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Review Article

## A Review on Herbal Plants used in Brain Ischemic and Reperfusion Injury

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### ABSTRACT

A stroke causes serious and long term brain disability due to disruption in the blood flow to the brain. Clinically major changes occur in brain functions are seen after brain ischemia and reperfusion. Patients show emotional, behavioural, and cognitive alterations during retrieval time. Cerebral injury by transient ischemia distresses the number of patients globally with death or long term disability. In recent years a great deal of research has been carried out to find the effectiveness of the herbal drug for the treatment of stroke. Both thrombolytic and neuro-protective activities of herbal drugs may be a new strategy for effective stroke treatment. This article reviews the list of universally used plants effective for brain stroke therapies. The purpose of this article was to collect the herbal drugs useful in brain stroke therapies.

**Keywords:** ischemia-reperfusion, brain injury, stroke, herbal drugs, tissue

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### Introduction

A **stroke** is a medical condition in which flow of blood is poor to the brain results in cell death. Stroke plays a central role in public health. More than 80% of all stroke events is due to ischemic stroke, causing a transient or permanent reduction in cerebral blood flow. Most of the cases are caused by thrombotic occlusions. 600,000 people suffering from stroke every year with serious, long-range disability by stroke <sup>1</sup>. Difficulties like Memory, thinking, talking, and partial paralysis and mobility problems caused by stroke <sup>2</sup>. Ischemia-reperfusion injury is a condition in which physicians control the damage to cells and organ preservation for the function of tissue and organ during storage so that the graft will function at re-perfusion. Ischemia is defined as the reduced amount of blood flow (hypoperfusion) of tissue. Tissue hypoperfusion may cause various conditions, like sepsis, acute coronary syndrome, organ transplantation and limb injury; studies suggested that reducing the time of blood flow to preserve the function of tissue and organ. Stroke is the rapid development of focal and global disorder of brain function, with various symptoms that can earlier more than 24 h or cause death, with no obvious cause other than the vascular origin <sup>3</sup>. Intravenous

recombinant tissue plasminogen activator (rt-PA) is the only drug used for the thrombolytic treatment of acute ischemic stroke. rt-PA decreases neurological injury and enhances the functional outcome of stroke survivors. Only 6% of patients are survivors, many patients with brain stroke do not reach the hospital within time, that's why most patients do not receive rt-PA treatment <sup>4</sup>.

Neutrophils utilize the vicious capabilities of free radicals to kill the bacteria, and there is confirmation that they also act on reper fused tissue. Morphological injury to the muscle fibers was evident only after reperfusion. Muscles biopsies showed that infiltration with granulocytes, mainly neutrophils, throughout ischemia and reperfusion and enhance the number of circulating neutrophils. It confirmed that neutrophils entered the cardiac tissue during reperfusion. Ischemia may accumulate neutrophils in such numbers that they block the microvasculature <sup>5</sup> and also seems to be associated with endothelial damage and also part of the inflammatory response, coordinated by a network of inflammatory cytokines and chemokines that is not absolutely understood. A rat leg model of ischemia/reperfusion is used to study the kinetics of cytokine production by some scientist. Reperfusion

increased markedly the level of IL-1, TNF-alpha and IL-6. TNF-alpha and IL-1 level reach at high after two hours and IL-6 continued to rise throughout the four hour recording period. Additionally, the amount of damage to both the leg muscles and the lungs was decreased significantly by antibodies to IL-1 and TNF, by IL-1 receptor antagonist and by soluble TNF receptor. Where large volumes of tissue are reperfused, as in this study, the post-ischemic syndrome may develop. There are many features with the systemic inflammatory response syndrome (SIRS) that occurs in sepsis, as well as respiratory and other organ disorder, and it is in the same way related with an increased level of inflammatory cytokines in the systemic circulation. Further move towards decreasing neutrophil-mediated reperfusion injury is to reduce neutrophil infiltration of the ischemic tissue. Adhesion molecules are essential for neutrophils to extravasate, and numerous studies have shown that the levels do certainly increase during ischemia/reperfusion. As a result, antibodies to adhesion molecules, including ICAM-1 and P-selectin, have been tried as possible therapies in animals, with significant success. A selectin blocker that binds to the neutrophil ligand for both E- and P-selectin also decreased infarct size <sup>6</sup>.

