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Traditional Chinese herbal medicine and cerebral ischemia

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1. ABSTRACT

Stroke is an important cause of mortality and morbidity worldwide but effective therapeutic strategy for the prevention of brain injury in patients with cerebral ischemia is lacking. Although tissue plasminogen activator (t-PA) has been used to treat stroke patients, this therapeutic strategy is confronted with ill side effects and is limited to patients within 3 hours of a stroke. Stroke-mediated cell death is a complex interplay of aberrant events involving excitotoxicity, acidosis, inflammation, oxidative stress, peri-infarct depolarization, and apoptosis. Due to the complexity of the events and the disappointing results from single agent trials, the combination of thrombolytic therapy and effective neural protection therapy may be an alternative strategy for patients with cerebral ischemia. Traditional Chinese herbal medicine has been described in ancient medicine systems as a treatment for various ailments associated with stroke. Recently, there have been reports of its benefits in treating stroke. This review will focus on various traditional Chinese herbal medicines and their neuroprotective effects on cerebral ischemia.

2. INTRODUCTION

Stroke is a leading cause of death and disability worldwide (1). Annually, there are an estimated 4.5 million deaths from strokes and over 9 million stroke survivors. The overall incidence for strokes is around 2 - 2.5 per thousand of the population. The risk of recurrence over 5 years is 15 – 40 %. This estimate suggests that by 2023, the number of patients experiencing an initial stroke is increased by approximately 30 % as compared with that in 1983. The prevalence rate of stroke is around five per thousand of the population. Stroke comprises the major cause of adult disabilities; 65 % of survivors are functionally independent one year after stroke (2). In the United States stroke is the third largest cause of death and the leading cause of disability with the highest disease-burden cost (3). Strokes can be subdivided into two categories, namely ischemic and hemorrhagic strokes. Ischemic strokes are more prevalent than hemorrhagic strokes making up approximately 87 % of all cases, and have been the target of most drug trials (4). A thrombosis results in a restriction of blood flow to the brain and this result in insufficient oxygen and glucose delivery to

support cellular homeostasis (5). These processes share overlapping biochemical abnormalities causing injury to neurons, glia, and endothelial cells. Within the core of ischemic territory, where blood flow is most severely restricted, excitotoxic and necrotic cell death occurred within minutes (5). This elicits multiple processes that lead to brain injury, such as free radical production, excitotoxicity, ionic imbalance, oxidative stress, inflammation, apoptosis, and peri-infarct depolarization (6-8). Targeting these mechanisms is important to provide therapeutic opportunities (6).

Drugs currently used for stroke, such as aspirin and anticoagulants, are utilized as preventative therapies (9). Thrombolytic therapy is an effective strategy for the prevention of brain injury in patients following stroke. A tissue plasminogen activator (t-PA) has been used to release blood clots in stroke patient (10). However, the narrow therapeutic window (within 3 h after stroke) and the hemorrhagic side effects put limitations on the use of this drug (11-12). Cell death following stroke is associated with a complex interplay of excitotoxicity, acidosis, inflammation, oxidative stress, peri-infarct depolarization, and apoptosis (5). Due to the complex events associated with cerebral ischemia and the disappointing results from single agent trials, the combination of thrombolytic therapies and effective neuronal protection therapy may be an alternative strategy for patients with cerebral ischemia.

2.1. Pathophysiology of cerebral ischemia

Appropriate blood supply to the nervous system is required for maintaining proper neuronal function. When the blood supply drops below 25% of normal values, neuronal activity declines rapidly. If the ischemic condition persists for a prolonged period of time, neuronal death occurs rapidly in the core areas and activation of multiple death pathways is accompanied by a secondary cell death in the penumbra (13).

