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Natural Polyphenols Against Cerebral Ischemia and Mechanism of Action: A Review

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Abstract: Cerebral ischemia is a disorder characterized by insufficient blood flow to the brain, which can lead to severe neurological deficits and brain damage. Given the complexity of cerebral ischemia and the limitations of current pharmacological treatments, there is a growing scholarly interest in natural polyphenols. Polyphenols are a diverse group of secondary metabolites, and these compounds have a strong antioxidant capacity, and oxidative stress is one of the main causes of post-ischemic brain damage. A major consequence of ischemia is the interruption of normal cellular processes due to oxygen and glucose deprivation, resulting in the production of reactive oxygen species (ROS). These ROS damage cellular structures, trigger an inflammatory response, and exacerbate neuronal death. In addition, some polyphenols have a direct effect on the cerebral vasculature; they improve endothelial function and enhance microcirculation, which is essential for restoring blood flow and oxygenation to ischemic brain tissue. Polyphenols can also affect mitochondrial function by promoting mitochondrial biogenesis and reducing mitochondrial dysfunction, which plays a key role in cell death during ischemic episodes. Therefore, this paper reviews the potential therapeutic effects of natural polyphenols on cerebral ischemia, focusing on their anti-ischemic effects and related mechanisms.

Keywords: Natural polyphenols; antiischemic; phytochemistry; pharmacology.

1. Introduction

Cerebral hemorrhage is a common clinical disease, is non-traumatic in the brain parenchyma blood vessel breakage and lead to bleeding, accounting for about 25% of stroke patients, its clinical acute mortality rate is about 35%, the patient's morbidity and smoking, hyperlipidemia, vascular

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aging, diabetes mellitus and hypertension and so on are closely linked. The patient is generally due to the effort to force, emotional excitement is the sudden onset of the early mortality rate is very high, and most of the surviving patients and the existence of different degrees of speech and swallowing disorders, cognitive impairment and movement disorders and other complications, on the patient's quality of life has a serious impact [1-3]. Cerebral hemorrhage manifests itself in many forms, including acute (ACI), transient (TIA), and chronic (CCI) cerebral ischemic attacks of vascular disease. Ischemia deprives brain cells of vital oxygen and nutrients they need, leading to cell death, inflammation, and oxidative stress. Despite advances in modern medicine, treatments for cerebral ischemia are limited, focusing on thrombolytic therapy and the use of neuroprotective drugs, and hampered by side effects, narrow therapeutic windows, and the complexity of ischemic injury [6-7]. The pathophysiology of cerebral ischemia involves several interrelated processes, each of which leads to neuronal damage and death. One of the most immediate and devastating responses to ischemia is the production of ROS due to the lack of oxygen and glucose.ROS, including free radicals such as superoxide and hydrogen peroxide, cause damage to cellular components such as lipids, proteins, and DNA. This oxidative stress disrupts cellular homeostasis, leading to inflammation, mitochondrial dysfunction and activation of cell death pathways. At the same time, ischemia triggers an inflammatory response that activates microglia, astrocytes, and releases pro-inflammatory cytokines and chemokines. This neuroinflammation exacerbates neuronal damage and impedes recovery.

It is in this context that natural polyphenols show promise. The antioxidant properties of polyphenols play a key role in neutralizing ROS and reducing oxidative damage and have emerged as a promising area of research. Polyphenols are secondary metabolites that are widely found in nature. Their antioxidant properties play a key role in scavenging ROS and alleviating oxidative damage. By scavenging free radicals, polyphenols help maintain cellular integrity and protect neurons from the deleterious effects of ischemic injury. In addition to their antioxidant properties, they also exert anti-inflammatory effects by modulating key signaling pathways involved in inflammation. Polyphenols such as resveratrol and curcumin have been shown to inhibit the nuclear factor-κB (NF-κB) pathway, a central regulator of inflammatory responses in the brain. By reducing the production of pro-inflammatory cytokines, polyphenols may limit neuroinflammation and improve neuronal survival [8-9] .

In addition, polyphenols have been found to affect several signaling pathways critical for cell survival and death. For example, activation of the Nrf2 (nuclear factor-red factor 2-related factor 2) pathway enhances the expression of antioxidant enzymes and detoxification proteins, providing additional protection against oxidative stress. Polyphenols such as curcumin have also been shown to regulate apoptotic pathways by balancing pro- and anti-apoptotic proteins, thereby promoting neuronal survival under ischemic conditions. In addition, polyphenols can modulate mitochondrial function, which is critical for maintaining neuronal energy production and cell survival. Through these mechanisms, polyphenols offer a potential therapeutic strategy against neurological damage caused by cerebral ischemia [10].

Natural polyphenols are a promising frontier for the treatment of cerebral ischemia. Through their potent antioxidant, anti-inflammatory and neuroprotective effects, they have the potential to mitigate the devastating consequences of ischemic brain injury. The aim of this paper is to organize and summarize the effects and related mechanisms of natural polyphenols con cerebral ischemia, so as to provide scientific references for the further exploration of natural polyphenols and the

expansion of polyphenol utilization and application.

2. Search Methodology

In this paper, a comprehensive review and analysis of existing literature was conducted to investigate the anti-ischemic effects of natural polyphenols. Relevant literature was obtained from several databases, including Medline PubMed, Science Direct, Web of Science, Baidu Scholar, Google Scholar, and CNKI. The keywords natural polyphenols, anti-ischemic effect, and mechanism of action were used in the search (Displayed in **Figure 1**). Some relevant studies were also retrieved by manually searching the reference lists of the selected articles. The chemical structures were generated using Chem Draw Professional 20.0 software and the diagrams were drawn using Fig Draw and WPS.

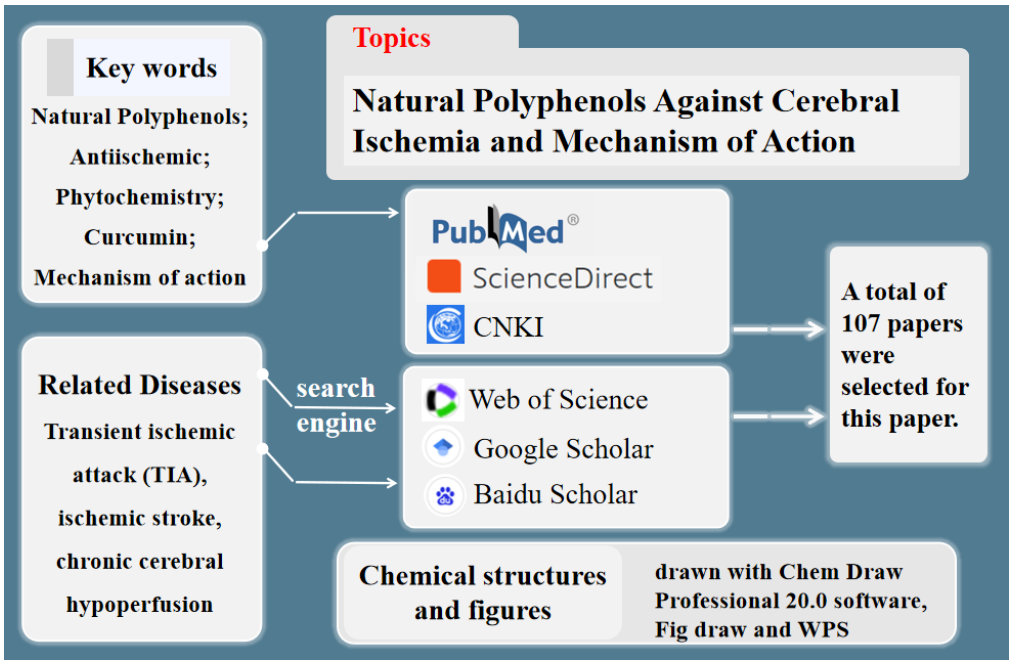

Figure 1. List of search channels

3. Disease Types and Causes

3.1 Acute Cerebral Ischemia

Acute cerebral ischemia (cerebral infarction) is classified as “stroke” in Chinese medicine, which has the characteristics of acute onset, rapid progression, high disability and mortality, and is the most common type of stroke, accounting for about 70% of all strokes. It refers to the ischemic and hypoxic necrosis of brain tissues caused by interruption of the cerebral blood supply without adequate compensatory blood supply from the collateral circulation, and then the neurological symptoms that result.

