WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 5.045
Volume 4, Issue 2, 1653-1667. Research Article ISSN 2277– 7105

CEREBRAL ISCHEMIC-REPERFUSION INJURY AND NEUROPROTECTIVE ACTIVITY OF HERBAL DRUGS

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Article Received on
09 Dec 2014,

Revised on 03 Jan 2015,
Accepted on 28 Jan 2015

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ABSTRACT

Cerebral ischemia/reperfusion injury is one of the leading causes of human death and disability throughout the world and has attracted more and more attention in the field of drug discovery. Focal (stroke) and Global (cardiac arrest) cerebral ischemia represents diseases that are common in the human population. Stroke and cardiac arrest, which are major causes of death and disability, affect millions of individuals around the world and are responsible for the leading health care costs of all diseases. After cerebral ischemia/reperfusion, the reactive oxygen species production is dramatically increased and overwhelms endogenous antioxidant systems, leading to oxidative stress. The brain is particularly vulnerable to oxidative stress injury due to its high consumption of oxygen, abundant polyunsaturated fatty acids and low levels of endogenous antioxidants. Antioxidants are significant substances which can protect the body from oxidative damage. The extensive prescription of synthetic antioxidants is ruled out owing to their toxicity and unavoidable side effects. There is an increasing interest in the use of natural antioxidants for prophylaxis or treatment of oxidative stress-related diseases. According to the pharmacological mechanisms underlying neuroprotection, we evaluated some important natural drugs from traditional medicinal herb that posses the neuroprotective effects on cerebral ischemic-reperfusion injury.

KEYWORDS: Cerebral ischemia, Oxidative stress, Herbal drugs, Stroke.

INTRODUCTION

Stroke was the leading cause of death 30 years ago when hypertensive intracerebral hemorrhage was the most common cause of stroke deaths. At present, stroke is the second leading cause of death in most of the countries; it ranks behind only cancer deaths. The

decline in the death rate from stroke over the last 20 years has been attributed to improved control of hypertension and advances in the management of cerebral hemorrhage in the acute stage. However, the incidence of cerebral infarction resulting in disability in the survivors of ischemic stroke appears to be on the increase, at a time when the proportion of elderly individuals is rapidly increasing in India.[1] Of all types of stroke, the incidence of hemorrhagic cerebrovascular disease, including subarachnoid hemorrhage and intracerebral hemorrhage, is about 20-25%; the incidence of ischemic stroke is 75-80%. By 2020 heart disease and stroke will become the leading cause of death and disability worldwide with the number of fatalities projected to increases to over 20 million a year and by 2030 to over 24 million a year.[2] The increase in the number of individuals with mental and physical handicaps after stroke presents considerable problems in terms of quality of life and socioeconomic costs.

Permanent brain damage caused by ischemia and reperfusion accompanies disease processes such as stroke and resuscitation from cardiac. In ischemic stroke, only part of the brain is involved, and the ischemia is dense or complete only in the center of the affected area. This area of dense ischemia is surrounded by a penumbral zone in which the blood flow is diminished but not completely lost. In cardiac arrest and resuscitation, the entire brain is subjected to a transient period of complete ischemia followed by reperfusion.[3, 4]

During reperfusion after ischemia, while restoration of oxygen and glucose supply reinstates the oxidative phosphorylation that helps to normalize energy demanding physiologic processes, a parallel cascade of deleterious biochemical processes can be triggered that may paradoxically antagonize the beneficial effect of reperfusion.[5, 6]

This phenomenon has been demonstrated in various tissues, especially in the brain, and has been termed reperfusion injury (RI).[7] The understanding and treatment of RI is an important objective in the new era of reperfusion therapy for stroke. Recently it is demonstrated that 3 hours of focal ischemia followed by 3 hours of reperfusion in the rat produces more damage than 6 hours of continuous ischemia without reperfusion.[8]

Global and Focal cerebral ischemia

Ischemia is defined as diminution of cerebral blood flow (CBF) to a critical threshold that propagates brain damage involving the entire brain or a selective region. Global cerebral ischemia entails diminution in CBF over the entire brain, encountered clinically as sequelae

