Herbal Medicine for Stroke

Claire Zimmerman, ND, RH (AHG), and Eric Yarnell, ND, RH (AHG)

Abstract

Ischemic stroke is a major cause of mortality and disability around the world. Currently, there is very little that can be done to treat a stroke other than using recombinant tissue-plasminogen activator for ischemic stroke, but the use is limited to within three hours of an acute episode and has high risks for possible hemorrhagic events. This paper examines a wide spectrum of herbs with research supporting their use for stroke events, whether preventative or for neurologic rehabilitation post stroke. Many of these herbs have a long history of use, primarily in the Chinese medicine system, and there is more and more preclinical and some clinical research supporting their use. The herbs discussed in this paper include *Panax ginseng* (Asian ginseng), *Panax notoginseng* (tienchi ginseng), *Salvia miltiorrhiza* (red sage, dan shen), *Astragalus membranaceus* (astragalus), Bu Yang Huan Wu Tang (Great Yang Restoration Decoction), *Centella asiatica* (gotu kola), *Withania somnifera* (ashwagandha), *Bacopa monnieri* (brahmi), *Ginkgo biloba* (ginkgo), and *Rosmarinus officinalis* (rosemary).

Keywords: stroke, herbal medicine, *Panax notoginseng*, *Ginkgo biloba*

Introduction

Stroke is a major cause of disability and mortality around the world. According to the Stroke Council of the American Heart Association/American Stroke Association, stroke is characterized as a neurological deficit attributed to an acute focal injury of the central nervous system by a vascular cause, including cerebral infarction, intracerebral hemorrhage, and subarachnoid hemorrhage.[1] Stroke is a neurological condition caused by the interruption of the blood supply to the brain from a local vascular abnormality, resulting in the loss of oxygen and nutrients to the brain.[2] Stroke is caused by either an ischemic event or a hemorrhagic event in the cerebral vasculature, with around 80% of all strokes presenting as ischemic.[3] This article will focus largely on the far more common ischemic strokes, except as noted.

The conventional approach to prevention of stroke is through use of oral thrombolytics such as warfarin or aspirin, as well as controlling blood pressure, mainly via prescription medications. Acute treatment of acute ischemic stroke is by recombinant tissue-plasminogen activator (tPA). Recombinant tPA is only effective if administered within three hours of stroke, and its use is somewhat dangerous, as it can result in intracranial hemorrhage. There really is no safe and effective widely used treatment for ischemic stroke.[4]

Another approach to treatment is to provide neuroprotective agents that interfere with the cascade that leads to cell death in the brain, with the goal of preventing the long-term damage and clinical symptoms leading to severe grades of disability. No neuroprotective agents have been shown to be effective enough to be widely used in the Western world, but this is largely due to a lack of research (not the same thing as negative trials). Neuroprotective and neuro-regenerative herbs are considered key therapeutic agents after ischemia/stroke in herbal medicine, though more research is needed to confirm their place in therapy. Neurologic cell death post stroke is associated with glutamate toxicity, glucose deprivation, oxidative cascades, inflammation, and apoptosis.

Inflammation is a double-edged sword in stroke, as excessive inflammation causes significant neurologic damage. However, inflammation is also necessary for the healing of these tissues. Botanical medicines present a unique therapeutic value in terms of inflammation, as they generally have the benefit of modulating inflammation rather than outright suppressing it. The pathologic process of stroke as well as the therapeutic interventions used to treat it can be separated into acute (minutes to hours), subacute (hours to days), and chronic (days to months). In general, the inflammatory processes that occur in the acute and subacute phases of stroke are the most damaging to tissues, whereas the inflammation that develops in the chronic stage tends to be more regenerative.[5] Therefore, adding inflammation-modulating herbs at various stages of the disease process, as well as preventatively, is an important therapeutic tool to include in treatment.

Asian Ginseng

A great deal of research has been conducted on traditional Chinese herbs, herbal formulas, and their constituents related to stroke. There are some basic mechanisms of action these share that are theorized both to prevent stroke and to treat neurological damage, including anti-inflammatory or antioxidant effects, vasodilation, improvement in cerebral blood flow, inhibition of platelet aggregation, and protection against

reperfusion injury.[6,7] Phenolics, particularly flavonoids, are highly suggestive for therapeutic use post stroke due to their antioxidant effects, which are likely to be protective against brain injury from ischemia and reperfusion.[8] Herbs contain a broad range of constituents, which can make it difficult to predict the exact therapeutic value when using a whole herb. However, many constituents have been well researched in regards to ischemia, both in preclinical trials and in vitro.

Panax ginseng (Asian ginseng, rén shēn) of the Araliaceae family has a long history of use in Chinese medicine for a wide range of conditions, reflected in its genus name, which is derived from the Greek concept of a panacea. Asian ginseng's main active constituents that have been identified are triterpenoid saponins known as ginsenosides, though complex carbohydrates and other compounds cannot be overlooked in terms of therapeutic potential. Note that the fruit of this plant may be equally as effective as the root, the usual part used as medicine.

