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- Review -

Protective Effects of Traditional Korean Medicine Preparations, Herbs, and Active Compounds on the Blood–brain Barrier in Ischemic Stroke Models

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Stroke is among the leading causes of death and long-term physical and cognitive disabilities worldwide, affecting an estimated 15 million people annually. The pathophysiological process of stroke is complicated by multiple and coordinated events. The breakdown of the blood–brain barrier (BBB) in people with stroke can significantly contribute to the development of ischemic brain injury. Therefore, BBB disruption is recognized as a hallmark of stroke; thus, it is important to develop novel therapeutic strategies that can protect against BBB dysfunction in ischemic stroke. Traditional medicines are composed of natural products, which represent a promising source of new ingredients for the development of conventional medicines. Indeed, several studies have shown the effectiveness of Korean medicine on stroke, highlighting the value of Korean medicinal treatment for ischemic stroke. This review summarizes the current information and underlying mechanisms regarding the ameliorating effects of the formula, decoction, herbs, and active components of traditional Korean medicine on cerebral ischemia-induced BBB disruption. These traditional medicines were shown to have protective effects on the BBB in many cellular and animal ischemia models of stroke, and experiments in various animal species, such as mice and rats. In addition, they showed brain-protective effects by protecting the BBB through the regulation of tight junction proteins and matrix metalloproteinase-9, reducing edema, neuroinflammation, and neuronal cell death. We hope that this review will help promote further investigation into the neuroprotective effects of traditional Korean medicines and stimulate the performance of clinical trials on Korean herbal medicine–derived drugs in patients with stroke.

Key words : Blood-brain barrier, matrix metalloproteinase, stroke, tight junction protein, traditional Korean medicine

Introduction

Stroke is a neurological abnormality in which blood vessels supplying blood to the brain are blocked or burst, causing damage to the brain. Most strokes are ischemic strokes, with this type accounting for 87% of all strokes [65]. Risk factors for stroke can be categorized as congenital and lifestyle. Age, sex, and race/ethnicity are hereditary risk factors for stroke, while hypertension, smoking, diet, and physical inactivity are among some of the more commonly reported lifestyle-related factors [4]. Stroke is dangerous not only because it can cause death but also because it can leave some people with permanent disabilities. Stroke is the second leading cause of mortality globally, accounting for almost 11% of all deaths, according to the World Health Organization in 2020. In 2017, 6.2 million died due to stroke worldwide [65]. In those who survive, stroke can result in long-term disability, which reduces productivity and increases medical costs, causing economic and psychological burdens on society and individuals. The symptoms of stroke, such as consciousness disorder, half-body exercise paralysis, speech disorder, abdominal vision (one object appears to be two), and dysfunction of swallowing, can make daily life difficult [24]. Furthermore, only one drug has been approved by the Food and Drug Administration to treat stroke [84], and there are many limitations to its use. Although there is a significant enhancement effect when tPA

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is used within 3 hr, only 6-16% of stroke patients can receive tPA treatment [27]. While many neuroprotective agents have been developed and have shown protective efficacy in stroke animal models, clinical trials have failed to show positive effects in patients with ischemic stroke. Therefore, stroke research is important, and a new paradigm is required.

The pathological process of stroke is complicated, with multiple and coordinated events. A number of pathophysiological events occur following stroke, including energy failure, glutamate excitotoxicity, oxidative stress, leukocyte infiltration, inflammation, breakdown of the blood-brain barrier (BBB), and edema [71]. The BBB is a gateway that strictly regulates the movement of ions, molecules, and cells between the central nervous system (CNS) and systemic circulation [19]. It is formed by endothelial cells of the capillary wall, astrocyte end-feet ensheathing the capillary, and pericytes embedded in the capillary basement membrane [3]. In the early stages of damage to the BBB, the tight junction proteins are loosened, and cerebrovascular permeability increases, which causes extravasation and extracellular accumulation of circulatory immune cells and fluid into the cerebral parenchyma [53]. It aggravates inflammation and generates neurotoxicity in the damaged site, thereby resulting in neuron cell death. Therefore, the protection of BBB breakdown is a major strategy for the treatment of damaged brains after ischemic injury.

Traditional medicines are composed of natural products, which represent a promising source of new ingredients for the development of conventional medicines. Indeed, researchers have begun to consult the traditional medicine literature in the search for novel therapeutic strategies [33, 52]. Compiled by the Korean royal physician Heo Jun during the 17th century, the *Dongui Bogam* contains information regarding several prescriptions and systematic screening methods that have been applied to both experimental and clinical settings [16, 57]. In addition, several studies have shown the effectiveness of Korean medicine on stroke, highlighting the potential role of Korean medicinal treatment in the treatment of stroke. This review selected recent studies and discussed further considerations for the critical reevaluation of the neuroprotection hypothesis of traditional Korean medicines against BBB disruption in ischemic brain injury. We hope that this review will further help investigate the neuroprotective effects of Korean medicines and stimulate the performance of clinical trials of Korean herbal medicine-derived drugs in patients with stroke.

Structure and function of the BBB

The BBB is a physiological and biochemical barrier that separates the CNS from the systemic circulation, which controls CNS homeostasis and protection of the brain tissue from exposure to potentially toxic substances. The BBB is a specialized barrier that consists of endothelial cells, tight junction proteins, pericytes, astrocytic end-feet processes, and the basement membrane. It is crucial in the regulation of the passage of ions, proteins, and inflammatory cells between the plasma and brain (Fig. 1) [3]. Tight junctions in the brain endothelial cells maintain the integrity of the BBB and consist of different proteins, such as zonula occludens 1 (ZO-1), claudin, and occludins [70]. In acute stroke, there is the degradation of the tight junctions resulting in the loss of vascular integrity [56].

