REVIEW

# Therapeutic potential of natural compounds from Chinese medicine in acute and subacute phases of ischemic stroke

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## Abstract
Stroke is one of the leading causes of death and disability in adults worldwide, resulting in huge social and financial burdens. Extracts from herbs, especially those used in Chinese medicine, have emerged as new pharmaceuticals for stroke treatment. Here we review the evidence from preclinical studies investigating neuroprotective properties of Chinese medicinal compounds through their application in acute and subacute phases of ischemic stroke, and highlight potential mechanisms underlying their therapeutic effects. It is noteworthy that many herbal compounds have been shown to target multiple mechanisms and in combinations may exert synergistic effects on signaling pathways, thereby attenuating multiple aspects of ischemic pathology. We conclude the paper with a general discussion of the prospects for novel natural compound-based regimens against stroke.

***Key Words:*** *cell death; herbal compound; immune response; ischemic stroke therapy; neuroplasticity; neuroprotection; oxidative damage; traditional Chinese medicine*

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## Introduction
Stroke, including ischemic and hemorrhagic types, is the leading cause of death and the most common cause of disability in the adult population worldwide (Donnan et al., 2008), inflicting tremendous social and financial burdens on individuals and society. Ischemic stroke accounts for approximately 85% of all stroke cases (Donnan et al., 2008), and can be further categorized into lacunar stroke and large artery atheromatous or embolic stroke based on its etiology and clinical symptoms. Lacunar stroke (~25% of all ischemic stroke) is small in size (2–20 mm) and can be "silent" (symptom-free), while large artery atheromatous or embolic stroke generally results in a massive infarct volume and more severe symptoms (Donnan et al., 2008). Although tissue plasminogen activator (tPA) treatment and thrombectomy are the most effective methods to restore blood flow in the ischemic area in the acute phase, only a small portion of patients meet the criteria for such therapies (Yong, 2014; Powers et al., 2018; Wang and Wang, 2018). Nevertheless, in the subacute phase stroke patients can benefit from proper supportive regimen and physical rehabilitation (Powers et al., 2018).

To achieve improved stroke outcome, vast resources have been-and are being-devoted to develop safe, effective therapeutic interventions (Junhua et al., 2009; Behravan et al., 2014). These efforts have led to the discovery of various compounds that achieve neuroprotection when delivered in preclinical models. However, because of the complex nature of stroke, treatment-related efficacy has not been validated in clinical trials. Meanwhile, the last decades have witnessed the resurgence of interest in herbal usage for medicinal and/or health promoting applications (Feng et al., 2006; Gurib-Fakim, 2006; Feigin, 2007; Bousser, 2013). Traditional Chinese medicine (TCM) has a long history of empirical usage of herbal and mineral products for medical purposes, representing an extensive, practice-based and information-rich foundation of regimens and medical knowledge. A variety of herbs have been utilized in TCM and in complementary therapies from other world regions for the treatment of stroke and stroke-associated symptoms (Junhua et al., 2009) for thousands of years (Craig, 1999; Dufresne and Farnworth, 2001; Balunas and Kinghorn, 2005; Ganesan, 2008; Wu et al., 2010; Bousser, 2013). From these herbs, bioactive herbal compounds have been extracted and extensively tested (Kumar and Khanum, 2012; Shen et al., 2015; Ting et al., 2018). Even so, the majority of this treasure of herbal compounds is still waiting to be explored (Gong and Sucher, 1999; Bauer and Bronstrup, 2013).

This review focuses on natural compounds that have been extracted from TCM herbs and tested for their efficacy in the treatment of ischemic stroke at acute and subacute phases (**Figure 1**).

