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REVIEW ARTICLE

THERAPEUTIC POTENTIAL OF HERBAL DRUGS IN CEREBRAL ISCHEMIA

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Abstract : Stroke is one of the most important causes of mortality and morbidity in the world. Prevention and effective treatment of stroke is of the utmost importance. Cerebral ischemia causes disturbances in a variety of cellular and molecular mechanisms, including oxidative phosphorylation, membrane function, neurotransmitter release, and free radical generation. It has been years since tissue-type plasminogen activator (t-PA) became the first medication approved by the FDA for the management of stroke, with limited success. Thrombolytic therapy is the most effective therapeutic strategy for the prevention of brain injury and reduction of mortality in patients with cerebral infarction. However, a combination of established thrombolytic therapy and effective neuronal protection therapy may have more beneficial effects for patients with cerebral infarction. Because clinical trials of pharmacological neuroprotective strategies in stroke have been disappointing, attention has turned towards approaches which include herbal drugs that can be used in limiting the neurological damage associated with stroke. Herbal drugs may be used as prophylactic treatment in patients with high risk of stroke. Herbals drugs have been described in ancient systems of medicine for the treatment of various ailments associated with stroke and have more recently been reported to be beneficial in treating stroke. However, the strength of evidence to support the use of these herbal drugs is unclear. This review focuses on putative mechanisms underlying the beneficial effects of herbal drugs in patients with stroke and on the possibility of herbal drugs to increase the therapeutic time window in patients with cerebral ischemia.

Key words : cerebral ischemia herbal drugs stroke

INTRODUCTION

Stroke is a major cause of death and disability worldwide. The resulting burden on the society continues to grow with increase in the incidence of stroke. Brain

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attack is a new term introduced to describe the acute presentation of stroke, which emphasizes the need for urgent action to remedy the situation (1). Among the pathophysiological changes that are postulated to occur as a response to stroke are free radical productions, excitotoxicity, disruption of sodium and calcium influx, enzymatic changes, stimulation of the inflammatory process, endothelin release, activation of platelets and leukocytes, delayed coagulation and endothelial dysfunction. All of these pathophysiological reactions may contribute to the brain injury following the onset of stroke (2, 3) (Fig. 1).

Based on this, drugs classified as neuroprotective, that can intervene in/during

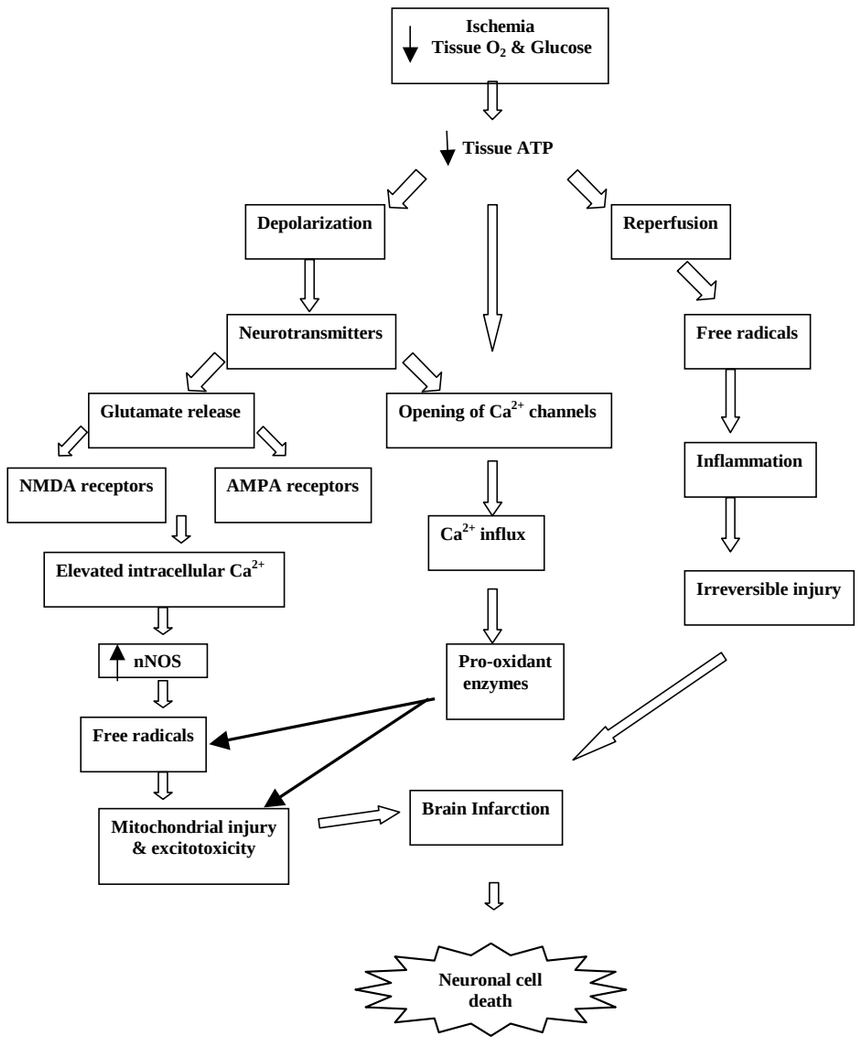

Fig. 1: Diagrammatic representation of mechanisms of ischemic brain damage.

these biochemical events were introduced so as to prevent the ischemic injury. However, although these drugs have been found useful in animal studies, they have shown mixed efficacy in clinical trials (4).

Recombinant plasminogen activator (rt-PA) is the only drug approved by FDA to date for the treatment of stroke. Thrombolysis reduces stroke morbidity but is only applicable to a small percentage of stroke patients (5, 6).

