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REVIEW ARTICLE

# A Review on Use of Some Herbal Medicinal Plants in Treatment of Cerebral Stroke

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## ABSTRACT

Cerebral ischemia (stroke) is one of the foremost causes of high morbidity and mortality for both developed and developing countries. Cerebral ischemia impairs the normal neurological functions which are triggered by a complex series of biochemical and molecular mechanism. Studies in experimental ischemia models have contributed vastly in understanding the pathophysiology of stroke. Moreover animal models provide a testing ground for novel compounds before their launching into any clinical trials. Animal models of tissue injury in stroke are designed to generate reproducible infarcts in a high throughput manner with a minimum of surgical manipulation to determine mechanisms of cell death and to test novel drugs as recanalyzing, neuroprotective, neuroregenerative and anti- inflammatory therapies. 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. This paper commonly reviews the number of herbal medicinal plants effective for the treatment of stroke.

## KEYWORDS

Cerebral Stroke, Pathophysiology, Neuroprotective, Tissue Injury, Herbal Drugs

## INTRODUCTION

Ischemia a deficiency of blood in a part, due to functional constriction or actual obstruction of a blood vessel. Brain ischemia, also known as cerebral ischemia, is a condition in which there is sufficient blood flow to the brain to meet metabolic demand. Cerebral ischemic stroke is a neurological disease where neuronal cell death is caused by serial pathophysiological events, so called 'ischemic cascade' like energy failure, excitotoxicity, oxidative stress, inflammation, apoptosis etc.

- Leading to poor oxygen supply or cerebral hypoxia
- Leading to brain tissue or cerebral infarction ischemic stroke.
- Subtype of stroke along with subarachnoid hemorrhage or intracerebral hemorrhage.

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### Stroke Pathophysiology

The two major mechanisms causing brain damage in stroke are ischemia and hemorrhage.

 

In ischemic stroke, which represents about 80% of all strokes, decreased or absent circulating blood deprives neurons of necessary substrates. The effects of ischemia are fairly rapid because the brain does not store glucose, the chief energy substrate and is incapable of anaerobic metabolism. Non-traumatic intracerebral hemorrhage represents approximately 10% to 15% of all strokes. Intracerebral hemorrhage originates from deep penetrating vessels and causes injury to brain tissue by disrupting connecting pathways and causing localized pressure injury.

Stroke can be divided into three categories:

- Brain ischemia
- Subarachnoid hemorrhage
- Intracerebral hemorrhage

Brain ischemia can be subdivided by cause into

- Thrombotic
- Embolic
- Hypo-perfusion

**Types of Cerebral Ischemia**

***Focal Brain Ischemia***

- Occurs when blood clot has occluded a cerebral vessel.
- Reduces blood flow to specific brain region,
- Increasing the risk of cell death to that particular area.
- E.g. caused by thrombosis or embolism.

***Global Brain Ischemia***

- Occurs when blood flow to the brain is halted or drastically reduced
- E.g. caused by cardiac arrest.

**Mechanism of Neuronal Injury**

Formation of microscopic thrombi responsible for impairment of microcirculation in the cerebral arterioles and capillaries is a complex phenomenon. Formation of a micro thrombus is triggered by ischemia-induced activation of destructive vasoactive enzymes that are released by endothelium, leukocytes, platelets and other neuronal cells. Mechanical "plugging" by leukocytes, erythrocytes, platelets and fibrin ensues.

At a molecular level, the development of hypoxic-ischemic neuronal injury is greatly influenced by "overreaction" of certain neurotransmitters, primarily glutamate and aspartate. This process called "excitotoxicity" is triggered by depletion of cellular energy stores. Glutamate, which is normally stored inside the synaptic terminals, is cleared from the extracellular space by an energy dependent process. The greatly increased concentration of glutamate (and aspartate) in the extracellular space in a depleted energy state results in the opening of calcium channels associated with N-methyl-D-aspartate (NMDA) and alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionate (AMPA) receptors. Persistent membrane depolarization causes influx of calcium, sodium, and chloride ions and efflux of potassium ions. Intracellular calcium is responsible for activation of a series of destructive enzymes such as proteases, lipases, and endonucleases that allow release of cytokines and other mediators, resulting in the loss of cellular integrity.