Ginsenoside Rd is one compound that has been studied in China for its benefits in ischemic stroke patients. Ginsenoside Rd is found primarily in Asian ginseng root hairs and leaves, but is also present in the fruit as well as hydroponically grown plants and *Panax quinquefolius* (American ginseng) roots and leaves.[9–12] In one double-blind clinical trial, 199 Chinese patients who had had suffered an acute ischemic stroke were randomized to receive an intravenous (i.v.) infusion of ginsenoside Rd 20 mg daily, 10 mg daily, or placebo for 14 days.[13] Both doses of ginsenoside Rd were associated with significantly better National Institutes of Health Stroke Scale results compared to placebo, which strongly predicts survival. There was no difference in neurological impairment or adverse effects at 15 days post stroke between the groups. A larger follow-up trial randomized 386 Chinese ischemic stroke patients to i.v. ginsenoside Rd or placebo for a similar 14-day period.[14] Unfortunately, there was no difference in mortality between the two groups, though stroke-related disability was significantly less in the ginsenoside Rd group compared to placebo. Whether use of injectable ginsenoside Rd is beneficial in ischemic stroke patients therefore remains debatable, and access to this medicine is limited anyhow.

One small clinical trial looked at 25 Korean patients who were undergoing warfarin therapy after suffering from ischemic stroke.[15] They were randomized either to continue warfarin alone or to add Asian red ginseng (made from steamed, dried roots of four-year-old plants) aqueous dried extract 500 mg t.i.d. for two weeks. There was no difference in international normalized ratio between the groups, and no serious bleeding events occurred in either group, suggesting that contrary to popular belief, Asian ginseng has no meaningful clinical interaction with warfarin. While stroke-related benefits were not proven, this at least provides a stronger basis for safe combination of Asian ginseng and warfarin. Case studies suggesting a potential problem combining these two do not outweigh the evidence from a randomized trial in this high-risk, real-world population. One clinical trial also found Asian ginseng was safe in combination with aspirin.[16]

A typical dose of crude Asian red ginseng root is 1–3 g t.i.d., either in capsules as a decoction or in granulations. The expense of this treatment can be limiting.

Lesser-Known Tienchi Ginseng

Panax notoginseng (tienchi ginseng, sān qī), in the Araliaceae family, is obviously related to Asian ginseng, given that they are in the same genus. However, it has a history in Chinese medicine in the treatment of a wide range of what we would recognize today as cardiovascular conditions, including ischemic cerebrovascular events, atherosclerosis, and cerebral hemorrhage.[17,18] These indications are quite distinctive from those of Asian ginseng. Tienchi ginseng is said to be unique in its ability to stop bleeding without causing blood stasis, and this is not related to tannins in the herb (most anti-hemorrhagic herbs are highly astringent). The non-protein amino acid dencichine has been credited with having hemostatic properties, though it is also considered a neurotoxin, at least for the higher concentrations present in *Lathyrus sativus* (grass pea).[19,20] Other constituents may also contribute to the hemostatic activity.

Numerous clinical trials have examined the role of tienchi ginseng saponins in patients with hemorrhagic stroke. In a meta-analysis of 20 clinical trials, 1,891 Chinese patients were randomized to current supportive therapies or those conventional therapies plus i.v. sān qī saponins for 10–70 days.[21] Mortality was significantly less, overall efficacy significantly better, neurological deficit significantly less, and intracerebral hematoma volume significantly less in the tienchi ginseng saponins group compared to controls. Of the six trials that gave mortality reports, 3.6% of patients died in the sān qī saponins group compared to 9.9% of controls. Adverse effects, where reported, were mild and transient. Though these small, low-quality studies are not definitive, they do suggest a potential role of tienchi ginseng saponins in patients with hemorrhagic strokes.

The jump from the anti-hemorrhagic properties of tienchi ginseng to its use for brain ischemia is somewhat mysterious. Preclinical studies, however, support that saponin extracts from *P. notoginseng* provide a protective effect against ischemic brain damage.[22] These saponin-containing injections have been shown to promote neuronal plasticity, attenuate apoptosis, and caspase activation, and to reduce pro-inflammatory cytokine production and blood–brain barrier permeability.

One meta-analysis of eight randomized clinical trials of tienchi ginseng saponins included 660 Chinese patients with acute ischemic stroke.[23] Seven of the eight trials were rated as having a high risk of bias for a variety of reasons. One trial was double blind, and all but one of the remainder were single blind. No study reported results beyond one month, with treatment being initiated within 24 h to one month of the acute stroke. Six studies used an extract of sān qī saponins: one at an oral dose of 240 mg q.d. for one month and five i.v. 200–525 mg q.d. for 14–20 days. This extract is referred to as xueshuantong, xuesetong, lulutong, and zhengkangnaoming in

Chinese medicine. Two studies used a subset of these compounds known as panaxatriol saponins (particularly ginsenoside Rg1, which shows strong anti-platelet activity) orally, 200 mg t.i.d. for one month. This extract is often referred to as sanchitongshu. Two trials reported a significant reduction in death and dependence compared to controls one month after stroke. All but one study reported significantly improved neurological deficits when taking sān qī saponins compared to controls. Reported adverse events were rare and mild. At least two of the trials paired tienchi ginseng saponins with aspirin, and at least one used various anticoagulants and antiplatelet agents in combination.

Another double-blind, randomized, multicenter clinical trial involving sanchitongshu has been published since the above meta-analysis was performed.[24] In it, 140 Chinese patients who had suffered an acute ischemic stroke in the past 30 days were randomized to either panaxatriol saponins extract 200 mg t.i.d. plus aspirin 50 mg q.d. or placebo plus the same dose of aspirin for one month. Subjects were followed for three to six months. Neurological deficits were significant lower and ability to perform activities of daily living significant better in the combination group compared to aspirin/placebo. There were no deaths in either group during the follow-up period. Adverse effects were mild and mostly consisted of gastrointestinal upset that went away without treatment, being equally infrequent between both treatment groups.