2.1.1. Brain inflammation and cerebral ischemia

Inflammation contributes to stroke related brain injury. Nevertheless, individual components of the inflammatory cascade may have detrimental or beneficial effects depending on the stage of tissue injury, the magnitude of the response, and whether these components may stimulate neuroprotective pathways (5, 14-16). The inflammatory response is a composite process that involves many different cell types, inflammatory mediators, and extracellular receptors. Stroke causes neutrophilia, lymphocytopenia, and an increase in the number of circulating monocytes (17). Neutrophils accumulation in the brain can be detected as early as 30 minutes after permanent middle cerebral artery occlusion (MCAO). Transmigration is mediated by three classes of cell adhesion molecules and by cytokine signaling (18). The recruitment of neutrophils to the ischemic brain begins with their rolling on activated endothelial blood vessel walls, which is followed by activation and adherence. Once attached to cerebral blood vessel walls, neutrophils transmigrate into the cerebral parenchyma and are facilitated by disruption of the blood brain barrier (BBB). The recruitment of neutrophils can obstruct the microcirculation and prevent complete restoration of cerebral blood flow after reperfusion. This blockage may cause further tissue damage after ischemia and is described as the ischemic no-reflow phenomenon (18). As shown in Figure 1, these processes are associated with neurodestructive gene expression responses in the injured brain. The inflammatory responses after these initial changes contribute to the development of tissue injury. Inflammatory interactions occurring at the blood-endothelium interface involve cytokines, adhesion molecules, chemokines, and leukocytes, and are critical to the pathogenesis of tissue damage in cerebral infarction. Exploring these pathophysiological mechanisms underlying ischemic tissue damage may direct a future rational drug design in the therapeutic treatment of stroke (18).

2.1.2. Excitotoxicity, oxidative stress, and apoptosis in cerebral ischemia

After global ischemia, lack of oxygen for adenosine triphosphate (ATP) synthesis in the mitochondria leads to ATP being consumed within two minutes. In turn, this causes neuronal plasma membrane depolarization, release of potassium into the extracellular space, and entry of sodium into cells (19). Membrane depolarization leads to neurotransmitter release, with the release of the excitatory neurotransmitter, glutamate, playing a critical role in ischemic pathology. Glutamate mediates excitatory synaptic transmission through activation of ionotropic glutamate receptors sensitive to NMDA (N-methyl-D-aspartic acid), AMPA (a-amino-3- hydroxy-5-methyl-4-isoxazolepropionic acid), or kinate. NMDA receptors are sodium and calcium permeable. Opening of these channels leads to further membrane depolarization and greater calcium influx, which in turn exacerbate intracellular calcium overload (excitotoxicity) (20). Ischemic stroke is associated with a number of neuronal changes, including reduction of energy production and release of excitatory glutamate receptors, increase in cytosolic calcium that causes mitochondrial calcium overload, and extensive breakdown of cellular phospholipids due to activation of calcium-dependent phospholipases. Free radicals (e.g. nitric oxide, superoxide) are produced in the process and contribute to membrane lipid peroxidation, protein and nuclear DNA damage, and subsequently cell death by necrosis and/or apoptosis (Figure 2). High levels of intracellular Ca^{2+}, Na^{+} and ADP cause mitochondria to produce deleterious levels of reactive oxygen species (ROS). Unlike other organs, the brain has relatively low levels of endogenous antioxidants and is thus especially vulnerable to ROS (21). Excess production of ROS causes the destruction of cellular macromolecules and is the basis of signaling mechanism leading to apoptotic cell death (22-23). Ischemic condition also activates nitric oxide synthase (NOS) and nitric oxide (NO) produced can combine with superoxide to produce peroxynitrite, a potent oxidant. Thus, reperfusion is accompanied by a surge in production of superoxide, NO, and peroxynitrite. Formation of these radicals in the vicinity of blood vessels plays an important role in reperfusion-induced injury. These radicals activate matrix metalloproteases (MMPs), enzymes known for disrupting the integrity of the vascular wall and increase