Atherosclerosis is the most common cause of ACI [13], and cardiogenic embolism accounts for 15% to 30% of the causes [14]. In addition, arterial occlusive type, which is caused by intracranial small arterial lesions, arterial entrapment, intracranial arterio-venous malformations, central nervous system vasculitis, etc. are also causative factors. Studies have shown that patients with ACI are caused by atherosclerotic thrombosis, and atherosclerosis may be the primary cause

of the development of cerebral infarction [15], and patients with atherosclerosis may have a greater chance of developing multisegmental embolisms, and there is a risk of synchronized formation and dislodgement of vulnerable plaques and generation of multisegmental emboli [16]. However, Chen et al [17] found that the incidence of multiple embolic events (MSE) was significantly higher in patients with cardiogenic embolism than in patients with large atherosclerotic arteries, which is presumably related to the physical properties of the emboli and the hemodynamic environment. Literature [18] has shown that headache and nausea can occur in 10%-25% of posterior inferior cerebellar artery (PICA) ischemic strokes and cerebellar ischemic strokes, and that acute ischemic strokes leading to isolated vertigo are mostly located in the cerebellum (16/18), suggesting that cerebellar ischemic strokes are an important cause of central acute vestibular syndrome, with vertigo as a common symptom [19]. In addition, isolated vertigo can be triggered by selective injury to the nucleus vestibularis or the medullary junction VIII of the pons pallidus, a region of the brain where nerves enter the pons [20-23].Another study found that a large influx of Ca2+ activates phospholipase and membrane proteases, which damages the cell membrane structure, leading to brain tissue necrosis and edema, and ultimately irreversible brain damage [24-25].

In summary, the etiology and pathogenesis of ACI are diversified, involving different pathological pathways such as atherosclerosis and cardiogenic embolism, and specificity in clinical symptoms; at the same time, the high sensitivity of brain tissues to ischemia and the complex pathophysiological cascade triggered by it suggests that early identification of acute cerebral infarction, precise diagnosis of its etiology, and timely intervention are essential for avoiding irreversible damage to brain tissues and improving the outcome of ACI [26].

3.2 Transient Ischemic

Transient cerebral ischemia (TIA) refers to the occurrence of a temporary insufficiency of blood supply to the cerebral blood supply system, resulting in transient localized cerebral functional deficits that do not reach the level of acute cerebral infarction [27]; the typical clinical symptoms of TIA last mostly 10 to 15 minutes, with the symptoms resolving within one hour in most cases, and the maximum duration of the symptoms is not more than 24 hours. It is characterized by the absence of permanent neurological impairment after the seizure, the absence of positive signs on physical examination, and the inability to detect the corresponding responsible lesion on imaging [28]. In Chinese medicine, TIA belongs to the category of “vertigo”, which is mainly caused by phlegm, dampness, blood stasis, obstruction of cerebral collaterals, and qi and blood dysfunction, and the etiology of TIA usually includes vascular lesions, abnormalities of blood components, and hemodynamic alterations [29]. Studies [30-31] have shown that TIA is an independent risk factor for cerebral infarction, and 15% to 20% of patients with TIA progress to cerebral infarction within 90 d of onset.

The pathogenesis of TIA is complex and involves a number of aspects such as vasospasm, microthromboembolism, and hemodynamic alterations, and studies have suggested that noncoding RNA molecules such as cyclic RNA and microRNA may be involved [32-33]. Among them, the microthrombus-embolism doctrine is considered to be the central mechanism, in which atherosclerotic plaque rupture at the bifurcation of carotid and intracranial large arteries, or microembolus dislodgement of cardiogenic origin (e.g., in patients with atrial fibrillation) enters the cerebral vasculature along with the blood flow, and the obstruction of distal blood vessels triggers clinical symptoms. Hemodynamic factors and hematological disorders should also not be

overlooked, as they account for a certain proportion of TIAs. Additionally, intracranial arteritis and cerebral artery steal syndrome are also important etiological factors for TIAs.

3.3 Chronic Cerebral Ischaemia

Ischemic cerebrovascular disease is a group of diseases triggered by insufficient cerebral tissue perfusion, cerebral vascular stenosis, thrombosis or embolism, which mainly includes CI and CCI [34-35]. Among them, CCI is a cerebral perfusion inefficiency syndrome caused by long-term vascular or circulatory diseases. Epidemiologic data show that CCI has a significant age predisposition, with approximately 70% of patients over 80 years of age [36-37]. With the deterioration of the disease, the symptoms of chronic insufficient blood supply to the brain tissue will gradually worsen [38-39]. From the perspective of Chinese medicine, the onset of CCI is closely related to emotional and emotional disorders, dietary disorders, overwork, old age and physical decline and the decline of internal organs, and its core pathomechanism is an imbalance of yin and yang, deficiency of the liver and kidney, which ultimately leads to a loss of moistening of the cerebral orifices [40].

At the histopathological level, CCI can lead to typical changes such as cerebral cortical and hippocampal neuronal cell atrophy, glial cell compensatory hyperplasia and cerebral white matter laxity [41]. Study [42] confirmed that nitric oxide (NO) can sustain damage to brain tissue in both acute and chronic stages of chronic cerebral ischemia. Yu Fen et al [43] found that neuronal apoptosis triggered by an imbalance between DNA damage and repair is the key pathogenesis of CCI, while Du Yehong et al [44] pointed out that CCI can accelerate the process of neuronal loss. In addition, Emerich et al [45] showed that cerebral ischemia activates endothelial cells, astrocytes, and perivascular inflammatory cells, exacerbating brain injury by triggering an inflammatory cascade. Cognitive dysfunction and energy metabolism disorders likewise play important roles in the pathologic process of CCI [46-47]. In summary, CCI is a chronic progressive disease with multifactorial and Mult mechanistic effects. An in-depth understanding of the pathogenesis of CCI is of great significance for optimizing clinical diagnosis and treatment strategies and delaying disease progression. This section is summarized in Figure 2.