A typical oral dose of crude sān qī ginseng is 1–3 g t.i.d. This can be administered by capsule, decoction, or granulation. As with Asian ginseng, cost is a significant issue with this herb.

Other Neuroprotective Chinese Herbs

One retrospective, case-control study of 1,236 Taiwanese adults who had suffered strokes and had type 2 diabetes mellitus found that those who had used Chinese medicine had significantly less mortality than those who had not, after controlling for multiple confounding variables.[25] Shū Jīng Huó Xuè Tāng (Relax the Channels and Invigorate the Blood Decoction), a complex formula with 17 component herbs that originated in the *Wàn Bìng Huí Chūn* (*All Diseases Return to Spring*), written by Gōng Tíng-Xián in approximately 1585 CE, was the most used formula in this cohort. *Salvia miltiorrhiza* (red sage, dān shēn) root was the most used herb in this cohort. This herb, in the Lamiaceae family, is widely recognized to have many positive effects on the cardiovascular system. Many low-quality clinical trials have been published in the Chinese medical literature, mostly involving injectable extracts of red sage.[26,27] Although these studies generally report improved neurological outcomes after acute ischemic stroke compared to various control groups, methodological problems prevent any firm conclusions. One small randomized trial in 106 Chinese adults who had recovered from an ischemic stroke found that a combination of red sage, tienchi ginseng, and *Dryobalanops aromatica* (Borneo camphor tree) resin (known as dan shen dripping pills) significantly lowered stroke recurrence compared to no additional therapy.[28] Further research is warranted on red sage for the prevention and treatment of acute ischemic stroke. A typical dose of the herb as crude powder, granulation, or in decoction is 5–10 g/day in divided doses.

Astragalus membranaceus (astragalus, huáng qí) root is used in Traditional Chinese Medicine for many purposes, in particular as a *qi* tonic. It is a member of the Fabaceae family. The clinical manifestation of deficient *qi* can be compared to fatigue, which is very common in post-stroke patients. A double-blind clinical trial randomized 64 Chinese adults with post-stroke fatigue to either 2.8 g astragalus extract or placebo t.i.d.[29] After one month, astragalus improved fatigue and social and cognitive functioning significantly compared to placebo. Another double-blind trial randomized 68 Chinese adults who had suffered acute hemorrhagic stroke to either astragalus extract 3 g or placebo t.i.d. for two weeks.[30] The percentage of patients who achieved functional independence was significantly higher in the astragalus group compared to placebo. There were numerous severe adverse effects, but they were equivalent between groups and not considered medication related (including four deaths due to re-bleeding, one in the astragalus group and three in the control group). More research is needed, but astragalus looks promising as a treatment after any kind of stroke. A typical dose of crude astragalus root as powder, granule, or decoction is 5 g t.i.d. A typical dose of astragalus tincture or glycerite is 3–5 mL t.i.d.

Astragalus makes up the vast proportion of Bǔ Yáng Huán Wǔ Tāng (Great Yang Restoration Decoction), a formula commonly used as a treatment for stroke in China and Taiwan. This formula originated in the *Yī Lín Gǎi Cuò* (*Correction of Errors Among Physicians*), written by Wáng Qīng-Rèn in 1830 CE. Its ingredients are listed in Table 1. Much preclinical research supports the traditional use of this formula for stroke patients.[31,32]

A meta-analysis assessed 19 clinical trials on Great Yang Restoration Decoction in 1,580 Chinese patients who had suffered acute ischemic stroke.[33] All trials were considered at high risk of bias due to multiple methodological flaws. Neurological deficits post stroke were significantly less likely in the herbal formula group compared to conventional medical treatment alone. Only one trial assessed mortality benefits, and thus this outcome was too unreliable to know if the formula had any effect. Adverse effects were rare and minor in those trials that reported them.

Many other traditional Chinese herbs have real potential to help stroke patients. Table 2 reviews a range of these herbs with significant research on their purported mechanisms of action in patients with stroke. Clinical trials are warranted for all of these herbs.

Other Neuroprotective and Restorative Herbs

Centella asiatica (gotu kola) of the Lamiaceae family has been used in various traditional healing systems throughout

Table 1. Components of Bǔ Yáng Huán Wǔ Tāng (Great Yang Restoration Decoction)

Herb	Common names	Part used	Percentage
Astragalus membranaceus	Astragalus, huáng qí	Root	75%
Angelica sinensis	Dong quai, dāng guī wěi	Root tips	7.5%
Ligusticum chuanxiong	Sichuan lovage, chuān xiōng	Root	3.5%
Paeonia lactiflora	Red peony, chì sháo	Root with bark	3.5%
Prunus persica	Peach seed, táo rán	Seed	3.5%
Carthamnus tinctorius	Safflower, hóng huā	Flower	3.5%
Pheretima spp.	Earthworm, dì líng	Whole animal	3.5%

Asia, prominently Ayurvedic medicine. The aerial parts and roots of this wetland-loving plant are used. Gotu kola has neuroprotective, neuroregenerative, and nootropic (enhancing cognitive function including memory) effects.[34] Research has suggested that this very safe herb helps to decrease oxidative stress in the brain, increase levels of antioxidant enzymes, affect neuronal morphology and acetylcholine esterase activity, as well as generally improve learning and memory.[35,36] Many preclinical studies support that gotu kola has actions that are beneficial for preventing and treating strokes.[37–39]