## Search Strategy and Selection Criteria
We searched original studies and reviews in regard to TCM therapy for stroke on PubMed, Google Scholar, and ScienceDirect in the range of 1980–2018, with a focus on the peer-reviewed publications in the last two decades. Key words utilized in search were "Traditional Chinese medicine (TCM)", "stroke", "herbal medicine", and those involved in each section subtitles. Initially over 500 reports were identified, of which

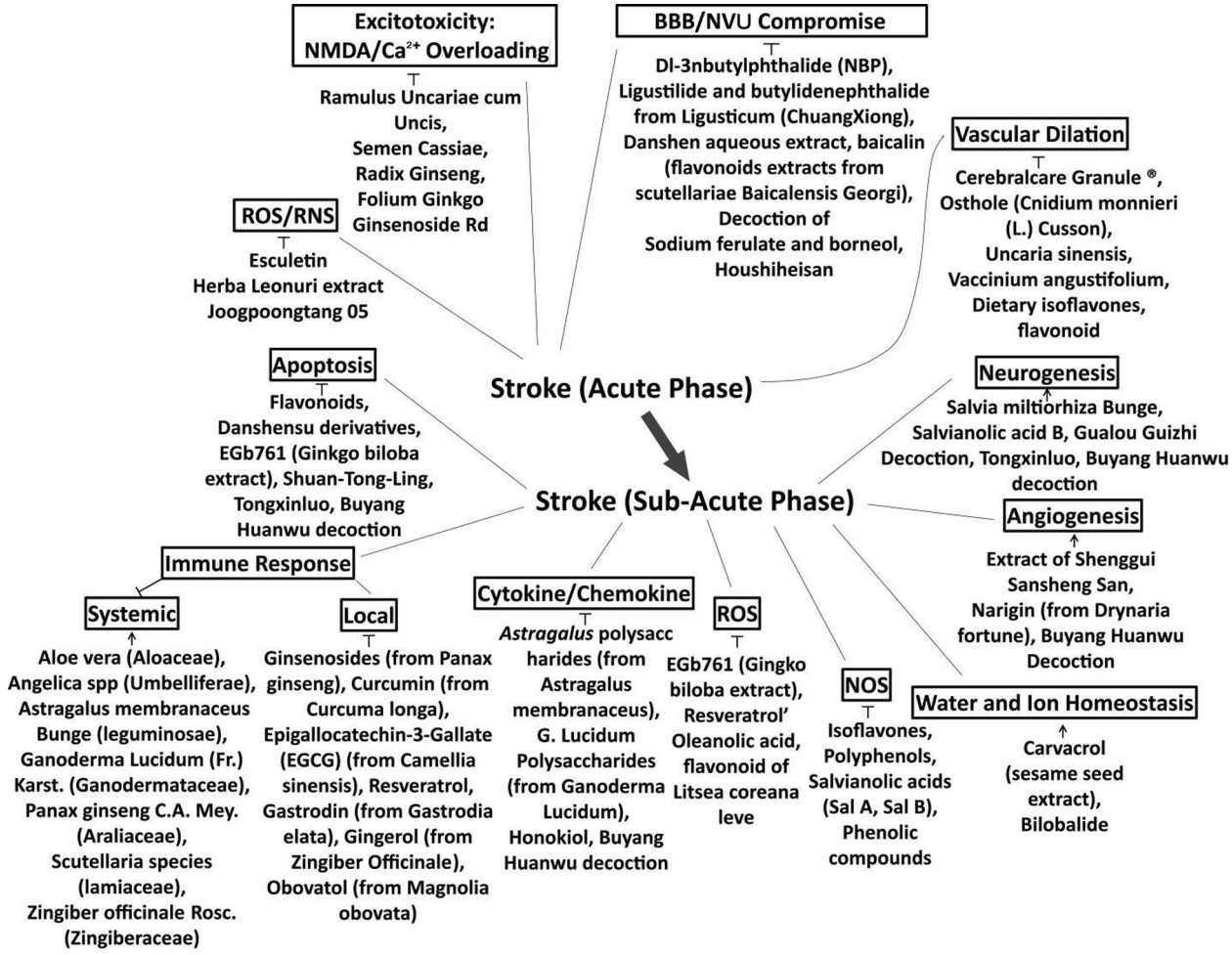


**Figure 1 Natural compounds for stroke therapy involved in the current review.**
At acute and sub-acute phases of stroke, natural compounds can perform pluripotent functions to ameliorate stroke injury (⊤) and promote reparative mechanisms (↑) through various mechanisms. BBB: Blood-brain barrier; NMDA: N-methyl-D-aspartate; NOS: nitric oxide synthase; NVU: neurovascular unit; RNS: reactive nitrogen species; ROS: reactive oxygen species.