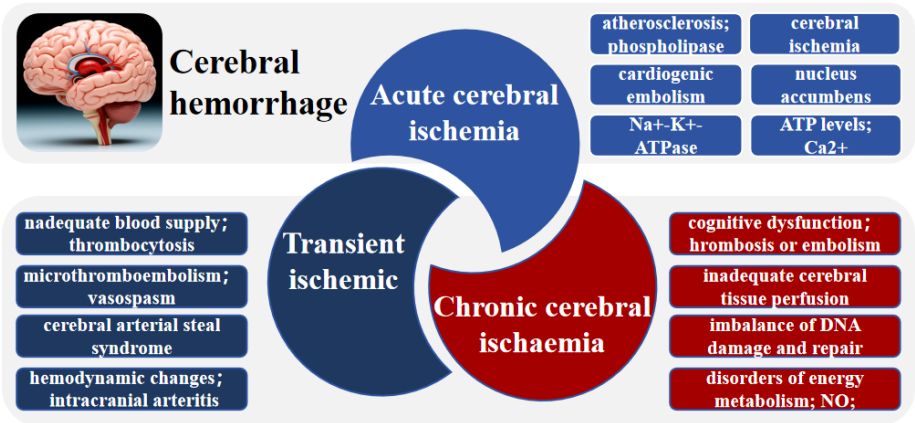

Figure 2. ACI, TIA, CCI and their related causes

4. Sources and Classification of Natural Phenols

Natural polyphenols are a class of secondary metabolites widely found in the plant kingdom, and may be found in abundance in various parts of plants such as skin, roots, leaves, flowers, fruits and seeds. Polyphenols contain multiple phenolic hydroxyl groups in their structure, which gives them unique chemical properties, and they play a role in defense against ultraviolet radiation and pathogens in plants [48] . Polyphenols are complex in structure and chemically active, and are often found in plants as mixtures of a large number of homologs with similar properties. Currently, four types of polyphenols can be categorized based on the number of phenolic rings and the coupling of these rings: phenolic acids, flavonoids, stilbenes, and lignans. Simple phenols are relatively simple in structure, such as hydroquinone, etc. Phenolic acids introduce functional groups such as carboxyl groups on the basis of phenols, like gallic acid, etc. Flavonoids have the basic C_6-C_3-C_6 skeleton and are the most diverse class of polyphenols, including flavonoids, flavonols, dihydroflavonoids, and other subtypes; stilbenoids have 1,2-diphenylethene as the basic structural unit, and resveratrol is a typical representative of them. Lignans are plant compounds present in dietary fiber, and among natural resources, flaxseed provides the richest source of lignans, followed by grains, legumes, vegetables and fruits [49-52] (summarized in Figure 3).

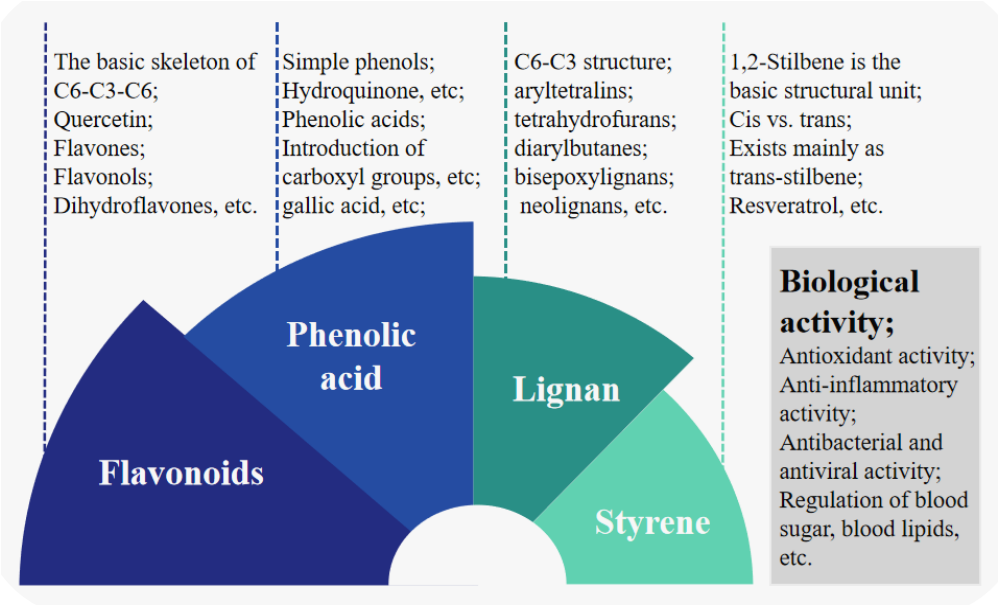

Figure 3. Polyphenol structure types and biological activities

Pharmacological studies have shown that polyphenols have a variety of biological activities. Polyphenols such as resveratrol and curcumin have been shown to inhibit the NF-κB pathway, a central regulator of inflammatory responses in the brain. By reducing the production of pro-inflammatory cytokines, polyphenols can limit neuroinflammation and improve neuronal survival. Polyphenols prevent cardiovascular disease by improving vascular endothelial function, lowering blood lipids, and inhibiting platelet aggregation. The antioxidant properties of polyphenols play a key role in neutralizing ROS and reducing oxidative damage.

Table 1. Natural polyphenols against cerebral ischemia

No.	Name	**formula**	**Ref.**
1	Resveratrol	$C_{14}H_{12}O_3$	[56]
2	Caffeic acid	$C_9H_8O_4$	[57]
3	Kaempferol	$C_{15}H_{10}O_6$	[58]
4	Pterostilbene	$C_{16}H_{16}O_3$	[59-60]
5	Hydroxysafflor Yellow A	$C_{27}H_{32}O_{16}$	[61-62]
6	Schisandrin B	$C_{23}H_{28}O_6$	[63]
7	Epigallocatechin gallate	$C_{22}H_{18}O_{11}$	[64]
8	Carthamin yellow	$C_{43}H_{42}O_{22}$	[65]
9	6-Gingerol	$C_{17}H_{26}O_4$	[66]
10	Flavanols	$C_{15}H_{14}O_2$	[67]
11	Phyllanthin	$C_{24}H_{34}O_6$	[68]
12	Apigenin	$C_{15}H_{10}O_5$	[69]
13	Hexahydrocurcumin	$C_{21}H_{26}O_6$	[70]
14	Curcumin	$C_{21}H_{20}O_6$	[70]
15	Xanthohumol	$C_{21}H_{22}O_5$	[71]
16	Quercetin	$C_{15}H_{10}O_7$	[72]
17	Isorhapontigenin	$C_{15}H_{14}O_4$	[73]
18	Cajaninstilbene acid	$C_{21}H_{22}O_4$	[74]
19	Silymarin	$C_{25}H_{22}O_{10}$	[75]
20	Juglanin	$C_{20}H_{18}O_{10}$	[76]
21	Rosmarinic acid	$C_{18}H_{16}O_8$	[77]
22	Scutellarin	$C_{21}H_{18}O_{12}$	[78]
23	3,5-dicaffeoylquinic acid	$C_{25}H_{24}O_{12}$	[78]
24	Tectorigenin	$C_{16}H_{12}O_6$	[79]
25	Salvianolic acid C	$C_{26}H_{20}O_{10}$	[80]
26	Trilobatin	$C_{21}H_{24}O_{10}$	[81]
27	2,3,5,4'-Tetrahydroxystilbene-2-O-β-D-Glucoside	$C_{20}H_{22}O_9$	[82]
28	Sesamol	$C_7H_6O_3$	[83]
29	Syringic acid	$C_9H_{10}O_5$	[84]
30	Ferulic acid	$C_{10}H_{10}O_4$	[85]
31	Luteolin	$C_{15}H_{10}O_6$	[86]
32	Calycosin	$C_{16}H_{12}O_5$	[87-88]
33	Formononetin	$C_{16}H_{12}O_4$	[87-88]
34	Daidzein	$C_{15}H_{10}O_4$	[87-88]
35	Isorhapontigenin	$C_{15}H_{14}O_4$	[89]
36	Aloe-emodin	$C_{15}H_{10}O_5$	[90]
37	Chlorogenic acid	$C_{16}H_{18}O_9$	[91-92]
38	Vanillic acid	$C_8H_8O_4$	[93]
39	Ellagic acid	$C_{14}H_6O_8$	[94]
40	Taxifolin	$C_{15}H_{12}O_7$	[95]

