparetic area, increased PI3K/AKT pathway activity leads to an increase in GSK3β expression [119]. In addition to its direct impact on apoptosis, the PI3K/AKT pathway plays additional roles, including regulating autophagy and blocking apoptosis. By suppressing caspase-3 expression and increasing the Bcl-2/Bax ratio, baicalein decreased neuronal death, as shown by a Western blot analysis of proteins linked to autophagy and apoptosis. Additionally, baicalein promoted the phosphorylation of PI3K/Akt/mTOR signaling pathway components, increasing autophagy in I/R model rats, which indirectly inhibited neuronal apoptosis [120].

Furthermore, in ischemic brain injury, neuronal death is triggered by glutamate-mediated excitotoxicity [125]. Thus, GLT-1 is essential for neuronal protection. Zhou et al. reported that baicalein upregulated PI3K/AKT expression and increased glutamate transporter protein-1 (GLT-1) expression. The PI3K/AKT/GLT-1 pathway is responsible for protecting brain cells from apoptosis in neonatal rats with hypoxic-ischemic encephalopathy [126].

4.3.1.2.2. BDNF. BDNF is a crucial neurotrophic factor that plays a significant role in supporting the survival of neurons and facilitating changes in the connections between them, known as synaptic plasticity [121]. By binding to the high-affinity receptor TrkB, BDNF activates intra- and extracellular kinases and exerts multiple neuroprotective effects. The results of real-time RT−PCR and Western blot analyses demonstrated notable upregulation of BDNF expression. Moreover, the production of caspase-3, which is closely associated with apoptosis, appeared to be downregulated in I/R model gerbils after baicalein treatment [122]. This result may be related to the role of the BDNF-activated signal-regulated kinases ERK and PI3K. A neuron−astrocyte coculture system revealed that astrocytes subjected to OGD/R became reactive astrocytes and released BDNF, which bound to TrkB to activate a downstream cascade of responses—the PI3K/AKT pathway and the mitogen-activated protein kinase (MAPK)/extracellular signal-regulated kinase (ERK) pathway. Through the activation of the PI3K/AKT pathway, baicalein decreased the protein levels of Bax, caspase-3, and caspase-9 via the BDNF/TrkB pathway. Thus, baicalein successfully decreased oxidative stress, inflammation, and apoptosis following I/R [123].

4.3.1.2.3. PAR-1. In another study, baicalin reduced the brain tissue water content and neuronal apoptosis in rats with acute cerebral hemorrhage, possibly by inhibiting PAR-1 expression [124]. Ju et al. also reported that the percentages of apoptotic cells were 15.5 %, 11.3 % and 7.4 % in the 5, 10, and 20 μM baicalin treatment groups, respectively, and these results were accompanied by a decrease in caspase-3 expression after the inhibition of PAR-1 mRNA and protein expression. These findings suggest that baicalein may attenuate neuronal damage after brain I/R by inhibiting PAR-1 to reduce caspase-3 levels. Previous research has demonstrated that activated PAR-1 increases NMDA receptor sensitivity and exacerbates glutamate-mediated neuronal apoptosis [125] or induces apoptosis by exacerbating intracellular Ca + overload [126]. However, some studies have shown that baicalin has an inhibitory effect on PAR-1. However, few studies have examined its impact on apoptosis via PAR-1, and the precise underlying mechanism still requires investigation.

4.3.2. Alzheimer's disease

The ERK pathway, which is a well-established inflammatory pathway, is involved in regulating cell differentiation, proliferation, and death. The ERK protein is located in the axons and dendrites of neuronal cells, and its phosphorylation transmits stimulatory signals to the nucleus. Overactivation of the ERK pathway causes neuronal cell death. Abnormal activation of the Ras-ERK pathway can