Astrocytes are the most common glia cell in the CNS and affect the brain's endothelial cell function, blood flow, and ion balance through close association with cerebrovascular interactions. Their close interaction with endothelial cells within the BBB, particularly via astrocyte end-feet, strengthens the regulation and maturation of the BBB [47]. The astrocyte end-foot protein strongly implicated in BBB function

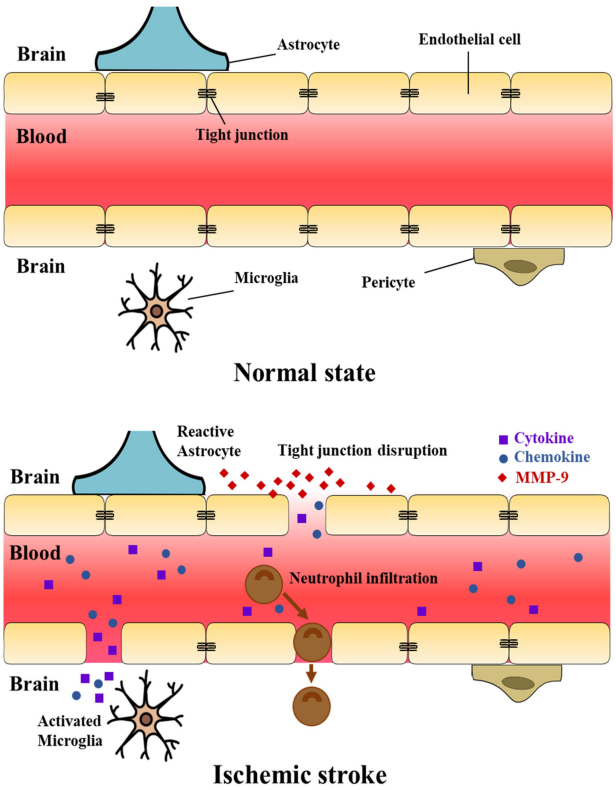


Fig. 1. Pathological changes in the blood vessels after ischemic stroke.

is the water channel aquaporin 4 (AQP4), which is involved in the pathogenesis of cerebral edema, facilitates water movement through the plasma membrane of several cell types in the brain, including endothelial cells, and contributes to permeability regulation [28]. Additionally, astrocytes play a role in mediating neuroinflammation and thus are significant in neuroinflammatory pathologies, including ischemic stroke [17].

Another cell type implicated in promoting BBB function are pericytes. Pericytes are located along the basement membrane of BBB endothelial cells, encircling the vessel wall and promoting overall BBB function. Although pericytes also exist in the peripheral vasculature, the CNS microvasculature has the highest degree of pericyte coverage, potentially contributing to vascular permeability and small vessel stability [20]. They also display an ability to self-renew and differentiate into neural and vascular lineage cells in the setting of stroke [54].

The basement membrane connects endothelial cells to astrocytic end-feet and has been implicated in BBB maintenance. Specifically, damage to the basement membrane caused by increased expression of matrix metalloproteinases (MMPs) is believed to be related to alterations in BBB permeability in numerous pathologies. In particular, MMP-9 plays a key role in protease-mediated physiological and pathological changes in BBB breakdown [59]. In ischemic stroke, increased MMP-9 in the damaged brain is one of the significant causes of BBB breakdown. BBB-constituting cells, including the brain microvascular endothelial cells, astrocytes, and brain pericytes, can release MMP-9 upon thrombin stimulation. Following this breakdown, a sustained increase in permeability likely occurs due to a neuroinflammatory response, which contributes to longer-term or permanent loss of neurological function, combined with other consequences such as brain edema [59].

Protective effects of traditional Korean medicines on BBB disruption in ischemic stroke

Formula and decoction (Table1, Table 2)

(1) Shuanghe-Tang is a traditional Korean medicine formula that has long been utilized to treat fatigue and promote recuperation following sickness in Korea. In a study of focal

Table 1. Composition of the Traditional Korean medicine formulas and decoctions

Formula and Decoction	Composition
Shuanghe-Tang	*Radix Paeoniae, Radix Astragali, Radix Rehmanniae, Radix Angelicae Gigantis, Rhizoma Cnidii, Cortex Spissus Cinnamomi, Radix Glycyrrhizae*
Weisheng-Tang	*Radix Astragali, Radix Angelicae Gigantis, Radix Paeoniae Alba, Radix Glycyrrhizae*
Sijunzi decoction	*Radix Ginseng, Rhizome Atractylodis macrocephala, Poria, Radix Glycyrrhizae*
Buyang Huanwu decoction	*Radix Astragali seu Hedysari, Radix Angelicae Sinensis, Radix Paeoniae Rubra, Rhizoma Ligustici Chuangxiong, Semen Persicae, Flos Carthami, Lumbricus*
Tong-Qiao-Huo-Xue decoction	*Moschus, Flos Carthami, Rhizoma Ligustici Chuanxiong, Semen Persicae, Fructus Jujubae, Radix Paeoniae Rubra, Bulbus Allii Fistulosi*
Angong Niuhuang Wan	*Borneolum, Moschus, Cornu Rhinocerotis, Radix Curcumae, Realgar, Cinnabaris, Margarita, Radix Scutellariae, Rhizoma Coptidis, Bezoar Bovis, Fructus Gardeniae*
Qingkailing injection	*Radix Isatidis, Flos Lonicerae, Fructus Gardeniae, Buffalo horn, Concha Margaritifera, Radix Scutellariae, Bezoar Bovis*
Shuxuetong injection	*Hirudo, Lumbricus*
Danhong injection	*Radix Salviae Miltiorrhizae, Flos Carthami*
YiQiFuMai injection	*Radix Ginseng, Radix Ophiopogonis, Fructus Schizandrae*
Longshengzhi capsules	*Radix Astragali, Flos Carthami, Radix Angelicae Sinensis, Rhizoma Ligustici chuanxiong, Semen Persicae, Radix Paeoniae Rubra, Radix Aucklandiae, Rhizoma Acori Atranorin, Taxilli Ramulus, Extract of Acanthopanax Senticosus, Hirudo, Lumbricus*
Tongxinluo capsule	*Radix Ginseng, Hirudo, Scorpio, Radix Paeoniae Rubra, Periostracum Cicadae, Eupolyphaga seu Steleophaga, Scolopendra, Lignum Santali Albi, Lignum Dalbergiae Odoriferae, Olibanum, Semen Ziziphi Spinosae, Bomeolum*
Tongfu Xingshen capsule	*Folium Sennae, Rhizoma Polygoni Cuspidati, Tabasheer, Semen Trichosanthis, Artificial Bovis*

Table 2. Traditional Korean medicine formulas and decoctions targeting the BBB in cerebral ischemia rodent models