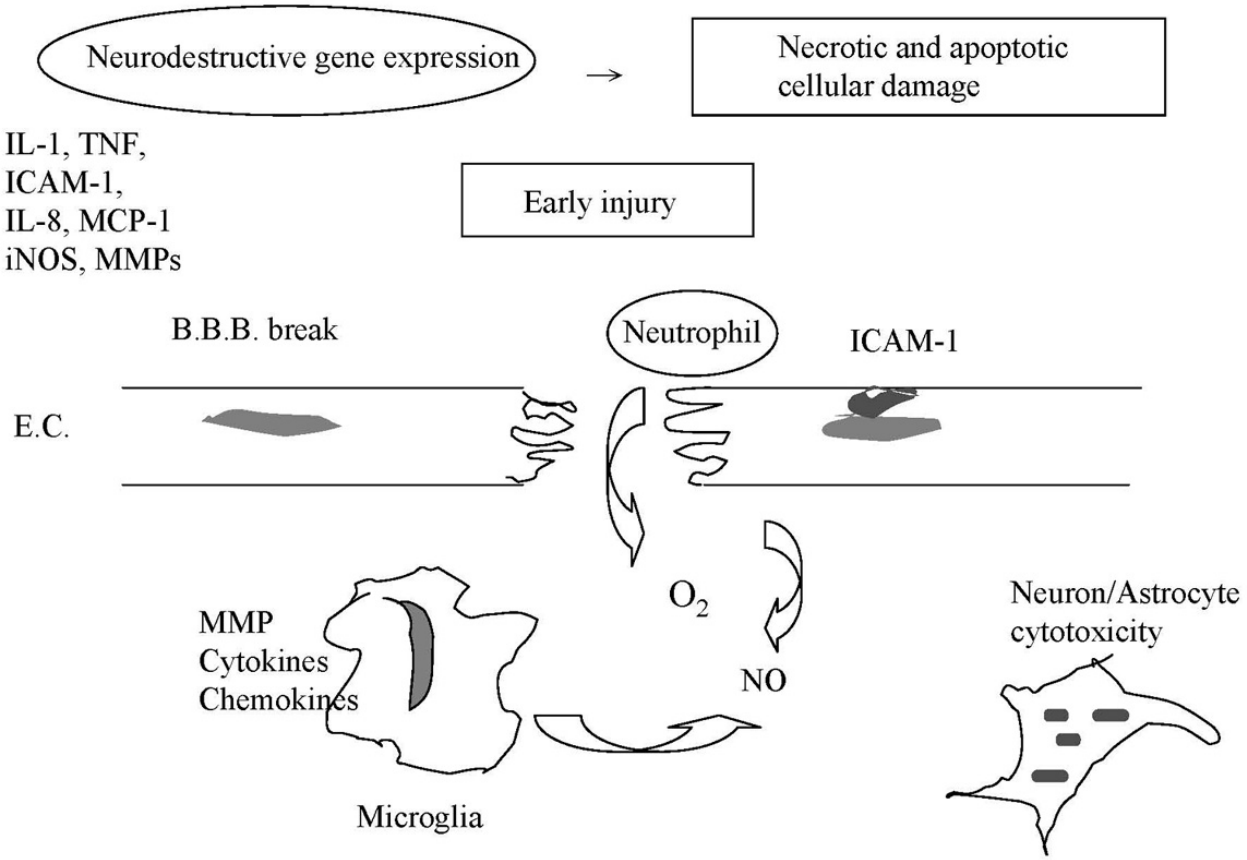

Figure 1. Progression of neurodestructive gene expression and brain injury following stroke. Abbreviation: B.B.B.: Blood-brain-barrier; E.C.: endothelial cells; ICAM-1:intracellular adhesive molecule-1; IL-1: interleukin-1 beta; IL-8: interleukin-8; iNOS: inducible nitric oxide synthase; MMPs: matrix metalloproteinases; MCP-1: monocyte chemotactic protein-1; NO: nitric oxide; TNF: tissue necrosis factor alpha.

blood brain barrier (BBB) permeability. Oxidative and nitrative stress triggers recruitment and migration of neutrophils and other leukocytes to the cerebral vasculature, and these cells further release enzymes and factors to increase basal lamina degradation and vascular permeability (as shown in Figure 2). These events can lead to parenchyma hemorrhage, vasogenic brain edema, and neutrophil infiltration into the brain (24). Therefore, factors leading to neuronal apoptosis include ROS, death receptor ligation, DNA damage, protease activation, and ionic imbalance. The release of cytochrome c from the outer mitochondrial membrane also plays a central role in triggering apoptotic pathways in response to ischemia.

2.2. Traditional Chinese medicines and cerebral ischemia

2.2.1. Proposed mechanisms of action underlying the neuroprotective effects of traditional Chinese herbal medicines

Cumulative evidence suggests that traditional Chinese herbal medicines (TCM) may play a role in the prevention or treatment of stroke (25-28). Some TCM can dilate blood vessels, suppress platelet aggregation, protect against ischemic reperfusion injury, and enhance the tolerance of ischemic tissue to hypoxia (27). After extensive pharmacological research and clinical trials, a number of remedies for the treatment of stroke based on TCM have been introduced onto the market (25). Therapeutic strategies of TCM on cerebral ischemia are based on the pathophysiology of stroke, as TCM are classified as antioxidants, and anti-inflammatory and antithrombotic agents (14). Although TCM has been used for the treatment of various types of neurologic ailments since the ancient times, they have also been reported to be beneficial in treating stroke in recent years. Clearly, large, well-designed trials are necessary to avoid preconceived notions resulting from admission, selection, reporting, or publication bias (25).

