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# Review on herbal medicine on brain ischemia and reperfusion

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ABSTRACT

Brain ischemia and reperfusion is the leading cause of serious and long-range disability in the world. Clinically significant changes in central nervous system function are observed following brain ischemia and reperfusion. Stroke patients exhibit behavioral, cognitive, emotional, affective and electrophysiological changes during recovery phase. Brain injury by transient complete global brain ischemia or by transient incomplete brain ischemia afflicts a very large number of patients in the world with death or permanent disability. In order to reduce this damage, we must sufficiently understand the mechanisms involved in brain ischemia and reperfusion and repair to design clinically effective therapy.
Cerebral ischemia and reperfusion is known to induce the generation of reactive oxygen species that can lead to oxidative damage of proteins, membrane lipids and nucleic acids. A decrease in tissue antioxidant capacity, an increase in lipid peroxidation as well as an increase in lipid peroxidation inhibitors have been demonstrated in several models of brain ischemia. This paper reviews the number of commonly used types of herbal medicines effective for the treatment of stroke. The aim of this paper was to review evidences from controlled studies in order to discuss whether herbal medicine can be helpful in the treatment of brain ischemia and reperfusion.

## 1. Introduction

Stroke is the leading cause of serious, long-range disability with about 600 000 people suffering stroke each year [1]. Stroke survivors may develop difficulties with memory, thinking, talking, partial paralysis, and mobility problems. In the Western world, over 70% of stroke survivors are over age 65. Since life expectancy continues to grow, the number of stroke survivors will further increase in the future [2]. Three months after stroke, 15%–30% of patients will be permanently disabled and 20% require institutional care [2]. Brain injury by transient complete global brain ischemia and regional incomplete brain ischemia afflicts a very large number of patients with death or permanent disability [1]. Stroke is the rapid progress of clinical signs of focal and global disturbance of cerebral function, with symptoms that can last more than 24 h or lead to death, with no apparent cause other than vascular origin [3]. The only drug that is used for the thrombolytic treatment of acute ischemic stroke in the US is intravenous recombinant tissue plasminogen activator (rt-PA). When delivered within 3 h after symptom onset, rt-PA reduces neurological damages and improves the functional outcome of stroke survivors. This improvement in recovery is achieved at the expense of an increased incidence in symptomatic intracranial hemorrhage, which occurs in ~6% of survivors. However, a large number of patients with acute ischemic stroke do not go to the hospital within the first hours after brain ischemia onset, so most of these patients do not receive rt-PA treatment [4].

## 2. Brain ischemia and reperfusion pathogenesis

In brain ischemia oxidants that are initiators of intracellular cell death signaling pathways may lead to apoptosis [5]. In focal or global cerebral ischemia, cerebral blood flow is reduced in the regions of brain that are nourished with oxygen by the occluded vessels [5]. Damage to cerebral capillaries due to ischemia and post-ischemic reperfusion results in a progressive alteration in the permeability of the blood–brain barrier that can subsequently result in formation of edema and hemorrhagic conversion. In case of blood–brain barrier permeability, substances such as

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$Na^+$, water, serum proteins, and blood can enter into the extracellular space of the brain tissue and cause swelling [6–8]. Swelling is deleterious for brain tissue because its effects on adjacent tissues is also magnified by the fixed volume of the skull. Swelling of brain tissue induced by brain ischemia and reperfusion exert a mechanical force on the surrounding shell of brain tissue, displacing it and causing increasing tissue pressure within it. When brain tissue pressure exceeds capillary pressure, capillary inflow is compromised, leading to ischemia and formation of edema [9].

Brain edema is of interesting topics for neurologists who daily cope with their damaging consequences. During brain ischemia, the glucose utilization of brain is increased substantially *via* the reliance of brain on anaerobic glycolysis, so the brain glucose levels rapidly fall, despite near normal plasma levels [10].

During brain ischemia and reperfusion a complex cascade of metabolic events initiated, several of them involve the production of nitrogen and oxygen free radicals. These free radicals mediate much of damages that occur following transient brain ischemia [11].

During brain ischemia, the reduction in cerebral blood flow and oxygen utilization initiates a cascade of deleterious biochemical events. Decrease of oxygen precludes oxidative phosphorylation and results in anaerobic metabolism [12].