during extracorporeal circulation following cardiac arrest (CA) from ventricular fibrillation or asystole that lasts 5 to 10 minutes. Global ischemia from CA results in a predictable pattern of histologic injury in which specific neuronal populations are affected (selective ischemic necrosis) [9-11]. Although reperfusion restores CBF and it can lead to secondary brain injury from influx of neutrophils and to increases in reactive oxygen species (ROS), cerebral edema and hemorrhage. Elevated levels of ROS may lead to damage of intracellular proteins and DNA by way of oxidation and by activating a number of pathways that lead to cell death. Unlike global cerebral ischemia, focal cerebral ischemia entails reduction in regional CBF in a specific vascular territory and is usually encountered clinically as an ‘‘ischemic stroke’’ due to thromboembolic or artherothrombotic vaso-occlusive disease. Normal CBF ranges from 50 to 75 ml/100 g of brain tissue per minute and can differ between the white and gray brain matter. Ischemic depolarization occurs when CBF decreases to levels of approximately 18 ml/100 g of brain tissue per minute, and neuronal cell death ensues if CBF is less than 10 ml/100 g of brain tissue per minute. In focal ischemia, the ischemic vascular bed comprises an area with severe CBF reduction that consists of an ‘‘ischemic core’’ and a more distal ‘‘ischemic penumbra’’ and includes regions that are marginally perfused and might be served by collateral vascular channels. Histopathologic outcome following focal ischemia largely depends on ischemic severity and duration. Increasing durations of depolarizing ischemia are associated with a spectrum of histopathologic correlates from reversible injury to irreversible cerebral infarction.[9, 12]

In spite of the growing understanding of the mechanisms of neuronal damage and death accompanying brain ischemia and reperfusion, effective therapy has remained elusive. Preclinical and clinical trials of calcium channels blockers have shown some evidence of neuronal protection. Drugs that block glutamate receptors have been largely ineffective in neuronal preservation after complete ischemia, although they appear somewhat more promising in neuronal salvage in the penumbral zone surrounding the area of severe ischemia in stroke models.

Drugs directed at inhibiting radical reactions either by inactivating the iron or by directly inactivating the radical species do appear to reduce biochemical evidence of cellular damage during post ischemic reperfusion but show only marginal effects in the preservation of neuronal viability and brain function. The most obvious strategy to counteract ongoing ischemia caused by vascular occlusion is to recanalize the obstructed vessel. Spontaneous

recanalization caused by endogenous thrombolysis is a complex process that depends on the size, composition, and anatomic location of the thrombus, and frequently takes hours to days to occur.[13] Numerous preclinical and clinical studies using thrombolytic agents, especially tissue plasminogen activator, demonstrated pharmacological recanalization and restoration of cerebral circulation (reperfusion) within minutes of the onset of treatment. Tissue plasminogen activator recently was shown to be effective and approved for urgent treatment of ischemic stroke in humans. Because recanalization of occluded vessels in the clinic is becoming a daily practice, careful inspection of the possible negative influence of reperfusion (apart from the risk related to hemorrhage) must be taken into consideration.[14]

The lack of effective, widely applicable and safe pharmacological treatments for ischemic stroke patients may explain a growing interest towards the traditional medicines, for which extensive observation and vast experience has accumulated over the past years. It has been suggested that some herbal medicines or their products, may improve microcirculation in the brain, protect against ischemic reperfusion injury, possess neuroprotective properties and inhibit apoptosis, thus justifying their use in ischemic stroke patients.[15, 16]

The details of plants showing protection against cerebral ischemic-reperfusion injury along with their name of families, used parts, system of medicine, type of extracts including responsible active chemical constituents, induction model of cerebral injury and neuroprotective activity with their possible mechanism/ outcomes are discussed in table 1.

Table 1: Details of plants showing neuroprotection against cerebral ischemic-reperfusion injury

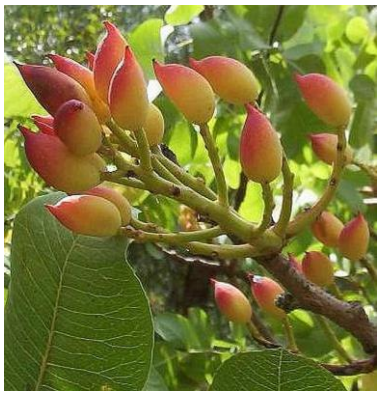
Name of Plant	Family/ Species	Part used	Locality/ system of medicine	Extract/ known Responsible chemical constituents	Model of cerebral injury	Possible mechanism/out comes
Pistacia vera L.	Anacardiaceae	Gum	Iran	Ethanolic & aqueous extract	Four-vessel occlusion model	Increases antioxidant defense and suppressed free radical production in brain [17].
Olea europaea L.	Oleaceae	Leaf	Serbia	Ethanolic extract/ Oleuropeine, Iridoide Monoterpenes	Global ischemic model	The extract having potent antioxidative Properties [18].
Wedelia calendulacea	Asteraceae	Stem	India	Methanolic extract/ Wedelolactone	Bilateral common carotid artery (BCCA) occlusion induced global cerebral ischemia model	Wedelolactone and norwedelo-lactone are mainly responsible for neuroprotection [19].
Phoenix dactylifera L.	Arecaceae	Fruits	Arabian gulf	Methanolic extract/ Dactyiferic acid & Flavonoid glycoside	BCCA occlusion model	Potent action by their high polyphenolic Content [20].
Moringa oleifera Lam.	Moringaceae	Leaves	Thailand	Alcoholic extract/ Betacaroten	MCCA (middle common carotid artery) occlusion induced focal ischemia	Extract contain Betacaroten, vitamin C & vitamin E responsible for stroke model [21].
Punica granatum	Punicaceae	Fruit	India	Aqueous extract	Global ischemia	Extract decreases the brain levels of NF-κB p65, TNF-α and increases level of IL-10 in stroke condition [22].
Embelia ribes Burm	Myrsinaceae	Fruits	India	Aqueous extract	Rt. MCCA occlusion induced focal ischemia	Promising shrub that increased the activity of endogenous antioxidant enzymes [23].
Centella asiatica	Umbelliferae	Whole herb	India	Methanolic extract/ Madecassoside	BCCA occlusion model	Madecassoside reduced the levels of malondialdehyde nitric oxide,