Given the few options currently available for patients following ischemic stroke and the recent disappointing failures of several large-scale Phase III clinical trials with neuroprotective drugs, the search for novel therapeutic approaches has become even more critical (7, 8). One such approach is the idea of combined therapy. Combinations of thrombolysis and a neuroprotecting agent or a combination of two neuroprotecting agents have been effective in experimental stroke (9). Another approach towards treatment of stroke can be prophylactic protection. It has been seen that in animal models of stroke, with many drugs, pretreatment yields better outcome than post onset treatment. Further suggestions from the clinical trials have shown that the very early treatment after stroke may be necessary for the drugs to be effective. Therefore in a sub group of patients that are at a substantial risk for ischemic stroke, e.g. patients with a mild episode of stroke or transient ischemic attacks, prophylactic neuroprotection might offer a useful approach and a better outcome than can be expected normally. The agent to be used prophylactically should be efficacious, safe, orally available and affordable (10). Herbal drugs have been described in ancient systems of medicine for the treatment of various ailments. These are nowadays revalued by extensive research on different plant species and their therapeutic principles. Since they have a relatively higher therapeutic window, lesser side effects, and are economical, herbal drugs have gained a lot of acceptance in the recent years and can be potential candidates for prophylactic treatment in stroke. A number of traditional Chinese medicines have been tried both in animal models of stroke and human patients and have been found to be effective. Indian traditional medicines, though tried and found useful in various neurological disorders, have not been studied in stroke models. We have evaluated the CNS active Indian drugs *Withania somnifera, Centella asiatica, Shilajit, Tinospora cordifolia* and *Convolvulus pluricaulis* as prophylactic treatment in the middle cerebral artery occlusion model of stroke in rats (11). However, there is no comprehensive review related to herbal products in the prophylaxis and treatment of stroke. The present review is an attempt to discuss the role of herbal products in the management of stroke.

Stroke: a major health problem

Stroke is the third largest cause of mortality after cancer and coronary heart disease and is the second largest cause of disability in adults (8). The incidence of stroke is 1 per 1000 people (12). However, this incidence varies according to age and sex. In the age group of 80+ yrs, the incidence of stroke reaches values of 20 per 1000 people (13). The incidence rate is higher among males of all age groups. A community based survey from different regions of India

showed a crude prevalence rate of 200 per 100,000 people. Overall 9400 strokes (first-ever and recurrent) were estimated to be hospitalized in 1999, with an attack rate of 208 per 100,000 (13).

Status of the presently available drugs in stroke

(a) Vascular approach

Thrombolytic agents : Evidence from various experimental stroke models that thrombolytics agents could minimize the effect of ischemia provided the impetus for the evaluation of thrombolytic therapy in acute ischemic stroke (8). Various thrombolytic agents like urokinase, streptokinase and recombinant tissue plasminogen activator (rt-PA) have been tried in experimental studies. These drugs also reached clinical trials, however all except rt-PA were withdrawn from the clinical trials because they neither showed acceptable efficacy nor safety (increased risk of intracranial hemorrhages being the major limitation) (14). Despite the risk of potential side effects associated with rt-PA (0.9 mg/kg, iv), it is the only drug approved by FDA so far for emergency treatment within three hours of onset of ischemic stroke. This emphasizes the limited resources available for improving ischemic stroke mortality and morbidity (Fig. 2).

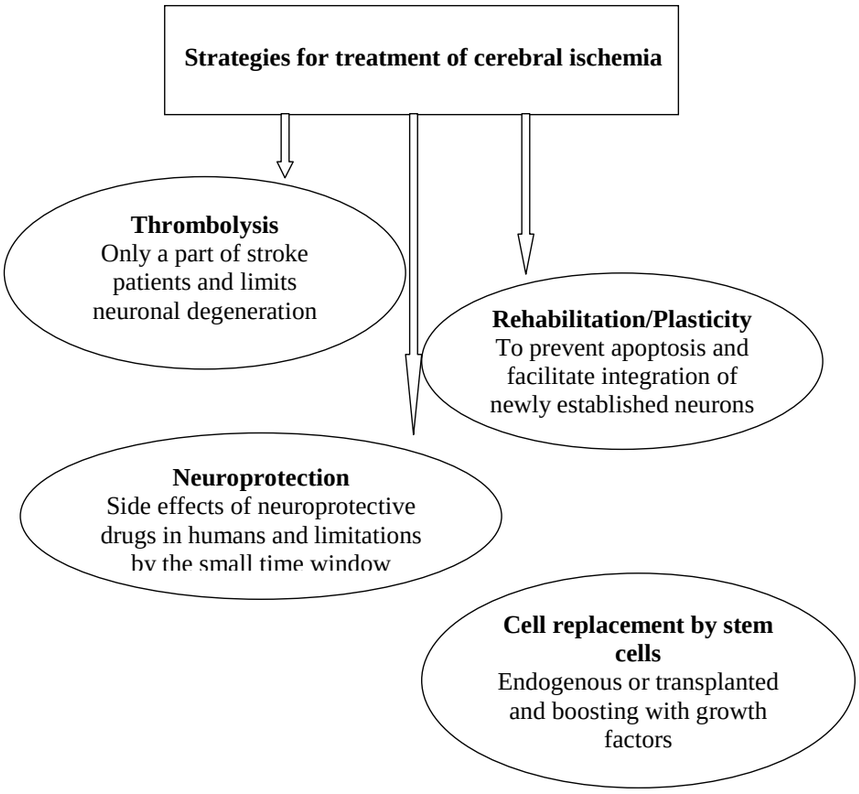

Fig. 2: Diagrammatic representation of strategies for treatment of cerebral ischemia.

(b) Neuroprotective approach

Neuroprotection is a mechanism based approach. Several mechanisms of neuronal injury have been proposed including increased excitotoxicity, calcium overload, formation of free radicals and inhibition of protein synthesis (15). These factors may not be sequential but certainly are interlinked. The neuroprotective drugs inhibit the ongoing ischemic cascade by acting at various sites that ultimately lead to neuronal death.

Experimental models of cerebral ischemia

Innumerable *in-vitro* and *in-vivo* models of cerebral ischemia have been described over the years. The *in-vitro* models include cultured neurons with or without synaptic formation, glia and cultured brain slice. However, these models can only indicate the level of cytotoxicity of the therapy. Because living experimental systems (animals) that contain whole elements, neurons, glia, vasculature and cerebrospinal fluid are closer to the human system, significant efforts have been made by neuroscientists to develop models that mimic closely the physiological and pathophysiological changes associated with stroke. A good in vivo animal model of stroke must reproduce the etiology, anatomical, functional and metabolic consequences of human pathology and must also permit the study of anti-ischemic drugs in conditions pertinent to the clinical therapeutics (16). The major models of stroke available for screening of drugs can be broadly classified into three subgroups as global ischemia, focal ischemia and forebrain ischemia (Table I).

TABLE I: Major animal models of stroke.