Mitochondrial respiratory chain is the major source for the production of reactive oxygen species (ROS) and following the destruction of the mitochondria, necrotic cell death occurs. Death of endothelial cells causes damage to blood–brain barrier resulting in cerebral edema [13]. Transcellular ion pump failure results in the intracellular accumulation of $Na^+$, $Ca^{2+}$ and water. The membrane depolarization results in a release of excitatory neurotransmitters from axon terminals. The glutamate then activates specific cell surface receptors resulting in an influx of $Na^+$ and $Ca^{2+}$ into postsynaptic neurons. In neurons, the intracellular calcium induces the production of nitric oxide (NO) that diffuses to adjacent cells susceptible to nitric oxide toxicity. When NO combines with superoxide the proxy nitrites were produced that can cause lipid peroxidation [14].

Impermeability of the blood–brain barrier is maintained by tight junctions and basal lamina of microvascular endothelial cells. During the first hours of ischemia, dissolution of the endothelial basal lamina starts [15].

Recently, focus on plant research has increased worldwide and most evidences have been collected to determine the immense potential of medicinal plants. Medical plants have therapeutic benefits and fewer side effects in comparison with synthetic drugs. Herbs may provide a source of new compounds including many drugs that are derived from plant sources.

## 3. Medicinal plants used for the treatment of brain ischemia and reperfusion

### 3.1. Artemisia absinthium (A. absinthium)

*A. absinthium* L. (family: Asteraceae) commonly known as wormwood is an aromatic herb with fibrous roots. The stems are straight, growing to 0.8–1.2 m, grooved, branched, and silvery-green. Ethnopharmacological literature documents the use of *A. absinthium* in various countries as an antiseptic, antispasmodic, febrifuge, cardiac stimulant, for the restoration of declining mental function and inflammation of the liver, and to improve memory [16].

*A. absinthium* contains 14 phenolic acids including caffeic acid, ferulic acid, sinapic acid, *p*-hydroxyphenol acidic acid, vanillic acid, salicylic acid, *p*-coumaric acid that are responsible for some therapeutic effects. Absinthin and artabsin also have sesqueterpines lactones, sesqueterpinoids alpha thujone, beta tujone, chrysanthenyl acetate thujone [17].

*A. absinthium* contains thujone, a $GABA_A$ receptor antagonist that can cause epileptic-like convulsions [17].

*A. absinthium* extracts have both *in vitro* and *in vivo* free radical scavenging activity [18]. The *A. absinthium* extract exhibited neuroprotection as it is evident from the reduction of infarct volume and lipid peroxidation, and restoration of endogenous antioxidants. Focal cerebral ischemia was induced by middle cerebral artery occlusion (MCAO) for 90 min followed by reperfusion for 24 h. It is well documented that transient focal MCAO causes neurological abnormality. The focal MCAO-induced increase in lipid peroxidation and administration of *A. absinthium* before focal cerebral ischemia markedly decreased ischemia and reperfusion-induced increase in the level of thiobarbituric acid reactive substances [18]. *A. absinthium* contains flavonoids such as quercetin, rutin and other flavonoid glycosides such as isoquercitrin, quercitin-3-O-d-glucoside, quercitin-3-O-rhamnoglucoside, isorhamnetin-3-O-rhamnoglucoside, isorhamnetin-3-glucoside, and phenolic acids such as chlorogenic, syringic, coumaric, salicylic and vanillic acids that are probably involved in the mechanism of oxidative damage [19]. Several researches have shown *A. absinthium* to possess potent antioxidant, free radical scavenging and anti-inflammatory activity [20].

### 3.2. 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 [21]. It has been used traditionally for treatment of anxiety, headaches, nerve pain, diabetes, cardiovascular diseases, digestive disorders, fevers, and migraines, sinusitis, and also as anticonvulsant, anti-inflammatory as well as a variety of neurodegenerative disorders [22].

The major aroma constituents of *O. basilicum* were 3, 7-dimethyl-1, 6-octadien-3-ol (linalool; 3.94 mg/g), 1-methoxy-4-(2-propenyl) benzene (estragole; 2.03 mg/g), methyl cinnamate (1.28 mg/g), 4-allyl-2-methoxyphenol (eugenol; 0.896 mg/g), and 1, 8-cineole (0.288 mg/g) [22].

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 antioxidants [23]. 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 [24]. Pre-treatment with ethyl acetate extract of *O. basilicum* significantly elevated brain glutathione content [23].