2.2.2. Traditional Chinese herbal medicine

Examples of traditional Chinese herbal medicine, prescription, active component, and mechanisms of action for cerebral ischemia are listed in Table 1.

2.2.2.1. *Angelica sinensis* (Oliv.) Diels, *Ligusticum chuanxiong* Hort

Angelica sinensis (Oliv.) Diels (AS) and *Ligusticum chuanxiong* Hort. (LC) have been widely used in traditional Chinese medicine to treat atherosclerosis and hypertension. The extract of *Ligusticum chuanxiong* and

Table 1. Examples of traditional Chinese herbal medicine, prescription, active components, and action mechanisms for cerebral ischemia

TCM or prescription	Active compound of TCM	Action mechanisms	References
TCM			
Angelica sinensis (Oliv.) Diels and *Ligusticum chuanxiong* Hort.	Ferulic acid	↓ROS, ICAM-1, NF kappa B ↑SOD, CAT, GPX, ERK phosphorylation, eNOS expression	28, 29
Ligusticum wallichii Franchat	Tetramethylpyrazine	↑coronary blood flow ↓ADP-induced platelet aggregation	30-34
Paeonia suffruticosa Andrews	Paeonol	↓platelet aggregation, ED1, IL-1, superoxide anion, lucigenin-CL counts	35
Paeonia lactiflora Pall	Paeoniflorin	↓NF kappa B, ED1, IL-1 beta, TNF alpha, ICAM-1, MPO immunoreactive cells, NMDA evoked f-EPSP, NMDA evoked Ca^{2+} influx	36
Panax ginseng and *Panax notoginseng* Burk.	Ginsenoside Rd	↓ROS, MDA, ↑GPx, SOD, ED1, BDNF	37-42
Salvia miltiorrhiza Bunge		↓MDA, ↑SOD	43-47
Sophora japonica L.		↓microglia activation, IL-1 beta release, apoptotic cells	48, 49
Stephania tetrandra S. Moore	Tetrandrine	↓Ca^{2+}, lipid peroxide, neutrophilic recruitment, ICAM-1 mRNA ↑NFkappa B	50, 51
TCM prescription			
Kueichih-Fuling-Wan		↑Glu, Asp, Gly, GABA, ↓Ca^{2+} ↑SOD,↓MDA, ROS, MMP	52-54
Sheng-mai-san		↓TBARS, ↑GPX, ↓NO, inflammatory cytokines, cerebral water and Na^{+} content, LDH, CPK, MDA	55-60