By scavenging free radicals, polyphenols help maintain cellular integrity and protect neurons from the harmful effects of ischemic injury. These compounds have shown potential in various preclinical models of cerebral ischemia, demonstrating their ability to reduce oxidative damage, modulate neuroinflammation, enhance neurogenesis and protect neurons from apoptosis. In addition, polyphenols have been found to promote cerebral blood flow and improve endothelial function, which is essential for restoring oxygen and nutrient supply to ischemic brain tissue [53-55]. The names, chemical structures of polyphenols are listed in Table 1 and Figure 4.

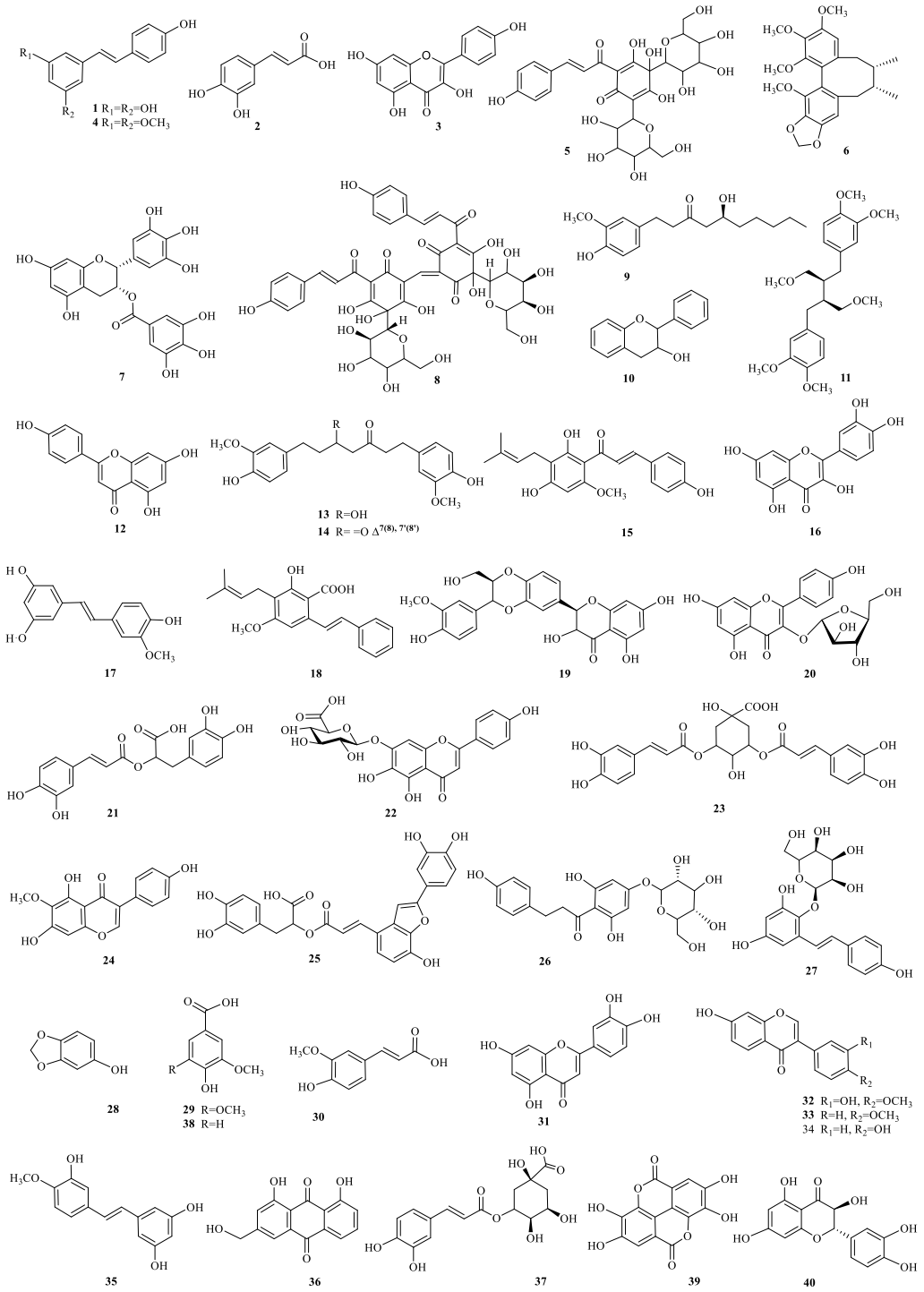

Figure 4. Structures of natural polyphenols against cerebral ischemia

5. Anti-cerebral Ischemic Effects and Mechanisms

5.1. Antioxidant Stress

When cerebral ischemia occurs, the supply of oxygen and glucose to the ischemic region is interrupted, and the mitochondrial respiratory chain is damaged, resulting in the production of ROS in large quantities, triggering oxidative stress.ROS can oxidize lipids, proteins, and DNA, destroying the cellular structure and function, which is a key factor in cerebral ischemic injury. Natural polyphenols, such as resveratrol, have multiple phenolic hydroxyl structures, which can provide hydrogen atoms to bind with ROS and terminate the free radical chain reaction, thus effectively scavenging ROS and reducing oxidative stress damage.

A study found that after experimental rats were given resveratrol (20 mg/kg/d) for 10 consecutive days and after cerebral ischemia was surgically induced, the concentration of trace elements such as magnesium, zinc and selenium, as well as their antioxidant activities (SOD and CAT) were significantly elevated, while the degree of lipid peroxidation and concentration of the toxic metal lead were markedly reduced in their cerebral cortices, when compared to untreated rats with cerebral ischemia. This suggests that the neuroprotective effect of resveratrol is related to its regulation of trace elements and toxic metal lead concentrations, as well as lipid peroxidation and antioxidant activity levels [56]. In vitro experiments have shown that caffeic acid can improve ROS levels, regulate related enzyme activity and gene expression, and inhibit inflammation and vascular marker changes. In vivo experiments have shown that polyphenols can alleviate cerebral infarction and hemorrhage caused by hyperglycemia, regulate endothelial proteins, and reduce neuroinflammation [57]. Wang et al. reported that kaempferol protects the brain from I/R-induced injury by regulating the expression of proteins such as p-Akt and Nrf-2, attenuating oxidative and inflammatory stress, elevating the activity of SOD and GSH, decreasing the content of MDA, and restoring the level of expression of inflammatory factors, such as TNF-α, by a mechanism that may be related to the inhibition of apoptosis triggered by oxidative and inflammatory stress [58].