						pro-inflammatory cytokines and NF-κB p65 in ischemic condition [24].
Hypericum perforatum	Hypericaceae	Whole Plant	Ayurveda	Ethanolic extract/ Hyperforin	BCCA occlusion induced global cerebral ischemia	The presence of hyperforin in extract, increases in cyclic AMP levels that reversing the stroke [25].
Ocimum basilicum L.	Lamiaceae	Leaf	India	Ethyl acetate extract	Global cerebral ischemia	Plant showing the reduction of cerebral infarct size and lipid peroxidation, restoration of GSH content, and attenuation of motor dysfunctions [26].
Pongamia pinnata (L) Pierre	Leguminosae	Root	Ayurveda	Ethanolic extract	BCCA occlusion induced global cerebral ischemia	Bioflavonoid contents of the root improved cerebral perfusion and microcirculation by inhibiting the lymphatic infiltration, astrocytosis & edema [27].
Eclipta alba (Linn.) Hassk	Asteraceae	Aerial part	India	Hydroalcoholic extract/ Wedelolactone	Global cerebral ischemia	The presence of Wedelolactone, that inhibit the pro-inflammatory cytokine IL-1β maturation and pathological neuronal apoptosis [28].
Withania somnifera Dunal	Solanaceae	Root	Ayurveda	Aqueous extract/ Sitoindosides VII-X & Withaferin A	Acute ischemia-reperfusion injury induced by BCCAO model	Plant shows beneficial in learning & memory symptoms of stroke [29].
Araucaria bidwillii Hook	Araucariaceae	Leaves	Himalaya regions	Ethyl acetate extract/ Biflavone	Global ischemia	Extract Inhibit the free radical generation, reactive oxygen species scavenging and modulation of Intracellular antioxidant [30].
Artemisia absinthium L.	Asteraceae	Aerial part	Traditional Chinese	Methanolic extract/ Flavonoid	MCCA occlusion induced focal ischemia	Plant markedly reduced brain infarction, oxidative stress and also

			medicine			improved behavioral outcome during cerebral I/R injury [31].
Momordica charantia L.	Cucurbitaceae	Fruits	Asia, Africa and Latin America	Lyophilized juice/ Charantin, insulin-like peptide, Cucurbutanoids, Momordicin	BCCAO induced global ischemia	Potent action due to its high reactive oxygen species scavenging activity [32].
Cordyceps militaris	Cordyceps	Fungus	Traditional Chinese medicine	Aqueous extract/ Cordycepine	Global ischemia	The active cordycepine decreases the excitotoxicity of excitatory amino acids, inhibit the production of the matrix metalloproteinase -3 as well as block free radicals in stroke model [33].
Lithospermm erythrorhizon	Boraginaceae	Root	Traditional Chinese medicine	Maize oil extract/ Shikonin	Focal ischemia	Antioxidant ability appears to be a basic and important mechanism of the neuroprotective effect of shikonin [34].
Hemidesmus indicus	Asclepideaceae	Root	Ayurveda, Unani & Siddha	Methanolic extract	Four-vessel occlusion model	Drug decreases in the levels of Cholinesterase, Glutamate, Mono amino Oxidase-B, increases in levels of dopamine & serotonin, both ways get beneficial effect in stroke patients [35].
Ageratum conyzoides L.	Compositae	Whole plant	Kenya	Pet. Ether extract	BCCAO induced Global ischemia	Plant shows the reduction in behavioral score, hyper locomotion and neuronal damage in brain injury [36].
Vanda tessellata	Orchidaceae	Leaves	Ayurveda & Unani	Pet. Ether extract	Global ischemia	Plant possesses significant activity against ischemic injury [37].
Allium sativum L.	Alleaceae	Fruits	India	Aqueous extract	Focal ischemia	Extract improves neurobehavior and decreases glutamate and