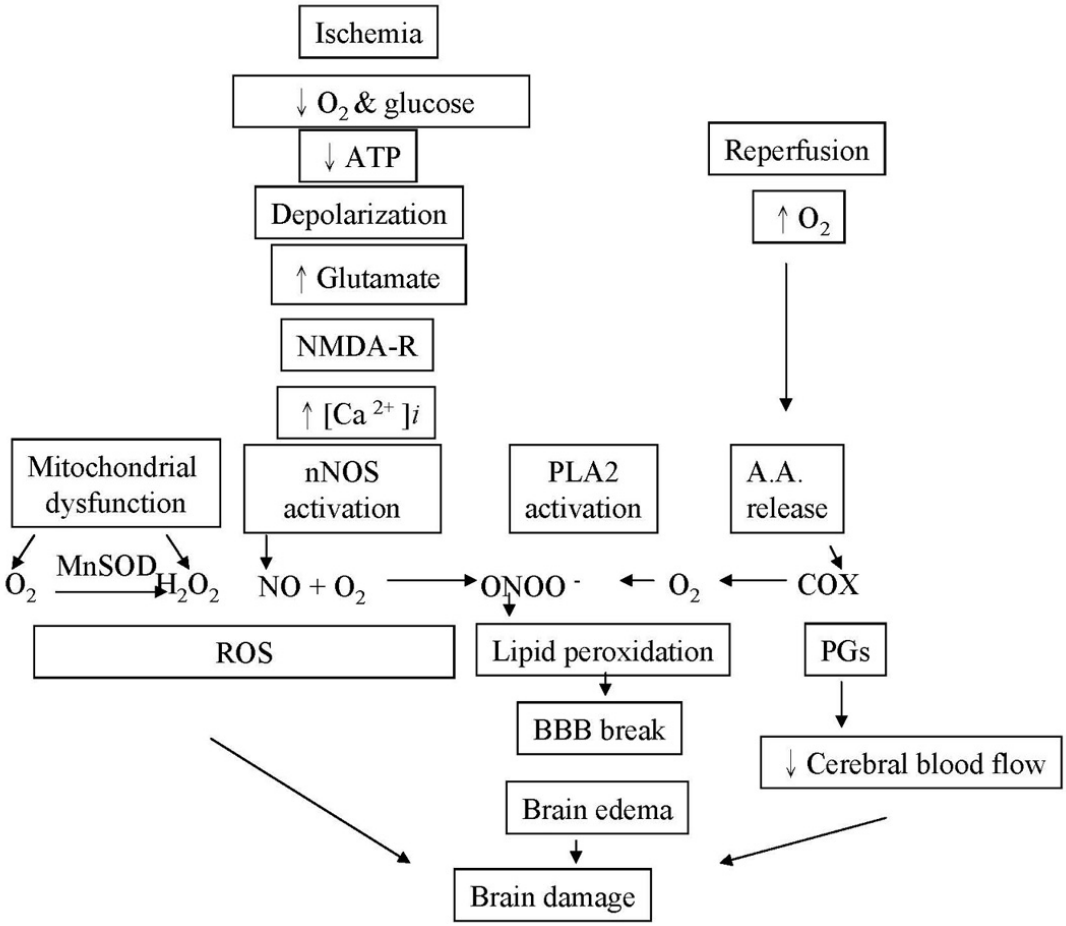

Figure 2. Possible pathways of ischemic brain damage. Abbreviations: ATP: adenosine triphosphate; A.A: arachidonic acid; B.B.B.: blood-brain-barrier; COX: cyclooxygenase; MnSDO: manganese superoxide dismutase; nNOS: neuron nitric oxide synthase; NMDA-R: n-methyl-D-aspartic acid receptor; PLA2: phospholipase A2; PGs: prostaglandins; ROS: reactive oxygen species

Angelica sinensis (ELCAS), can dose- and time-dependently protect human umbilical vein endothelial cells (ECV304) against hydrogen peroxide damage and suppress ROS production. The decrease of ROS may be associated with increase in enzyme activity, such as superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPX). Western blot analysis revealed that ELCAS significantly increased ERK phosphorylation and eNOS expression. These observations indicate that LC and AS can prevent cardiovascular and cerebrovascular diseases that are due to their antioxidative activity and activation of the ERK and eNOS-signaling pathway (29). Ferulic acid (FA), an active component in AS and LC, is thought to play a role in neuroprotection. FA treatment effectively suppressed superoxide radicals in the parenchyma lesions and intracellular adhension molecule-1 (ICAM-1) immunoreactive vessels in the ischemic striatum after 2 hours of reperfusion. FA reduced the expression of ICAM-1 and nuclear factor-kappa-B (NF-kappaB) in the ischemic cortex and striatum, and also down-regulated myeloperoxide (MPO) immunoreactive cells in the ischemic cortex after 24 hours of reperfusion. These results showed that the effects of FA on reducing the cerebral infarct area and neurological deficit-score are at least partially attributed to the inhibition of superoxide radicals, ICAM-1, and NF-kappaB expression in MCAo rats (28).

2.2.2.2. *Ligusticum wallichii* Franchat

Ligusticum wallichii Franchat (LW) is one of the most commonly used traditional Chinese herbal medicines for the treatment of ischemic stroke. Tetramethylpyrazine (TMP), one of the most important anti-inflammatory components of LW, protects the brain against ischemic brain injury (30). TMP has been shown to increase coronary blood flow and inhibit ADP induced platelet aggregation. These effects account for an efficacy in the treatment of disorders associated with blood vessel occlusion like cerebral ischemia (31). Moreover, TMP is effective within a 4 h time period of post-transient focal stroke, and can reduce cerebral ischemic reperfusion damage (32) and the infarct volume in ischemia-reperfusion brain injury (33). Hence, LW or TMP treatment may provide an alternative way to lower the risk or improve the function of, ischemia/reperfusion brain injury (34).