Presently, there are no clear cut therapies as per studies of reperfusion injury and attempts to control it. Probably due to a variety of experimental protocols, none of the potential therapies to bound the production of free radicals on reperfusion has been constantly advantageous in controlled trials. The association of inflammatory cytokines and their effects on neutrophils is a relatively current discovery, and it opens a new possibility for investigation. Conceivably in the longer term, better techniques for fast reperfusion with the use of anti-oxidants and neutrophil inhibitors will cut the massive cost.

### Pathogenesis of Brain Ischemia-reperfusion

In brain, intracellular cell death signalling pathways may lead to the death of cells due to ischemia <sup>7</sup>. Reduced cerebral blood circulation in the region of the brain that is comfortable with oxygen by the occluded vessels in case of focal/global cerebral ischemia <sup>[7]</sup>. Ischemia and post-ischemic reperfusion injured brain capillaries result in a progressive alteration in the permeability of the blood-brain barrier (BBB) that can later consequence in the development of edema and hemorrhagic conversion. Substances such as Na<sup>+</sup>, water, serum proteins, and blood infiltrate into the extracellular space of the brain tissue and cause swelling in case of changing the BBB permeability <sup>8-10</sup>. Swelling is deadly for cerebral tissue as its effects on neighbouring tissues are also magnified by the proper volume of the skull. Swelling of cerebral tissue induced by brain ischemia and reperfusion apply an involuntary force on the nearby shell of brain tissues, displacing it and causing ever-increasing tissue pressure within it. The pressure of brain tissue exceeds capillary pressure; increased capillary infiltration is compromised and cause ischemia and development of edema <sup>11</sup>.

The use of glucose in the brain is rise considerably during brain ischemia, by the dependence of brain on anaerobic glycolysis, due to this brain glucose levels fall rapidly, in spite of near-normal plasma levels <sup>12</sup>. A complex cascade of metabolic events initiated during brain ischemia and reperfusion, most of involve in the manufacture of nitrogen and oxygen-free radicals. These free radicals arbitrate more damages that occur subsequent transient brain ischemia <sup>13</sup>. The diminish in cerebral blood flow and oxygen consumption initiates a cascade of harmful biochemical actions during brain ischemia. Decrease of oxygen precludes oxidative phosphorylation and consequence in anaerobic metabolism <sup>14</sup>. The mitochondrial respiratory chain is the origin for the formation of reactive oxygen species (ROS) and following the damage of the mitochondria, necrotic cell death occurs. Death of endothelial cells causes harm to blood-brain barrier resulting in cerebral edema <sup>15</sup>. Failure of transcellular ion pump outcomes in the intracellular accumulation of Na<sup>+</sup>, Ca<sup>2+</sup> and water. The membrane depolarization results in the release of excitatory neurotransmitters from axon terminals. The glutamate then activates specific cell surface receptors resulting in an influx of Na<sup>+</sup> and Ca<sup>2+</sup> 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 attach with superoxide the proxy nitrites have formed that lead to lipid peroxidation <sup>16</sup>. 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 <sup>17</sup>.

The traditional medicine all over the globe is at the present time revalued by an extensive performance of the research on the different plant species and their potential. Herbal drugs have gained a lot of approval in recent years just because they have higher therapeutic potential, minute side effects and economically. Herbs may afford a source of various types of new compounds including many drugs that are derived from plant sources.

### Conclusion

Herbal drugs play a vital role in the management of deadly neurological diseases. As brain stroke is a complex progressive injury relating to numerous mechanisms. The progress of neuroprotective agents from the herbal plant is a promising way in the treatment of brain stroke and related neurodegenerative diseases. In the future, more concentration should be paid to herbal compounds that can slant the BBB and have broad therapeutic time windows, accurate pharmacological targets and lesser side effects.

### Conflict of interest statement

We declare that we have no conflict of interest.

