https://doi.org/ 10.33472/AFJBS.6.5.2024. 6364-6373

African Journal of Biological Sciences

Herbal Plants and its implication in Brain Stroke

Yuvaraj Sivamani[1]Ankan Chakraborty[2], Dhruv Rao[2], Nabh Chandra[2], Sumitha Elayaperumal*

1. Department of Pharmaceutical Chemistry, Cauvery College of Pharmacy, Mysore, Karnataka, India.

2. Department of Biotechnology and Bioinformatics JSS Academy of Higher Education and Research, *Mysore, Karnataka, India*

*Correspondence to:

Sumitha Elayaperumal, PhD.

Assistant Professor,

Department of Biotechnology and Bioinformatics,

JSS Academy of Higher Education and Research,

Mysore, Vellore: 632 004, India.

E-mail: sumithae@jssuni.edu.in/sunsmitha@yahoo.co.in

Article History
Volume 6, Issue 5, 2024
Received: 25 May 2024
Accepted: 02 Jun 2024
doi: *10.33472/AFJBS.6.5.2024. 6364-6373*

Abstract

Stroke is the second most common cause of death in the world, accounting for over 5.5 million fatalities each year and current treatment involves intravenous thrombolytics, fibrinogen-depleting agents, antihypertensive therapy, antidiabetic drugs, stem cell therapy, and others. Many risk factors are associated with stroke condition which includesthyroid disorder, diabetes mellitus, hypertension, obesity and age. Intravenous thrombolytic remain the main therapeutic agent in modern medicine, however several treatment approaches have been discovered to prevent and treat the stroke cascade. As herbal medicine gaining the importance in treating various diseases, they can play vital role in the maintenance of health and improvement or treatment of stroke. Numerous phytochemicals have demonstrated significant neuroprotective potential in pathogenesis of stroke through a variety of mechanisms, such as antioxidants anti-inflammation and BBB protection, mitochondrial protection and antiapoptosis. This review will discuss the source of different plants with phytochemicals and its potential clinical applications in ischemic stroke.

Key words: Stroke, Herbal Plants, Atherosclerosis, Phytochemicals, Neuroprotection

Introduction

Stroke

The first mention of brain stroke comes from Hippocrates between 460 to 370 CE. The term used to describe the symptoms of convulsions and paralysis caused by a stroke was "Apoplexy"[4]. In the following several hundreds of years, research was focused on the physical symptoms and its possible causes. Enemas, (injecting fluid into the lower bowel by way of the rectum) and bloodletting (old medical practice of removing the patient's blood as a treatment) were frequently used to treat patients[5]. During the early 1900s, nursing literature started to concentrate more on the treatment of stroke patients. It was also around this time that the term "stroke" replaced apoplexy. In modern era acute Stroke is the second leading cause of death worldwide. Approximately 18,00,000 people are affected by stroke in India in a year[7]. Strokes are classified into two types: ischemic and hemorrhagic. An ischemic stroke occurs when blood flow to a specific part of the brain is interrupted. Ischemic stroke is responsible for most strokes globally[8]. Release of blood into the brain or ventricles causes hemorrhagic strokes. Acute hemorrhagic strokes are further classified as intracerebral hemorrhage (ICH) and subarachnoid hemorrhage (SAH)(figure 1)[8].