5.2. Anti-inflammatory Effect

Inflammatory response occupies a key position in cerebral ischemic injury. Ischemia triggers activation of microglia and astrocytes, releasing pro-inflammatory cytokines such as TNF-α, IL-1β, IL-6, etc., which further exacerbate inflammatory injury. Natural polyphenols inhibit inflammation through NF-κB signaling pathway, TLR4 signaling, and so on. In MCAO/R rat model and LPS-stimulated BV-2 cell experiments, Pterostilbene reduced rat neurological scores, brain water content and infarct volume, and decreased the number of activated microglial cells and the expression of iNOS and IL-1β; in vitro experiments showed that it inhibited inflammatory cytokines, NAPDH activity and NF-κB pathway activation, indicating that its effects on cerebral ischemic alleviation was associated with the inhibition of ROS/NF-κB-mediated inflammatory pathway in microglia [59-60].

By constructing a mouse model of cerebral ischemia and in vitro experiments, it was found that resveratrol could reduce the expression of miR-155 in ischemic brain and activated BV2 microglial cells, promote the polarization of microglial cells toward M2, and reduce neuroinflammation, which could provide a new strategy for the treatment of cerebral ischemia-associated neuroinflammation [96]. Hydroxysafflor Yellow A reduces infarct volume and lowers

neurological deficit scores in MCAO rat models and OGD primary neuronal cultures, exerts anti-inflammatory and anti-apoptotic effects, and improves ischemic reperfusion injury by regulating GSK3β phosphorylation and inhibiting iNOS, NF-κB, and caspase-3 activation [61-62]. Schisandrin B was able to significantly reduce infarct volume, neurological scores, number of apoptotic neurons, and inflammatory signaling molecules in the treatment of MCAO/R model rats, confirming that its therapeutic effect on cerebral ischemia-reperfusion injury is associated with the inhibition of TLR4 signaling and inflammatory response [63].Epigallocatechin gallate (EGCG) can reduce brain tissue water content and MPO activity, down-regulate pro-inflammatory factor IL-1β, up-regulate anti-inflammatory factor IL-10 expression, and effectively inhibit inflammatory response in rats with cerebral ischemia/reperfusion injury [64].In a rat model of stroke, treatment with Carthamin yellow for two weeks improved neurological deficits, brain tissue water content, and infarct area. It also inhibited specific inflammatory signaling pathways, reduced pro-inflammatory factor concentrations, and regulated ferroptosis-related indicators. Its protective effect stems from its inhibition of inflammation and ferroptosis [65]. Research has shown that 6-Gingerol can significantly improve the cerebral ischemia/reperfusion (I/R) injury condition in experimental rats, which can effectively reduce the volume of cerebral infarction, alleviate cerebral edema, elevate neurological scores, and reverse the morphological damage of brain tissues. Mechanistically, it can significantly inhibit NLRP3 inflammasome-mediated inflammatory response and neuronal apoptosis, while up-regulating autophagy levels, demonstrating a favorable neuroprotective effect [66]. The degree of polymerization and relative molecular mass of polyphenols affects their spatial conformation, which in turn alters phenolic hydroxyl activity. For example, increasing the degree of polymerization of flavanols enhances their scavenging ability for a wide range of free radicals. Yang et al. studied kelp polyphenols with different relative molecular masses and polarities and found that their antioxidant capacity was inversely related to their relative molecular masses and polarities, revealing an important correlation between the structural properties of polyphenols and their antioxidant properties [67].

5.3. Anti-apoptosis

Neuronal apoptosis induced by cerebral ischemia is a key factor leading to neurological deficits, and natural polyphenols can play a protective role by regulating apoptotic signaling pathways. For example, EGCG reduces neuronal apoptosis by up-regulating the anti-apoptotic protein Bcl-2, down-regulating the pro-apoptotic protein Bax, and inhibiting the activation of caspase-3; while quercetin inhibits the p38 MAPK signaling pathway and reduces the activities of caspase-9 and caspase-3 to achieve the anti-apoptotic effect. In a focal cerebral ischemia model in adult male rats, preoperative intraperitoneal injection of EGCG (50 mg/kg) significantly improved neurological deficits, reduced the volume of cerebral infarction, attenuated histopathological damage, and decreased the number of TUNEL-positive cells. Mechanistically, EGCG exerts neuroprotective effects by regulating caspase-3 and PARP protein expression [100]. For the Wistar rat cerebral ischemia-reperfusion (CIR) model, Phyllanthin (2.5-10 mg/kg) was found to improve neurological function, regulate the AMPK/Nrf2-mediated NF-κB signaling pathway, reduce the release of inflammatory cytokines, and alleviate the oxidative stress and apoptosis of the tissues, demonstrating the neuroprotective potential of CIR [68]. In the cobalt chloride-induced oxidative stress model of PC12 cells and the rat MCAO model, Apigenin pretreatment significantly enhanced cell viability, reduced ROS levels, attenuated apoptosis, and improved mitochondrial membrane

potential; in vivo experiments showed that it improved neurological deficit scores and reduced infarct size, and its neuroprotective mechanism may be related to the activation of mitochondrial function [69]. Studies on rat cerebral ischemia/reperfusion model showed that intraperitoneal injection of Hexahydrocurcumin (40 mg/kg) at the initial stage of reperfusion reduced neurological function scores, decreased infarct size, and attenuated histomorphological damage. It reduces cerebral edema and protects the blood-brain barrier by regulating tight junction protein (TJP), attenuating neutrophil infiltration, decreasing Aquaporin-4 expression [70].

Xanthohumol: In MCAO and OGD in vitro and in vivo models, Xanthohumol reduces infarct size, improves neurological function, reverses neuronal damage, and reduces oxidative stress and apoptosis. Mechanistically, it exerts neuroprotective effects against ischemic stroke by inhibiting p38-MAPK phosphorylation and activating Nrf2 [71]. Oral quercetin pretreatment attenuated neurological deficits, cerebral infarction, blood-brain barrier disruption, and oxidative stress after cerebral ischemia/reperfusion in rats, and inhibited TNF-α and IL-1β mRNA expression and Caspase 3 activity. It plays a key role in brain injury repair by regulating ERK/Akt phosphorylation and protein phosphatase activity [72].Studies in the MCAO/R rat model showed that intraperitoneal injection of Isorhapontigenin dose-dependently suppressed cerebral infarct volume and neurological deficits, increased cerebral blood flow, and improved histopathological changes. It exerts neuroprotective effects by decreasing MDA levels, elevating SOD and GSH-PX activities, regulating the Bcl-2/Bax ratio, inhibiting Caspase-3, and activating the PI3K/Akt signaling pathway [73].