Endothelial cells are one of the first cell types to respond to hypoxia. This response occurs at morphological, biochemical and immunological levels, causing a variety of physiological and pharmacological effects. Morphologically, endothelial cells swell and form "microvilli" at the luminal surface of the cell. This results in a reduction in the luminal patency of the capillary vessel. Mechanical plugging by erythrocytes, leukocytes, and platelets ensues. At a biochemical level, endothelial cells mediate the effects of vasoactive agents such as endothelin peptides, eicosanoids, and smooth muscle relaxant (probably nitric acid), which in part modulate the vascular tone of the microcirculation.[1,2]

**Clinical Relevance**

Depending upon the pathophysiology of cerebral ischemia, three major categories of flow reduction have to be distinguished:

***Transient Global Ischemia:*** The most important clinical cause of global ischemia is cardiac arrest which produces complete cessation of cerebral blood flow, followed by more or less efficient recirculation, depending on the success of cardiac resuscitation.

Global ischemia also results from strangulation, severe shock or intracranial hypertension, but under these conditions flow decline is incomplete and heterogeneous. The clinical prototype of focal brain ischemia is stroke which is most frequently caused by thrombotic occlusion of the middle cerebral artery.

***Transient Focal Ischemia:*** are produced by vascular clipping in the course of neurosurgical interventions or by severe vasospasms.

**Mechanism Responsible for Causing Ischemic Strokes**

The three main mechanisms causing ischemic strokes are: (a) thrombosis, (2) embolism and (3) global ischemia (hypotensive) stroke:

***Thrombosis***

Atherosclerosis is the most common pathological feature of vascular obstruction resulting in thrombotic stroke. Atherosclerotic plaques can undergo pathological changes such as ulcerations, thrombosis, calcifications, and intra-plaque hemorrhage. The susceptibility of the plaque to disrupt, fracture or disrupt or ulcerate depends on the structure of the plaque, and its composition and consistency. Disruption of endothelium that can occur in the setting of any of these pathological changes initiates a complicated process that activates many destructive vasoactive enzymes. Platelet adherence and aggregation to the vascular wall follow, forming small node of platelets and fibrin. In addition to atherosclerosis, other pathological conditions that cause thrombotic occlusion of a vessel include clot formation due to hypercoagulable state, fibromuscular dysplasia, arteritis (Giant cell and Takayasu), and dissection of a vessel wall.

***Embolism***

Embolic stroke (ES) can result from embolization of an artery in the central circulation from a variety of sources. Besides clot, fibrin, and pieces of athermanous plaque, materials known to embolize into the central circulation include fat, air, tumor or metastasis, bacterial clumps, and foreign bodies. Superficial branches of cerebral and cerebellar arteries are the most frequent targets of emboli. Most emboli lodge in the middle cerebral artery distribution because 80% of the blood carried by the large neck arteries flow through the middle cerebral arteries.

***Global–Ischemic or Hypotensive Stroke***

Profound reduction in systemic blood pressure due to any reason is responsible for "hypotensive stroke." Some neurons are more susceptible to ischemia than others. These include the pyramidal cell layer of the hippocampus and the Purkinje cell layer of the cerebellar cortex. Cerebral gray matter is also particularly vulnerable. Abundance of glutamate in these neurons renders them more susceptible to global ischemia.[3,4]

**Various Animal Model Used for Cerebral Ischemia**

Stroke models can be divided into two main categories:

1. Models to study how risk factors (both environmental and genetic) may contribute to vascular damage that ultimately leads to stroke and therapeutical approaches to prevent stroke events.
2. Models for the study of the pathophysiological consequences of stroke, and for testing therapeutical strategies (recanalyzing, neuroprotective and neuroreparative approaches).