Formula and Decoction	Rodent type	BBB target	Cerebral ischemia model	Reference
Shuanghe-Tang	Mice	EB leakage↓, ZO-1↑, occludin↑, AQP4↑	Photothrombosis	[31]
Weisheng-Tang	Mice	EB leakage↓, ZO-1↑, claudin-5↑, MMP-9↓, PAR-1↓,	Photothrombosis	[32]
Sijunzi decoction	Rat	EB leakage↓, COL IV↑, MMP-9↓, apoptosis↓, TIMP1↑,	MCAO	[77]
Buyang Huanwu decoction	Mice	EB leakage↓, ZO-1↑, occludin↑, MMP-2/9↓, apoptosis↓(caspase3↓), Alb↓, Fga↓, Trf↓, neuronal death↓(CaMKII↑)	MCAO/CIR	[22], [13]
Tong-Qiao-Huo-Xue decoction	Rat	EB leakage↓, ZO-1↑, occludin↑, claudin-5↑, MMP-9↓, AQP4↓	MCAO	[72], [35]
Angong Niuhuang Wan	Rat	EB leakage↓, ZO-1↑, claudin-5↑, MMP-2/9↓	MCAO	[63]
Qingkailing injection	Mice/Rat	EB leakage↓, ZO-1↑, occludin↑, claudin-5↑, VE-Cadherin↑, MMP-9↓, apoptosis↓ (caspase-3↓), HIF-1α↓,	tMCAO/ICH	[49], [81], [48]
Refined Qingkailing injection	Rat	EB leakage↓, apoptosis↓	tMCAO	[50]
Shuxuetong injection	bEnd.3	TEER↑, FITC-dextran concentration↓, ZO-1↑, occludin↑, claudin-5↑, VEGF↓	OGD	[61]
Danhong injection	Rat	EB leakage↓, ZO-1↑, occludin↑, JAM-1↑, MMP-2/9↓	MCAO/pMCAO	[69], [80]
YiQiFuMai injection	Mice	EB leakage↓, ZO-1↑, occludin↑	MCAO	[6]
Longshengzhi capsules	Rat	MMP-2/9↓, VEGF↓, HIF-1α↓	MCAO	[78]
Tongxinluo capsule	Mice/Rat	EB leakage↓, ZO-1↑, occludin↑, claudin-5↑, LRP-1↓, AQP4 polarization loss↑, activate the Shh pathway	pMCAO/MCAO	[8], [66], [44]
Tongfu Xingshen capsule	Rat	EB leakage↓, natural stem cell↑, astrocytes↑	ICH	[18]

BBB: blood-brain barrier, MCAO: middle cerebral artery occlusion, pMCAO: permanent middle cerebral artery occlusion, tMCAO: transient middle cerebral artery occlusion, OGD: oxygen-glucose deprivation, ICH: intracerebral hemorrhage, EB: evans blue, ZO-1: zonula occludens-1, AQP4: aquaporin4, MMP-2/9: matrix metalloproteinase-2/9, PAR-1: protease-activated receptor-1, COL IV: collagen IV, TIMP1: tissue inhibitor of metalloproteinase 1, Alb: albumin, Fga: fibrinogen alpha chain, Trf: transferrin, CaMKII: Ca^{2+}/calmodulin-dependent protein kinase II, VE-Cadherin: vascular endothelial cadherin, HIF-1α: hypoxia-inducible factors 1 alpha, TEER: trans-epithelial electrical resistance, VEGF: vascular endothelial growth factor, JAM-1: junctional adhesion molecules-1, LRP-1: lipoprotein receptor-related protein 1, FITC-dextran: fluorescein isothiocyanate-dextran.

cerebral ischemia mice, this formula significantly reduced the cerebral infarction volume, decreased BBB breakdown, attenuated edema, and improved neurological and motor functions. Shuanghe-Tang increased the expression of occludin, ZO-1, and aquaporin 4 (AQP4) [31].

(2) Weisheng-Tang is a traditional Korean formula that has been used in individuals who suffer from exhaustion and indigestion causing diarrhea. Weisheng-Tang significantly reduced infarct volume and edema and improved neurological and motor functions. Weisheng-Tang resulted in less BBB damage via downregulation of the tight junction proteins and suppression of protease-activated receptor-1 (PAR-1) and MMP-9 in the ischemic brain [32].

(3) Sijunzi decoction is widely used to invigorate 'Qi.' In the middle cerebral artery occlusion (MCAO) rat model, Sijunzi decoction treatment enhanced neurobehavioural scores and prevented BBB disruption. Permeability of the BBB was maintained by increasing the expression of tissue inhibitor of metalloproteinase 1 (TIMP1) and collagen IV and reducing the expression of MMP-9 and apoptotic rate in the hippocampus [77].

(4) Buyang Huanwu decoction has long been used to treat

stroke. It improved the function recovery of MCAO mice, reduced the volume of cerebral infarction, and attenuated BBB disruption. It increased the level of tight junction proteins, ZO-1, and occludin and reduced MMP-2/9 activities and NK cells infiltrating the brain [22]. Moreover, in a study of cerebral ischemia/reperfusion mice, albumin, fibrinogen alpha chain, and transferrin, which increased due to stroke, were reduced by Buyang Huanwu decoction, and the integrity of the BBB was preserved. In addition, neuronal death and apoptotic cell death were also suppressed by Buyang Huanwu [13].

(5) *T*ong-Qiao-Huo-Xue decoction is a traditional formula that has long been used clinically for stroke treatment. This decoction improved neurological function and reduced the infarct volume and BBB injury in the cerebral ischemia-reperfusion rat model [72]. It protected the permeability of the BBB by increasing the expression of tight junction proteins such as ZO-1, occludin, and claudin-5 and reducing the expression of AQP4 and MMP-9 in MCAO rats [35].

(6) Angong Niuhuang Wan is a traditional formula to treat stroke, but it contains arsenic- and mercury-containing materials, so it should be used carefully. In the MCAO rat model, it reduced the infarct size and protected BBB permeability by increasing the expression of tight junction proteins, including ZO-1 and claudin-5, and inhibiting MMP-2/9 [63].

(7) Qingkailing injection is a traditional Chinese medicine based on Angong Niuhuang Wan. It has been widely used for the treatment of stroke for almost 30 years in China [50]. *Qingkailing* protects against BBB disruption, improves neurological function, inhibits inflammatory responses, and decreases infarct volume [49, 81]. It was shown that tight junction proteins such as ZO-1, claudin-5, vascular endothelial cadherin (VE-Cadherin), and occludin were increased in the transient MCAO mice model [81]. In addition, it reduced apoptosis [49] and the activation of MMP-9 and hypoxia-inducible factor-1 (HIF-1), which affects the structural hardness of the basement membrane and the collapse of the BBB [81]. However, refined Qingkailing was developed due to safety concerns and contains four major components of traditional Qingkailing (baicalin, geniposide, cholic acid, and hyodeoxycholic acid (4.4:0.4:3:2.6)). Refined Qingkailing has been reported to reduce apoptosis, inflammatory response, and infarction rates in cerebral ischemia [50]. Moreover, Qingkail*ing* decreased apoptosis by inhibiting the activation of caspase-3 in the intracerebral hemorrhage rat model [48].