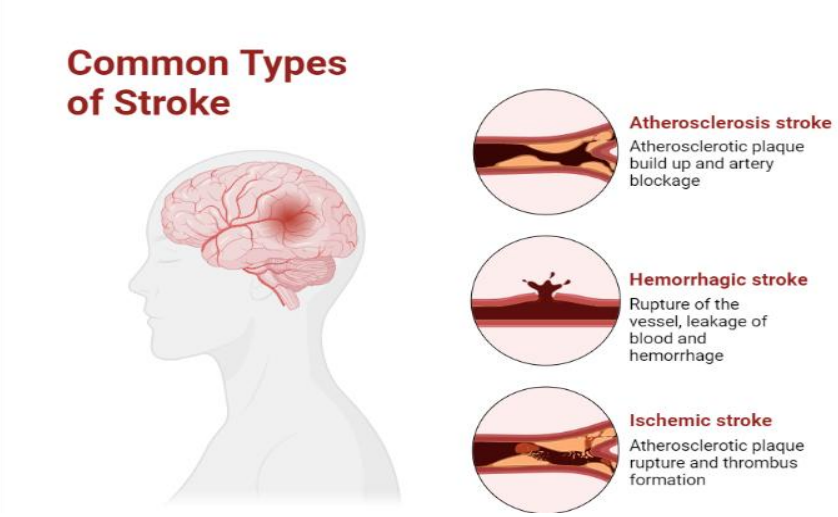

Figure 1: Types of Stroke

Major Causes of Stroke

There are many risk factors or causes of Acute stroke, including old age, hypertension, smoking, diabetes mellitus, cardiovascular disease, congestive heart failure[9]. Dissection, fibromuscular dysplasia, arteritis/vasculitis, and vasoconstriction are further causes of ischemic strokes. Cocaine abuse has been linked to acute ischemic strokes caused by vasoconstriction, particularly in the posterior circulation[10].Hypertension is the most important risk factor for strokes. Approximately 75% of all stroke patients have hypertension. Hypertension weakens the arterial walls, which can result in both ischemic and hemorrhagic strokes[11]. Strokes in small vessels (lacunar infarcts) are most usually caused by uncontrolled chronic hypertension, which leads to arteriolosclerosis. The basal ganglia, internal capsule, thalamus, and pons are all affected by these strokes. Hypertensive intracerebral hemorrhages can also result from uncontrolled hypertension in these locations (ICH)[12].Hemorrhagic strokes account for 15% of stroke cases globally. The most common cause for hemorrhagic stroke is hypertension. Another cause for this type of stroke is Cerebral amyloid angiopathy, a disorder in which amyloid plaques develop in small and medium arteries, causes vessels to become stiff and more sensitive to tearing[12]. Cocaine abuse has also been linked to acute stroke and frequently results in hemorrhagic strokes (ICH and SAH) in patients with underlying aneurysms and vascular abnormalities[13].

Atherosclerosis is the most prevalent and significant underlying pathology that leads to the creation of an atherothrombotic plaque. It is caused by a buildup of low-density lipoprotein cholesterol (LDL) in the arteries supplying the brain[14]. These plaques can obstruct or narrow the neck or intracranial arteries, causing distant ischemia of the brain. Plaques can also rupture and when that happens, exposes the cholesterol plates. These crystals attract platelets and fibrin, leading to stroke in the arteries.When an artery is blocked, the neurons nearby lose their supply of oxygen and nutrients. The Na+/K+ ATPase pumps malfunction because of the inability to undergo aerobic metabolism and create ATP, resulting in an accumulation of Na+ inside of the cells and K+ outside of the cells[15]. The buildup of Na+ ions cause cell depolarization and, as a result, the release of glutamate. Glutamate activates NMDA (N-Methyl D-Aspartate) and AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) receptors (receptors for glutamate), allowing calcium ions to enter cells. Continuous calcium influx causes continuous neuronal activation and, eventually, cell death (figure 2) [16].

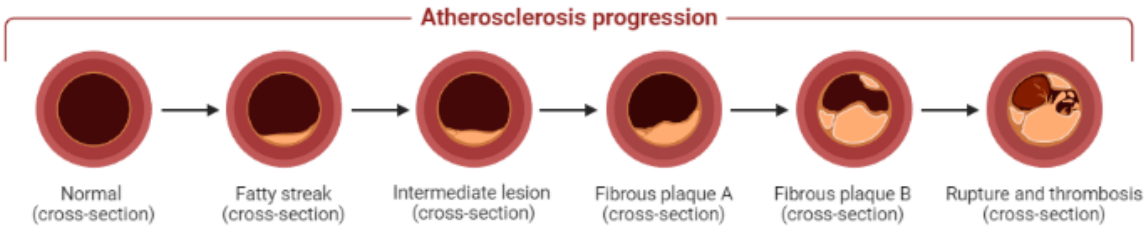

Figure 2: Atherosclerosis stages

Current Treatment Methods

i. Ischemic Strokes:
Tissue plasminogen activator (tPA) is the primary treatment for an ischemic stroke. It dissolves blood clots that are impeding blood flow to your brain[20]. Anticoagulants are blood thinning medicines that may also be used to reduce the blood clotting. A thrombectomy is a medical procedure to remove the clot from the blood vessel, and is used in treating ischemic strokes. This kind of thrombolytic therapy must be administered in the first 3 to 4 hours after the onset of stroke[21].