Treatment of SH-SY5Y cells with OGD simulating cerebral ischemia and t-BHP-induced oxidative stress, as well as studies in the MCAO rat model, revealed that intraperitoneal injection of cajaninstilbene acid (2.5, 5 mg/kg) reduced cell death, decreased infarct size and improved neurological function. It reduces oxidative stress and mitochondrial dysfunction through antioxidant activity and activates Nrf2 to exert neuroprotective effects, and AMPK is a key kinase regulating this effect, activating the AMPK/Nrf2 pathway is its neuroprotective mechanism [74]. Silymarin nanoparticles were prepared by encapsulating Silymarin with collagen-based polymer nanoparticles, and male Wistar rats were pretreated intraperitoneally for 7 days, followed by MCAO-induced focal cerebral ischemia. Significant improvements in neurobehavior, infarct analysis, biochemistry, histopathology, and immunohistochemistry were observed in the nano-Silymarin-treated group compared to the free Silymarin-treated group, suggesting that nanoparticle encapsulation increases drug bioavailability and targeting, and enhances neuroprotective effects [75]. In the mouse MCAO model, juglanin injected at a dose of 20 mg/kg for 3 weeks reduced the volume of cerebral infarction and improved neurological function scores. It prevents neuronal damage caused by cerebral ischemia by inhibiting BBB hyperpermeability, downregulating VEGF and VEGFR2 expression, restoring normal expression of tight junction proteins occludin and ZO-1, and regulating the VEGF/VEGFR2 signaling pathway [76]. Scholars gave different doses of Rosmarinic acid to cerebral ischemic rats, which could reduce neurological deficits, decrease infarct volume, attenuate the reduction of SOD and CAT activities and GSH levels in the ischemic semidark band, and also improve depressive behavior. It induced an increase in Nrf2 expression, which is involved in mediating the neuroprotective effects of Rosmarinic acid in stroke and post-stroke depression (PSD) [77]. Both Scutellarin and 3,5-dicaffeoylquinic acid reduced the incidence of cerebral infarction, alleviated neurological abnormalities, attenuated cerebral tissue in rat cerebral ischemia models lesions, increase the number of Nissl somatic cells, repair neuronal ultrastructure, attenuate BB

ultrastructural damage, reduce the content of Evans blue in ischemic brain tissues, down-regulate the expression of iNOS and MMP-9 proteins, and have a therapeutic effect on BBB and neuronal damage [78].Tectorigenin reverses cognitive deficits, hippocampal damage, and reduced myelin density caused by CCI, inhibits expression of inflammatory factors and factors related to the TLR4/NF-κB pathway, and overexpression of TLR4 reversed its effects, suggesting that it attenuates cognitive deficits through inhibition of the TLR4/NF-κB signaling pathway [79]. Salvianolic acid C improves neurological function, inhibits microglial cell activation and inflammatory factor expression, upregulates ZO-1 and CD31 expression to maintain BBB function, inhibit microglia polarization, promote endothelial cell tubule formation, and exert neural repair function after cerebral ischemia [80].

5.4. Improvement of Cerebrovascular Function

Maintaining normal cerebrovascular function is of great significance in the treatment of cerebral ischemia. Natural polyphenols can improve endothelial function, enhance microcirculation, and restore cerebral blood flow through a variety of pathways, and some of the polyphenols can also promote angiogenesis and regulate vascular tone. For example, resveratrol can enhance NO synthesis in cerebrovascular endothelial cells, dilate blood vessels and increase cerebral blood flow. In the mouse cerebral microvascular endothelial cells bEnd.3 and MCAO-induced CIRI rat model, Trilobatin can concentration-dependently promote the proportion of bEnd.3 cells in the S-phase, increase the expression of SIRT6, SIRT7, and VEGFA proteins, alleviate neurological function damage after CIRI, enhance post-stroke neoangiogenesis and functional vascularization of the cerebral ischemia penumbra region It upregulates CDK4, cell cycle protein D1, VEGFA and its receptor VEGFR-2 protein expression. It promises to be a novel restorative agent for ischemic stroke by mediating the SIRT7/VEGFA signaling pathway to promote angiogenesis by directly binding to and increasing SIRT7 expression [81].

2,3,5,4'-Tetrahydroxystilbene-2-O-β-D-Glucoside significantly promotes postoperative recovery, reduces the volume of cerebral infarction and improves neurological dysfunction in a dose- and time-dependent manner in rats. It can increase the density of microvessels in the brain, upregulate CD31 expression in the ischemic penumbra region, and increase the expression levels of vascular endothelial growth factor, angiopoietin 1 and angiopoietin receptor-2 at the site of cerebral injury to promote angiogenesis [82]. In addition, resveratrol has neuroprotective effects during the delayed phase of focal cerebral ischemic injury, and elevated levels of MMP-2 and VEGF may be important for its role by inducing angiogenesis [98]. In a rat femoral artery ligation model, it was found that a high dose of red wine polyphenol compounds (20 mg/kg/day) decreased arterial, small arteries and capillary density and blood flow, inhibited the PI3 kinase-Akt-eNOS pathway, reduced vascular endothelial growth factor expression, and decreased metalloproteinase (MMP) activation; a low dose of RWPC (0.2 mg/kg/day) resulted in a reduction of the left/right (L/R) leg ratio back to control levels, increased blood flow and microvessel density, was associated with overexpression of the PI3 kinase-Akt-eNOS pathway and increased vascular endothelial growth factor production, and had no effect on MMP activation. It was shown that low and high doses of red wine polyphenol compounds have promotional and anti-angiogenic effects on post-ischemic neovascularization in vivo, respectively, providing a new direction for the treatment and prevention of cerebral ischemic diseases [99].

5.5. Autophagy

Galuteolin purified from *Lonicera japonica* was administered to rats with middle cerebral artery occlusion/reperfusion and treated with Galuteolin or Galuteolin and rapamycin. Galuteolin was found to significantly reduce infarct volume, brain water content and neurological deficits in a dose-dependent manner, attenuate neuronal damage in the 1st pyramidal layer of the carotid artery in the hippocampus, and increase the expression level of neuron-specific enolase (NSE), as well as significantly reduce the expression level of autophagy-related proteins. In addition, Galuteolin reduced rapamycin-associated neuronal injury and autophagy activation, suggesting that it can inhibit ischemic brain injury by modulating autophagy-related indicators in I/R [100].

Sesamol exhibits multifaceted neuroprotective effects in brain I/R injury. It prevents neuronal structural damage and attenuates demyelination; restores oxidant/antioxidant balance by increasing total antioxidant capacity and attenuating lipid peroxidation; reduces inflammatory and apoptotic indicators; restores GFAP, Cx43, and autophagy signaling, and shuts down the Notch-1/NLRP3 inflammasome trajectory. The findings suggest that Sesamol exerts neuroprotective effects against I/R injury by attenuating injury events, promoting autophagy, and abolishing Notch1/NLRP3 inflammasome signaling [83]. Summarize 5 sections in Table 2 and Figure 5-6.

Table 2. Pharmacological effects of natural polyphenols

compounds	Models	Dose	Effects/mechanisms	Ref
Antioxidant stress				
Resveratrol	Rats	20 mg/kg/d	SOD, CAT↑	[56]
Caffeic acid	Mouse stroke model	25, 50, 100, 200, and 400 g/mL	Regulation of NAPDH oxidase 4 and Nrf2 gene expression	[57]
Kaempferol	wistar strain albino rats	0-1200 μg/mL	SOD, GSH↑ MDA↓; Regulation of p-Akt, Nrf-2	[58]
Taxifolin	Male Long-Evans Rats	0.1, 1 g/kg	iNOS, COX-2, ICAM-1, NF-κB↓	[95]
Anti-inflammatory effect				
Pterostilbene	MCAO/Rats	200, 400 mg/kg	iN OS, IL-1βmRNA, IκBα↓ IκBα↑	[59-60]
Resveratrol	MCAO/Mice	100 mg/kg	miR-155, BV2↓	[96]
Hydroxysafflor Yellow A	MCAO/Rats	2, 4, 8 mg/kg	NLRP3, ASC, Caspase-1, GSMDD, IL-1β, IL-18, LDH, NF-κB↓	[61-62]
EGCG	cerebral ischemia-reperfusion injury Rats	12.5, 25, 50 mg/kg	MPO, IL-10↑ IL-1β↓	[64]