Type of model	*Representative models*
Global Ischemia	1. Total body ischemia Decapitation Cardiac arrest with resuscitation Profound systemic hypotension
	2. Global cerebral ischemia Increased intracranial pressure Combination of occlusion of the major arteries
Forebrain Ischemia	1. Bilateral common carotid occlusion in mongolian gerbil hypotension.
	2. Four vessel occlusion in the rats
	3. Bilateral common carotid occlusion in spontaneously hypertensive rats
	4. Two vessel occlusion with hypotension in rats
Focal Ischemia	1. Middle cerebral artery occulsion Intraluminal arterial occlusion without craniotomy Mechanical or electrical arterial occlusion with craniotomy and dural opening
	2. Photochemically induced focal cerebral thrombosis
	3. Cerebral embolism Blood clot embolization Microsphere embolization

Failure of neuroprotective agents in clinical trials

Despite numerous agents that can prevent the cascade of events leading to ischemic neuronal death in animal models (8), there is no neuroprotective agent that has been shown to conclusively improve stroke outcome (17, 18). Numerous experimental treatment strategies have been developed to gain new options for stroke treatment. However, all approaches using neuroprotective agents that have been successfully evaluated in rodents have subsequently failed in clinical trials (19, 20). The discrepancy between animal results and clinical trials could be due to many reasons.

The heterogeneity of human stroke

(a) Morphological and functional differences between the brain of humans and animals.

(b) Difficulty in timing when the neuroprotective agents may be of benefit. In animals the time of stroke onset is known precisely whereas in human this is not the case. In animals, the administration of drugs is at precise times; either at the time of ischemia, immediately after reperfusion or various times after reperfusion whereas in humans, pharmacological agents are administered many hours after the onset of symptoms perhaps in the presence of a persisting occlusion.

(c) Better experimental control of variables like temperature, blood pressure and glucose in animal models. Since the variations in these parameters are sufficient enough to affect the outcome, there is better experimental control of variables like temperature, blood pressure, and glucose in animal models. These variables should be monitored for a long time and should be accounted for and controlled whenever possible in humans.

(d) Finally, the parameters used to assess brain damage and the effects of therapeutic agents are different in clinical trials and in experimental models. In animal models the extent of the lesion is assessed frequently and usually after only a few hours of survival whereas the endpoints of clinical trials make reference to the clinical and functional conditions of the patient not only in the acute stage but also in the long term. It is critical that when testing a potential neuroprotective agent in animals, the experiments should be performed in a randomized and blinded fashion. Outcomes measured in animal models should also include functional tests (behavioral responses) apart from histology (21–23). The failure of presently available neuroprotective agents in clinical trials has led to the emergence of newer approaches for the treatment of acute ischemic stroke (Table II).

TABLE II : Why do most therapeutic strategies work in experimental animals and none in humans ?

In animals :
• Trial conditions optimized to show protection
• Models adapted to pathophysiology rather to clinical condition
• Only positive results published
• Grey vs white matter
• Low statistical power
In Humans :
• Complicating pathology: High blood pressure, diabetes, medication etc.
• Heterogeneity of stroke types
• Age
• To avoid side effects: dosages too low
• Timing of therapy does not match pathophysiology

Is multifactorial pathophysiology a cause for single approach failure?

Stroke is a multifactorial disease with a complex etiopathogenesis. The pathogenesis and etiology of this prevalent, incapacitating disease remain a clinical enigma (24). Given the complexity of its pathophysiology, it is possible that drugs of different mechanisms of action may be more effective than an individual approach alone.

Current approaches in management of stroke

Combination therapy

The rational for combination therapy is based on the increasing knowledge of the pathophysiological mechanisms of ischemic brain damage. A number of independent lethal mechanisms (excitotoxicity, radical damage, proteolytic activation, induction of apoptosis) are involved in the ischemic process that ultimately lead to cell death. Each agent affects only one of the several mechanisms in the ischemic cascade whereas combination therapy has the potential to affect various points in the cascade (25, 26). Combining neuroprotection with thrombolytics may decrease or eliminate the untoward effects of thrombolysis i.e. hemorrhagic conversion, frank parenchymal hemorrhage, and reperfusion injury, which may partially or totally eliminate the benefits of reperfusion itself. Neuroprotective agents if administered early may prolong the time interval that the brain can tolerate ischemia before reperfusion. In our laboratory, we have shown the better functional outcome and reduction in cerebral infarction using various neuroprotective agents (27–32).

Thrombolytic agents and neuroprotective agents may act synergistically and may result in more complete attenuation of ischemic damage and better functional outcome than either of the two treatments (33). There is substantial evidence in experimental studies that a combination of neuroprotective and thrombolytic agents or two or more neuroprotective agents with a different mechanism of action is more effective than the any single agent (34–38).

In humans, use of pre-hospital antiexcitotoxic and calcium antagonist therapies, early thrombolysis on arrival followed by free radical scavenger and anti-inflammatory therapies, and finally anti-apoptotic and growth factor therapies can be a beneficial approach.

Prophylactic treatment

The aim of neuroprotective maneuvers is to influence the ischemic cascade so as to maximize the proportions of ischemic volume that will survive and recover. Results of clinical as well as experimental studies have stressed the earliest possible treatment of ischemic stroke and led to the concept of prophylactic neuroprotection. The duration of prophylactic neuroprotection depends upon the conditions of the patients. Patients undergoing procedures such as cardiac surgery, endarterectomy, or endovascular therapy, which have a risk of cerebral ischemic events during a defined period, might be considered for short-term, periprocedure prophylactic neuroprotection. In addition high risk populations suffering from transient ischemic attacks and atrial fibrillation as well as those at risk for stroke recurrence after minor strokes are readily identifiable and perhaps appropriate for long-term prophylactic neuroprotection. Patients with hypertension and cerebrovascular atherosclerosis have a high stroke risk and therapies directed at these underlying disorders are available that also have concomitant neuroprotective effects (10, 39, 40).

If a neuroprotective drug is available orally, safe and relatively inexpensive, it could be considered for prophylactic use in people at risk for stroke and could be used

to counter the biochemical changes as a result of vascular occlusion thereby preventing the extent of neuronal injury.

Herbal drugs

The traditional medicine all over the world is nowadays revalued by an extensive activity of research on different plant species and their therapeutic principles. Herbal drugs have gained lot of acceptance in the recent years because they have a relatively higher therapeutic window, less serious side effects, and are economical. They have been extensively studied in many diseases such as cancer, liver diseases, and infectious diseases as well as in neurological disorders like stroke with promising results.