ii. Hemorrhagic strokes:
A medicine to lower the blood pressure may be given to reduce strain on blood vessels. Other medical procedures to treat hemorrhagic stroke may include Aneurysm clipping, Blood transfusion, Coil Embolization or surgery to remove the pooled blood, or to temporarily remove a part of skull to reduce pressure on the brain[22]. Just as in ischemic strokes, the quicker the treatment, the higher the chance of recovery will be

Herbal Plants in used Stroke

Asian ginseng

Asian ginseng also referred to as Panax ginseng(figure 3). It is a perennial plant that thrives in East Asian mountains.Chinese, Korean, and eastern Siberia are among the countries in the Far East where Asian ginseng is indigenous. It has been utilised in traditional Chinese medicine for thousands of years for medical purposes. Root is the most beneficial part of the plant and is frequently used for treating health problems. It heals neurological damage, has antioxidant or anti-inflammatory effects, vasodilation, improves cerebral blood flow, prevents platelet aggregation, and protects against reperfusion injury. Triterpenoid saponins known as

ginsenosides have been found to be the primary active ingredients in Asian ginseng, although complex carbohydrates have also been implicated.

Figure 3: Asian ginseng

Ginseng, particularly its active components like ginsenosides and ginsenoside-Rd, presents a promising neuroprotective strategy in stroke treatment. These compounds exhibit various mechanisms of action, including attenuating excitotoxicity, regulating Ca2+ levels, preserving blood-brain barrier integrity, reducing inflammation, and inhibiting apoptosis and pyroptosis. Specifically, ginsenoside-Rd has been found to block Ca2+ overload by acting on NMDA receptors and inhibiting NR2b phosphorylation through calcineurin activity attenuation. Moreover, combination of Panax Ginseng and Ginkgo biloba extracts have shown effectiveness in reducing inflammatory responses and maintaining glutamate/GABA balance via the CAMK4/CREB pathway.In a study by Zhu et al. in a rat model of transient middle cerebral artery occlusion (MCAO), it was observed that administration of 12.5 mg/kg of ginsenoside Rb1 via intranasal route led to a decrease in both the total infarct volume and the modified Neurological Severity Score (mNSS), indicating an improvement in neurological function.Ye et al. demonstrated a reduction in infarct volume and mNSS in a rat model of transient MCAO upon intraperitoneal administration of 50 mg/kg of ginsenoside Rd. Similarly, Park et al. showed that intraperitoneal administration of 30 mg/kg of compound K in a mouse model of transient MCAO resulted in a decrease in total infarct volume.These findings suggest that ginsenosides like Rb1, Rd, and compound K have potential neuroprotective effects by modulating microglial activation and reducing inflammation in the stroke, which could be beneficial in mitigating the damage caused by cerebral ischemia.

Ginkgo Biloba

Ginkgo biloba is one of the most widely used herbal supplements in the world. Ginkgos are big trees that can grow to be 20-35 m tall (figure 4). Ginkgos are extremely resilient due to a combination of disease resistance, insect-resistant wood, and the capacity to generate aerial roots and sprouts, with some specimens claiming to be over 2,500 years old. Terpenoids and flavonoids, which are chemicals known for their powerful antioxidant capabilities, are abundant in ginkgo. It supports heart health and blood circulation and also helps lessen stress, anxiety, and Alzheimer's disease symptoms.Ginkgo biloba has two principal active components in various concentrations: terpene lactones (most notably ginkgolides and diterpenes) and ginkgo flavone glycosides (most notably ginkgetin, bilobetin, and sciadopitysin). Ginkgo biloba is a Chinese medicinal herb. It is a member of the Ginkgoaceae family. Ginkgo leaf extracts contain phenolic acids, proanthocyanidins, flavonoid glycosides such myricetin, kaempferol, isorhamnetin, and quercetin, as well as terpene trilactones like

Computed Tomography (CT): ginkgolides and bilobalides. Ginkgo biflavones, alkylphenols, and polyprenols are also found in the leaves[24].