One double-blind, preliminary trial assessed 48 Indonesian adults suffering from cognitive dysfunction while recovering from ischemic stroke.[40] Randomization was not described, but the subjects were treated with either 750 or 1,000 mg of a crude gotu kola extract or folic acid 3 mg daily for six weeks. All three treatments were equally effective at improving overall cognitive function compared to baseline. Gotu kola at both doses was significantly better at improving memory than folic acid. There were no adverse effects in the trial. Although small, this provides initial evidence for use of gotu kola to help patients recover cognitive function after a stroke. Long-term use is recommended for optimal benefits. A daily dose of gotu kola extract standardized to triterpenoid saponin content 30–60 mg t.i.d. or of fresh whole plant tincture or glycerite 3–5 mL t.i.d. is recommended. Though in vitro evidence suggests flavonoids such as quercetin and kaempferol (which are hardly unique to

Table 2. Traditional Chinese Herbs for Stroke and Relevant Actions

Herb	Proposed Actions	Citation
Uncaria rhynchophylla (cat's claw, gōu téng) stems	Neuroprotection, inflammation modulation, antioxidant, anti-diabetic, anti-hypertensive	[a]
Ligusticum chuanxiong (Sichuan lovage, chuān xiōng) root	Platelet activation inhibition, inflammation modulation, antioxidant, vasodilation, neuroprotection	[b]
Carthamnus tinctorius (safflower, hóng huā) flower	Inflammation modulation, antioxidant, neuroprotection	[c]
Salvia miltiorrhiza (red sage, dān shēn) root	Neuroprotection, antioxidant, inflammation modulation	[d]
Scutellaria baicalensis (Chinese skullcap, huáng qín) root	Neuroprotection, antioxidant, inflammation modulation, anti-thrombotic, antifibrotic, anti-diabetic	[e]
Prunella vulgaris (heal all, xìa kū cǎo) herb	Inflammation modulation, anti-thrombotic, anti-hyperlipidemic	[f]
Eleutherococcus senticosus (eleuthero, cì wǔjiā) root	Antioxidant, anti-hyperlipidemic, neuroprotection, inflammation modulation	[g]
Camellia sinensis (green tea) leaf	Antioxidant, neuroprotection	[g]
Pueraria montana var *lobata* (kudzu, ge gen)	Antioxidant, neuroprotection	[g]
Magnolia officinalis (magnolia)	Antioxidant, anti-thrombotic, inflammation modulation, neuroprotection	[g]

[a]Chik SCC, Or TCT, Luo D, et al. Pharmacological effects of active compounds on neurodegenerative disease with *Gastrodia* and *Uncaria* decoction, a commonly used poststroke decoction. Sci World J 2013:1–22; [b]Donker PO, Chen Y, Ding L, Qiu F. Locally and traditionally used *Ligusticum* species—A review of their phytochemistry, pharmacology and pharmacokinetics. J Ethnopharmacol 2016;194:530–548; [c]Xu H. Liu WX, Liu TL, et al. Synergistic neuroprotective effects of danshensu and hydroxysafflor yellow A on cerebral ischemia–reperfusion in rats. Oncotarget 2017;8:115434–115443; [d]Bonaccini L, Karioti A, Bergonzi MC, Bilia AR. Effects of *Salvia miltiorrhiza* on CNS neuronal injury and degeneration: A plausible complementary role of tanshinones and depsides. Planta Med 2015;81:1003–1016; [e]Gaire BP, Moon S-K, Kim H. *Scutellaria baicalensis* in stroke management: Nature's blessing in traditional Eastern medicine. Chin J Integr Med 2014;20:712–720; [f]Park SH, Koo HJ, Sung YY, Kim HK. The protective effect of *Prunella vulgaris* ethanol extract against vascular inflammation in the TNF-α-stimulated human aortic smooth muscle cells. BMB Rep 2013;46:352–357; [g]Kim H. Neuroprotective herbs for stroke therapy in traditional Eastern medicine. Neurol Res 2005;27:287–301.