Traditional Chinese Medicine and cerebral ischemia

Traditional Chinese medicine (TCM) has been extensively studied in stroke therapy. There are more than 100 traditional chinese medicines which have been studied for stroke treatment both in animals as well as in patients. A number of commercial stroke treatments based on TCM have been introduced into the market recently after extensive pharmacological research and clinical trials. Similar to western medicine, chinese medicine therapies are based on the pathophysiology of stroke and are classified as antioxidants, anti-inflammatory, antithrombotic etc. (41, 42). The various Chinese herbs that have been used in cerebral ischemia reperfusion injury include:

Radix salviae miltiorrhizae : RSM is a powder which is extracted and processed from dried root and rhizome of *Salvia miltiorrhiza Bunge*, family Labiatae. It as been used for increasing the cerebral blood flow and therefore has a potential against cerebral ischemia (43). It has been tried against various models of cerebral ischemia like ligation of carotid artery in gerbils and 4-vessel occlusion model in rats and has been found to be effective. Various studies have been carried out to find out the possible mechanisms of the underlying protective effect. Kuang et al demonstrated that Radix Salviae Multiorrhizae reduced the lipid peroxidation and afforded cerebral protection against reperfusion injury (44). Recently, it has been shown that Radix Salviae Miltiorrhizae has the actions of improving blood circulation and resolving stasis to promote regeneration in traumatic intracranial hematoma (45) and also has been used for the management of cardiovascular disease (46).

Tetramethylpyrazine (TMP): Tetramethyl-pyrazine is widely used in the treatment of ischemic stroke by Chinese herbalists and is one of the most important active ingredients of the traditional Chinese herbal medicine, *Ligusticum wallichii* Franchat (Chung Xiong). However, the mechanism by which TMP protects the brain is still not clear, although neuroprotective effects of TMP against ischemic brain injury might involve its anti-inflammatory potential (47). Experimentally tetramethylpyrazine has been shown to induce vasodilatation, to increase coronary blood flow and inhibit ADP induced platelet aggregation. These properties of tetramethylpyrazine apparently account for its efficacy in the treatment of disorders associated with blood vessel occlusion like cerebral ischemia (48). Recently, it has been shown that administration of TMP, within a 4 h time period post-transient focal stroke, may reduce cerebral ischemic reperfusion

damage (49). It has been shown that TMP administration results in a reduction in the infarct volume in ischemia-reperfusion brain injury (50). Thus, TMP treatment may represent a good approach to lowering the risk of or improving function in ischemia-reperfusion brain injury-related disorders.

Ginseng: Ginseng, the root of *Panax ginseng*, is a well-known traditional Chinese herbal medicine. It is a slow-growing perennial plant with fleshy roots, in the *Panax* genus, in the family Araliaceae. It grows in the Northern Hemisphere in eastern Asia (mostly northern China, Korea, and eastern Siberia), typically in cooler climates. *Panax ginseng*, attenuates H_2O_2– induced oxidative injury. Ginsenoside Rd (GSRd), one of the main active ingredients in *Panax ginseng*, exhibited remarkable neuroprotection when presented during oxygen glucose deprivation and reoxygenation, which may be ascribed to its anti-oxidative properties by reducing the intracellular reactive oxygen species and malondialdehyde production; increasing glutathione content; and enhancing the antioxidant enzymatic activities of catalase, superoxide dismutase and glutathione peroxidase (GPx). These findings suggest that it may be a potential neuroprotective agent for cerebral ischemic injury and further studies are required to explore the potential neuroprotective efficacy of GSRd (51). The roots of *Panax notoginseng* (PN) are commonly used as a therapeutic agent to stop hemorrhage in traditional Korean medicine. Results suggest that anti-inflammatory effects of the PN extract may contribute to its neuroprotective effects in brain ischemia (52). It has also been shown that *P. ginseng* might be neuroprotective against cerebral ischemia-induced injury in rat brain by decreasing lipid peroxides and increasing the expression of GPx and SOD (53). These days, combination of Oriental herbal medicines and western pharmaceuticals has been used but is still controversial. Case reports and healthy volunteer trials show conflicting results on the effect *Panax ginseng* has on warfarin's pharmacologic action, some reporting a reductive and others a potentiating influence. Clinical study by Lee et al suggests that co-administration of *P. ginseng* and warfarin in ischemic stroke patients does not influence the pharmacologic action of warfarin (54). Ginsenoside Rb1 (GRb1), a major component of the traditional herb ginseng, has been reported to show a neuroprotective effect in a rodent ischemic model. Results also demonstrated that GRb1 ameliorated both early and delayed injuries in the thromboembolic stroke model in non-human primates (55).

Siberian ginseng: Siberian ginseng, also known as eleuthero, has been used for centuries in Eastern countries, including China and Russia. Although a distant relative of American (*Panax quinquefolius*) and Asian ginseng (*Panax ginseng*), with some overlap in its uses, Siberian ginseng is a distinct plant with different active chemical components. Siberian ginseng, the root and stem bark of *Acanthopanax senticosus* has been used as a tonic and adaptogen to strengthen in traditional Korean medicine. The studies have shown the neuroprotective effects of water extracts of *Acanthopanax senticosus* (ASW) in transient middle cerebral artery occlusion (MCA occlusion, 90 min occlusion, 24 h reperfusion). Immunohistochemical studies have also shown that ASW markedly

inhibited both cyclooxygenase-2 and OX-42 expressions in the penumbral region at 24 h after MCA occlusion. These studies suggest that *Acanthopanax senticosus* has a neuroprotective effect by inhibiting inflammation and microglial activation in brain ischemia (56).

Jasminoidin: The effect of jasminoidin was studied in focal cerebral ischemia in rats. It has been found that Jasminoidin had good effect on repressing the expression of tumor necrosis factor-alpha and interlukin 1 beta as well as vonWillebrand factor caused by cerebral ischemia, thus it manifested the effects of relieving the damage to vascular endothelial cell and blocking the progress of cascade damage of cerebral ischemia through inhibiting the process of inflammation (57). A study was conducted to see the effects of baicalin and jasminoidin on cerebral ischemia-reperfusion injury, and test whether the combined administration of baicalin and jasminoidin can improve the therapeutic effect. It was found that the combination of baicalin and jasminoidin can significantly improve their effectiveness (58).