Figure 4: Ginkgo Bilob

The recommended dosage ranges 120 to 240 mg every day for 20 to 28 days. The dosage ranges from 15 ml to 20 ml (Ginkgo biloba extract 17.5 mg per 5 ml) each day for 14 to 30 days of Ginkgo biloba extract when administered through intravenous injection [24].

Danshen

Salvia miltiorrhiza is a perennial plant in the genus Salvia that is prized for its use in traditional Chinese medicine (figure 5). It is also known as red sage, Chinese sage, tan shen, or danshen. Although there is no reliable scientific evidence to support the use of Danshen for disorders such as cancer, heart and blood vessel health, or other ailments.

Figure 5: Danshen

Danshen seems to prevent blood and platelet coagulation, which thins the blood. Additionally, it widens blood arteries, which enhances circulation. Salvinolic acid (also known as salvianolic acid B), is one of the chemical compounds identified from Salvia miltiorrhiza[25]. There isn't much proof that Danshen works because the RCTs that already exist are of poor quality and don't control for placebo. The idea that Danshen might help with the improvement of disability following acute ischemic stroke is not supported by a systematic review on RCTs comparing Danshen with other medications[25].Patients with heart trouble were assisted by taking danshen orally since it lessened their chest pain. The symptoms of chronic asthmatic bronchitis are lessened by injecting danshen in addition to other bronchitis medications. The use of danshen may lessen issues with blood circulation. Danshen is beneficial for treating insomnia[25].

Gotu Kola

Gotu kola, also known as Centellaasiatica(figure 6). It is utilised in traditional medicine as well as being eaten as a vegetable in food. Gotu kola possesses neuroprotective, neuroregenerative, and nootropic properties that improve memory and other cognitive

abilities[26]. The brain's oxidative stress is reduced, antioxidant enzyme levels are elevated, neuronal shape and acetylcholine esterase activity are impacted, and learning and memory are typically improved. Saponins (also known as triterpenoids), which include asiaticoside, madecassoside, and madasiatic acid, are the main biologically active components of gotu kola.As measured by the improvement in cognitive impairment following stroke infarction as measured by the improvement in MoCA-Ina scores from the start to the conclusion of therapy, gotu kola extract at doses of 750 mg and 1000 mg per day for six weeks indicated effective compared to folic acid treatment, gotu kola medication demonstrated better improvement in delayed memory recall. Both the 750 mg and 1000 mg doses of gotu kola extract were well tolerated and had little negative side effects[30].

Figure 6: Gotu Kola

Gotu aids in improving cognitive function following a stroke. It helps to enhance memory and nerve function[28]. Gotu kola is said to be used to treat arthritis since it has a lot of anti-inflammatory qualities. Gotu kola may help to ease insomnia. Because of how gotu kola affects brain activity, it might be a powerful antidepressant.

Table 1: Herbs used for treatment of stroke, there scientific name and dosage

Herb	Scientific Name	Dosage
Asian Ginseng	Panax quinquefolius	50 mg/kg in mouse and rat model studies
Gingko Biloba	Gingko biloba	120 to 240 mg every day for 20 to 28 days.
Danshen	Salvia miltiorrhiza	Unknown
Gotu Kola	Centella asiatica	750 mg and 1000 mg per day for six weeks

Potential Risks of Herbal Medicines

The risk of an adverse reaction to a herbal medicine varies depending on consumer-related factors such as age, heredity, co-occurring conditions, and concurrent drug use, in addition to its source and dosage [31]. The quality of herbal treatments is also a significant factor in determining their toxicity. Herbal treatments can undermine the efficacy of conventional drugs or delay or replace a more effective form of conventional treatment, which can have an indirect negative impact on health.An herbal medciation hazardous potential is determined by the pharmacological properties and dosage levels of its bioactive

ingredients rather than its natural origin. Adverse reactions of herbal medicines can also be categorized into numerous types, like adverse reactions to modern drugs.