(8) Shuxuetong injection is a formula that consists of leeches (*Hirudo nipponica Whitman*) and earthworms (*Pheretima asperfillum*). It has been long used for the treatment of stroke in China. Shuxuetong increased the expression of the BBB tight junction proteins, claudin-5, occludin, and ZO-1 in the oxygen-glucose deprivation/reperfusion (OGD/R) bEnd.3 cell model to prevent the disruption of the BBB, reactive oxygen species (ROS), mitochondrial superoxide production, inflammation via downregulation of NF-κB, vascular endothelial growth factor (VEGF), and p-ERK1/2 [61].

(9) Danhong injection is a traditional Chinese formula composed of *Radix Salviae miltiorrhizae* and *Flos Carthami tinctorii* that has been used in the treatment of acute ischemic stroke. Danhong treatment reduced infarct volume and improved neurological deficit in the MCAO rat model. In addition, Danhong decreased neutrophil infiltration and protected the BBB by increasing occludin and reducing MMP-9 [69]. Mannitol, a representative treatment for brain edema, was found to be effective in reducing edema temporarily but can further worsen the destruction of the BBB. However, when mannitol is used in combination with Danhong, BBB destruction was improved by increasing the expression of occludin, junctional adhesion molecules-1 (JAM-1), and ZO-1 and inhibiting the activation of MMP-2/9 [80].

(10) YiQiFuMai injection is a modern formula based on Sheng-Mai-San. It is used to treat microcirculatory disturbance-related diseases in China. In the MCAO mouse model, it reduced the cerebral infarct volume and brain edema and improved neurological behavior outcomes. In addition, it increased ZO-1 and occludin, thereby preventing damage to the BBB [6].

(11) Longshengzhi capsules contain a formula based on Buyang Huanwu decoction and is used at the recovery stage of ischemic stroke in China. It was found to decrease infarct volumes and brain edema and improve neurological deficits via anti-inflammatory effects. It protects against BBB disruption by reducing MMP-2/9, VEGF, and HIF-1α [78].

(12) Tongxinluo capsule is a traditional Chinese medicine approved in China in 1996 for stroke treatment. It attenuates BBB disruption by increasing the expression of tight junction proteins (occludin, claudin-5, and ZO-1), decreasing lipoprotein receptor-related protein 1 (LRP-1), restoring AQP4 polarization loss, and activating the sonic hedgehog (Shh) pathway [8, 44, 66]. In addition, it was found to have an anti-inflammatory effect, reduce apoptosis, and alleviate pyroptosis [66].

(13) Tongfu Xingshen capsule is a traditional Chinese medicine formula developed in China to treat hemorrhagic stroke. It is known to attenuate BBB deficits and cerebral

edema and improve neuronal function by increasing brain-derived neurotrophic factors to proliferate the number of natural stem cells and astrocytes in the intracerebral hemorrhage rat model [18].

Herbs (Table 3)

(1) *Lycium barbarum* is widely used in traditional Chinese medicine and food supplements. It is known to have health-promoting effects and anti-aging effects. *L. barbarum* polysaccharides account for more than 40% of the *Lycium barbarum* fruit extract. *L. barbarum* polysaccharides decreased the infarct volume, water content, and hemispheric swelling, reduced apoptotic cell and oxidative stress, and improved neurological deficits in the MCAO mouse model. In addition, they attenuated BBB breakdown by downregulation of MMP-9 and AQP4 and up-regulation of occludin [76].

(2) *Gastrodia elata Blume* has long been widely used in traditional Chinese medicine to treat many neurological disorders, including ischemic stroke. Ethyl acetate extracts of *G. elata Blume* was found to have a protective effect on cerebral ischemia by reducing apoptosis and inhibiting platelet aggregation. In addition, *Gastrodia elata Blume* in the MCAO rat model was found to reduce the expression of AQP4 and increase the expression of tight junction proteins such as occludin and claudin-5, illustrating its BBB protective effect. Moreover, it has an anti-inflammatory effect by reducing the release of NO and the activity of nitric oxide synthase (NOS) [25].

(3) Kudiezi injection consists of components extracted from *Ixeris sonchifolia* Hance. *I. sonchifolia* H. is used in the treatment of angina, coronary artery diseases, and cerebral infarction in traditional Chinese medicine. Kudiezi prevented ischemic brain injury and BBB disruption by enhancing tight junction proteins (ZO-1, claudin-5, and occludin) and JAM-1 and attenuating the expression and activation of caveolin-1 in the MCAO rat model [10]. In addition to animal studies, a study on patients with acute cerebral ischemia also showed that Kudiezi had anti-inflammatory properties and reduced the expression of MMP-9 [45].

(4) *Carthamus tinctorius* L. has been known to have a protective effect on myocardial ischemia and cerebral ischemia. It was found that *C. tinctorius* L. reduced infarct volume and neurological damage via decreasing apoptosis in the MCAO rat model. In addition, it alleviates BBB damage by reducing MMP-2/9 expression and increasing TIMP [9].

(5) *Cordyceps sinensis* is known to have anti-cancer, antioxidant, anti-diabetes, anti-aging, and immunomodulative effects and has been used in traditional Chinese medicine for thousands of years. It was found that *C. sinensis* extract protects the BBB and ischemic brain injury by reducing apoptosis in the oxygen-glucose deprivation (OGD) brain microvascular endothelial cell (BMEC) model and MCAO rat model [2].

(6) *Erigeron breviscapus* injection consists of *E. brevisca-*

Table 3. Traditional Korean medicine herbs targeting the BBB in cerebral ischemia rodent models

Herb	Rodent type	BBB target	Cerebral ischemia model	Reference
Lycium barbarum polysaccharides	Mice	EB leakage↓, occludin↑, MMP-9↓, AQP4↓	MCAO	[76]
Gastrodia elata Blume	Rat	EB leakage↓, occludin↑, claudin-5↑, AQP4↓	MCAO	[25]
Kudiezi	Rat/Patient	EB leakage↓, ZO-1↑, occludin↑, claudin-5↑, JAM-1↑, MMP-9↓, caveolin-1↓	MCAO/Acute cerebral infarction	[10], [45]
Carthamus tinctorius L.	Rat	MMP-2/9↓, TIMP↑	MCAO	[9]
Cordyceps sinensis	Rat/BMEC	apoptosis↓	MCAO/OGD	[2]
Erigeron breviscapus	Rat	EB leakage↓, ZO-1↑, occludin↓, claudin-5↑, MMP-9↓, iNOS↓	MCAO	[43]
partially purified components of *Uncaria sinensis*	Mice	EB leakage↓, ZO-1↑, occludin↑, MMP-9↓	Photothrombosis	[60]
Total Glycosides of *Cistanche deserticola*	Rat	EB leakage↓, ZO-1↑, occludin↑, claudin-5↑	MCAO	[67]