154 were selected for the current review. Exclusion criteria included: not TCM herb-based study or therapy, therapy window beyond the subacute phase, opinion or commentary without peer review, and outside the focus of current review (such as side effects, toxicity, formulation development and fabrication, and patient/hospital management).

## Natural Compounds in the Treatment of Ischemic Stroke: Acute Phase

In the acute phase (from minutes to hours) of an ischemic stroke, interruption of blood supply leads to events including rapid cell necrosis, cellular membrane and subcellular organelle injury, DNA damage, excitotoxicity, acidotoxicity, oxidative stress, mitochondria swelling and dysfunction, ionic homeostasis disturbance and cell lysis-related cell oedema (Dirnagl et al., 1999; Donnan et al., 2008; Doyle et al., 2008; Lo, 2008). Prevention or attenuation of any of these pathological factors can be beneficial and may ameliorate the damage to the brain.

### Attenuation of cellular oxidative stress

Occlusion of the cerebral artery deprives the brain of metabolic substrates and oxygen to mitochondrial enzymes, disrupts the respiratory chain and results in leakage of superoxide, along with activated NADPH oxidase and inducible nitric oxide synthase (iNOS). Together these lead to the overproduction of reactive oxygen species (ROS) and reactive nitrogen species (RNS), inducing further damage to organelle membranes, lipids, proteins and DNA (Soobrattee et al., 2008; Loh et al., 2009; Wang et al., 2009; Jiang et al., 2010). These injuries can be alleviated by treatment with antioxidant molecules, including a large array of natural compounds, such as members of the phenol and/or flavonoid families (Perron et al., 2009). For example, neural protection against stroke by flavonoid of Litsea coreana leve, esculetin (a coumarin derivative) (Wang et al., 2012), Herba Leonuri extract (Loh et al., 2009), and Joongpoongtang 05 (Lagouge et al., 2006) can be attributed, in part, to their oxidant-scavenging effects when applied in the acute phase of stroke (Lagouge et al., 2006).

### Alleviation of excitotoxicity

Ischemia drives the neuronal release of excitatory neurotransmitters, such as glutamate, and disrupts their ab-

sorbance or clearance by neurons and astrocytes. Excessive extracellular glutamate results in overactivation of N-methyl-D-aspartic acid receptors (NMDA-Receptor, NMDA-R), cellular $Ca^{2+}$ overload, and eventually neuronal death. This phenomenon, called excitotoxicity, has been identified as a crucial therapeutic target in stroke treatment (Brouns and De Deyn, 2009; Debet al., 2010; Moskowitz et al., 2010).

Several herbal compounds have been identified as having NMDA-R antagonist properties or the capability of inhibiting $Ca^{2+}$ responses, including those from *Ramulus Uncariae cum Uncis*, *Semen Cassiae*, *Radix Ginseng*, and *Folium Ginkgo* (Sun et al., 2005; Kaneko et al., 2010; Wu et al., 2010; Zhao et al., 2011; Liang et al., 2013). Similarly, entry of $Ca^{2+}$ through NMDA linked receptor-operated calcium channels (ROCC), which is the main reason for cytosolic $Ca^{2+}$ elevation after stroke, can be blocked by *Ginsenoside Rd*, a dammarane-type steroid glycoside extracted from ginseng plants (Ye et al., 2013). Interestingly, TCM herbal reagents may exert their protective function through direct blockage of $Ca^{2+}$ channels or through secondary mechanisms, such as modulation of the PKC cell signaling pathway (Li et al., 2007; Wang et al., 2008; Chen, 2012). Although their effects against excitotoxicity need confirmation *in vivo*, these reagents' therapeutic potential is worthy of further exploration.

**Maintenance of blood-brain barrier and neurovascular unit functions**

The cerebral microvasculature is crucial for two physiological processes which maintain brain homeostasis: 1) prevention of blood-borne pathogen intrusion into the parenchyma via the blood-brain barrier (BBB), which relies on the unique tight junction proteins that seal along the endothelial cells in the brain microvasculature; and 2) maintenance of cerebral blood supply and the active exchange of oxygen/metabolites and $CO_2$/metabolic waste between the blood and brain. Both processes rely on the normal functioning of the neurovascular unit (NVU), which is composed of cerebral endothelial cells, pericytes, astrocytes and neurons (Peknyand and Nilsson, 2005; Giaume et al., 2010; Sofroniew and Vinters, 2010).