- Type A reactions, which are pharmacologically predictable and usually dose-dependent.
- Type B reactions, which cannot be predicted on the basis of the principal pharmacological properties
- Type C reactions, which develop during long term therapy.
- Type D reactions, which consist of delayed effects, such as carcinogenicity and teratogenicity.

Many herbal remedies are potent and safe; however, this is not the case for many of them, mostly because of insufficient data and scientific investigation. Many individuals believe that herbal medicines are safe since they are natural. On the other hand, a lot of natural medicines have serious adverse effects. The quality of herbal medicines, which is sometimes inadequately tested, is another concern regarding safety. Furthermore, there's a chance that herbal treatments will get contaminated, which could be harmful. Although several human investigations have directly shown that phytochemicals can be absorbed and then excreted in urine, phytochemicals in food must first be absorbed in order to exert biological effects.The ability of phytochemicals to cross the blood-brain barrier (BBB) and reach the target areas of the CNS is another important characteristic of an effective neuroprotective drug. The complexity of brain vascularity and BBB permeability additionally restricts herbal medicine's therapeutic potential for various CNS illnesses, including stroke[32].Herbal medications utilised in traditional communities have often not been associated with toxic side effects. Even severe adverse effects, such the kidney failure and liver damage induced by some plant species, went unrecognised until recently due to the lack of systematic observation. In 61% of the preparations, excessive quantities of lead, cadmium, and arsenic were discovered in a recent investigation of traditional Chinese medicine items in Australia. These levels were high enough to cause severe poisoning. It was discovered that several preparations contained pesticides or pollutants linked to poor storage.

Adverse effects

Ginseng

Insomnia is the most common side effect of herbs. Other includesbreast soreness, faster heartbeat, high or low blood pressure, headache, decrease in appetite, and digestive issues. Certain data suggests that Asian ginseng could affect blood sugar levels and can be dangerous to take orally during pregnancy. It has also been linked to birth defects in animals. There are concerns about potential pharmacological interactions between ginseng and certain medications, such as calcium channel blockers, other high blood pressure medications, statin medications, and some antidepressants. Research on the effects of Asian ginseng on the blood thinner warfarin (Coumadin) has yielded contradictory findings.

Ginkgo Biloba

Ginkgo leaf extract is probably safe for most people to consume. A few mild side effects, including as headaches, light-headedness, nausea, and allergic skin reactions, are possible. But it might also increase your risk of bruises, bleeding, and arrhythmia. Consuming the raw plant material or the roasted seed could be dangerous as it can induce serious adverse effects, such as seizures.Some people may experience a reduction in the effects of alprazolam if they take along with ginkgo. Ginkgo may lessen the effects of diabetes drugs when used in

conjunction with them and may increase the blood sugar levels. The risk of seizures may rise when using ginkgo due to the its effect on anticonvulsant drugs used to stop seizures.

Gotu Kola
Most people may be able to safely consume its extract when taken orally for up to a year. But in some cases it may cause nausea and stomach discomfort. It can be used topically for up to ten weeks without risk above that it might cause redness and irritatation. Hepatotoxic drugs, sedatives and CNS depressants may interact with gotu kola.

Danshen
Adverse effects of Dan shen include itching, stomach problems, and decreased appetite. Clinical results indicate that taking Digoxin with Danshen reduces its effectiveness and may make its side effects. It also interacts with medications used to treat hypertension. Aspirin levels in the blood may increase if it is combined with aspirin.

References

1 Ekor M. The growing use of herbal medicines: issues relating to adverse reactions and challenges in monitoring safety. *Front Pharmacol* Frontiers Media SA; 2013; **4**.

2 Msomi NZ, Simelane MBC, Msomi NZ, Simelane MBC. Herbal Medicine. *Herb Med* IntechOpen; 2018; .

3 Gyasi RM, Siaw LP, Mensah CM. Prevalence and pattern of traditional medical therapy utilisation in Kumasi metropolis and Sekyere south district, Ghana. *J Ethnopharmacol* Elsevier; 2015; **161**: 138–46.