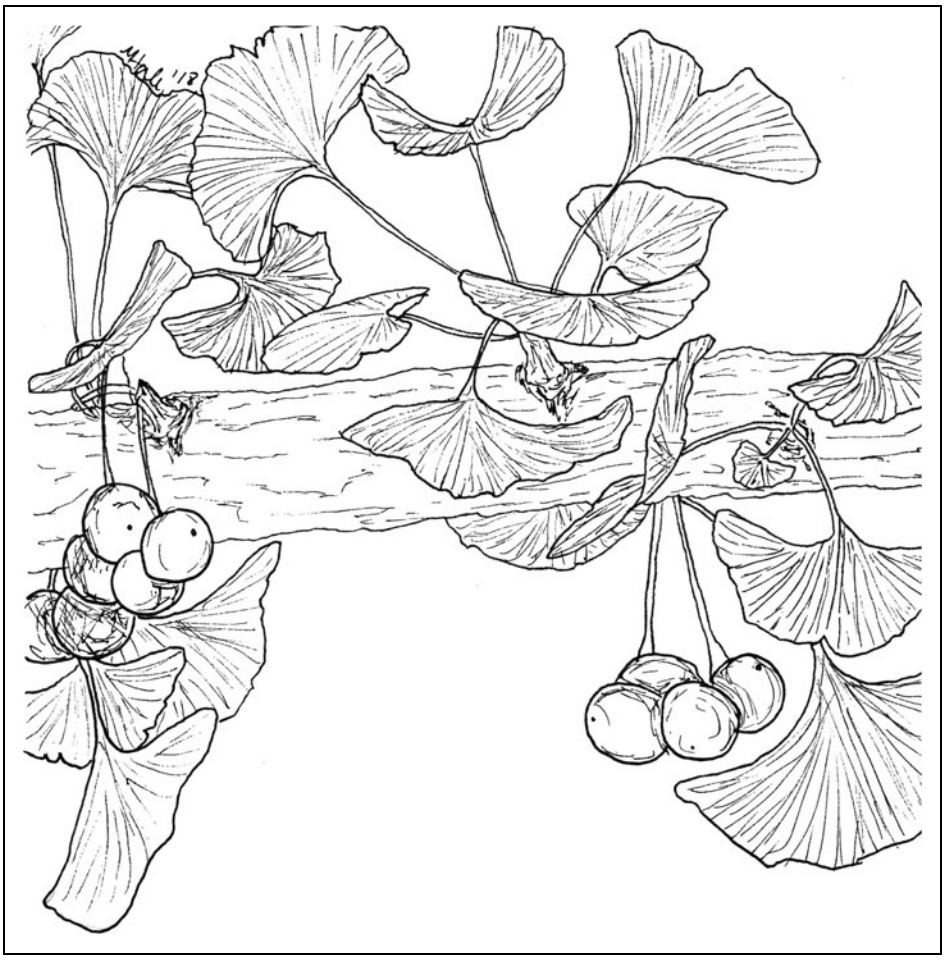

Figure 1. ***Ginkgo biloba*. Drawing by Meredith Hale and reprinted with permission.**

gotu kola, being found in most other plants) from gotu kola inhibit CYP3A4 and 2D6, there is no clinical evidence of any interactions between gotu kola and any drug.[41]

The roots of *Withania somnifera* (ashwagandha), a member of the Solanaceae family, have a long history of use in Ayurvedic medicine as a remedy for a wide range of neurologic disorders.[17] In addition to being antioxidant and neuroprotective, ashwagandha decreased the size of cerebral infarcts in preclinical research.[42–44] Administration of the herb for 30, but not 15, days prior to middle cerebral artery occlusion in rats led to significant neuroprotection with reduced clinical consequences of the induced ischemic strokes.[45] This suggests that ashwagandha might be worth researching as a stroke preventative in humans. The dose of crude ashwagandha root in capsules or as powder is 1–3 g t.i.d. The dose of tincture of the fresh (preferably) or dried root is 2–3 mL t.i.d. There are no anticipated adverse effects with this herb.

Bacopa monnieri (brahmi) of the Plantaginaceae family has $>3{,}000$ years of use in Ayurvedic medicine primarily for promoting cognitive and mental health.[46] Its common name refers to Brahmā, the Hindu god who created all life (but not the universe itself). Brahmi grows in wetland areas, and is native to every continent except Antarctica. Preclinical research in rat models of stroke have shown improvements in cognitive function, memory restoration, neuro-regeneration, neuroprotective effects, and reduction of infarct size.[47] Several mechanisms of action have been suggested, including increasing cerebral blood flow, restoration of cholinergic function, GABA modulation, promoting antioxidant defenses, augmentation of 5-HT levels, neuroprotection, reduction in neuro-inflammation, and modulation of brain stress hormones.[48,49] An appropriate dosage of brahmi extract is 300 mg daily in healthy patients, and some research suggests that this dose can be doubled to 600 mg daily in patients with compromised cognitive function.[50] The dose of tincture of the fresh aerial parts is 3–5 mL t.i.d. It is extremely safe.

Ginkgo biloba (ginkgo; Figure 1), the last remaining member of the Ginkgoaceae family, yields leaves that are not a traditional medicine (though the seed was traditionally used in Chinese medicine), having only been discovered to have medicinal value in the 20th century by European researchers. Standardized extracts of the leaves have been extensively researched for several decades in the treatment of circulatory conditions to increase peripheral and cerebral blood flow, and in the treatment of dementia.[13] Ginkgo leaf as a standardized extract contains flavonoid glycosides consisting of quercetin,

kaempferol, isorhamnetin, terpene lactones, ginkgolides, and bilobalide, which has been shown to exert antioxidant activity as well as a beneficial effect on neuronal cell metabolism and cerebral circulation.[13,51] In preclinical trials, this extract has also been shown to be highly protective to the brain and neuronal tissue while also reducing stroke volume, suggesting it may be a useful preventative treatment for stroke.[13] Note that the standardized extract also removes most of a set of toxins called ginkgolic acids, which are similar to urushiol from poison ivy and have actually shown neurotoxicity in vitro.[52] Therefore, crude extracts of ginkgo leaves are not recommended for use.

Several clinical trials have been conducted on ginkgo leaf standardized extracts in people who have had a stroke. A meta-analysis of 10 randomized trials conducted prior to 2005 found that overall ginkgo extract significantly improved neurological outcomes in ischemic stroke patients.[53] Unfortunately, the best quality trial up to that point did not show a difference between ginkgo and placebo in improving function, but it was safe.[54] A more modern trial randomized 102 Iranian adults to either ginkgo extract 40 mg t.i.d. or placebo after acute ischemic stroke for four months.[55] Post-stroke functional recovery was significantly better in the ginkgo group compared to controls, with a number needed to treat of just 2.5 to see a 50% reduction in the clinical score used to assess neurological function. A much larger multicenter trial randomized 348 Chinese adults who had suffered an ischemic stroke within seven days to take either ginkgo extract 450 mg/day or no additional treatment. All subjects were treated with aspirin 100 mg/day.[56] Neurological and cognitive function were significantly better in the ginkgo + aspirin group compared to aspirin alone, with no difference in recurrent vascular events or adverse effects. Note that this strongly supports that ginkgo is safe to take with aspirin. Another more recent trial randomized 90 Croatian adults who were recovering from ischemic stroke to receive ginkgo extract 120 mg or 60 mg or placebo daily for six months.[57] At these much lower doses, only one of four measures showed that ginkgo was superior to placebo at improving neurological or cognitive function, though the ginkgo group suffered fewer adverse effects than the placebo group. The totality of this research strongly suggests that very high doses of ginkgo (450 mg, about twice as high as the 240 mg dose used in some of the highest dose ginkgo extract studies) along with aspirin is quite promising and safe after ischemic stroke.