Carthamin yellow	MCAO/Rats	20, 40 mg/kg	TNF-α, IL-1β, IL-6↓ SOD, MDA↑	[65]
Anti-apoptosis				
EGCG	MCAO/Rats	50 mg / kg	cAOase-3, PARP↑	[97]
Phyllanthin	CIR-injured rats	2.5, 5, 10 mg / kg	Bax, Bcl-2, caspase-3, PGE2, LOX-1↑	[68]
Apigenin	PC12 cell	10 μg/mL	ROS↓ MMP↑	[69]
Hexahydrocurcumin	MCAO/Rats	40 mg/kg	ICAM-1, AQP4, VCAM-1↓ TJP↑	[70]
Isorhapontigenin	MCAO/Rats	2/24 h	SOD, p-Akt , GSH-PX↑ MDA↓	[73]
Cajaninstilbene acid	SH-SY5Y cell	2.5, 5 mg / kg	Adjustment of AMPK/Nrf2 pathway	[74]
Silymarin	Wistar Rats	10,100, 1,000 μg/kg	EDC-HC, MDA↑	[75]
Juglanin	MCAO/Rats	20 mg / kg	ZO-1↑ VEGF, VEGFR2↓	[76]
Tectorigenin	CCI-induced cognitive impairment in mice	12.5, 25, 50 mg/kg	TLR4/NF-κB pathway↓	[79]
Calycosin	I/R injured rats	12.5, 25, 50 mg/kg	neurologicalfunction↑ ischemicvolume, neuraldeath, Bax/Bc1-2 ratio↓	[88]
Resveratrol	Rats	2, 4, 6 μl (20 nM/ml)	p-JAK2, p-STAT3, p-AKT, p-mTOR, BCL-2↑ caspase-3, BAX↓	[101-102]
Chlorogenic acid	SD Rats	20, 100, 500 mg/kg	BDNF NGF, SOD, GSH↑ MDA, ROS↓	[90-91]
Vanillic Acid	SD rats	50, 100 mg/kg	IL-6, IL-1β, TNF-α, NF-κBp65↓	[93]
Ellagicacid	Male SD rats	10, 30mg/kg	Bc1-2↑	[94]
Taxifolin	Rats	0.1 and 1.0 μg/kg	Mac-1, ICAM-1, ROS, NO↓	[95]
Improvement of cerebrovascular function				
Trilobatin	Mice	7.5, 15, 30 μg/g	SIRT6, SIRT7, VEGFA, CDK4, SIRT7↑	[81]
resveratrol	MCAO/Mice	50 mg/kg/d	MMP-2, VEGF↑	[98]

Red wine polyphenol compounds	rats	0.2, 20 mg/kg/d	PI3K, eNOS, MMP↓	[99]
Autophagy				
Galuteolin	I/R injured rats	25, 50, 100 mg/kg	Infarct volume, brain water content↓	[100]
Sesamol	I/R injured rats	100 mg/kg	GFAP、Cx43↑ Notch-1/NLRP3↓	[83]

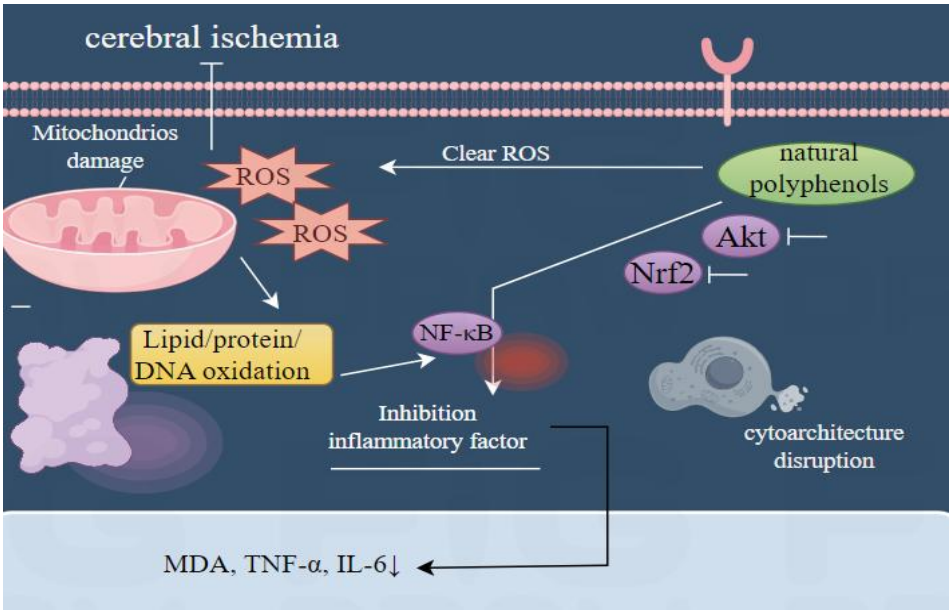

Figure 5. Schematic diagram of natural polyphenols against cerebral ischemia 1

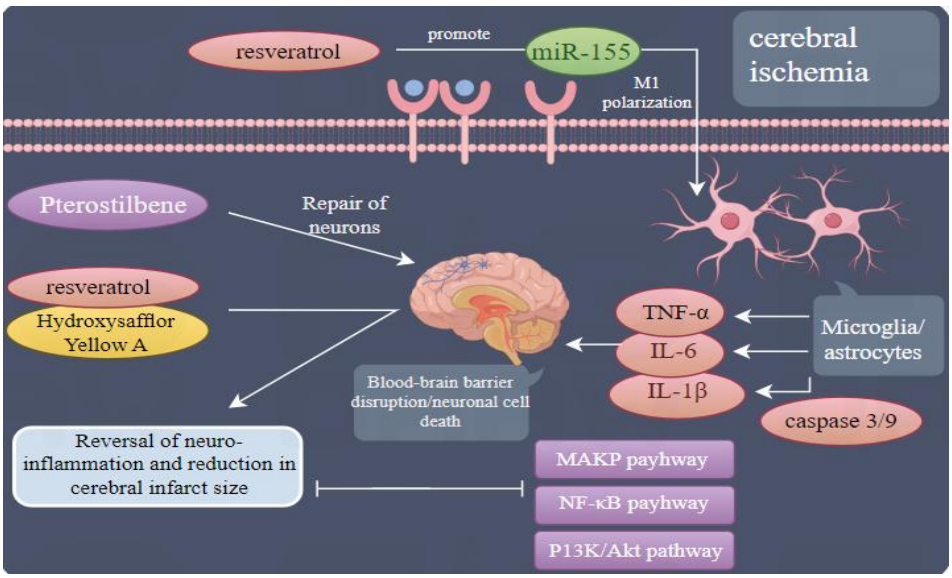

Figure 6. Schematic diagram of natural polyphenols against cerebral ischemia 2

6. Bioavailabilityand Nanotechnology Applications

6.1. Bioavailability

Although natural polyphenols are widely found in plants, their oral bioavailability is generally low, which has become a major bottleneck in the treatment of cerebral ischemia. On the one hand, most polyphenols are easily degraded by gastric acid and digestive enzymes in the gastrointestinal tract, and the intestinal absorption efficiency is low; after entering the blood circulation, the first-pass metabolism in the liver further leads to a significant decrease in the concentration of the prototype drug, and it is difficult to reach an effective therapeutic concentration in the brain through the blood-brain barrier. Among them, 6-Gingerol, as an antioxidant component in ginger, shows potential in the treatment of cerebral ischemia, but its poor aqueous solubility and low intestinal absorption rate lead to insufficient bioavailability in the brain; the antioxidant and neuroprotective effects of Ferulic acid are limited by the low bioavailability, which affects the therapeutic efficiency of Ferulic acid.