BBB: blood-brain barrier, BMEC: brain microvascular endothelial cell, MCAO: middle cerebral artery occlusion, OGD: oxygen-glucose deprivation, EB: evans blue, ZO-1: zonula occludens-1, AQP4: aquaporin4, MMP-2/9: matrix metalloproteinase-2/9, TIMP: tissue inhibitor of metalloproteinase, JAM-1: junctional adhesion molecules-1, iNOS: inducible nitric oxide synthase.

pus (Vant.) Hand-Mazz. *E. breviscapus* has long been used by ethnic minorities in China because of its effectiveness in treating heart and liver diseases and activating blood circulation. *E. breviscapus* injection was found to reduce infarct size and brain edema and improve neurological function in the MCAO rat model by increasing tight junction proteins (claudin-5 and ZO-1) and suppressing MMP-9 activation and iNOS synthesis [43].

(7) *Uncaria sinensis* is a medicinal herb used in traditional Korean medicine for neurological symptoms and high blood pressure. Pretreatment with partially purified components of *U. sinensis* restored the integrity of the BBB by reducing MMP-9 and increasing tight junction proteins ZO-1 and occludin in a focal cerebral ischemia mouse. In addition to the protective effect on the BBB, it reduced the infarct volume and improved the neurological function in ischemic stroke [60].

(8) *Cistanche deserticola* is used to invigorate 'Yang' in traditional Chinese medicine and is known to mainly act in the kidneys [37]. Total glycosides of *C. deserticola* reduced brain damage via promoting angiogenesis and decreasing oxidative stress in ischemic stroke. It also attenuated BBB disruption by increasing the expression of tight junction proteins such as ZO-1, claudin, and occludin [67].

Active components (Table 4, Table 5)

(1) Borneol is extracted from the chrysanthemum family and is used in traditional Chinese medicine to treat many brain diseases. D-borneol, L-borneol, and synthetic borneol (DL-borneol) are commonly used [39]. D-borneol, L-borneol, and synthetic borneol were found to reduce cerebral infarction and edema in the MCAO rat model. In addition, it was found that all three types have a preventive effect on BBB damage by increasing the expression of tight junction proteins, claudin-5 [21]. Other experiments showed that borneol preserves BBB integrity by increasing tight junction proteins ZO-1 and TIMP1 and reducing VEGF, MMP-2/9, and AQP4 [15, 39, 55]. Borneol has also been shown to have anti-inflammatory, anti-apoptosis, and angiogenic effects against ischemic stroke [21].

(2) Scutellarin and 3,5-dicaffeoylquinic acid are the active components of *Erigeron breviscapus* injection. *E. breviscapus* injection has been found to reduce the infarct size, improve neurobehaviorals, and protect the BBB via reducing MMP-9 and increasing tight junction proteins such as claudin-5 and ZO-1. In particular, 3,5-dicaffeoylquinic acid was found to be effective in reducing brain edema and significantly increasing claudin-5 [43].

(3) *Panax notoginseng* saponins are extracted from *Panax notoginseng Radix*. Furthermore, it is an effective component of Xuesaitong injection used to treat ischemic stroke. It inhibits ROS and prevents the destruction of the BBB by increasing the expression of ZO-1 and claudin-5 [26].

(4) Ginsenoside Rg1 and Ginsenoside Rb1 are major active ingredients of *Panax ginseng* and *Panax notoginseng,* which have been widely used in traditional Chinese medicine for a long time. Ginsenoside Rg1 and Ginsenoside Rb1 are known to decrease the infarct volume and BBB disruption and improve neurological deficits [1, 41]. Ginsenoside Rg1 decreased AQP4 in the MCAO rat model [82], and Ginsenoside Rb1decreased MMP-9 and prevented the loss of tight junction proteins (occludin and ZO-1) in the MCAO mouse model [14]. In addition, Ginsenoside Rb1 also reported the anti-inflammatory, anti-apoptotic and antioxidant effects in ischemic stroke [73].

(5) Ligustrazine is the main active compound of *Ligusticum wallichii* Franchat (Chuan Xiong) and *Ligusticum chuanxiong* Hort. It is also known as 2,3,4,5-tetramethylpyrazine. Chuan Xiong is used in traditional Chinese medicine for cerebral ischemia and cardiovascular disease. Ligustrazine was found to reduce infarct volume, brain edema, neurological deficits, neuroinflammation, and BBB dysfunction in the ischemic brain. It was also found to preserve BBB permeability by increasing tight junction proteins, such as occludin and claudin-5, and reducing MMP-9 expression and activation [30, 62].

(6) Oridonin is a component extracted from a herb called *Rabdosia rubescens*. It reduced infarct volume, apoptosis, and neuroinflammation in the cerebral ischemia model. In addition, it was found that oridonin protected the BBB by increasing tight junction proteins (ZO-1, claudin-5, and occludin) in both *in vivo* and *in vitro* models (tMCAO mouse model and OGD and reperfusion bEND.3 model) [34].

(7) Baicalin is a natural flavonoid component extracted from the roots of *Scutellaria baicalensis* [12]. *S. baicalensis* is a widely used herb in traditional Chinese medicine under the name Huang-qin. Baicalin has been reported to have anti-oxidative, anti-thrombotic, anti-apoptosis, and anti-tumor effects on ischemic stroke [40]. Baicalin was found to prevent BBB damage and cerebral edema by reducing MMP-9 and enhancing tight junction protein expression in the ischemic rat [11, 64] and OGD BMEC models [83].