Rosmarinus officinalis (rosemary) has a long history of use in Western Europe's herbal tradition, particularly in the Mediterranean region where it grows in abundance. It is a member of the Lamiaceae family, and the leaf is the medicinal part. Rosemary also has been extensively studied for its effects on cognition, memory, and cardiovascular protective mechanisms. Alcohol extracts of rosemary have been shown to have protective effects on both the cardiovascular system and the brain.[58] Rosemary has been shown to have significant antioxidant effects in the vascular system, which suggests that it may be useful in the prevention of ischemic stroke events if taken long term.[59] Preclinical trials have shown that rosemary extract demonstrates effective improvement of cerebral infarction and neurologic regeneration while also affecting blood–brain barrier permeability. This resulted in a reduction in brain edema and therefore a reduction in neurologic damage.[60] The broad scope of research and historic use of this plant suggest it may be helpful both preventatively and as a post-stroke treatment. The effects on atherosclerotic prevention are notable in the prevention of stroke, as are the significant benefits to the blood–brain barrier, brain edema, and neuro-regeneration through notable antioxidant and nootropic activity.[61] A typical dose of crude rosemary powder is 500–1,000 mg t.i.d. and of tincture 1–2 mL t.i.d.

Conclusion

Many of the herbs and herbal formulas discussed in this article have a long history of use for stroke, with new supporting evidence elaborating on their possible mechanisms of action (or suggesting new herbs for this purpose). Clinical trials remain largely preliminary but promising. The potential of creating new and effective ways to prevent and treat ischemia and hemorrhagic stroke is great. The herbs discussed have been shown to be very safe and can work either alone or in formulas. Given the ongoing relative lack of therapies for stroke and post stroke, clinical implementation of these treatments is viable, and research on them should be prioritized.

References

1. Sacco RL, Kasner SE, Broderick JP, et al. An updated definition of stroke for the 21st century: A statement for healthcare professionals from the American Heart Association/American Stroke Association. Stroke 2013;44:2064–2089.

2. Han S-Y, Hong Z-Y, Xie YH, et al. Therapeutic effect of Chinese herbal medicines for post stroke recovery: A traditional and network meta-analysis. Medicine 2017;96:1–13.

3. Shi X, Yu W, Yang T, et al. *Panax notoginseng* saponins provide neuroprotection by regulating NgR1/RhoA/ROCK2 pathway expression, in vitro and in vivo. J Ethnopharmacol 2016;190:301–312.

4. Powers WJ, Derdeyn CP, Biller J, et al. AHA/ASA Guideline: 2015 American Heart Association/American Stroke Association focused update of the 2013 guidelines for the early management of patients with acute ischemic stroke regarding endovascular treatment: A guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke 2015;46:3024–3039.

5. Jin R, Liu L, Zhang S, et al. Role of inflammation and its mediators in acute ischemic stroke. J Cardiovasc Transl Res 2013;6:834–851.

6. Gu Y, Chen J, Shen J. Herbal medicines for ischemic stroke: Combating inflammation as therapeutic targets. J Neuroimmune Pharmacol 2014;9:313–339.

7. Kim H. Neuroprotective herbs for stroke therapy in traditional Eastern medicine. Neurol Res 2005;27:287–301.

8. Sun AY, Wang Q, Simonyi A, Sun GY. Botanicals phenolics and brain health. Neuromol Med 2008;10:259–274.

9. Kang OJ, Kim JS. Comparison of ginsenoside contents in different parts of Korean Ginseng (*Panax ginseng* CA Meyer). Prev Nutr Food Sci 2016;21:389–392.

10. Kim YK, Yoo DS, Xu H, et al. Ginsenoside content of berries and roots of three typical Korean ginseng (*Panax ginseng*) cultivars. Nat Prod Commun 2009;4:903–906.

11. Choi SY, Cho CW, Lee YM, et al. Comparison of ginsenoside and phenolic ingredient contents in hydroponically-cultivated ginseng leaves, fruits, and roots. J Ginseng Res 2012;36:425–429.

12. Li TS, Mazza G, Cottrell AC, Gao L. Ginsenosides in roots and leaves of American ginseng. J Agric Food Chem 1996;44:717–720.

13. Liu X, Xia J, Wang L, et al. Efficacy and safety of ginsenoside-Rd for acute ischaemic stroke: A randomized, double-blind, placebo-controlled, Phase II multicenter trial. Eur J Neurol 2009;16:569–575.

14. Liu X, Wang L, Wen A, et al. Ginsenoside-Rd improves outcome of acute ischaemic stroke—a randomized, double-blind, placebo-controlled, multicenter trial. Eur J Neurol 2012;19:855–863.