2.2.2.3 *Paeonia suffruticosa* Andrews and *Paeonia lactiflora* Pall

Moutan cortex of *Paeonia suffruticosa* **Andrews** (MC) and the root of *Paeonia lactiflora* **Pall.** (PL) are important Traditional Chinese herbs commonly used to treat inflammatory and pyretic disorders. Paeonol, a common component of MC causes anti-platelet aggregation and scavenges free radicals. Paeonol 15 and 20 mg/kg pretreatment, and 20 mg/kg post-treatment reduced cerebral infarct area; and paeonol at 15 and 20 mg/kg pretreatment reduced the neuro-deficit score. In addition, paeonol at 20 mg/kg pretreatment reduced the lucigenin-enhanced chemiluminescence counts (lucigenin-CL counts) after 2 h period of reperfusion. The numbers of ED1 and interleukin1 beta (IL-1beta) immunoreactive cells were reduced in the cerebral infarction region. Paeonol can suppress and scavenge superoxide anion, and inhibit microglia activation and IL-1beta expression in ischemia-reperfusion injured rats. The ability for paeonol to reduce cerebral infarct and neuro-deficit in rats suggests that this herb may similarly be effective in reducing cerebral infarction in humans (35). Paeoniflorin, a component in *Paeonia lactiflora* Pall., inhibits nuclear factor-kappaB expression in chronic hypoperfusion rats and has anti-inflammatory properties. Paeoniflorin can reduce cerebral infarction area and improve the neurological deficit score. Pre-treatment with paeoniflorin also reduced the increased counts of ED1, IL-1beta, TNF-alpha, the ICAM-1 of microvessels, MPO immunoreactive cells, and apoptotic cells in the cerebral infarction region (36). Furthermore, paeoniflorin also inhibited the field excitatory postsynaptic potential (f-EPSP) evoked by NMDA in hippocampus slice. Paeoniflorin dose-dependently inhibited the calcium influx evoked by NMDA. In addition, both the increase of NMDA-induced calcium influx by Ruthenium red and inhibition of NMDA-induced calcium influx by omega-conotoxin MVIIC were reversed by paeoniflorin. These results indicate that the inhibitory effects of paeoniflorin on NMDA-induced f-EPSP or calcium influx in the hippocampus may be due to inactivation of the NMDA receptor (author's unpublished data). Paeoniflorin may prove to be a suitable compound for treatment of stroke.

2.2.2.4. *Panax ginseng* and *Panax notoginseng* Burk

Ginseng, the root of *Panax ginseng*e, is a well-known traditional Chinese herbal medicine and can attenuate H_2O_2– induced oxidative injury (37). Ginsenoside Rd (GSRd), one of the active ingredients of *Panax ginseng*, exhibits neuroprotection when presented during oxygen glucose deprivation and reoxygenation (38). The anti-oxidative properties of GRSd include reducing the intracellular ROS and malondialdehyde (MDA) production, increasing glutathione content, and enhancing the antioxidant enzymatic activities of catalase, superoxide dismutase, and glutathione peroxidase (GPx). Additionally, GSRd can stabilize the mitochondrial membrane potential and attenuate apoptotic death of hippocampal neurons after oxygen-glucose-deprivation (OGD) exposure. These findings suggest that GSRd may be a potential neuroprotective agent to ameliorate cerebral ischemic injury (39). *P. ginseng* may protect against cerebral ischemia-induced injury in rat brain by decreasing lipid peroxides and increasing the expression of antioxidative enzymes such as GPx and SOD (40). Ginsenoside Rb1 (GRb1), a major component of the traditional herb ginseng, has been reported to ameliorated early and delayed injuries in the thromboembolic stroke model in nonhuman primates (41). *Panax notoginseng* Burk. (PN) has been reported to improve blood circulation, as well as learning and memory functions. PN also increased ED1, brain-derived neurotrophic factor (BDNF), and beta-secretase immunoreactive cells and attenuated the reduction in learning and memory functions in rats after cerebral ischemia-reperfusion. The data suggest that PN may exert its effect by increasing BDNF generated by activated microglia (42).