Tianma gouteng fang : Studies have been carried out to see the effect of *Tianma gouteng fang* (TGF) on the amino acid transmitters in the hippocampus extracellular liquids in freely moving rats subjected to incomplete brain ischemia. It was found that TGF can increase the concentration of inhibitory amino acids in hippocampus extracellular liquids of rats and inhibit the excessive release of excitatory amino acids and raise the concentration of the inhibitory amino acids during the ischemia-reperfusion periods. Therefore, TGF can play the neuroprotective role (59).

***Uncaria sinensis*:** *Uncaria* is a genus of flowering plants in the family Rubiaceae, native to Asia, Africa, and South America. They are known colloquially as Gambier, Cat's Claw or Uña de Gato. Studies have shown that oral administrations of Choto-san, a Kampo formula, and the hooks and stems of *Uncaria sinensis* Haviland (Rubiaceae), a medicinal plant comprising Choto-san, enhanced superoxide anion and hydroxyl radical scavenging activities in the hippocampus, and prevented delayed neuronal death of pyramidal cells in the hippocampal CA1 region in a transient forebrain ischemia gerbil model. Studies have also been carried out clarifying whether the endogenous antioxidant enzymes contribute to the effect of these mechanisms on superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (GSH-Px) activities in the brain. The data suggest that one of the mechanisms of the protective effects of CSE and USE against transient brain ischemia-induced neuronal damage may be their enhancing effect on CAT activity in the brain (60, 61). Studies also suggest that the oral administration of *Uncaria sinensis* provides a protective effect against transient ischemia-induced delayed neuronal death by reducing oxidative damage to neurons. The ethanol extract from the hooks and stems of *Uncaria sinensis* Havil and (Rubiaceae) exhibited significant inhibitory activity on oxidative stress (62).

Tetrandrine: Tetrandrine is an active compound obtained from *Radix stephaniae* Tetrandrae. Tetrandrine has a calcium antagonizing property and has been tried against ischemia reperfusion injury. In one

study the effects of tetrandrine and nicardipine were carried out against ischemia reperfusion injury in gerbils. Pretreatment with tetrandrine (15 mg/kg, iv) and nicardipine (0.25 mg/kg, iv) decreased the calcium content, water content and lipid peroxide and attenuated the ultra structural abnormalities of cortex and hippocampus in the ischemia reperfusion group produced by 10 min occlusion of bilateral carotid arteries followed by reperfusion in gerbils. The effects of tetrandrine were similar to but less potent than nicardipine (63). The effect of tetrandrine on neutrophilic recruitment response to brain ischemia/reperfusion (I/R) has been studied. Results indicate that tetrandrine inhibited neutrophilic recruitment, expression of ICAM-1 mRNA, and activation of NF-kappaB after brain I/R (64).

Tanshinone is an active compound isolated from Radix Salviae Multiorrhizae and has been reported to show good clinical effect in improving the blood circulation. It also been shown to have an inhibitory effect on the adhesion molecules (ICAM-1 and P-selectin) and can be a potential candidate in the evaluation against stroke. Tanshinone (TSB) is a major active constituent of the roots of *Salvia miltiorrhiza* (Danshen) widely used in the treatment of stroke and coronary heart disease in Asian countries (65). Recently, it has been evaluated whether tanshinone IIA was neuroprotective in permanent focal cerebral ischemia and what the possible mechanisms of its neuroprotection could be. Results from this study illustrated that TSA protected the brain from ischemic injury by suppressing the oxidative stress and the radical-mediated inflammatory insult (66). Further studies are warranted to investigate the role of other apoptosis-related signaling proteins and reperfusion-related mechanisms in the protective effect of TSB on neurons.

Zuzhongping was studied against middle cerebral artery occlusion model in rats. The rats received 1 ml/kg/day of Zuzhongping. Ischemic volume of Zuzhongping group was significantly smaller than that of the saline treated group (67).

Polyherbal preparations

Shengmai san is a traditional Chinese herbal medicine consisting of three herbal components *Panax ginseng*, *Ophiopogon Japonicus*, and *Schisandra chinenisis* and is being used for treating coronary heart disease and termed as a polyherbal preparation (68). Shengmai san, in a model of bilateral carotid occlusion, when administered directly into the duodenum 2 h before cerebral ischemia suppressed thiobarbituric acid reactive substance (TBARS) formation and also prevented the loss of glutathione peroxidase (GSH-Px) as compared to the control. It has also been shown that Shengmai san prevents cerebral oxidative damage in rat (69). Recently, it has been shown that Shengmai san or aminoguanidine protects against heat stroke-induced arterial hypotension and cerebral ischemia by inhibition of iNOS-dependent NO overproduction in the brain and excessive accumulation of several inflammatory cytokines in the peripheral blood stream (70). The multifunctional aspect of traditional herbal prescription was useful in terms of preventing oxidative injury in the brain using Shengmai San as a typical prescription (71). Studies have also indicated that the

Shengmai San may reduce hepatic lipids and lipid peroxidation in rats as it has antioxidant property (72, 73).

Zhenxuanyin composed of *gastrodia tuber, poria cocos* and *ligusticum wallichii* was tried against 4-O vessel occlusion model in rats. It was administered 3 times a day. Twenty hours later N-isopropyl-p-[*123I*]-iodoamphetamine (*123I-IMP)* uptake was evaluated in the brain as an index of cerebral blood flow. The results show that 0.3 g/kg of *Zhen*xuanyin increased the cerebral blood flow to the normal levels (74).

BHUx: It is a novel polyherbal formulation, consisting of 5 medicinal plants namely *Terminalia arjuna, Strychnox nux-vomica, Boswellia serrata, Commiphora mukul,* and *Semecarpus anacardium,* which have history of clinical use alone or in other combinations, but these plant fractions were never tried collectively in this ratio as in BHUx, which has been found to be effective on all the etiological factors, together. Sandhika is a polyherbal formulation, (water soluble fraction of *Commiphora mukul, Boswellia serrata, Semecarpus anacardium* and *Strychnos nux vomica*), which has been in clinical use in India for last 20 years. Its modified formulation BHUx has shown specific inhibition of cyclooxygenase (COX)-2 (75). The antioxidant, anti-inflammatory, hypo-lipidemic, anti-proliferative properties of BHUx have been studied on several experimental models and prove its safety margin in therapeutic doses (76). Studies suggest that BHUx, acting mainly at three levels, i.e., as a potent natural antioxidant, by reduction of key inflammatory mediators of arachidonic acid cascade and by preventing LDL oxidations, may be found effective in stroke (77).