6.2. Nanodelivery Systems Enhance Bioavailability

The advantages of nanotechnology in optimizing the pharmacokinetic properties of natural polyphenols have been widely validated, and there are significant performance differences among various types of nanodelivery systems. Among these, nanolipid carriers demonstrate particularly outstanding comprehensive performance in enhancing bioavailability.

Taking ferulic acid delivery as an example, nanolipid carriers exhibit significant advantages over free drugs in terms of efficacy and therapeutic strength. In an in vitro OGD model, free ferulic acid significantly reduced cellular LDH release and ROS accumulation only one hour after treatment, but these indicators rebounded to levels close to those of the model group after eight hours. In contrast, ferulic acid encapsulated in nanolipid carriers maintained significant effects even after eight hours [104]. In vivo experiments using a rat I/R model showed that the nanolipid carrier group had lower motor neuron dysfunction scores (mNSS) and reduced MDA levels compared to the model group, while the free ferulic acid group had no statistically significant differences in mNSS scores or MDA levels, confirming its inability to cross the blood-brain barrier and exert effects [104]. This difference stems from the nanolipid carrier's biomimetic membrane-like structure, which protects the drug from enzymatic degradation while enhancing cellular uptake via endocytosis, thereby prolonging the duration of action and improving targeted delivery efficiency.

Applications of nanotechnology also include curcumin-collagen nanocomposites, which are stabilized by crosslinking agents and can effectively alleviate oxidative stress associated with cerebral ischemia-reperfusion injury [106]. Chitosan nanoparticles loaded with silymarin have targeted delivery as their primary advantage. Surface-modified TAT peptides can bind to receptors on the surface of vascular endothelial cells. This system reduces the forced swimming immobility time in rats with depressive-like behavior and lowers IL-6 levels, but the drug encapsulation rate is significantly lower than that of nanolipid carriers [107]. By constructing natural polyphenol nanocomposites, the therapeutic efficacy of cerebral ischemia treatment can be improved by effectively enhancing drug utilization and avoiding certain adverse effects (as shown in Figure 7).

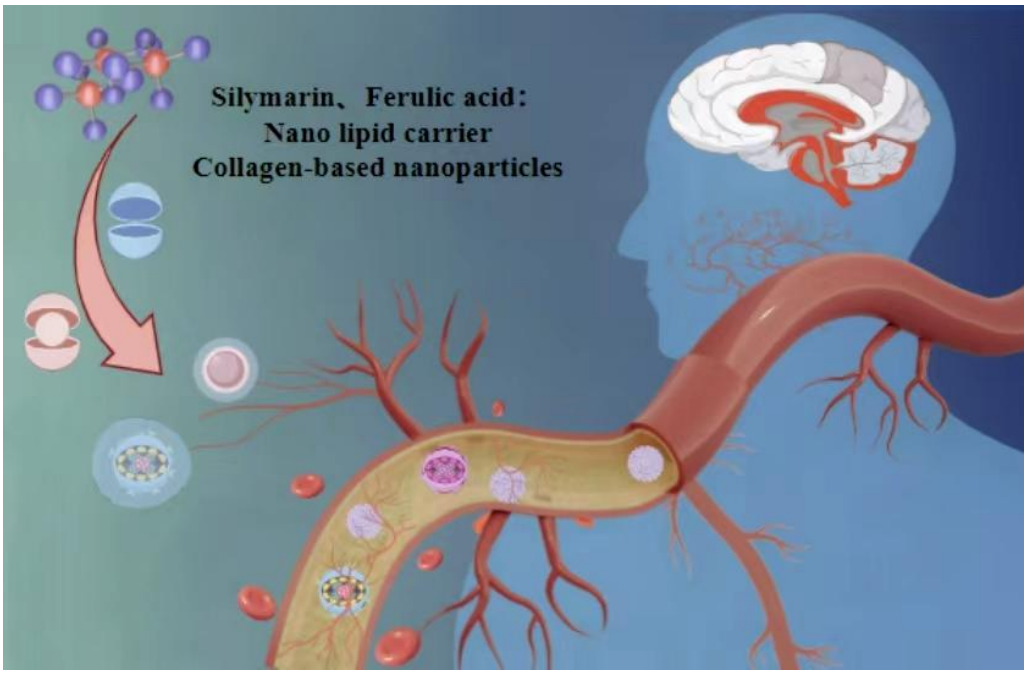

Figure 7. Applications of nanomaterials

7. Conclusion and Perspectives

Natural polyphenols, as secondary metabolites widely found in plant foods, have attracted attention in the prevention and control of cardiovascular diseases, neurodegenerative diseases and cancers due to their antioxidant, anti-inflammatory and neuroprotective properties, and have shown great potential in the treatment of cerebral ischemia in particular. When cerebral ischemia occurs, the interruption of oxygen and glucose supply triggers the production of ROS, which destroys cellular structure, exacerbates inflammation and leads to neuronal death. Natural polyphenols can effectively remove ROS, reduce oxidative stress, and become an important line of defense against post-ischemic brain damage.

Natural polyphenols such as resveratrol, quercetin, curcumin, EGCG and anthocyanins have been shown to possess neuroprotective effects in experimental models of cerebral ischemia. Resveratrol enhances cerebral blood flow and reduces neuronal apoptosis; quercetin reduces oxidative damage and inflammation and improves neuronal survival; curcumin reduces neuroinflammation and promotes neurogenesis; and EGCG protects neurons by regulating signaling pathways. Its mechanism of action involves various aspects, regulating inflammation, oxidative stress and cell death-related signaling pathways, inhibiting the NF-κB pathway to reduce pro-inflammatory factors, activating the Nrf2 pathway to enhance the expression of antioxidant enzymes, and regulating the balance of apoptotic proteins, and can also act directly on the cerebral vasculature to improve endothelial function and enhance microcirculation, and by regulating the mitochondrial function to reduce cell death.

However, there are still many challenges in bringing natural polyphenols to the clinic for the treatment of cerebral ischemia. First and foremost is the issue of bioavailability, as polyphenols are extensively metabolized in the liver and gastrointestinal tract, making it difficult for them to reach the brain at effective concentrations. In addition, the concentration of polyphenols varies significantly from source to source, and determining optimal dosage, standardized regimens, and

synergistic use with other therapies urgently needs to be validated in large-scale, long-term clinical trials. Although the results of preclinical studies are promising, long-term safety and efficacy assessments and pharmacokinetic studies also need to be further developed.

It is worthwhile to expect that natural polyphenols have multi-target therapeutic advantages, which can simultaneously act on oxidative stress, inflammation, neuronal survival and vascular function, and so on, complementing the traditional single-target therapy. In the future, as research continues, natural polyphenols may become an important part of comprehensive treatment for cerebral ischemia and play an important role in improving patients' prognosis, but there is still a need for unremitting exploration in optimizing clinical application, clarifying dosage regimens and evaluating long-term effects.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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