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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].

3.3. 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. Leaves have petioles, up to 5 cm long, usually slightly toothed [25].

Traditionally, fresh juice or decoction of *O. sanctum* leaves is used to promote health and also in treatment of various disorders as advocated in Ayurveda. *O. sanctum* possesses significant anti-inflammatory, antioxidant, immunomodulatory and antistress properties [26].

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 [27].

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 [26].

3.4. Ginkgo biloba L (G. biloba)

G. biloba is a large tree, reaching a height of 20–35 m. The tree has an angular and long crown, and is usually deep rooted and resistant to wind and snow damage.

G. biloba has been used medicinally for thousands of years. Today, it is one of herbs that more consumed in the United States. Available evidence supports ginkgo for managing dementia, anxiety, schizophrenia, and cerebral insufficiency (insufficient blood flow to brain). Ginkgo should be used cautiously in individuals with clotting disorders or taking blood thinners, or prior to some surgical or dental procedures, due to reports of bleeding [28].

G. biloba extracts used for medicinal purposes are usually standardized to contain 24% ginkgo-flavone glycosides and 6% terpenoids. The terpenoids includes bilobalide and the ginkgolides A, B, C, M, and J that are 20-carbon cage molecules with six 5-membered rings. Ginkgo extract has the flavonoids that may contribute to ginkgo's antioxidant and free radical scavenging effects [29].

G. biloba extract reduces the cell membrane lipid peroxidation in experimental spinal cord injury similarly to methylprednisolone, reduces bromethalin-induced cerebral lipid peroxidation and edema. *G. biloba* extract protect brain neurons against oxidative stress induced by peroxidation, decrease neuronal injury following ischemia or electroconvulsive shock [30].

G. biloba extract inhibits dose-dependently synthesis of nitric oxide through inhibition of inducible NO synthase [31].

Cerebral edema increases intracranial pressure and exacerbates vascular dysfunction impairing cerebral blood flow. The brain edema in the hippocampal region is increased following global cerebral ischemia and reperfusion, and in a dose-dependent way, reduced by pre-treatment with the *G. biloba* extract [32].

G. biloba extract pre-treatment reduces nitrite and nitrate overproduction after transient bilateral carotid occlusion, thus indicating an inhibitory effect of the extract on nitric oxide formation following transient brain ischemia and reperfusion [32].

3.5. Gastrodia elata (G. elata)

G. elata is an herb of the Orchidaceae family. The herb has been used in Traditional Chinese medicine. Medicinally, it is used for 'calming the liver' and for treating headaches, dizziness, tetanus, and epilepsy. *G. elata* root has analgesic activity and inflammatory-mediating activities, as well as *in vivo* and *in vitro* inhibitory activity on NO production [33].

G. elata extract inhibited glutamate-induced neuronal apoptosis of an *in vitro* system. *G. elata* extract has protective effect on the hippocampal neuronal damages following transient global ischemia in gerbils [34]. Several antioxidants are known to inhibit the neuronal damage caused by the transient global ischemia and excitotoxicity [35]. *G. elata* extract has been reported to have the free radical scavenging and antioxidant activity [35].

In another study, *G. elata* extract pretreatment significantly reduced the cortical and striatum of brain tissue infarct sizes. *G. elata* extract provides neuroprotection by preventing brain damage through the increased expression of genes encoding antioxidant proteins after transient focal cerebral ischemia and reperfusion. This may be effective as neuroprotective agents at the cellular and molecular levels in the brain [36].

3.6. Camellia sinensis

Green tea is made from *Camellia sinensis* leaves that has 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 [37]. Varieties of green tea have been used in the countries where it is grown. These varieties can differ substantially due to variable growing conditions, production processing, and harvesting time [38].

Fresh tea leaf is unusually rich in the flavanol group of polyphenols known as catechins which may constitute up to 30% of the dry leaf weight. Other polyphenols include flavonols and their glycosides, and depsides such as chlorogenic acid, coumarylquinic acid, and one unique to tea, theogallin (3-galloylquinic acid). Caffeine is present at an average level of 3% along with very small amounts of the other common methylxanthines, theobromine and theophylline [39].

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 [37].

3.7. Leaf of Olea europaea (O. europaea)

Olive leaf is the leaf of the olive tree (*O. europaea*). While olive oil is well known for its flavor and health benefits, the leaf

has been used for medicinal purposes in various cultures [40]. Clinical evidence has been conflicting regarding any blood pressure lowering effect of olive leaf extracts. A liquid extract made directly from fresh olive leaves gained international attention when it was shown to have an antioxidant capacity almost double green tea extract and 400% higher than vitamin C [41].

Mediterranean diet contains high consumption of olive products constitute a rich source of polyphenols such as oleuropein and its derivatives including hydroxytyrosol [42].

Oleuropein exhibits antioxidative, anti-ischemic, hypolipidemic and cardioprotection effects [43].

The pretreatment with olive leaf extract dietary may reduce infarct volume, brain edema, blood brain permeability, and neurobehavioral deficit scores in a reliable and reproducible animal model of stroke followed by reperfusion [44].

The administration of olive leaf extract down regulates the expression of tumor necrosis factor-β. Therefore, necrosis factor-β activation and the formation of lipid peroxidation are inhibited. Oxidative stress *via* increased production of ROS and low density lipoprotein oxidation induces inflammatory response; olive phenols with high antioxidant capacity can thus inhibit low density lipoprotein oxidation and block inflammatory response [45].