Ischemia induces necrosis in the infarct core and disrupts the normal function of the NVU and BBB in the penumbra. This results in vasculature leakage and disturbance of astrocyte-neuron communication (Peknyand and Nilsson, 2005; Giaume et al., 2010).

Recovery of the disrupted endothelium is critical for the functional restoration of the BBB and the NVU after stroke. Natural compounds such as dl-3n-butylphthalide (NBP) have demonstrated the capacity for improving endothelium function of cerebral microvessels through increasing numbers of perfused microvessels in infarct area in a stroke model using stroke-prone renovascular hypertensive rats (Liu et al., 2007). Extracts from *Ligusticum* (*Chuanxiong*), namely ligustilide and butylidenephthalide, can relax the vascular constriction of rat arteries induced by norepinephrine bitartrate and calcium chloride ($CaCl_2$) (Liang et al., 2005). Moreover, in a cerebral ischemia-reperfusion model in rats, treatment with Danshen aqueous extract decreased serum levels of hs-C-reactive protein, interleukin-8, interleukin-10, and tumor necrosis factor-α (TNF-α), and attenuated secondary endothelium damage (Liang et al., 2013). Experimental evidence suggests that BBB function can be preserved following stroke by modifying the levels and/or localization of tight junction proteins with baicalin (flavonoid extracts from *Scutellariae Baicalensis Georgi*) (Lin, 2011) treatment or decoction that is composed of sodium ferulate and borneol (Chen et al., 2010).

**Salvage of the penumbra**

The ischemic penumbra is the tissue in the vicinity of the stroke core which is not yet necrotic/lost, but is damaged and receives lower than normal perfusion (Dirnagl et al., 1999; Weinberger, 2006; Lo, 2008). Penumbra salvage is a therapeutic target in both acute and sub-acute phases of stroke. Natural compounds contribute to such salvage through multiple mechanisms, such as anti-apoptotic, anti-inflammatory responses and regulation of local blood flow.

Improvement of collateral blood flow from surrounding areas supports the penumbra's survival (Wei et al., 2001). It has been reported that natural compounds with vascular dilation effects, including Cerebralcare Granule® (Sun et al., 2010), osthole (*Cnidium monnieri* (*L.*) Cusson) (Fusi et al., 2012), *Uncaria sinensis* (Park et al., 2011), *Vaccinium angustifolium* (Kristo et al., 2010), dietary isoflavones (Mann et al., 2009; Siow and Mann, 2010) and industrialized flavonoid (Lapchak, 2012), increase collateral blood flow through 1) vascular dilation in the acute phase or 2) reconstruction of the vascular network through angiogenesis in the sub-acute phase (Vauzour et al., 2008; Bu et al., 2013). Their biological effects include increased nitric oxide (NO) availability and induction of angiogenic growth factors.

## Natural Compounds in the Treatment of Ischemic Stroke: Sub-Acute Phase

More complicated mechanisms and regulatory factors are involved in the sub-acute phase than in the acute phase. The mechanisms include shifting of cell death mechanisms from necrosis to apoptosis, activation of local and systemic immune responses, infiltration of neutrophils and monocytes, increased cytokine and ROS production, oedema from water and ion imbalances, and activation of protective mechanisms and repair processes, including neurogenesis and angiogenesis (**Figure 1**).

**Prevention of apoptotic cell death**

In the sub-acute phase, damaged cells, especially neurons, can be rescued by preventing them from entering the apoptotic cascade (Akpan and Troy, 2013). Thus, attenuation of mitochondrial damage, maintenance of ion homeostasis, inhibition of caspase activities and other mediators of the apoptotic cascade will contribute to the survival of neurons after stroke.