15. Lee SH, Ahn YM, Ahn SY, et al. Interaction between warfarin and *Panax ginseng* in ischemic stroke patients. J Altern Complement Med 2008;14:715–721.

16. Fung FY, Wong WH, Ang SK, et al. A randomized, double-blind, placebo-controlled study on the anti-haemostatic effects of *Curcuma longa*, *Angelica sinensis* and *Panax ginseng*. Phytomedicine 2017;32:88–96.

17. Bu Y, Lee K, Jung H-S, Moon S-K. Therapeutic effects of traditional herbal medicine on cerebral ischemia: A perspective of vascular protection. Chin J Integr Med 2013;19:804–814.

18. Xu D, Huang P, Yu Z, et al. Efficacy and safety of *Panax notoginseng* saponin therapy for acute intracerebral hemorrhage, meta-analysis, and mini review of potential mechanisms of action. Front Neurol 2015;5:1–19.

19. Huang LF, Shi HL, Gao B, et al. Decichine enhances hemostasis of activated platelets via AMPA receptors. Thromb Res 2014;133:848–854.

20. Rao SL, Adiga PR, Sarma PS. The isolation and characterization of β-N-oxalyl-L-α,β-diaminopropionic acid: A neurotoxin from the seeds of *Lathyrus sativus*. Biochemistry 1964;3:432–436.

21. Xu DY, Huang P, Yu ZS, et al. Efficacy and safety of *Panax notoginseng* saponin therapy for acute intracerebral hemorrhage, meta-analysis, and mini review of potential mechanisms of action. Front Neurol 2014;5:274.

22. Shi X, Yu W, Yang T, et al. *Panax notoginseng* saponins provide neuroprotection by regulating NgR1/RhoA/ROCK2 pathway expression, in vitro and in vivo. J Ethnopharmacol 2016;190:301–312.

23. Chen X, Zhou M, Li Q, et al. Sanchi for acute ischaemic stroke. Cochrane Database Syst Rev 2008;4:CD006305.

24. He L, Chen XY, Zhou MK, et al. Radix/rhizoma notoginseng extract (Sanchitongtshu) for ischemic stroke: A randomized controlled study. Phytomedicine 2011;18:437–442.

25. Tsai FJ, Hoa TJ, Chen CF, et al. Effect of Chinese herbal medicine on stroke patients with type 2 diabetes. J Ethnopharmacol 2017;200:31–44.

26. Wu B, Liu M, Zhang S. Dan Shen agents for acute ischaemic stroke. Cochrane Database Syst Rev 2007;2:CD004295.

27. Sze FK, Yeung FF, Wong E, Lau J. Does danshen improve disability after acute ischaemic stroke? Acta Neurol Scand 2005;111:118–125.

28. Xu G, Zhao W, Zhou Z, et al. Danshen extracts decrease blood C reactive protein and prevent ischemic stroke recurrence: A controlled pilot study. Phytother Res 2009;23:1721–1725.

29. Liu CH, Tsai CH, Li TC, et al. Effects of the traditional Chinese herb *Astragalus membranaceus* in patients with poststroke fatigue: A double-blind, randomized, controlled preliminary study. J Ethnopharmacol 2016;194:954–962.

30. Chen CC, Lee HC, Chang JH, et al. Chinese herb *Astragalus membranaceus* enhances recovery of hemorrhagic stroke: Double-blind, placebo-controlled, randomized study. Evid Based Complement Alternat Med 2012;2012;708452.

31. Mu QC, Liu PF, Hu XT, et al. Neuroprotective effects of Buyang Huanwu decoction on cerebral ischemia-induced neuronal damage. Neural Regen Res 2014;9:1621–1627.

32. Wei RL, Teng HJ, Yin B, et al. A systematic review and meta-analysis of buyang huanwu decoction in animal model of focal cerebral ischemia. Evid Based Complement Alternat Med 2013;2013:138484.

33. Hao CZ, Wu F, Shen JG, et al. Clinical efficacy and safety of buyang huanwu decoction for acute ischemic stroke: A systematic review and meta-analysis of 19 randomized controlled trials. Evid Based Complement Alternat Med 2012;2012;630124.

34. Shinomol GK, Muralidhara, Bharath MM. Exploring the role of "brahmi" (*Bocopa* [sic] *monnieri* and *Centella asiatica*) in brain function and therapy. Recent Pat Endocr Metab Immune Drug Discov 2011;5:33–49.

35. Gupta YK, Veerendra KMH, Srivastava AK. Effect of *Centella asiatica* on pentylenetetrazole-induced kindling, cognition and oxidative stress in rats. Pharmacol Biochem Behav 2003;74:579–585.

36. Veerendra KMH, Gupta YK. Effect of different extracts of *Centella asiatica* on cognition and markers of oxidative stress in rats. J Ethnopharmacol 2002;79:253–260.

37. Thong-asa W, Tilokskulchai K, Chompoopong S, Tantisira MH. Effect of *Centella asiatica* on pathophysiology of mild chronic cerebral hypoperfusion in rats. Avicenna J Phytomed 2018;8:210–226.

38. Luo Y, Yang YP, Liu J, et al. Neuroprotective effects of madecassoside against focal cerebral ischemia reperfusion injury in rats. Brain Res 2014;1565:37–47.

39. Tabassum R, Vaibhav K, Shrivastava P, et al. *Centella asiatica* attenuates the neurobehavioral, neurochemical and histological changes in transient focal middle cerebral artery occlusion rats. Neurol Sci 2013;34:925–933.