**Models for the Study of the Pathophysiology and Therapies for Stroke**

Models of cerebral ischemia can be separated into focal and global ischemia models:

***Models for Inducing Focal Cerebral Ischemia***

Stroke caused by an acute cerebral vessel occlusion can be reproduced by different

techniques, namely by mechanical occlusion of either the proximal middle cerebral artery (pMCAo) (large vessel occlusion) or distal MCA (dMCAo) (small vessel occlusion), or by thrombotic occlusion either via injection of blood clots or thrombin into the MCA or by photo-thrombosis after intravenous injection.

### *Mechanical Occlusion of the MCA*

pMCAo models belong to the most frequently used procedures in stroke research. pMCAo is usually induced by direct mechanical occlusion, most often through the insertion of a silicon-coated nylon suture into the internal carotid artery that is subsequently advanced to the circle of Willis to occlude the MCA at its origin. The severity of ischemic injury can be modeled by leaving the suture filament in place either transiently for a variable duration of time (time usually ranges between 30-120 min) before the suture is removed to allow tissue reperfusion.

### *Thromboembolic Models*

Embolic strokes can be induced in animals through injection of large-sized synthetic macrospheres (300-400 µm diameter) or small-sized microspheres (less than 50 µm) into the internal carotid artery. In the first case, large infarcts similar to those produced by the permanent occlusion of the MCA are induced. In the latter case, smaller, multifocal infarcts can occur.

a) **Endothelin and Photothrombosis Model**: Consist of intracerebral injection of vasoconstrictor substances as endothelin-1 (ET-1) that causes a lesion by reducing acutely the blood flow in the circumscribed injected area. In photothrombosis model, consists of the photothrombosis of an injected photosensitive dye. This is induced by the transcranial illumination of the brain after the systemic delivery of a photosensitive dye (Rose Bengal), obtaining the coagulation of the irradiated tissue.

b) **Cerebral Venous Thrombosis Models**: CVT can be induced by different methods occlusion of the superior sagittal sinus can be induced by direct injection of various chemical substances (cyanoacrylate, ethanolamine or other sclerosing agents) into the sinus.[5,6]

## Models for Inducing Global Cerebral Ischemia

Global cerebral ischemia, characterized by the critical reduction of cerebral blood flow in the whole brain, induces selectively neuronal injury in the CA-1 region of the hippocampus as long as the duration of ischemia is limited.

Models of global cerebral ischemia are usually used to study brain damage that occurs in cardio-circulatory resuscitation. Global ischemia can be induced by means of different approaches. The so called ‘four vessel occlusion method’ (4VO) consists of a reversible CCA occlusion, which, combined with permanent interruption of the vertebral arteries via electro cauterization, results in bilateral forebrain and brainstem ischemia with a highly predictable brain damage.[7]

## New Stroke Models

### *Transgenic Mice Models*

Using these models one can investigate the efficacy of anti-apoptotic proteins in preventing delayed neuronal death after focal cerebral ischemia in transgenic mice. The major problems that are being faced in the development of transgenic mice models for cerebral ischemia is the variability in the vascular territories in the different species of mice used to generate transgenic mice.

### *Neonatal Hypoxia Model*

Cerebral hypoxia-ischemia remains a major contributor to perinatal morbidity and mortality. It is estimated that between 0.2 to 0.4% of full-term infants and up to 60% of premature infants experience asphyxiation at or before birth. An established model of neonatal hypoxia/ ischemia is being used recently. Ligation of the right common carotid artery and treatment with 8% oxygen produces ipsilateral brain damage. Oxygen sensitive genes, apoptosis, and neurological evaluations can investigate using this model.[8]

## Treatment Approaches in Management of Stroke

### *Combination Therapy*

A number of independent lethal mechanisms (excitotoxicity, radical damage, proteolytic activation, induction of apoptosis) are involved in the ischemic process that ultimately leads 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.

Combining neuroprotection with thrombolytic 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. Thrombolytic agents and neuroprotective agents may act synergistically and may result in more complete attenuation of ischemic damage and better functional outcome. For e. g: In humans, use of prehospital anti-excitotoxicity 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. 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, periprocedural 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. 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 Medicinal Plants in Treatment of Brain Ischemia

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.