In many cases natural compounds can at least partially

achieve these effects, and the mechanisms involved have been investigated. Flavonoids are known to affect the phosphatidylinositol 3 kinase (PI3K)-Akt/PKB pathway, and subsequently inhibit the activation of central proteins in the cell death machinery, such as the proapoptotic Bcl-2 family member BAD and members of the caspase family (Spencer, 2008; Zhou et al., 2010; Zhang et al., 2010, 2013; Su and Hsieh, 2011; Wang et al., 2012; Pan et al., 2013). Flavonoids also show effects in modifying mitogen-activated protein kinase signaling pathway through changes in extracellular signal-regulated kinase 1/2 and c-jun amino-terminal kinase. Similarly, Danshensu derivatives can dose-dependently attenuate cell damage and death, lower ROS production, preserve mitochondrial potential, and modulate Bcl-2, Bax, caspase-3 and p53 protein expression in cells that are challenged with oxidants *in vitro* (Pan et al., 2013). Such observations have been further confirmed *in vivo*. One of the Danshensu derivatives has demonstrated antioxidant capacity through increasing the activity of superoxide dismutase (SOD) and glutathione peroxidase while decreasing the level of malondialdehyde and ROS production (Seetapun et al., 2013).

Ginkgo biloba extract EGb761 has been shown to ameliorate apoptosis through attenuation of caspase activation, thus blocking the extrinsic apoptotic pathway in a permanent middle cerebral artery occlusion model using female ovariectomized mice (Tulsulkar et al., 2016). The extract is also known to increase heme oxygenase-1 (a potent antioxidant enzyme) expression and activate the Wnt signaling pathway (Saleem et al., 2008; Nada and Shah, 2012, 2015; Nada et al., 2014). Oleanolic acid, a well-characterized triterpenoid from medicinal plants and herbs, can also increase heme oxygenase-1 expression and improve stroke outcome in preclinical studies (Caltana et al., 2015). Alternatively, gavage feeding a mixture of various herbal compounds following a traditional Chinese prescription attenuated neuronal loss and mitigated stroke volume in a transient cerebral ischemia/reperfusion model in rats (Mu et al., 2014).

**Regulation of immune responses: microglia and infiltrating macrophages**

Stroke induces both systemic and local immune responses (Iadecola and Anrather, 2011). Systemic immune depression after stroke can worsen patients' prognosis due to higher occurrence of infectious complications such as pneumonia (Kamel and Iadecola, 2012). Chinese herbal medicines contain compounds that selectively modulate immune cells such as lymphocytes and natural killer cells and thus can be used to support the immune system through regulation of immune cells' population and activation, and manipulation of circulatory cytokines to fight infectious complications (Tan and Vanitha, 2004). Among the most commonly used are *Aloe vera*. (Aloaceae), *Angelica spp*. (Umbelliferae), *Astragalus membranaceus Bunge*. (Leguminosae), *Ganoderma lucidum* (Fr.) Karst. (Ganodermataceae), *Panax ginseng* C.A. Mey. (Araliaceae), *Scutellaria species* (Lamiaceae) and *Zingiber officinale Rosc*. (Zingiberaceae) (Tan and Vanitha, 2004).

In contrast, local immune responses at the site of stroke damage are highly activated, and these responses have been reported to be determinant factors of stroke outcome. Microglia are the immune surveillance cells in the brain that can be directly activated upon stroke and, along with monocyte-derived macrophages that infiltrate through the disrupted BBB, are key contributors to the inflammatory responses in the ischemic brain (Yenari et al., 2010).

Activated microglia and newly migrated peripheral immune cells produce an array of factors (e.g., interleukins, TNF-α, NO, prostaglandins; refer to next section) that are toxic to neurons. Natural compounds regulate the local immune response by altering the production of cytokines and chemokines or acting as antagonists of cytokine receptors (Shao et al., 2004a, b; Zhang et al., 2010; Choi et al., 2011; Liang et al., 2011; Sun and Hsieh, 2011; Spencer et al., 2012; Fischer et al., 2013; Gu et al., 2014; Fu et al., 2018) to inhibit microglia-mediated neurotoxicity (see below).