						aspartate levels, possibly by increasing the endogenous defensive capacity of the brain [38].
Nigella sativa L.	Ranunculaceae	Seeds	Iran	Aqueous and ethanolic extracts	Four-vessel occlusion model	Both extract shows potent anti ischemic activity [39].
Allium cepa L.	Alleaceae	Bulb (outer scales)	India	Methanolic extract & Flavonoid rich fraction	Global ischemia	Flavonoid rich fraction reduced the cerebral damage and oxidative stress [40].
Angelica Sinensis Diels	Umbelliferae	Whole plant	Traditional Chinese medicine	Ligustilide	MCCAO induced focal ischemia	Ligustilide promoting EPO transcription *via* an ERK signaling pathway and inhibiting RTP801 expression in ischemic disorders [41].
Litsea coreana leve	Lauraceae	Aerial part	Traditional Chinese medicine	Total flavonoid fraction	Focal ischemia	Flavonoid suppressed the increase in the levels of nitrates, malondialdehyde and lactate dehydrogenase in cerebral injury [42].
Vitis vinifera L.	Vitaceae	Seed	Ayurvedic medicine system	Ethanolic extracts	Global ischemia	Promising effects of seed might be attributable partly to its antioxidant capacity and inhibitory effect on glutamate activities in the brain [43].
Cyperus rotundus	Cyperaceae	Rhizoms	Ayurvedic medicine system	Ethanolic extracts	Global ischemia	Extract can reduce the ischemia-induced apoptosis in CA1 sector of hippocampus after transient, global cerebral Ischemia [44].
Luffa acutangula	Cucurbitaceae	Whole plant	Tirupati, India	Petroleum ether extract	BCCAO ischemic model	Proves beneficial in hyper locomotion & brain damage [45].
Melissa officinalis	Labiatae	Leaves	Iran	Aqueous extract	Global ischemia	protective effect of leaves on ischemia due to inhibition of (hypoxia-inducible factor) HIF-1α, oxidative stress & apoptosis [46].

Achyrocline satureioides (Lam.) DC. (marcela)	Asteraceae	Flower	Uruguay	Aqueous extract/ Quercetin	Focal ischemia	Quercetin is responsible for the preventive benefits of extract due to the antioxidant and anti inflammatory Properties [47].
Dalbergia latifoliais	Fabeceae	Bark	Bundelkhand and Central India	Methanolic extract/ Flavonoid	Global ischemia	Flavonoid fraction prevents the cerebral injury *via* potent antioxidant property [48].
Kaempferia parviflora	Zingiberaceae	Rhizo-mes	Thailand	Ethanolic extracts/ Dimethoxy flavone	MCCAO induced focal ischemia	Extract inhibit over production of cytotoxic nitric oxide, enhance free radical scavenger and antioxidant activity [49].
Ginkgo biloba	Ginkgoceae	Leaf	Traditional Chinese medicine	EGb761 extract	MCAO model	EGb761 enhance the endogenous protective Gene, Heme oxygenase (HO-1) and reduced brain damage [50].



Pistacia vera L.

Olea europaea L.

Wedelia calendulacea

Phoenix dactylifera L.

Punica granatum

Embelia ribes

Pongamia pinnata

Withania somnifera

Momordica charantia L.

Lithospermum erythrorhizon

Allium sativum L.

Allium sativum L.

Vitis vinifera L. *Melissa officinalis* *Dalbergia latifoliais*

Figure 1: Parts of plants (selected) which are showing the Neuroprotective activity.

CONCLUSION

Herbs are staging a comeback and herbal 'renaissance' is happening all over the globe. The herbal products today symbolize safety in contrast to the synthetics that are regarded as unsafe to human and environment. Currently, there is an enormous increase in the use of herbs and other alternative medicines in the treatment of several disorders. As newer technologies developed, tremendous scope for further scientific exploration of therapeutic efficacy of herbal drugs generated. A review of the literature indicates that the medicinal plants are may be the most prolific source for treatment of stroke or related disorders. The Chinese and Indian system of medicine, especially Ayurveda, has several medicinal plants with proven beneficial claims towards these pathological conditions. The present paper directly reviewed and documented information on over medicinal plant species with links to cardiac arrest and stroke. Herbal extracts represent combinatorial chemistry of nature with vast complex effect on numerous cellular components and functions. There also difficulty in standardization, pharmacodynamics and pharmacokinetics of these herbal drugs. Therefore, the efficacy of herbals in the treatment of stroke needs to be further explored.

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