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**List of plants on which study has been done:**

S. No.	Name of the plant	Family	Common name	Plant part used	Extracts studied	References
1.	<i>Gastrodia elata</i>	Orchidaceae	Tianma	Herb Herb	Ethanolic extract	Jivad N, Rabiei Z et al., 2015. <sup>18</sup> Wang D et al., 2019 <sup>19</sup>
2.	<i>Ginkgo biloba L</i>	Ginkgoaceae	Maidenhair tree	Herb	Ethanolic extract	Jivad N, Rabiei Z et al., 2015. <sup>18</sup>
3.	<i>Panax ginseng</i>	Araliaceae	Korean ginseng	Roots	Ethanolic extract	Shamim M et al., 2019 <sup>20</sup>
4.	<i>Anchusa</i>	Boraginaceae	Bugloss	Flower	Ethanolic	Torki A et al., 2018 <sup>21</sup>
5.	<i>Danshen and Gegen</i>	Lamiaceae	Red sage, Chinese sage or Tan shen	Herb	Ethanolic	Deng Y et al., 2018 <sup>22</sup>
6.	<i>Lavandulaofficinalis</i>	Lamiaceae	English Lavender	Herb	Lavender oil	Jivad N, Rabiei Z et al., 2015. <sup>18</sup>
7.	<i>Withaniacoagulans</i>	Solanaceae	Indian cheese maker	Roots	aqueous extract	Sagheb H M et al., 2017 <sup>23</sup>
8.	<i>Vitisvinifera</i>	Vitaceae	Grape	Fruit	Ethanolic	Sarkaki A et al., 2016 <sup>24</sup>
9.	<i>Bacicalin &amp; Jasminoidin</i>	Lamiaceae & Rubiaceae	Cape jasmine, Gardenia	Root & Fruit	Ethanolic	Jivad N, Rabiei Z et al., 2015. <sup>18</sup>
10.	<i>Oil of O.europaea</i>	Oleaceae	Wild olive, Indian olive	Leaf	Olive oil	Jivad N, Rabiei Z et al., 2015 <sup>18</sup>
11.	<i>Nigella sativa</i>	Ranunculaceae	Black caraway or Kalonji	Leaf	Aqueous	Hobbenaghi R et al., 2014 <sup>25</sup>
12.	<i>Camellia sinensis</i>	Theaceae	Tea shrub , Tea tree	Leaf Leaf	Green tea	Jivad N, Rabiei Z et al., 2015. <sup>18</sup> Chakraborty M et al.,2014 <sup>26</sup>
13.	<i>Rosa laevigataMichx</i>	Rosaceae	Cherokee rose	Fruit	Flavonoid rich-extract	Zhang S et al., 2013. <sup>27</sup>
14.	<i>Punicagranatum</i>	Punicaceae	Anar	Seeds	Hydro-alcoholic	Sarkaki A et al., 2013. <sup>28</sup>
15.	<i>Zingiberofficinale</i>	Zingiberaceae	Ginger	Fruit	Aqueous	Jittiwat J et al., 2012. <sup>29</sup>
16.	<i>Apocynumvenetum</i>	Apocynaceae	Sword-leaf dogbane	Leaf	Hydro-alcoholic	Xiang j et al., 2012. <sup>30</sup>
17.	<i>Ocimum sanctum</i>	Lamiaceae	Holy basil or Tulsi	Leaf	Fresh juice	Jivad N, Rabiei Z et al., 2015. <sup>18</sup>
18.	<i>Ocimumbasilicum</i>	Lamiaceae	Sweet basil, Common basil, Thai basil.	Leaf	Ethyl acetate	Jivad N, Rabiei Z et al., 2015. <sup>18</sup>
19.	<i>Artemisia absinthium</i>	Asteraceae	Worm wood, Grand worm wood	Herb	Ethanolic	Jivad N, Rabiei Z et al., 2015. <sup>18</sup>
20.	<i>Oleaeuropaea</i>	Oleaceae	Wild olive, Indian olive, Brown olive	Leaf	Olive leaf	Jivad N, Rabiei Z et al., 2015. <sup>18</sup>

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