**Modulation of cytokine/chemokine production**

At the injury site, damaged cells and infiltrated neutrophils produce a variety of inflammatory cytokines and chemokines, including TNF-α, interleukin-1β, interleukin-6, intercellular adhesion molecule 1, and sphingosine-1-phosphate, which closely correlate with damage severity and extent. Restricting peripheral inflammatory cell recruitment through the preservation of endothelium function is therefore of primary importance in stroke therapy. Various natural compounds are reported to attenuate stroke-induced elevations of cytokines and lessen tissue damage (Shao et al., 2004a, b; Sun and Hsieh, 2011; Shichita et al., 2012; Spencer et al., 2012; Fischer et al., 2013), effects that can be observed with injection of combined herbal components as well (Chen et al., 2015). The most commonly studied components are Ginsenosides (from *Panax ginseng*), Curcumin (from *Curcuma longa*), Epigallocatechin-3-Gallate (from Camellia sinensis), Resveratrol, Gastrodin (from *Gastrodia elata*), Gingerol (from *Zingiber officinale*) and Obovatol (from *Magnolia obovata*) (Shao et al., 2004a, b; Zhang et al., 2010; Choi et al., 2011; Liang et al., 2011; Sun and Hsieh, 2011; Spencer et al., 2012; Fischer et al., 2013; Gu et al., 2014; Fu et al., 2018). For example, Ginsenosides suppresses nuclear factor-κB and mitogen-activated protein kinase activities, upstream signaling molecules in the inflammatory response. It also inhibits expression of iNOS and elevation of TNF-α under pathological stresses (Zhang et al., 2010; Su and Hsieh, 2011).

Interestingly, independent reports have shown that in a model of cerebral ischemia-reperfusion honokiol exhibits both anti-inflammatory effects through inhibition of nuclear factor-κB and cytokine production in glial cells (Zhang et al., 2013) and neuroprotective effects through inhibition of NMDA current and disruption of PSD95-nNOS interaction to alleviate excessive, toxic NO production (Hu et al., 2013). These reports support TCM's "one reagent, multiple targets" and "integral therapy through mutual effects" principles.

**Attenuation of oxidative stress/nitric oxide stress**

Ischemia induces oxidative stress and NO stress, both of which are deleterious in causing secondary damage. Anti-oxidant effects are among the earliest identified properties in phytochemicals. Initially they were considered as oxidant scavengers; later, extensive studies revealed their potential to reduce ROS and NO production through modulation of gene expression and signaling pathways (Soobrattee et al., 2005; Stevenson and Hurst, 2007; Lin, 2011; Rubio et al., 2013). Recent studies have shown long-term intake of resveratrol delays age-related deterioration and mimics transcriptional aspects of dietary restriction, suggesting a regulatory role in cellular metabolism (Pearson et al., 2008) and potential for maintaining long-term cardiac and cerebrovascular health. Of note, natural compounds execute their multi-functional effects through different mechanisms, including attenuation of ROS and NO production (see below), some of which are cell-specific (Conforti and Menichini, 2011; Lin, 2011; Rubio et al., 2013).

***Reduction of reactive oxygen species production***

Reduction of ROS production by natural compounds can be achieved through multiple mechanisms: (a) direct oxidant scavenging, which attenuates mitochondrial damage and reduces superoxide leakage; (b) upregulation of antioxidant genes; or (c) suppression of oxidant genes (Esposito et al., 2002; Soobrattee et al., 2005; Stevenson and Hurst, 2007; Perron and Brumaghim, 2009; Campos-Esparza Mdel and Torres-Ramos, 2010; Wu et al., 2010).