trigger apoptosis, a process that is closely associated with degenerative disorders, including AD [127]. In neuronal cells treated with oligomeric Aβ42, the levels of Ras and p-ERK were significantly increased. The level of the G1/S-specific cell cycle protein D1 (Cyclin D1) was elevated, which not only led to cell cycle deregulation but also was an important cause of AD-related neuronal loss [128]. Cyclin D1 is a protein that is encoded by the CCND1 gene in humans, and it plays a crucial role in controlling the activity of CDKs, which are protein-dependent kinases involved in the cell cycle. Cyclin D1 accumulation and aberrant cell cycle activation are thought to be directly related to neuronal apoptosis [129]. Abnormal stimulation of the cell cycle in terminally developed neurons results in Aβ1–42-induced SH-SY5Y cell apoptosis. This effect is achieved by activating MAPK-ERK1/2. During this process, a notable increase in the expression of the Ras protein and considerable increases in the p-ERK1/2 and Cyclin D1 levels are observed further leading to neuronal cell damage and apoptosis. After treatment with 10 μM or 20 μM baicalein, the number of cells in S phase is significantly reduced, which effectively alleviates the cell cycle arrest induced by Aβ. WB indicated that activation of the Ras-ERK pathway is suppressed, ameliorating cognitive impairment in the rats. These findings reveal that the ability of baicalein to preserve neurons is strongly associated with its ability to block the proapoptotic ERK pathway [130].

4.4. Suppression of mitochondrial dysfunction

By synthesizing ATP, regulating Ca + channels, and regulating OS, mitochondria maintain energy metabolism homeostasis in the body. Additionally, mitochondria can maintain their dynamic homeostasis through division, fusion, transport, and autophagy. Dysfunctional mitochondria produce more ROS, produce less ATP, and induce apoptosis. These changes are directly or indirectly associated with CNS pathology. Mitochondria, which are the main source of endogenous ROS, have a strong connection with the body's OS response [132]. In the mitochondrial electron transport chain, electrons that escape from complexes I, II, and III in the respiratory chain react with oxygen to produce either superoxide anion (O2-) or hydrogen peroxide (H_2O_2) [133]. During mitochondrial reverse electron transfer, NAD+ is reduced to NADH, the NADH/NAD + ratio increases, and the mitochondria are in a state of peroxidation, with an increased O2 content and the generation of large amounts of ROS [134].

4.4.1. MMP

The mitochondrial membrane potential (MMP) is critical for maintaining ATP production by the respiratory chain. A reduction in the activity of respiratory chain complex I results in the depolarization of the membrane potential and the accumulation of ROS. Conversely, an increase in ROS levels results in a subsequent decrease in the membrane potential, establishing a vicious cycle. The evidence indicates that mitochondrial damage, which is strongly associated with OS, plays a substantial role in the development of CNS diseases [134,135]. In PD patients, OS is severe in the substantia nigra, as evidenced by decreased GSH levels [136], mitochondrial respiratory chain complex I dysfunction [136,137], and DNA oxidative damage. Hence, mitigating the harmful effects of oxidative damage caused by malfunctioning mitochondria has emerged as a crucial focus in research on therapeutic options for PD. Eun Byul Jung reported that baicalein inhibited the increase in mitochondrial permeability caused by the depletion of cellular GSH, modulated changes in the cell membrane potential, and prevented the activation of the apoptotic cascade [138]. Additionally, a study of rats with chronic cerebral underperfusion revealed that baicalein improved oxidative phosphorylation and the membrane potential, as well as the mitochondrial production of ROS, demonstrating its therapeutic potential for treating chronic cerebral underperfusion-induced dementia [139].

4.4.2. DJ-1

Studies have shown that the DJ-1 gene protects cells from OS and mitochondrial damage [140]. In vivo, mice with both DJ-1 gene mutations and DJ-1 gene deficiencies display compromised mitochondrial respiration, a decreased mitochondrial membrane potential, increased amounts of mitochondrial ROS, and modified mitochondrial morphology [141]. Baicalein mitigated the decrease in mitochondrial redox activity and the significant decrease in the mitochondrial membrane potential in PD model rats treated with 6-OHDA. Additionally, baicalein increased the expression of the DJ-1 gene, leading to an attenuated OS response and protection of brain mitochondrial homeostasis and function [142].