(8) Ruscogenin is an active ingredient found at the root of *Ophiopogon japonicus* (Thumb.) under the name Ker-Gawl

Table 4. Chemical structure and source of the Traditional Korean medicine active components

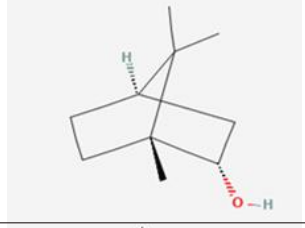
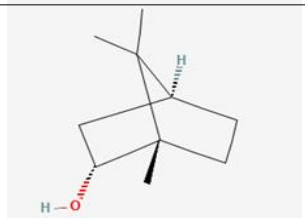
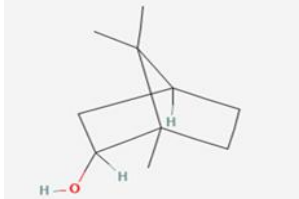
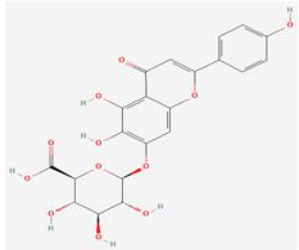
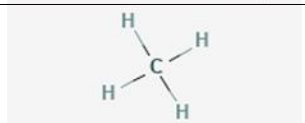
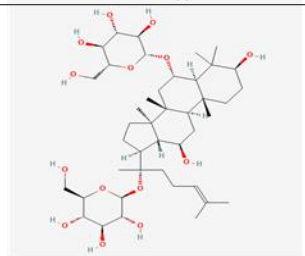
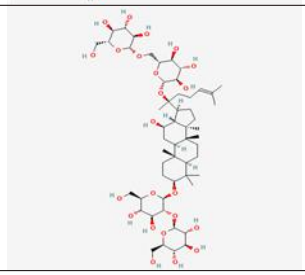
Active component	Chemical structure	Source
D-borneol		Blumea balsamifera (L.) DC., Cinnamomum camphora (L.) Presl.
L-borneol		Blumea balsamifera (L.) DC., Cinnamomum camphora (L.) Presl.
synthetic borneol (DL-borneol)		Blumea balsamifera (L.) DC., Cinnamomum camphora (L.) Presl.
Scutellarin		Erigeron breviscapus (Vant.) Hand-Mazz
3,5-dicaffeoylquinic acid		Erigeron breviscapus (Vant.) Hand-Mazz
Panax notoginseng saponins		Panax notoginseng (Burk) F. H. Chen
Ginsenoside Rg1		Panax ginseng C.A. Meyer
Ginsenoside Rb1		Panax ginseng C.A. Meyer

Table 4. Continued

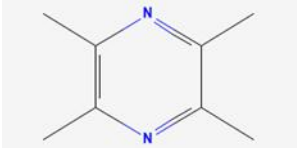
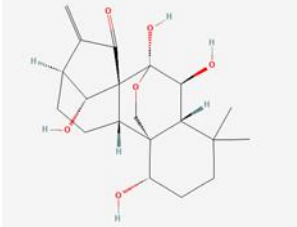
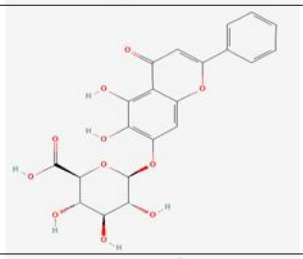
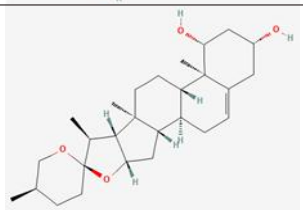
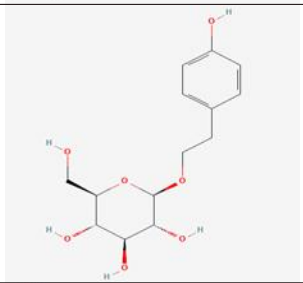
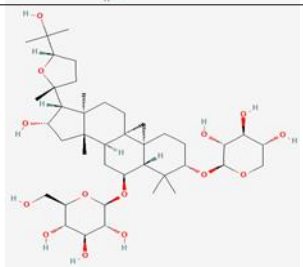
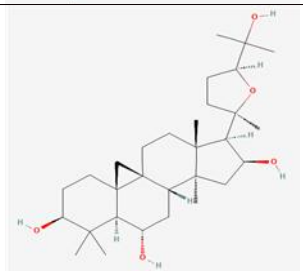
Active component	Chemical structure	Source
Ligustrazine (Tetramethylpyrazine)		Ligusticum wallichii Franchat, Ligusticum chuanxiong Hort
Oridonin		Rabdosia rubescens (Hemsl.) Hara
Baicalin		Scutellaria baicalensis Georgi
Ruscogenin		Ophiopogon japonicus (Thumb.) Ker-Gawl.
Salidroside		Rhodiola rosea L.
Astragaloside IV		Astragalus membranaceus Bunge
Cycloastragenol (active form of astragaloside IV)		Astragalus membranaceus Bunge

Table 4. Continued

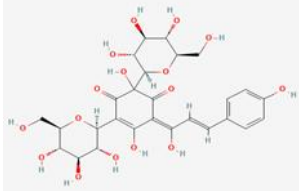
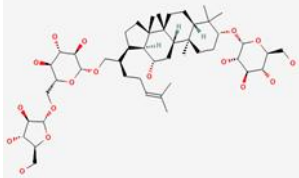
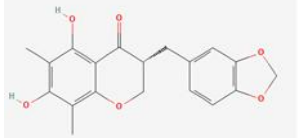
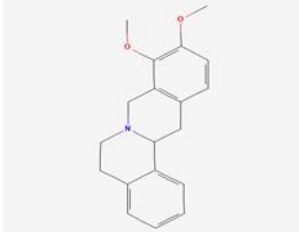
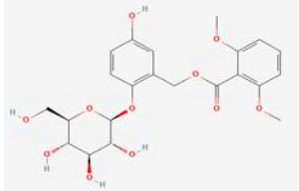
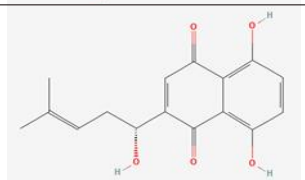
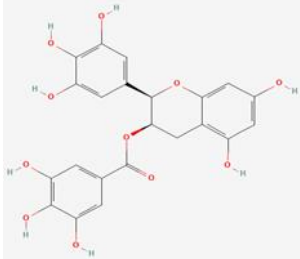
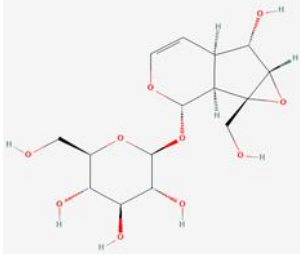
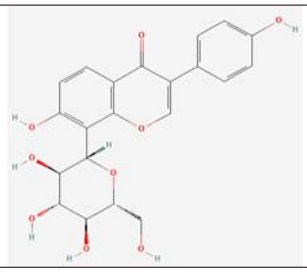
Active component	Chemical structure	Source
Hydroxysafflor Yellow A		Carthamus tinctorius L.
Notoginseng leaf triterpenes		Panax notoginseng (Burk) F. H. Chen
Methylophiopogonanone A		Ophiopogon japonicus (Linn. f.) Ker-Gawl
Levo-tetrahydropalmatine		Corydalis ambigua Cham
Curculigoside A		Curculigo orchioides Gaertn
Shikonin		Lithospermum erythrorhizon Siebold & Zucc.
Green tea polyphenols		Camellia sinensis L.
Catalpol		Rehmannia glutinosa Libosch