For example, resveratrol, a naturally occurring stilbene-class of polyphenol, is well recognized for its anti-oxidant benefits. The chemical structure of resveratrol allows it to behave directly as a free radical scavenger, which can decrease oxidative damage in a dose-dependent manner (Shang et al., 2009). The neuroprotective effect of resveratrol was first identified in a model of systemic injection of kainic acid in rats, as it ameliorated kainate-induced excitotoxicity in the hippocampus and olfactory bulb (Virgili and Contestabile, 2000). Since then, resveratrol has been shown to reduce pathology and improve behavioral outcomes in numerous animal models of CNS injuries, including stroke. Although the exact mechanism of resveratrol-related neuroprotection is not fully understood, the beneficial effects are thought to be related to activation of silent mating type information regulation 2 homolog 1 (Borra et al., 2005), AMP-activated kinase (Dasgupta and Milbrandt, 2007) and nuclear factor (erythroid derived 2)-like 2 (Chen et al., 2005; Ungvari et al., 2010). Activation of silent mating type information regulation 2 homolog 1 and AMP-activated kinase can both improve metabolism and lifespan, which promote a pro-survival environment in the injured CNS, while activation of nuclear factor (erythroid derived 2)-like 2 enhances the transcription of genes involved in anti-oxidative activity, such as SOD, heme oxygenase-1 (HO-1), catalase and many other phase II defense enzymes (Kansanen et al., 2013; Zhang et al., 2013). In a mouse cerebral ischemia-reperfusion model, resveratrol has been demonstrated to have neural protective effects through upregulation of HO-1 (Sakata et al., 2010). In addition, it has also been shown that resveratrol can activate PPARγ coactivator 1α (Lorenz et al., 2003; Lagouge et al., 2006), which then mitigates oxidative stress by modulating mitochondrial function and the expression of anti-oxidant enzymes, such as SOD2 and glutathione peroxidase 1 (St-Pierre et al., 2006; Lu et al., 2010). Similarly, treatment with EGb 761, an extract from Gingko biloba leaves, has been shown to produce anti-oxidant effects through increases in HO-1 expression in both transient and permanent ischemic stroke models (Saleem et al., 2008; Shah et al., 2011; Tulsulkar and Shah, 2013).

***Regulation of nitric oxide production***

NO, a critical molecule in cell signaling and regulation of local blood flow, is generated by neuronal nitric oxide synthase and endothelial nitric oxide synthase under physiological conditions. At the onset of stroke, however, NO reaches toxic levels due to the activation of iNOS.

Isoflavones and polyphenols regulate endothelial nitric oxide synthase production and transcriptional activation of antioxidant defense genes in the vasculature via the transcription factors NFκB and nuclear factor (erythroid derived 2)-like 2 (Siow et al., 2007). Salvianolic acids, especially salvianolic acid A and salvianolic acid B, have been identified to have similar transcriptional regulatory effects (Ho and Hong, 2011). Interestingly, some phenolic compounds from plants can also activate endothelial nitric oxide synthase and neuronal nitric oxide synthase, improving NO availability and blood flow in the damaged area. By inhibiting iNOS activation or expression, they prohibit NO overproduction and subsequent neural toxicity (Siow et al., 2007; Siow and Mann, 2010; Conforti and Menichini, 2011). Such observations partially explain these herbal compounds' antioxidant, antithrombic and vascular relaxing properties, suggesting their inclusion in the prevention and treatment of cardiovascular disease and reducing risk factors (Layne and Ferro, 2017; Peng et al., 2017).

**Maintenance of water and ion homeostasis**

Ischemia disturbs water and ion homeostasis in the brain (Brouns and De Deyn, 2009; Aronowski and Zhao, 2011; Mann, 2011; Kim et al., 2018). Dysfunction of astrocytes and the microvasculature leads to cytotoxic vasogenic edema, which further compromises transportation of oxygen and metabolic substrates from the vessels to the parenchyma.

Aquaporin-4, a water channel on the cell membrane of astrocytes, is critical for the elevation of ion and water levels in the damaged area (Brouns and De Deyn, 2009; Aronowski and Zhao, 2011; Mann, 2011; Kim et al., 2018). Carvacrol (a sesame seed extract) and bilobalide have been shown to have neuroprotective effects by attenuating cerebral edema through inhibition of aquaporin-4 expression in both intracranial hemorrhagic and ischemic animal models (Lee et al., 2012; Zhong et al., 2013).

**Activation of endogenous reparative function**

In addition to initiating cell damage and death, ischemic injury also activates the endogenous reparative functions of the brain. Those mechanisms include angiogenesis, which restores the cerebral vasculature and cerebral blood flow, and neurogenesis, which rebuilds the neural network to enhance neuronal function (Lin et al., 2015; Ma et al., 2015; Ruan et al., 2015; Cassidy and Cramer, 2017). Activation and proper regulation of these processes improve neurological function and stroke outcome. Accumulating evidence shows that active ingredients from natural compounds can manipulate these processes through various mechanisms (Liu et al., 2018; Chen et al., 2015; Ren et al., 2015; Udalamaththa et al., 2016; Zhao et al., 2018).