Pretreatment with olive leaf extract increased cholesterol, cholesterol ester, phosphatidylcholine, and cerebroside levels of brain. Pretreatment with olive leaf extract significantly decreased the brain ceramide levels [46]. Brain ischemia and reperfusion results in rapid accumulation of free fatty acids including arachidonic acid and docosahexaenoic acid as a consequence of the activity of both phospholipase A_2 and phospholipase C. Arachidonic acid has been implicated as a causative factor to stimulate sphingomyleinase to produce ceramide. Ceramide induces apoptosis by inhibiting the mitochondrial electron transport and releasing cytochrome C. Cytochrome C in turn initiate the apoptotic cellular cell death cascade by activation of caspase3 [47]. Olive leaf extract mediated neuroprotection is due to the increase of brain phosphatidylcholine levels [46].

3.8. Oil of O. europaea

Olive oil is a fat obtained from the olive (the fruit of *O. europaea*; family Oleaceae), a traditional tree crop of the Mediterranean Basin. Olive oil is used throughout the world.

There are many different olive varieties or olives, each with a particular flavor, texture and shelf-life [48].

The Mediterranean diet, rich in virgin olive oil, improves the major risk factors for cardiovascular disease, such as the blood pressure, glucose metabolism, lipoprotein profile, and antithrombotic profile. Inflammation and oxidative stress are also positively modulated. Some of these effects are attributed to minor components of virgin olive oil. Therefore, the definition of the Mediterranean diet should include virgin olive oil [49].

A key component of this diet is olive oil, which contains monounsaturated fatty acids and polyphenols, compounds with a clear antioxidant effect. Tyrosol and hydroxytyrosol are two such olive oil phenolic compounds; hydroxytyrosol administration increased plasma antioxidant capacity and lowered production of pro-inflammatory and pro-thrombotic mediators in experimental animals [50].

The pretreatment with dietary virgin olive oil reduced infarct volume, brain edema, blood–brain barrier permeability, and neurobehavioral deficit scores in animal model of stroke followed by reperfusion. Dietary virgin olive oil can affect brain water content and brain water homeostasis by increasing blood brain permeability integrity. The neuroprotection exerted by virgin olive oil was mainly seen in the penumbra (cortex). The lack of protective effects in the subcortical area could be due to the more severe damage in the subcortical area than in the cortex. The virgin olive oil mediated neuroprotection is due to the reduction of post-ischemic infarct volume and brain edema [51].

Histological analysis indicated that the disruption of the myelin structure occurs during the final period of ischemic tissue injury and myelin is more resistant to ischemic injury than other parts of neurons. Sulfatides and galactocerebrosides are the major lipid constituents of myelin sheath. Concentrations of cerebrosides and sulfatides are decreased during ischemia [52]. However, virgin olive oil consumption at 0.75 mL/kg/day can increase brain cerebroside levels [53].

3.9. 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. Some species produce colored bracts at the apices. The flowers may be blue, violet or lilac in the wild species, occasionally blackish purple or yellowish [54].

L. officinalis is well known as a powerful aromatic and medicinal herb. The plant is used in traditional and folk medicines of all over the world for the treatment of several gastrointestinal, nervous and rheumatic disorders [55].

Lavender is comprised of over 100 constituents, among which the primary components are linalool and linalyl acetate, α-pinene, limonene, 1, 8-cineole, cis-and trans-ocimene, 3-octanone, camphor, caryophyllene, terpinen-4-ol, and flavonoids [56].

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 [57].

The treatment with lavender oil significantly decreased neurological deficit scores, infarct size, the levels of MDA, carbonyl and ROS, and decreased neuronal damage, upregulated super oxide dismutase, catalase, glutathione peroxidase activities and glutathione/oxidized glutathione ratio. The neuroprotective effects of lavender oil against cerebral ischemia/reperfusion injury may be attributed to its antioxidant effects [58].

3.10. Baicalin and jasminoidin

Baicalin and jasminoidin are two major compounds extracted from Chinese herbs. Baicalin is extracted from the dried root of *Scutellaria baicalensis*, but jasminoidin is extracted from the dried fruit of *Gardenia jasminoides* Ellis [59]. The baicalin and jasminoidin could markedly decrease the infarction area in the rat brain [60]. In animal model of stroke, baicalin could decrease the lipid peroxidation and the releases of glutamate

and aspartate in the brain tissue. Baicalin showed the ability to interfere with its activations to N-methyl-D-aspartate receptor and nitric oxide synthase [61].

Jasminoidin could reduce the expression of monocyte chemoattractant protein-1 in ischemic brain in rats. Baicalin and jasminoidin attenuate the infarction volume in rat brains subjected to focal ischemia. The combined treatment of baicalin and jasminoidin resulted in significant decrease in infarction volume compared with that treated with baicalin or jasminoidin individually [60].

Baicalin markedly increased brain-derived neurotrophic factor (BDNF) mRNA expression in the hippocampus in rats undergoing focal cerebral ischemia–reperfusion injury; both baicalin and jasminoidin decreased caspase-3 mRNA expression [60]. BDNF and caspase-3 represent ameliorated and deteriorated orientations in the course of cerebral ischemic damage, respectively. BDNF can protect cell from ischemia, and inhibit cell apoptosis [62].

4. Conclusion

Medicinal plants play an important role in the treatment of many incurable diseases like neurological disease [63–71]. Since brain ischemia and reperfusion is a complex progressive injury involving a series of mechanisms such as cell survival and apoptosis, ROS accumulation, Ca^{2+} overload, inflammation, microglia aggregation, *etc.*, it is difficult to describe the mechanisms of protective agents against ischemia and reperfusion. In conclusion, development of protective agents from traditional herb medicine is a promising direction in the treatment of ischemic cerebral injury and related neurodegenerative diseases. In the future, more attention should be paid to natural compounds that can transverse the blood–brain barrier and have wide therapeutic time windows, clear pharmacological targets and fewer side effects.

Conflict of interest statement

We declare that we have no conflict of interest.

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