Indian medicinal plants

Traditional medicine system ‘Ayurveda’ has been in existence for thousand of years in India. With the associated side effects of western medicine, herbal preparations are gaining a lot of importance and are now being studied to find the scientific basis of their therapeutic actions. Although Indian plants have been extensively studied against various neurological disorders like stress, learning and memory diseases, depression and anxiety, there is scanty research on the Indian herbals in terms of stroke. However, Indian herbals that can increase the blood flow/antioxidant property/antiexcitoxic activity may have a potential against these disorders.

Bacopa monnieri, popularly known as *Brahmi,* is an annual creeping plant found through out India in damp and marshy areas. In the ancient Indian literature it has been described as a medicine to improve memory. Experimentally also it has been demonstrated to improve the learning process in both human and animals. In one comparative study the effect of alcoholic extract of Brahmi and chlorpromazine on the learning process was carried out. Authors have found that the alcoholic extract of Brahmi and chlorpromazine improved the performance of rats in motor learning. Besides its CNS actions it has also been shown to have antioxidant properties in experimental studies as demonstrated by Tripathi et al (78). Therefore it’s potential in cerebral ischemia cannot be ruled out. It has also been demonstrated that it has potential to modulate the activities of HSP70, cytochrome P450 and SOD, thereby possibly allowing the brain to be prepared

to act under adverse conditions such as stress (79). Studies have shown that neuroprotective effects of Brahmi appeared to be the results of its antioxidant to suppress neuronal oxidative stress and the acetylcholinesterase inhibitory activities. Therefore, treating patients with Brahmi extract may be an alternative direction for ameliorating neurodegenerative disorders associated with the overwhelming oxidative stress (80). It has been reported that it exhibited high antioxidant activity (81), so it may be worthwhile to study in stroke patients.

Nardoyscht jatamansi, commonly known as jatamansi, is a popular medicine of the ayurvedic system of medicine. It is an erect perinneal herb and grows in the alpine Himalayan region. It is described for epilepsy, leprosy, hysteria and convulsions in ayurveda showing that it is a CNS active plant. In a pharmacological study it was demonstrated that both alcoholic and hexane extracts of jatamansi prevented the lipid peroxidation induced by $FeSO_4$, which could be due to the presence of antioxidant phytochemicals in jatamansi (82). Because of its anti-lipid perxidative property, it may have a potential against cerebral ischemia. It has been reported that *Nardoyscht jatamansi* has antioxidant activity (83, 84) and may be a beneficial approach in the treatment of stroke as it suppresses the oxidative stress.

Withania Somnifera referred to as Aswagandha in Ayurveda has been described to promote memory and intellect. Studies with *Withania somnifera* have indicated that it exerts significant antiageing effects in aged subjects and has significant anxiolytic and antidepressant activity. The other pharmacological actions exerted by *Withania somnifera* include anti-inflammatory, immunostimulatory and antioxidant properties (85).

Free radicals are involved in the pathogenesis of the cerebral ischemia and inflammatory response during the late phase leads to delayed cytotoxicity. Since *Withania somnifera* which is a CNS active plant has demonstrated both antioxidant and anti-inflammatory properties its potential in stroke can not be ruled out. Our laboratory has shown the protective effect of *Withania somnifera* against focal cerebral ischemia in rats (11). It has been shown that *Withania somnifera* significantly reduced myocardial injury and emphasizes the beneficial action of *Withania somnifera* as a cardioprotective agent (86, 87). It has been reported that *Withania somnifera* has antioxidant property and is a potential drug in treating oxidative damage (88).

Centella asiatica is a tiny herbaceous plant found throughout India at the altitudes upto 610 m above the sea level. It grows abundantly in damp and marshy places in Bengal. The dried aerial parts, preferably leaves are used for medicinal purpose (89). In the Indian system of medicine, it has been used for different ailments like insanity, asthma, leprosy, ulcers, eczemas and wound healing. Brahmic acid, an active triterpenoid present in the plant, has therapeutic value in ulcerations, extensive wounds and eczemas (90, 91). Apart from these chemical constituents, *Centella asiatica* also contains asiatic and madecassic acid, which are known to possess neuroprotective properties (92).

The whole plant of *Centella asiatica* has

been shown to be beneficial in improving memory and reported to improve general mental ability in mentally retarded children. Recently it has been shown that *Centella asiatica* is cardioprotective against adriamycin induced cardiac damage in rats (93). Recently, it has been shown that *Centella asiatica* rendered radioprotection to DNA and membranes against radiation exposure. Extract can prevent a radiation-induced decline in antioxidant enzyme levels. This suggests that radioprotection by *Centella asiatica* extract could be mediated by mechanisms that act in a synergistic manner, especially involving antioxidant activity (94). Asiatic acid, a triterpenoid derivative from *Centella asiatica*, has also shown biological effects such as antioxidant, antiinflammatory, and protection against glutamate- or beta-amyloid-induced neurotoxicity. Findings suggest that asiatic acid may be useful in the treatment of cerebral ischemia (95). It has been indicated that *Centella asiatica* can impact the amyloid cascade altering amyloid beta pathology in the brains of PSAPP mice and modulating components of the oxidative stress response that has been implicated in the neurodegenerative changes that occur with Alzheimer's disease (96). Two new flavonoids named castilliferol 1 and castillicetin 2, as well as a known compound, isochlorogenic acid 3, were isolated from the whole plant of *Centella asiatica*. These compounds exhibited good antioxidant activity (97).

Shilajit : Shilajit is a pale-brown to blackish-brown exudation, of variable consistency, exuding from layers of rocks in many mountain ranges of the world, especially the Himalayas and Hindukush ranges of the Indian subcontinent. It has been found to consist of a complex mixture of organic humic substances and plant and microbial metabolites occurring in the rock rhizospheres of its natural habitat (98). It contains number of organic acids like fulvic acid, humic acid and hippuric acid. Traces of benzoic acid are also present. Besides these, a special group of compounds known as benzopyrones are also present. Also present are tirucallane triterpenes, phenolic lipids and small tannoids (99). In Ayurveda, Shilajit has been described to be beneficial against immune disorders, urinary tract disorders, sexual dysfunction, diabetes, ulcers, asthma, rheumatism and also known to arrest aging, induce rejuvenation, improve memory.