### *Ginseng (P. 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).

### *Brahmi (Bacopa monnieri)*

Brahmi is an annual creeping plant found throughout India in damp and marshy areas. 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. 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.

### *Jatamansi (Nardostachys jatamansi)*

It is a popular medicine of the ayurvedic system of medicine. It is an erect perennial herb and grows in the alpine Himalayan region. It has been reported as 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. Because of its anti-lipid peroxidative property, it has a potential against cerebral ischemia.

### *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 Hindu Kush ranges of the Indian subcontinent. It has been demonstrated that the antioxidant potential of processed Shilajit when 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.[9]

### *Ocimum basilicum (O. basilicum)*

O. basilicum L. commonly known as Sweet Basil is native to Asia, Africa, South America, and the Mediterranean. Basil grows between 30 and 130 cm tall, with opposite, light green, silky leaves. The flowers are small and white in color. The neuroprotective effect of O. basilicum was evaluated using transient global cerebral ischemia and reperfusion model. The O. basilicum extract exhibited neuroprotection with reduction of infarct size and lipid peroxidation as well as restoration of endogenous antioxidant. The overproduced oxidants are detoxified by endogenous antioxidants. Glutathione is considered as a central component in the antioxidant defenses of cells. Glutathione acts both to directly detoxify ROS and as a substrate for various peroxidases. Pre-treatment with ethyl acetate extract of O. basilicum significantly elevated brain glutathione content.

### *Ocimum sanctum (O. sanctum)*

Ocimum tenuiflorum, also known as O. sanctum, holy basil, is an aromatic plant in the family Lamiaceae which is native to the Indian and widespread throughout the Southeast Asia. It is an erect, many branched subshrub, 30–60 cm tall and simple opposite green or purple leaves. The occlusion of bilateral common carotid artery for 30 min followed by 45 min reperfusion caused up-regulation of superoxide dismutase (SOD) activity. The increased SOD activity is, therefore, an indication that the brain's antioxidant machinery is activated in response to excessive generation of free radicals. O. sanctum pretreatment significantly prevented the rise in methane dicarboxylic aldehyde (MDA) levels and up-regulation of SOD activity. O. sanctum pretreatment attenuates the excessive formation of free radicals to reperfusion injury.

### *Camellia sinensis*

Green tea is made from Camellia sinensis leaves that have undergone minimal oxidation during processing. Green tea originated in China, but it has become associated with many cultures throughout Asia and it has recently become relatively widespread in the West where black tea has been the traditionally consumed tea. The hydrogen peroxide level of brain was significantly increased by the ischemia/reperfusion. The 0.5% green tea extract pretreatment for 3 weeks significantly reduced the increased levels of hydrogen peroxide and also inhibited the increased production of lipid peroxidation products. Eicosanoid concentration was significantly elevated in the ipsilateral hemisphere by the ischemia/reperfusion compared to contralateral hemisphere and the

 

elevated eicosanoids concentrations were significantly reduced by the 0.5% green tea extract pretreatment for 3 weeks.

***Lavandula officinalis (L. officinalis)***

L. officinalis is a genus of 39 known species of flowering plants in the mint family, Lamiaceae. Flowers are borne in whorls, held on spikes rising above the foliage. The pretreatment of rats with 200 mg of lavender extract caused a significant decrease in the permeability of the blood–brain barrier. Lavender extract reduced serum and brain MDA levels, which proved lavender extract, may increase the antioxidant capacity in brain and serum. The treatment with lavender oil significantly decreased neurological deficit scores, infarct size, the levels of MDA, carbonyl and ROS, and decreased neuronal damage, upregulated superoxide dismutase, catalase, glutathione peroxidase activities and glutathione/oxidized glutathione ratio.[10]

## CONCLUSION

Medicinal plants play an important role in the treatment of many incurable diseases like neurological disease such as brain ischemia. Herbal extracts or mixtures represent combinatorial chemistry of nature with vast collection 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 future development of protective agents from traditional herb medicine could be a promising direction in the treatment of ischemic cerebral injury and related neurodegenerative diseases.

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