Table 4. Continued

Active component	Chemical structure	Source
Puerarin		Pueraria lobata Benth (Willd.) Ohwi

which is a herb used in traditional Chinese medicine. Ruscogenin reduced the infarct volume, brain edema, and neurological deficit by inhibiting NLRP3 inflammasome activation and IL-Iβ and caspase-1 expression in the MCAO mouse model. In addition, it attenuated BBB dysfunction by increasing tight junction proteins such as ZO-1 and occludin in both *in vivo* and *in vitro* models [5].

(9) Salidroside is a component extracted from a herb called *Rhodiola rosea L.*, which has long been used in traditional Chinese medicine. It has been reported that Salidroside has anti-apoptosis, anti-inflammatory, anti-oxidant, and anti-tumor neuroprotective effects [23, 38]. In addition, Salidroside was found to reduce BBB permeability by decreasing the activation of MMP-9 and increasing claudin-5 and occludin expression in the MCAO rat model [85].

(10) Astragaloside IV is an extraction component of *Astragalus radix* (Huang Qi). In traditional Chinese medicine, *A. radix* is used for cerebrovascular diseases, cardiovascular diseases, diabetes, and cancers. Astragaloside IV reduced the infarct volume and brain edema and restored neurological deficits due to its anti-inflammatory, anti-apoptosis, and anti-oxidant effects in ischemic stroke [58, 79]. Astragaloside IV protected BBB permeability by increasing the expression of tight junction proteins (ZO-1 and occludin) [58]. In addition, Cycloastragenol, an active form of Astragaloside IV, reduced MMP-9 and increased the expression of ZO-1 and occludin [36]. In addition to *in vivo* models, Astragaloside IV and Hydroxysafflor Yellow A inhibited cell death and increased proliferation *in vitro* in the OGD BMEC model [7].

(11) Notoginseng leaf triterpenes are total saponins extracted from the leaves and stems of *Panax notoginseng*. *P. notoginseng saponins* are mainly extracted from the roots of *P. notoginseng*. Although there are many effective ingredients in the stems and leaves of *P. notoginseng*, it is not used well. However, it has been found that Notoginseng leaf triterpenes reduced the infarct volume and brain edema and improved neurological function by decreasing apoptosis in ischemic stroke. In addition, Notoginseng leaf triterpenes showed BBB protective effects by decreasing MMP-2/9 expression and inflammation in the MCAO rat model [74].

(12) Methylophiopogonanone A (MO-A) is an isoflavonoid extracted from *Opiopogon japonicus*. *O. japonicus* is widely used to treat myocardial ischemia, thrombosis, and hypoxia in traditional Chinese medicine. MO-A reduced infarct volume and brain edema and improved neurological deficit in MCAO rats. In addition, MO-A attenuated BBB permeability by decreasing MMP-9 and increasing tight junction proteins such as claudin-5 and claudin-3. In the *in vitro* model, MO-A was also found to prevent BBB damage by reducing ROS generation [42].

(13) Levo-tetrahydropalmatine (L-THP) is an active component extracted from the *Corydalis* genus. L-THP reduced the infarction volume, improved neurological deficits, and attenuated BBB permeability by decreasing the expression of MMP-2/9 and caveolin-1 and attenuating the loss of tight junction proteins (ZO-1, occludin, claudin-5) in the MCAO mouse model [51].

(14) Curculigoside A is an active component extracted from the roots of *Curculigo orchioides*. *C. orchioides* is used to restore physical strength in traditional Chinese medicine. As a result of the administration of Curculigoside A to MCAO rats, the infarct volume was significantly reduced, and cerebral damage was alleviated. In addition, Curculigoside A inhibited HMGB1 expression and NF-κB activation associated with inflammatory reactions, reducing BBB breakdown [29].

(15) Shikonin has been known to have anti-inflammatory effects. It reduced the infarct volume and edema and improved neurological deficits by suppressing the pre-inflammatory mediators such as TLR-4 and TNF-α in the tMCAO mice model. In addition, Shikonin maintained the integrity of the BBB by increasing the expression of tight junction

Table 5. Traditional Korean medicine active components targeting the BBB in cerebral ischemia rodent models

Active component	Rodent type	BBB target	Cerebral ischemia model	Reference
Borneol	Rat	EB leakage↓, ZO-1↑, claudin 5↑, MMP-2/9↓, TIMP1↑, AQP4↓, VEGF↓	pMCAO/MCAO	[39], [21], [15], [55]
Scutellarin	Rat	EB leakage↓, ZO-1↑, occludin↓, claudin-5↑, MMP-9↓, iNOS↓	MCAO	[43]
3,5-dicaffeoylquinic acid	Rat	EB leakage↓, ZO-1↑, occludin↓, claudin-5↑, MMP-9↓, iNOS↓,	MCAO	[43]
Panax notoginseng saponins	bEnd.3	TEER↑, FITC-dextran concentration↓, ZO-1↑, claudin-5↑	OGD	[26]
Ginsenoside Rg1	Rat	EB leakage↓, AQP4↓	MCAO	[82]
Ginsenoside Rb1	Mice	EB leakage↓, ZO-1↑, occludin↑, MMP-9↓	MCAO	[14]
Ligustrazine (Tetramethylpyrazine)	Rat/Mice	EB leakage↓, occludin↑, claudin-5↑, MMP-9↓, MMP activity↓	MCAO	[62], [30]
Oridonin	Mice/bEND.3	EB leakage↓, ZO-1↑, claudin-5↑, occludin↑	tMCAO/OGD	[34]
Baicalin	Rat/BMEC/ Rat	TEER↑, HRP permeability↓, endogenous IgG immunoreactivity↓, ZO-1↑, occludin↑, claudin-5↑, MMP-9↓	pMCAO/OGD/ MCAO	[11, 64, 83]
Ruscogenin	Mice/bEND.3	EB leakage↓, ZO-1↑, occludin↑	MCAO/OGD	[5]
Salidroside	Rat/HBMEC	EB leakage↓, ocludin↑, claudin-5↑, MMP-9↓	MCAO/OGD	[85]
Astragaloside IV	BMEC/Rat	EB leakage↓, ZO-1↑, occludin↑, apoptosis↓	OGD/tMCAO	[7, 58]
Cycloastragenol (active form of astragaloside IV)	Mice	EB leakage↓, ZO-1↑, occludin↑, MMP-9↓	MCAO	[36]
Hydroxysafflor Yellow A	BMEC	apoptosis↓	OGD	[7]
Notoginseng leaf triterpenes	Rat	EB leakage↓, MMP-2/9↓	MCAO	[74]
Methylophiopogonanone A	Rat/bEnd.3	TEER↑, claudin-3↑, claudin-5↑, MMP-9↓	MCAO/OGD	[42]
Levo-tetrahydropalmatine	Mice	EB leakage↓, ZO-1↑, occludin↑, claudin-5↑, MMP-2/9↓, caveolin-1↓, Alb↓	MCAO	[51]
Curculigoside A	Rat	EB leakage↓	MCAO	[29]
Shikonin	Mice	EB leakage↓, claudin-5↑, MMP-9↓	tMCAO	[68]
Green tea polyphenols	Rat	EB leakage↓, ZO-1↑, occludin↑, claudin-5↑	MCAO	[46]
the lyophilized Powder of Catalpol and Puerarin	Rat/NVU	TEER↑, SF-absorbance↓, γ-GTP activity↑, claudin-5↑, apoptosis↓	MCAO/OGD	[75]