Studies have shown that pretreatment with Shilajit did not potentiate the hypnotic effect of barbiturate. The analgesic effect of Shilajit was evaluated using the tail flick method in mice. Shilajit at the dose of 200 mg/kg showed analgesic effect during the first 60 min (100). In a study the nootropic and anxiolytic activity of Shilajit was investigated using passive and active avoidance learning and elevated plus maze technique respectively. It was seen that Shilajit had a dose dependant effect on the retention latency in the passive avoidance learning, the effect being significant at 50 mg/kg. Also in active avoidance the rats pretreated with Shilajit required significantly less trials to learn as compared to the control animals. Shilajit exhibited anxiolytic effect as evidenced by greater time spent by the rats on the open arm as compared to the close arm. The effect of Shilajit is being maximal at 10 mg/kg.

Studies have also shown that it possesses

anti-inflammatory (100, 101) and antiulcer activity (100). In another study, the antioxidant potential of processed Shilajit was compared with unprocessed Shilajit and vitamin C (ascorbic acid). Peak levels of Shilajit occurred 12–15 hours after ingestion and took more than 72 hours to metabolize. Processed Shilajit showed significant antioxidant activity, may be beneficial in stroke.

Tinospora cordifolia is widely used in botanical formulations in India and China. It also exhibited strong free radical scavenging properties against reactive oxygen and nitrogen species as revealed by electron paramagnetic resonance spectroscopy, diminishing the expression of iNOS gene. *Tinospora cordifolia* therefore attenuate oxidative stress mediated cell injury during oxygen-glucose deprivation (OGD) and exerts the free radical scavenging effect in both the cytosolic as well as at gene expression levels and may be an effective therapeutic tool against ischemic brain damage (102). It has also been shown that the antiangiogenic activity of the plant *T. cordifolia* is related, at least in part, to the regulation of the levels of these cytokines and growth factors in the blood of the angiogenesis-induced animal (103). It has also been demonstrated that *T. cordifolia* has anti-tumor activity (104). *T. cordifolia*, when administered for a period of 60 days, indicated the preventive role of *T. cordifolia* against fructose-induced insulin resistance and oxidative stress; hence this plant could be used as an adjuvant therapy for the prevention and/or management of chronic diseases characterized by hyperinsulinemia, hypertriglyceridemia, insulin resistance and aggravated antioxidant status (105). *Tinospora cordifolia* is also used in anti-diabetic herbal drug preparations (106). It has been shown that the enhanced GSH level and enzyme activities involved in xenobiotic metabolism and maintaining antioxidant status of cells are suggestive of a chemopreventive efficacy of *T. cordifolia* against chemotoxicity, including carcinogenicity (104).

Convolvulus pluricaulis: Is an indigenous plant commonly mentioned in Ayurveda as a rasayana, which is mainly advocated for use in rejuvenation therapy (107). It is used as a tonic, alternative and febrifuge. It is a sovereign remedy in bowel complaints especially dysentery. The plant is reported to be a prominent memory-improving drug. It is used as a psychostimulant and tranquilizer and is reported to reduce mental tension. The ethanolic extract of the plant reduces total serum cholesterol, triglycerides, phospholipids and nonesterfied fatty-acid. There is a pertinent reference in Ayurvedic literature about the use of the drug as brain tonic in hypotensive syndromes. The pharmacological studies of the herb have shown varying degrees of its hypotensive and tranquilizing effects.

The antiulcerogenic effect of *Convolvulus pluricaulis* was due to augmentation of mucosal defensive factors like mucin secretion, lifespan of mucosal cells and glycoproteins rather than on the offensive factors like acid-pepsin (107). It has also been reported that the action of the plant extract on thyroid function is primarily mediated through the inhibition of 5'-DI enzyme activity, which has been investigated in the regulation of hyperthyroidism in female mice using *Convolvulus pluricaulis* root extract

(108). Clinical studies have exhibited demonstrable beneficial effects in patients with anxiety neurosis. The herb induces a feeling of calm and peace, good sleep and a relief in anxiety, stresses, mental fatigue, producing a significant reduction in the level of anxiety, neuroticism arising due to various levels of stresses. *Convolvulus pluricaulis* possesses neuroprotective potential, thus validating its use in stroke (109).

Curcumin: Curcumin, a member of the curcuminoid family of compounds, is a yellow colored phenolic pigment obtained from the powdered rhizome of *Curcumin longa* Linn (turmeric). It is a phenolic antioxidant, several times more potent than vitamin E (110), and has shown to protect the brain against lipid peroxidation (111). Recent studies have demonstrated the neuroprotective effect of curcumin in animal models of cerebral ischemia. The protective effect has been attributed to its antioxidant activity (112, 113). It was previously reported that 14-3-3gamma could be up-regulated by ischemia in astrocyte to protect cells from ischemia-induced apoptosis. It was also found that ischemia activates the JNK/c-Jun/AP-1 pathway to up-regulate 14-3-3gamma in astrocytes. Curcumin treatment inhibition of AP-1 also inhibited 14-3-3gamma up-regulation indicating that ischemia-induced up-regulation of 14-3-3gamma in astrocytes involves activation of the JNK/c-Jun/AP-1 pathway (66). Overall, curcumin appears to carry promise as a stroke preventive agent. It may be worthwhile to conduct future clinical trials of oral curcumin supplementation in persons with, or at risk for stroke, to investigate its appropriate dosing, safety, and therapeutic efficacy.

Ocimum sanctum commonly known as holy basil (Tulsi) is an herbaceous sacred plant found through out India. Indian material medica describes the use the plant in a variety of ailments. Different parts of plant like stem, flower, seed, leaves, root etc are known to possess therapeutic potential and have been used, by traditional medicinal practitioners, as expectorant, analgesic, anticancer, antiasthamatic, antiemetic, diaphoretic, antidiabetic, antifertility, hepatoprotective, hypotensive and antistress agents. Tulsi has also been used in treatment of fever, bronchitis, arthritis, convulsion etc. Various studies have shown the antioxidant property of *Ocimum sanctum.* It has been shown that lindane produced oxidative stress as indicated by increase in the levels of MDA and decrease in GSH levels. Treatment with *Ocimum sanctum* seed oil per se showed antioxidant activity and also reversed the oxidative stress produced by lindane. The results suggest that *Ocimum sanctum* seed oil can attenuate the immunotoxicity and oxidative stress produced by lindane (114, 115). Studies have shown that treatment with *O. sanctum per se* showed antioxidant activity and also reversed the oxidative stress produced in various neurodegenerative diseases (116, 117). A study indicated that extracts of *O. sanctum* have an important protective role against H_2O_2 injury in human lens epithelial cells by maintaining the normal cellular architecture. The protection could be due to its ability to reduce H_2O_2 through its antioxidant property (118).