4.4.3. $BNIP_3L$/NIX

Mitochondrial autophagy is a cellular process that specifically eliminates malfunctioning mitochondria, as well as their detrimental metabolites and oxidized substances, through autophagy regulatory systems. The pathways are mainly categorized into two main groups, namely, the PINK1/Parkin pathway and the mitochondrial autophagy receptor protein-related pathway. The mitochondrial autophagy receptor protein $BNIP_3L$/NIX pathway is an important pathway that mediates mitochondrial autophagy [143]. $BNIP_3L$ interacts with LC3 and connects damaged mitochondria to autophagosomes through its cytoplasmic-oriented LC3 interaction region motifs, initiating mitochondrial autophagy [144]. The LC3-II/LC3-I ratio indicates the status of autophagy [145]. Previous studies have shown that baicalein regulates apoptosis through the $BNIP_3$ pathway [146]. In a PD rat model, treatment with baicalein increased the LC3-II/LC3-I ratio and decreased the MMP. Moreover, downregulated miR-30b promoted the upregulation of NIX and BNIP3 expression [147].

Additionally, baicalein-mediated activation of the AMPK/PGC-1α pathway to promote NIX-mediated mitochondrial autophagy greatly reduces depression-like behavior in CUMS model mice [148]. Min Chen et al. suggested that reduced mitochondrial autophagy is the main cause of the pathological consistency and selective susceptibility of brain regions in PD patients. By inhibiting miR-30b, baicalein activated the AMPK/mTOR pathway, which is involved in the control of autophagy and neuronal apoptosis in PD, and ameliorated the low LC3-II/I ratio in PD model rats [149]. These findings suggest that baicalein and baicalein have diverse and

comprehensive effects on promoting mitochondrial autophagy and ameliorating mitochondrial dysfunction. The mechanisms by which baicalein and baicalin ameliorate mitochondrial dysfunction are shown in Table 4.

5. Safety and toxicological studies of baicalin and baicalein

As the pharmacological effects of baicalin and its glycoside baicalein have been explored in depth, their clinical safety and adverse effects have also received attention. Clinical data revealed that none of the 72 healthy people who participated in a randomized, double-blind experiment in which they were administered a single oral dose of baicalin and baicalein ranging from 100 to 2800 mg reported any negative side effects. Furthermore, laboratory assessments revealed no indications of liver or kidney toxicity [150]. In a study on the oral safety of baicalein, 36 healthy individuals were randomly assigned to receive 200, 400 or 600 mg baicalein tablets. The findings indicated that all negative occurrences were minor in nature and were handled without any need for intervention [151]. However, this does not indicate the safety of baicalin and its glycoside baicalein. There have also been trial results suggesting that some subjects experienced adverse events of elevated high-sensitivity C-reactive protein (hs-CRP) levels and elevated triglyceride levels while taking baicalein tablets [152]. Yi Cai et al. showed that high doses (800–1600 mg/kg) administered for 8 weeks may pose a risk of nephrotoxicity in rats [153].

Since the relevant trials have not explored the temporal correlation of hepatic and renal toxicity caused by baicalein and its glycoside baicalein. Therefore, we believe that further trials should be conducted to discuss in depth the hepato- and nephrotoxicity and other risks associated with the long-term use of baicalin and its glycoside baicalein. This would be beneficial for the safety of clinical trials conducted.

In view of the scarcity of clinical trials on baicalin and its glycoside baicalein, its use still carries a high degree of risk. We think that its known adverse reactions could be a potential threat to subjects. Therefore, the health status of subjects, especially their hepatic and renal functions, should be fully assessed before subsequent trials are conducted.

6. Conclusions

Baicalin and its aglycone baicalein are the primary constituents of flavonoid derivatives from *S. baicalensis* roots. As multitarget neuroprotective agents, these compounds play good therapeutic roles in treating degenerative diseases of the CNS, including stroke, AD, and PD. Researchers have paid substantial attention to these compounds. In recent years, the mechanisms underlying their neuroprotective effects have been revealed. Anti-inflammatory and antioxidant effects, a reduction in neuronal apoptosis, and the attenuation of mitochondrial dysfunction are among the favorable effects these compounds produce.