4 Gomez CR. Time Is Brain: The Stroke Theory of Relativity. *J Stroke Cerebrovasc Dis* J Stroke Cerebrovasc Dis; 2018; **27**: 2214–27.

5 Nalin DR. The History of Intravenous and Oral Rehydration and Maintenance Therapy of Cholera and Non-Cholera Dehydrating Diarrheas: A Deconstruction of Translational Medicine: From Bench to Bedside? *Trop Med Infect Dis* Multidisciplinary Digital Publishing Institute (MDPI); 2022; **7**.

6 Zhong X min, Huang Y, He L, Wang J. Effect of intensive education on stroke prevention and management ability of community doctors: a cross-sectional study. *BMC Med Educ* BioMed Central Ltd; 2022; **22**: 1–6.

7 Kamalakannan S, Gudlavalleti ASV, Murthy Gudlavalleti VS, Goenka S, Kuper H. Incidence & prevalence of stroke in India: A systematic review. *Indian J Med Res* Wolters Kluwer -- Medknow Publications; 2017; **146**: 175.

8 Donkor ES. Stroke in the 21st Century: A Snapshot of the Burden, Epidemiology, and Quality of Life. *Stroke Res Treat* Hindawi Limited; 2018; **2018**.

9 Arboix A. Cardiovascular risk factors for acute stroke: Risk profiles in the different subtypes of ischemic stroke. *World J Clin Cases WJCC* Baishideng Publishing Group Inc; 2015; **3**: 418.

10 Olin JW, Gornik HL, Bacharach JM, Biller J, Fine LJ, Gray BH, Gray WA, Gupta R, Hamburg NM, Katzen BT, Lookstein RA, Lumsden AB, Newburger JW, Rundek T, Sperati CJ, Stanley JC. Fibromuscular Dysplasia: State of the Science and Critical Unanswered Questions. *Circulation* Lippincott Williams & WilkinsHagerstown, MD; 2014; **129**: 1048–78.

11 Boehme AK, Esenwa C, Elkind MSV. Stroke Risk Factors, Genetics, and Prevention. *Circ Res* NIH Public Access; 2017; **120**: 472.

12 Caplan LR. Lacunar Infarction and Small Vessel Disease: Pathology and Pathophysiology. *J Stroke* Korean Stroke Society; 2015; **17**: 2.

13 Tsatsakis A, Docea AO, Calina D, Tsarouhas K, Zamfira LM, Mitrut R, Sharifi-Rad J, Kovatsi L, Siokas V, Dardiotis E, Drakoulis N, Lazopoulos G, Tsitsimpikou C, Mitsias P, Neagu M. A Mechanistic and Pathophysiological Approach for Stroke Associated with Drugs of Abuse. *J Clin Med 2019, Vol 8, Page 1295* Multidisciplinary Digital Publishing Institute; 2019; **8**: 1295.

14 Libby P, Buring JE, Badimon L, Hansson GK, Deanfield J, Bittencourt MS, Tokgözoğlu L, Lewis EF. Atherosclerosis. *Nat Rev Dis Prim 2019 51* Nature Publishing Group; 2019; **5**: 1–18.

15 Pivovarov AS, Calahorro F, Walker RJ. Na+/K+-pump and neurotransmitter membrane receptors. *Invertebr Neurosci* Springer; 2019; **19**: 1.

16 Fani G, Mannini B, Vecchi G, Cascella R, Cecchi C, Dobson CM, Vendruscolo M, Chiti F. Aβ Oligomers Dysregulate Calcium Homeostasis by Mechanosensitive Activation of AMPA and NMDA Receptors. *Cite This ACS Chem Neurosci 2021* 2021; **12**: 766–81.

17 Muir KW, Santosh C. Imaging of acute stroke and transient ischaemic attack. *J Neurol Neurosurg Psychiatry* BMJ Publishing Group Ltd; 2005; **76**: iii19–28.

18 Lövblad KO, Baird AE. Computed tomography in acute ischemic stroke. *Neuroradiology* Neuroradiology; 2010; **52**: 175–87.

19 García-Bermejo P, Castaño C, Dávalos A. Multimodal CT versus MRI in Selecting Acute Stroke Patients for Endovascular Treatment. *Interv Neurol* Karger Publishers; 2013; **1**: 65.