Allium sativum, commonly known as garlic, is a species in the onion family Alliaceae. Its close relatives include the onion, shallot, leek, and chive. Garlic has been used throughout recorded history for both culinary and medicinal purposes.

Experimental evidence has shown that some garlic-derived products have a protective effect against ischemic brain injury. The neuroprotective effect of garlic might be associated with control of the free-radical burst induced by reperfusion, preservation of antioxidant enzyme activity, and the delay of other pathophysiological processes (119). Diallyldisulfide (DADS), an active principle of garlic (*Allium sativum*), is known for its antihyperlipidemic properties, also having good anti-inflammatory and antioxidant properties. This drug may be beneficial in preventing the vascular complications in various diseases and provide a new therapeutic approach for the treatment of cerebrovascular and cardiovascular related diseases (120). Recently, it has been demonstrated that the administration of garlic can prevent nickel II- or chromium VI-induced alterations in blood glucose homeostasis while exerting a hepatoprotective effect on glycogen levels and antioxidant status in male albino rats (121).

Momordica charantia is a tropical and subtropical vine of the family Cucurbitaceae, widely grown for edible fruit, which is among the most bitter of all vegetables. English names for the plant and its fruit include bitter melon or bitter gourd and karela from the Panjabi, Hindi-Urdu name of the vegetable. *Momordica charantia* is a traditional herb commonly used for its antidiabetic, antioxidant, contraceptive and antibacterial properties. It is also used for the rapid healing of wounds (122). Momordica charantia is used to treat various diseases including inflammation. As it has antioxidant and anti-inflammatory properties (123), it could be a better approach for the treatment of stroke.

Compounds derived from herbal drugs

Oleogum resin (Guggul) is a resin from a tree native to India belonging to the family Burseraceae and its scientific name is *Commiphora mukul*. This resin has long been used in Ayurvedic medicine, combined with other plant products to cleanse and rejuvenate the body, especially the blood vessels and the joints. In Chinese medicine, guggul is known as mo yao and is used to activate blood flow, relieve pain, and speed recovery. Guggul found in India, Bangladesh, and Pakistan, has been used to treat various diseases including hyper-cholesterolemia, atherosclerosis, rheumatism, and obesity over several thousands of years. Guggulsterone isolated from guggul has been identified as the bioactive constituent responsible for guggul's therapeutic effects. Guggulsterone has been found to potently inhibit the activation of nuclear factor-kappaB (NF-kappaB), a critical regulator of inflammatory responses. Such repression of NF-kappaB activation by guggulsterone has been proposed as a mechanism of the antiinflammatory effect of guggulsterone (124). Guggulsterone and other natural products, which are inexpensive can modulate inflammatory responses, but lack side effects, will be beneficial for the treatment of arthritis (125). It has also been shown that the lipid peroxides, indicating oxidative stress, declined 33.3% in the guggulipid group without any decrease in the placebo group (126).

Korean ginseng tea (KGT), prepared from the roots of *Panax ginseng*, is widely used by Korean people for antistress, antifatigue, and endurance promoting effects. It has been reported that the protective action, exhibited by KGT against hypoperfusion/reperfusion

induced brain injury, suggests its therapeutic potential in cerebrovascular diseases (CVD) including stroke. KGT with wide usage is known to be a safe natural product (127).

Crataegus flavonoid is a large genus of shrubs and trees in the rose family, Rosaceae, native to temperate regions of the Northern Hemisphere in Europe, Asia and North America. It has been reported that Crataegus extract was safe to use in patients receiving optimal medication for heart failure. In addition, the data indicates that Crataegus extract can potentially reduce the incidence of sudden cardiac death, at least in patients with less compromised left ventricular function (128). The effect of Crataegus flavonoids (CF) on brain ischemic insults were investigated in Mongolian gerbil stroke model, and results suggest that oral administration of this antioxidant increases the antioxidant level in the brain and protects the brain against delayed cell death caused by ischemia/reperfusion injury (129, 130).

Spiramine T, an atisine-type diterpene alkaloid isolated from the Chinese herbal medicine *Spiraea japonica* var. acuta (Rosaceae), was shown to have neuroprotective effects on cerebral ischemia-reperfusion injury. The effects of spiramine T on antioxidant enzymes and nitric oxide production were also evaluated in gerbils subjected to global forebrain ischemia. Results suggested that the neuroprotective effects of spiramine T were related to modulation of endogenous antioxidant enzymatic activities and reduction of the formation of nitric oxide (131). It has also been demonstrated that spiramine T exhibited protective effects on cerebral ischemia and its mechanism might be related to reducing calcium accumulation and lipid peroxidation (132).

Conclusion:

Stroke is one of the foremost causes of morbidity and mortality, and poses a major socioeconomic problem in young patients, especially in developing countries. Despite the multifactorial pathophysiology underlying manifestations of stroke, there are strong reasons to believe that oxidative stress is a common factor playing a central role in the pathogenesis of these diseases. Production of reactive oxygen species in the brain has been implicated as a common underlying factor for the etiology of stroke. However, the treatment is yet far from satisfactory and lot of research is undergoing to find newer drugs and newer avenues for the treatment of stroke, which can satisfactorily treat stroke and can have a better safety profile. One such approach is the use of herbal drugs in stroke. Herbal extracts or mixtures represent combinatorial chemistry of nature with vast repertoire of chemical entities that have a complex effect on numerous cellular components and functions. They have great potential in the multi-target approach to diseases. In recent years, there is considerable interest to investigate anti-oxidative and anti-inflammatory effects of herbal drugs from different sources. A lot of work is being carried out to find the effectiveness of Indian and Chinese herbals in stroke. Both thrombolytic and neuroprotective properties of herbal drugs may be a novel strategy for effective stroke therapeutics. The Indian system of medicine, especially Ayurveda, has several medicinal plants with proven beneficial claims towards these pathological conditions. However, the potential of herbal drugs

as defined therapeutic agents is undermined by the difficulty in standardization, pharmacodynamics and pharmacokinetics of these multi-component mixtures and also the lack of enough experimental data. Therefore, the potential of Indian herbals in the treatment of stroke needs to be further explored.

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