2.2.2.5. *Salvia miltiorrhiza* Bunge

Salvia miltiorrhiza Bunge**,** the dried root and rhizome of *Salvia miltiorrhiza* Bunge, is recognized as

Radix salviae miltiorrhizae (Danshen). This herb has been used for increasing the cerebral blood flow and potentially protects against cerebral ischemia (43). According to the theory of traditional Chinese medicine, cerebral infarction results from blood stasis. A method of quickening the blood and dispelling stasis is used to treat cerebral infarct. Previous studies have been conducted to find out the possible mechanisms for the underlying protective effects of Danshen, which reduces lipid peroxidation, improves blood circulation, and resolves stasis to promote regeneration in traumatic intracranial hematoma (44-45). In Danshen-treated rats, the cerebral SOD activity is significantly increased, while the cerebral MDA level is significantly decreased when compared with untreated animals (45). Prevention and treatment of cerebral infarction by Danshen involves multiple pathways, including anti-atherosclerosis, anti-hypertension, anti-platelet aggregation, anti-inflammatory, and anti-oxidative effects (46-47).

2.2.2.6. *Sophora japonica* L.

The dried flowers and buds of *Sophora japonica* (SJ) are used as a medicinal herb in China to treat bleeding hemorrhoids and hematemesis. Previous studies found that SJ could reduce the size of cerebral infarction and neurological deficits, and reduced microglial activation, interleukin-1beta release, and the number of apoptotic cells in rats after ischemia-reperfusion injury. SJ partly reduces cerebral infarction because of its anti-oxidative and anti-inflammatory activities (48). Further more, SJ shows an effect on platelet aggregation and cardiovascular function, which suggests the potential as a treatment for cerebral infarction (49).

2.2.2.7. *Stephania tetrandra* S. Moore

Radix Stephaniae tetrandrae is the dried root of *Stephania tetrandra* S. Moore. Tetrandrine, an active compound of Radix *stephaniae* tetrandrae, has a calcium antagonizing property. Pretreatment with tetrandrine (15 mg/kg, iv) and nicardipine (0.25 mg/kg, iv) decreased the calcium content, water content, lipid peroxide, and attenuated the ultra structural abnormalities of the cortex and hippocampus in the gerbil ischemia model produced by a 10 min occlusion of the bilateral carotid arteries followed by reperfusion. The effects of tetrandrine were less potent than nicardipine (50). Tetrandrine also inhibited neutrophilic recruitment, expression of ICAM-1 mRNA, and activation of NF-kappaB after ischemia/reperfusion (I/R) in the brain (51).

2.2.3. Traditional Chinese medicine prescription

2.2.3.1. Kueichih-Fuling-Wan

Kueichih-Fuling-Wan (KFW), a traditional Chinese medicine prescription consisting of five herbal components *Cinnamomi ramulus*, *Poria cocos* (Schw.) Wolf., *Prunus persica* (L.) Batsch, *Paeonia suffructicosa* Andr., and *Paeonia lactiflora* Pall, has been used for the treatment of cerebral ischemia. The changes of glutamate (Glu), asparate (Asp), glycine (Gly), and gamma-aminobutyric acid (GABA) in serum and cerebral tissues was determined and the degrees of Ca^{2+} and the cerebral edema were analyzed in rats treated with KFW. In this study, the contents of Glu, Asp, Gly, GABA, and Ca^{2+} in the group treated with KFW were elevated compared with controls (52). KFW was also found to prevent the progress of atherosclerosis in cholesterol-fed rabbits (53) and increase SOD activity, reduce MDA content, and relieve neurological deficits in cerebral ischemia and reirrigation (CIR) rats (54). In addition, KFW reversed the increase of ROS and the decrease of the mitochondrial membrane potential (MMP) of neuronal SHSY-5Y cells during ischemia. These results indicate that KFW can be used to protect neurons against ischemia (author's unpublished data).