40. Farhana KM, Malueka RG, Wibowo S, Gofir A. Effectiveness of gotu kola extract 750 mg and 1000 mg compared with folic acid 3 mg in improving vascular cognitive impairment after stroke. Evid Based Complement Alternat Med 2016;2016:2795915.

41. Savai J, Varghese A, Pandita N, Chintamaneni M. Investigation of CYP3A4 and CYP2D6 interactions of *Withania somnifera* and *Centella asiatica* in human liver microsomes. Phytother Res 2015;29:785–790.

42. Sood A, Mehrotra A, Dhawan DK, Sandhir R. Indian ginseng (*Withania somnifera*) supplementation ameliorates oxidative stress and mitochondrial dysfunctions in experimental model of stroke. Metab Brain Dis 2018;33:1261–1274

43. Zhang QZ, Guo YD, Li HM, et al. Protection against cerebral infarction by withaferin A involves inhibition of neuronal apoptosis, activation of PI3K/Akt signaling pathway, and reduced intimal hyperplasia via inhibition of VSMC migration and matrix metalloproteinases. Adv Med Sci 2017;62:186–192.

44. Sood A, Kumar A, Dhawan DK, Sandhir R. Propensity of *Withania somnifera* to attenuate behavioural, biochemical, and histological alterations in experimental model of stroke. Cell Mol Neurobiol 2016;36:1123–1138.

45. Chaudhary G, Sharma U, Jagannathan NR, Gupta YK. Evaluation of *Withania somnifera* in a middle cerebral artery occlusion model of stroke in rats. Clin Exp Pharmacol Physiol 2003;30:399–404.

46. Abascal K, Yarnell E. Bacopa for the brain: A smart addition to Western medicine. Alt Complement Ther 2011;17:21–25.

47. Saraf MK, Prabhakar S, Anand A. Neuroprotective effect of *Bacopa monniera* [sic] on ischemia induced brain injury. Pharmacol Biochem Behav 2010;97:192–197.

48. Kamkaew N, Scholfied CN, Ingkaninan K, et al. *Bacopa monnieri* increases cerebral blood flow in rat independent of blood pressure. Phytother Res 2013;27:135–138.

49. Rastogi M, Ojha RP, Devi BP, et al. Amelioration of age associated neuroinflammation on long term bacosides treatment. Neurochem Res 2012;37:869–874.

50. Kongkeaw C, Dilokthornsakul P, Thanarangsarit P, et al. Meta-analysis of randomized controlled trials on cognitive effects of *Bacopa monnieri* extract. J Ethnopharmacol 2014;151:528–535.

51. Bora KS, Sharma A. Evaluation of antioxidant and cerebroprotective effect of *Medicago sativa* Linn against ischemia and reperfusion insult. Evid Based Complement Alternat Med 2011;2011:792167.

52. Ahlemeyer B, Selke D, Schaper C, et al. Ginkgolic acids induce neuronal death and activate protein phosphatase type-2C. Eur J Pharmacol 2001;430: 1–7.

53. Liu J. The use of *Ginkgo biloba* extract in acute ischemic stroke. Explore (NY) 2006;2:262–263.

54. Zeng X, Liu M, Yang Y, et al. *Ginkgo biloba* for acute ischaemic stroke. Cochrane Database Syst Rev 2005;4:CD003691.

55. Oskouei DS, Rikhtegar R, Hashemilar M, et al. The effect of *Ginkgo biloba* on functional outcome of patients with acute ischemic stroke: A double-blind, placebo-controlled, randomized clinical trial. J Stroke Cerebrovasc Dis 2013;22:e557–563.

56. Li S, Zhang X, Fang Q, et al. *Ginkgo biloba* extract improved cognitive and neurological functions of acute ischaemic stroke: A randomised controlled trial. Stroke Vasc Neurol 2017;2:189–197.

57. Demarin V, Bašić Kes V, Trkanjec Z, et al. Efficacy and safety of *Ginkgo biloba* standardized extract in the treatment of vascular cognitive impairment: A randomized, double-blind, placebo-controlled clinical trial. Neuropsychiatr Dis Treat 2017;13:483–490.

58. Posadas SJ, Cas V, Largo C, et al. Protective effect of supercritical fluid rosemary extract, *Rosmarinus officinalis*, on antioxidants of major organs of aged rats. Exp Gerontol 2009;44:383–389.

59. Sinkovic A, Suran D, Lokar L, et al. Rosemary extracts improve flow-mediated dilation of the brachial artery and plasma PAI-1 activity in healthy young volunteers. Phytother Res 2011;25:402–407.

60. Seyedemadi P, Rahnema M, Bigdeli MR, et al. The neuroprotective effect of rosemary (*Rosmarinus officinalis* L.) hydro-alcoholic extract on cerebral ischemic tolerance in experimental stroke. Iran J Pharm Res 2016;15:875–883.

61. Adsersen A, Gauguin B, Gudiksen L, Jäger AK. Screening of plants used in Danish folk medicine to treat memory dysfunction for acetylcholinesterase inhibitory activity. J Ethnopharmacol 2006;104:418–422.

Claire Zimmerman, ND, RH (AHG), is in private practice in Seattle, Washington and is adjunct faculty at Bastyr University in Kenmore, Washington. **Eric Yarnell, ND, RH (AHG),** is chief medical officer of Northwest Naturopathic Urology, in Seattle, Washington, and is a faculty member at Bastyr University in Kenmore, Washington.

To order reprints of this article, contact the publisher at (914) 740-2100.