BBB: blood-brain barrier, BMEC: brain microvascular endothelial cell, HBMEC: human brain microvascular endothelial cell, NVU: neurovascular unit, MCAO: middle cerebral artery occlusion, pMCAO: permanent middle cerebral artery occlusion, tMCAO: transient middle cerebral artery occlusion, OGD: oxygen-glucose deprivation, EB: evans blue, ZO-1: zonula occludens-1, AQP4: aquaporin4, MMP-2/9: matrix metalloproteinase-2/9, TIMP1: tissue inhibitor of metalloproteinase 1, Alb: albumin, TEER: trans-epithelial electrical resistance, VEGF: vascular endothelial growth factor, iNOS: inducible nitric oxide synthase, FITC-dextran: fluorescein isothiocyanate-dextran, HRP: horseradish peroxidase, SF-absorbance: sodium fluorescein-absorbance, γ-GTP: γ-glutamyl transpeptidase.

proteins, claudin-5, and reducing MMP-9 expression [68].

(16) Green tea polyphenols are a major active component in green tea and widely used in neurodegenerative diseases such as Alzheimer's and Parkinson's disease. Green tea polyphenols showed the effect of attenuating the disruption of the BBB via increasing the expression of tight junction proteins ZO-1, occludin, and claudin-5 in the MCAO rat model [46].

(17) The lyophilized powder of Catalpol and Puerarin are two active components extracted from the traditional Chinese

medicine herbs, *Rehmannia glutinosa Libosch* and *Radix Puerariae*. *Catalpol* and Puerarin were found to reduce the infarct volume and neurological deficiency by attenuating apoptosis, oxidative stress, and inflammation in both *in vivo* and *in vitro* cerebral ischemia models. In addition, they protected BBB integrity by increasing the expression of the claudin-5 *in vitro* model [75].

Conclusion and future perspectives

Ischemic stroke elicits BBB disruption that aggravates inflammation and generates neurotoxicity in the damaged site, resulting in neuron cell death. Therefore, new treatments targeting the protection and restoration of the BBB are needed to help protect tissue injury from increasing in the setting of ischemic stroke. Traditional Korean medicine has been recorded in the treatment of neurovascular disorders. This review has presented several traditional Korean medicines, including the herbal formula, decoction, herbs, and active components, which exert a neuroprotective effect on cerebral ischemia-induced BBB disruption. These traditional medicines were shown to have protective effects on the BBB in many cellular ischemia models such as OGD and hypoxia, various animal ischemia models of stroke such as MCAO and photothrombosis, and experiments in various animal species such as mice and rats. In addition, they showed brain-protective effects by protecting the BBB through regulation of tight junction proteins (ZO-1, occludin, and claudin-5) and MMP-9, reducing edema, neuroinflammation, and neuronal cell death. However, there are also several limitations to the existing studies that have focused on the neuroprotective effects of traditional Korean medicines on BBB dysfunction after ischemic stroke. Many traditional Korean medicines were found to exert a neuroprotective effect on ischemia-induced BBB disruption using rodent models, which differ greatly from human patients. Therefore, we hope that this review will stimulate the performance of clinical trials of Korean herbal medicine-derived drugs in patients with stroke.

Acknowledgment

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The Conflict of Interest Statement

The authors declare that they have no conflicts of interest with the contents of this article.

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초록 : 허혈성 뇌졸중 모델에서 혈액-뇌 장벽에 보호효과를 나타내는 한약처방, 한약재 및 활성화합물

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뇌졸중은 세계적으로 사망과 장기간인 신체적, 인지적 장애의 주요 원인들 중 하나이며, 매년 약 1,500만 명의 사람들에게 영향을 미친다. 뇌졸중의 병태 생리학적 과정은 다수의 사건들이 관여하는 복잡한 과정으로, 그 중 혈액-뇌 장벽(blood-brain barrier: BBB)의 붕괴는 허혈성 뇌손상의 진행에 크게 기여하는 것으로 알려져 있다. 따라서 BBB 붕괴는 뇌졸중의 특징으로 인식되므로 허혈성 뇌졸중에서 BBB 기능 장애를 보호할 수 있는 새로운 치료 전략을 개발하는 것이 뇌졸중 치료에 매우 중요하다. 전통한약은 천연물로 구성되어 있으며, 이는 뇌졸중 치료약 개발을 위한 유망한 원천이 될 수 있다. 실제로 여러 연구에서 뇌졸중에 대한 한의학의 효능이 밝혀져 허혈성 뇌졸중에 대한 한의학적 치료 가치가 부각되고 있다. 본 리뷰에서는 허혈성 뇌졸중으로 인한 BBB 붕괴에 대한 전통적인 한의학의 처방, 탕약, 약재 및 활성 성분의 개선 효과에 관한 현재 정보와 기본 메커니즘을 요약 정리하였다. 이러한 연구가 한의학의 신경보호 효과에 대한 추가 조사를 촉진하고 뇌졸중 환자에 대한 한방유래의 임상시험 시행을 활성화하는데 도움이 되기를 기대한다.