20 Warach SJ, Dula AN, Milling TJ. Tenecteplase Thrombolysis for Acute Ischemic Stroke. *Stroke* Lippincott Williams & WilkinsHagerstown, MD; 2020; : 3440–51.

21 Fisher M, Ringleb PA, Schellinger PD, Schranz C, Hacke W. Thrombolytic therapy within 3 to 6 hours after onset of ischemic stroke: Useful or harmful? *Stroke* Lippincott Williams & Wilkins; 2002; **33**: 1437–41.

22 Connolly ES, Rabinstein AA, Carhuapoma JR, Derdeyn CP, Dion J, Higashida RT, Hoh BL, Kirkness CJ, Naidech AM, Ogilvy CS, Patel AB, Thompson BG, Vespa P. Guidelines for the Management of Aneurysmal Subarachnoid Hemorrhage. *Stroke* Lippincott Williams & WilkinsHagerstown, MD; 2012; **43**: 1711–37.

23 Mohsin MM, Hanif MA, Ayub MA, Dharmadasa RM. Ginseng. *Med Plants South Asia Nov Sources Drug Discov* Elsevier; 2019; : 331–40.

24 Belwal T, Giri L, Bahukhandi A, Tariq M, Kewlani P, Bhatt ID, Rawal RS. Ginkgo biloba. *Nonvitamin Nonmineral Nutr Suppl* Elsevier; 2018; : 241–50.

25 Chen W, Chen G. Danshen (Salvia miltiorrhiza Bunge): A Prospective Healing Sage for Cardiovascular Diseases. *Curr Pharm Des* Curr Pharm Des; 2017; **23**.

26 Gohil KJ, Patel JA, Gajjar AK. Pharmacological Review on Centella asiatica: A PotentialHerbal Cure-all. *Indian J Pharm Sci* Wolters Kluwer -- Medknow Publications; 2010; **72**: 546.

27 Todorova V, Ivanov K, Delattre C, Nalbantova V, Karcheva-Bahchevanska D, Ivanova S. Plant Adaptogens—History and Future Perspectives. *Nutr 2021, Vol 13, Page 2861* Multidisciplinary Digital Publishing Institute; 2021; **13**: 2861.

28 Phoemsapthawee J, Ammawat W, Prasertsri P, Sathalalai P, Leelayuwat N. Does Gotu kola supplementation improve cognitive function, inflammation, and oxidative stress more than multicomponent exercise alone? – a randomized controlled study. *J Exerc Rehabil* Korean Society of Exercise Rehabilitation; 2022; **18**: 330.

29 Rastogi V, Santiago-Moreno J, Doré S. Ginseng: a promising neuroprotective strategy in stroke. *Front Cell Neurosci* Frontiers Media SA; 2014; **8**: 1–13.

30 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. *Evidence-based Complement Altern Med* Hindawi Limited; 2016; **2016**.

31 Ekor M. The growing use of herbal medicines: issues relating to adverse reactions and challenges in monitoring safety. *Front Pharmacol* Frontiers Media SA; 2013; **4**.

32 Liu Y, Chen Z, Li A, Liu R, Yang H, Xia X. The Phytochemical Potential for Brain Disease Therapy and the Possible Nanodelivery Solutions for Brain Access. *Front Oncol* Frontiers Media SA; 2022; **12**.

33 Pool H, Quintanar D, Figueroa JDD, Marinho Mano C, Bechara JEH, Godínez LA, Mendoza S. Antioxidant effects of quercetin and catechin encapsulated into PLGA nanoparticles. *J Nanomater* 2012; **2012**.

34 Kumar A, Nath A, Sunil P&, Jain K, Pandey AN, Jain SK. Nasal-nanotechnology: revolution for efficient therapeutics delivery. *https://doi.org/103109/107175442014920431* Taylor & Francis; 2014; **23**: 681–93.

35 Din FU, Aman W, Ullah I, Qureshi OS, Mustapha O, Shafique S, Zeb A. Effective use of nanocarriers as drug delivery systems for the treatment of selected tumors. *Int J Nanomedicine* Dove Press; 2017; **12**: 7291.