At the periphery of the injury site, endothelial progenitor cells can bud from the existing vasculature and develop into new microvessels, which elongate and penetrate through the glial barrier, and eventually form mature, functional microvessels and improve blood flow in the infarct area (Ma et al., 2015). For example, it has been shown that extract from Shengui Sansheng San increases VEGF signaling pathways, and facilitates vasculature formation in the infarct area *in vivo* and tube formation of cultured brain microvascular endothelial cells *in vitro* (Liu et al., 2018). In addition, narigin, a major active ingredient in the Chinese herb Drynaria fortune, has been shown to promote tube formation of endothelial progenitor cells *in vitro* through the activation of the CXCL12/CXCR4/PI3K/Akt signaling pathway (Zhao et al., 2018). In a rat model of focal cerebral ischemia, post-stroke gavage feeding of Houshiheisan preserved NVU integrity and salvaged neurons in the penumbra (Wang et al., 2014).

The majority of neurogenesis from activated neural stem cells takes place in the subventricular zone and hippocampal subgranular zone and contributes to neural replacement and restoration of neural circuits (Lin et al., 2015; Ruan et al., 2015; Cassidy and Cramer, 2017). Several studies have demonstrated that natural compounds or decoction can regulate the activation and proliferation of neural stem cells and mesenchymal stem cells, as well as guide their neural differentiation by manipulating multiple signaling pathways (Lin et al., 2013; Si et al., 2014; Chen et al., 2015; Ren et al., 2015; Gao and Shen, 2017; Qin et al., 2017). For example, Salvia miltiorrhiza Bunge attenuated apoptosis and improved cell viability of injected mesenchymal stem cells in a rat stroke model (Kim et al., 2018). Moreover, Salvianolic acid B promoted neural differentiation of induced pluripotent stem cells via the PI3K/Akt pathway (Shu et al., 2018) and active ingredients of radix astragali promoted neural stem cell proliferation and guided their differentiation into dopaminergic neurons *in vitro* (Gao et al., 2018).

## Summary and Future Prospects for the Clinical Use of Natural Compounds

In summary, natural compounds have been demonstrated to have neuroprotective actions including anti-oxidative, anti-apoptotic, anti-neuroinflammatory, and neuromodulatory effects, as well as promoting brain tissue repair and functional recovery (**Figure 1**) (Soobrattee et al., 2005; Sucher, 2006). Importantly, the efficacy of natural compounds, such as those derived from Danshen, may be derived from either a reduction of cardiovascular risk factors for stroke and/or through multiple bioactivities, including gene modulation and interactions with cell signaling cascades, rather than merely as classic oxidant scavengers. Most studies reviewed here reported beneficial treatment effects of natural compounds using *in vitro* and/or *in vivo* experimental stroke models, suggesting a promising therapeutic potential of natural compounds in treating stroke (Wu et al., 2010; Han et al., 2017; Gaire, 2018).

Moreover, studies using combined ingredients support the therapeutic principles of TCM, namely, "one reagent, multiple targets" and "integral therapy through mutual effects" (Chen et al., 2018). The benefits derived from prescriptions of multiple components can be from mutually enhancing or synergetic effects of the ingredients targeting multiple events in stroke pathology. Thus a combination of multiple natural compounds may be a better remedy achieving synergic effects (Liu et al., 2018). Indeed, several small-scale clinical trials for stroke have already been undertaken to examine the efficacy of herbal regimens consisting of multiple ingredients (Butler, 2008; Huang et al., 2015). Although current evidence is still incomplete, preliminary results from those trials show that administration of a single compound or a combination of different compounds, as an addition to the conventional western style therapeutic strategies, benefits patients in recovery after stroke (Gao et al., 2009; Junhua et al., 2009; Butler et al., 2014; Chen et al., 2015; Hung et al., 2015; Peng et al., 2017).

In conclusion, natural compounds and their derivatives are emerging as effective novel therapeutic reagents against stroke. While the mechanisms of their protective properties require further clarification as do issues with regard to quality control, mechanisms of drug-drug interactions and toxicity, we expect to see the increasing validation of these gifts from nature and acceleration of their translation into clinical regimens.

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