Inflammation and OS are two key steps in brain injury. These two steps are closely related concomitant reactions. Oxidative stress causes the inflammatory infiltration of neutrophils, increased protease secretion, and the production of proinflammatory substances. In addition to activating the NLRP3 inflammasome, ROS also increase the synthesis of proinflammatory cytokines and increase microglial polarization toward the M1 phenotype. Inflammation occurs with the secretion of inflammatory factors and exacerbates oxidative stress by stimulating cells to produce excess ROS. The protective effects of baicalin and its glycoside baicalein on the nervous system are closely associated with two core components: its anti-inflammatory and antioxidant effects. By triggering the Nrf2 pathway and lowering intracellular ROS levels, these compounds prevent oxidative stress-mediated NF-κB activation. The antioxidant enzyme HO-1 in the Nrf2 pathway also inhibits NF-κB-dependent inflammatory activity. In addition, we focused on the important role of iron accumulation in brain injury. Excessive iron accumulation in brain tissue leads to OS, contributes to neuronal cell damage and apoptosis, and accelerates the development of NSDs. Baicalin modulates programmed cell death by lowering iron accumulation and decreasing the generation of ROS and MDA in vivo. Ferroptosis, which has been a popular research topic in recent years, has been investigated in many studies. The link between baicalin and ferroptosis has been noted. However, few relevant studies are available on this topic, the specific mechanism involved is still unclear, and this topic still needs to be explored in depth. In addition, this paper only summarizes the main mechanisms by which baicalein and baicalin affect NSDs, but some mechanisms have not been included due to insufficient numbers of relevant studies and insufficient evidence. Many studies cited in this paper only discussed the effect of different

Table 4
Mechanisms by which baicalin and baicalein inhibit mitochondrial dysfunction.

Disease	Compound	Concentrations	Model	Molecular mechanisms	References
Alzheimer's disease	Baicalein	100 mg/kg	Wistar rats	Maintenance of the mitochondrial membrane potential and reduction in mitochondrial swelling	[139]
Parkinson's disease	Baicalein	10 and 25 μM	PC12 cells	Restoration of the mitochondrial membrane potential and reduction in cytochrome *c* release	[138]
	Baicalein	0.1, 1, and 10 μM	SH-SY5Y cells	Decreased lipid peroxidation and ROS generation by the upregulation of DJ-1 protein expression	[142]
	Baicalein	100 mg/kg	Sprague–Dawley rats	Upregulation of NIX and BNIP3 expression to decrease LC3 and P62 levels and stabilize the MMP	[147]
	Baicalein	100 mg/kg	Sprague–Dawley rats	Amelioration of mitochondrial dysfunction by the SIRT1/AMPK/mTOR pathway	[149]
Depression	Baicalin	20 mg/kg	CUMS model mice, HT22 cells	Increase in NIX and BNIP3 expression to downregulate LC3, P62, and TOM20 expression	[148]

doses of baicalein and baicalin on NSDs but did not elaborate on the relationship between the dosing concentration of baicalein or baicalin and time. Further research is needed to determine the optimal duration of drug retention in in vivo and in vitro models.

In conclusion, baicalin and its glycoside baicalein are natural plant compounds with many properties and good therapeutic effects on a variety of NSDs. However, their inherent structure results in low bioavailability, which limits their efficacy in damaged tissues. Considering this challenge, various drug delivery strategies, such as solid dispersions, inclusion complexes, phospholipid complexes, nanotechnology and micelles, have been explored, but more formulations are still needed to increase their bioavailability and maximize the pharmacological effects of baicalin and baicalein.

CRediT authorship contribution statement

Lujia Si: Writing – original draft. **Yupu An:** Formal analysis. **Jiahang Zhou:** Writing – original draft. **Yu Lai:** Writing – review & editing, Supervision, Funding acquisition.

Data availability statement

No original data were created in this literature review. Therefore, this article does not deposited data in a publicly repository.

Ethical approval and consent to participate

This is a literature review, the ethical statement do not apply here.

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Declaration of competing interest

All the authors declare that they have no conflicts of interest.

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