2.2.3.2. Sheng-mai-san

Sheng-mai-san (SMS) is a traditional Chinese medicine prescription consisting of three herbal components *Panax ginseng, Ophiopogon japonicus*, and *Schisandra chinenisis*. This prescription is used for the treatment of coronary heart disease (55). SMS, when administered directly into the duodenum 2 h before cerebral ischemia in a model of bilateral carotid occlusion, suppressed thiobarbituric acid reactive substance (TBARS) formation, and prevented the loss of glutathione peroxidase (GPX). SMS prevents cerebral oxidative damage in rats (56-57) by protecting against heat stroke-induced arterial hypotension and the inhibition of inducible nitric oxide synthase (iNOS)-dependent NO overproduction in the brain, and by preventing excessive accumulation of several inflammatory cytokines in the peripheral blood stream (58). After SMS treatment with rats subjected to cerebral ischemia-reperfusion, the cerebral water and Na^{+} content were lowered, lactate dehydrogenase (LDH) and creatine phosphokinase (CPK) released from brain during cerebral reperfusion were suppressed ($P<0.01$, $P<0.01$), and lactate and malondialdehyde (MDA) levels were decreased ($P<0.01$, $P<0.01$). These results indicate that SMS is effective in protecting rats from cerebral ischemia-reperfusion injury. The mechanisms directly relate to the inhibition of brain edema, intracellular enzymes release, lactate accumulation, and lipid-peroxidation (59). The multifunctional aspect of SMS was useful in preventing oxidative injury of the brain (60).

3. CONCLUSION

Stroke is a leading cause of death and disability worldwide. Prevention and effective treatment of stroke is imperative. Stroke can be subdivided into two categories, ischemic and hemorrhagic. Ischemic strokes are more prevalent than hemorrhagic strokes. A thrombosis results in a restriction of blood flow to the brain that can cause an ischemic stroke. Within the core of the ischemic territory, excitotoxic, and necrotic cell death occurs within minutes and elicits multiple processes that lead to brain injury. Free radical production, excitotoxicity, ionic imbalance, oxidative stress, inflammation, apoptosis, and peri-infarct depolarization causes brain injury. Targeting these mechanisms provides therapeutic opportunities. Traditional Chinese herbal medicine has been described in ancient medical systems as a treatment of various ailments associated with stroke. Recently, there have been reports of the benefits in treating stroke. TCM are classified as

antioxidants, anti-inflammatory, and antithrombotic. Therapeutic strategies for TCM on cerebral ischemia are based on the pathophysiology of stroke. Although TCM has been used for the treatment of various stroke ailments since ancient times, it has been reported to be recently beneficial in treating strokes and provides therapeutic opportunities. Clearly, large, well-designed trials are necessary to avoid partiality resulting from admission, selection, reporting, or publication bias.

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Abbreviations: ADP: adenosine diphosphate; ATP: triphosphate; AS: *Angelica sinensis* (Oliv.) Diels; Asp: aspirate; BBB: blood-brain-barrier; BDNF: Brain-derived neurotrophic factor; CAT: catalase; CPK: creatinine phosphokinase; I/R: ischemia/reperfusion; CL: lucigenin-chemiluminescence; ECV304: human umbilical vein endothelial cells; eNOS: endothelial nitric oxide synthase; ERK: extracellular signal-regulated kinase; FA: Ferulic acid; ED1: a cellular marker specific for activated rat microglia, monocytes & macrophages; f-EPSP: f-EPSP: field excitatory post-synaptic potential; GABA: gamma-aminobutyric acid; GRb1: Gunsenoside Rb1; GSRd: ginsenoside Rd; Glu: glutamate; GPX: glutathione peroxidase; ICAM-1: intracellular adhesion molecule-1; IL-1 beta: interleukin-1 beta; iNOS: inducible nitric oxide synthase; KFW: Kueichih-Fuling-Wan; LC: *Ligusticum chuanxiong* Hort.; LDH: Lactate dehydrogenase; LW: *Ligusticum wallichii* Franchat; Mn-SOD: manganese-superoxide dismutase; MMPs: matrix metalloproteases; MCAo: middle cerebral artery occlusion; MDA: malondialdehyde; MC: Moutan cortex of *Paeonia suffruticosa*; MPO: myeloperoxidase; NO: nitric oxide; NMDA: N-methyl-D-aspartic acid; ODG: oxygen-glucose-deprivation; PL: *Paeonia lactiflora* Pall; PN: *Panax notoginseng* Burk. ROS: reactive oxygen species; SJ: *Sophora japonica* L.; SOD: superoxidase dismutase; SMS: Sheng-mai-san; TCM: traditional Chinese herbal medicine; TBARS: thiobarbituric acid-reactive substances; TMP: tetramethylpyrazine; TNF alpha: tissue necrosis factor alpha; t-PA: tissue plasminogen activator

Key Words: Traditional Chinese herbal medicine, Cerebral ischemia, Stroke, Review

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