IJP (2018), Vol. 5, Issue 3 **(Review Article)**

IJP International Journal of Pharmacognosy

Received on 10 October 2017; received in revised form, 12 November 2017; accepted, 18 November 2017; published 01 March 2018

THE ROLE OF HERBAL COMPOUNDS IN THE TREATMENT OF CEREBRAL ISCHEMIA

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Keywords:

Stroke, Cerebral ischemia, Oxidative stress, Natural product

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ABSTRACT: Stroke is the sudden blockage or rupture of cerebral arteries that can lead to cerebral damage or clinical neurologic deficit. Generally, stroke is as ischemic and hemorrhagic. Ischemia caused by factors such as thrombosis, embolism, and systemic hypoperfusion. Stroke is one of the most important factors of mortality and disability worldwide. After a stroke, an increase of free radicals has the most important role in the breakdown of blood-brain and increase of cerebral edema. This study aimed to review the effect of compounds isolated from plants to reduce cerebral ischemia. Our review showed that natural compounds could exert a protective effect by reduction of oxidative stress and events related to it. We also suggest that consider special attention to natural product for the treatment of cerebral ischemia.

INTRODUCTION: As defined by the World Health Organization (WHO), stroke is the rapid loss of brain function during the impairment of brain perfusion [1]. Stroke is the main cause of mortality and disability and commonly occurs during the elderly so that it burdens high expenditure to health field to the reduction of complications related to stroke [2]. These patients are prone to other problems such as pneumonia and urinary tract infection and pulmonary embolism and foot deep vein thrombosis, and these complications can be reasons for mortality in patients [3]. Stroke is along with weakness, paralysis, numbness, and loss of sensation in the hands and feet at a side of the body and inability in cognitive and speech and visual and balance [4]. Patients with moderate to severe stroke are usually hospitalized and the possibility of again stroke at the patient is low but the possibility of dying in the first month after stroke is % 50 [5].

QUICK RESPONSE CODE

DOI: 10.13040/IJPSR.0975-8232.IJP.5(3).117-22

The article can be accessed online on www.ijpjournal.com

DOI link: http://dx.doi.org/10.13040/IJPSR.0975-8232.IJP.5(3).117-22

Ischemia influences limit and specific part of the brain, for example, internal capsule, caudate nucleus or cortex by middle cerebral artery occlusion. Also, this event can occur temporarily or permanently. The main Characterize of ischemic is inevitable death during the first minutes after the occurrence in regions that reduced blood flow and consequently ATP level. Then around this area, where there is a small amount of blood flow, occur necrosis [6] as well as neurochemical and neuro-inflammation damages [7] **Fig. 1**.

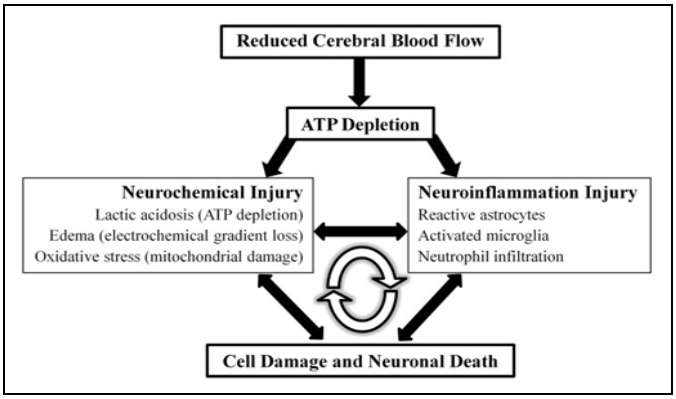

FIG. 1: DETRIMENTAL ACUTE EFFECTS OF ISCHEMIC STROKE CAN BE CONCEPTUALIZED INTO TWO SEPARATE BUT HIGHLY INTER-RELATED PHYSIO-LOGICAL ENTITIES, NEUROCHEMICAL AND NEURO-INFLAMMATION INJURY, THAT ULTIMATELY LEAD TO CELLULAR DAMAGE AND DEATH

Transient cerebral ischemia is characterized by hypoxia in a short period that then produces large amounts of free radicals during long period of reperfusion. This event leads to the destruction of macromolecules such as proteins, nucleic acids as well as membranes. The result of pathophysiologic is variables and depend on the amount affected intracellular organelles and macromolecules [8]. During ischemia, increasing of calcium concentration leads to activation of nitric oxide synthase depended on calmodulin so that non-physiological concentrations of nitric oxide lead to oxidative damage. Also, a combination of superoxide and nitric oxide result in the formation of proxy nitrite and ultimately induction of oxidative damage to macromolecules [9]. Another event that occurs during reperfusion is the increase of reactive oxygen species due to reoxygenation so that their accumulations increase the severity of damage [10] **Fig. 2**.

Nowadays, Studies on the development of neuroprotective agents to treat cerebral ischemia have been focused on antioxidants. Antioxidants have been investigated in many experiments under *in-vitro* and *in-vivo* conditions and have also been conducted several clinical trials [11]. The antioxidant activity of compounds isolated from plants seems very impressive for example flavonoids are known as an important factor to inhibit lipid peroxidation, platelet aggregation, control fragility and permeability of capillaries, cyclooxygenase and lipoxygenase activities.

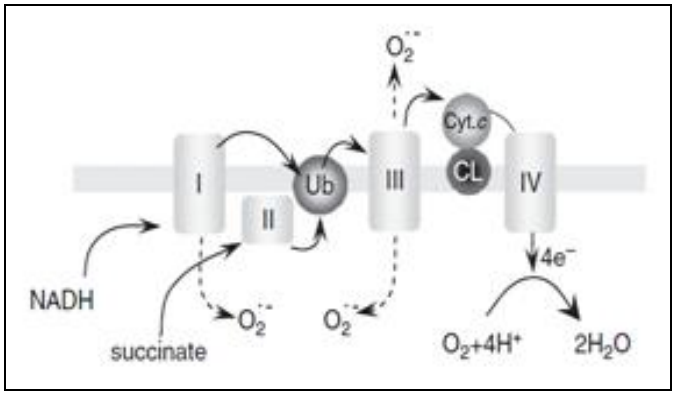

FIG. 2: FORMATION OF REACTIVE OXYGEN SPECIES BY THE MITOCHONDRIAL RESPIRATORY CHAIN. CL, CARDIOLIPIN; CYT. C, CYTOCHROME C; UB, UBIQUINONE

These actions are due to their antioxidant effects and their ability to scavenge free radicals [12-14]. It has been suggested that antioxidant compounds may prevent cerebral brain damage particularly cerebral damage caused by ischemia/reperfusion. Therefore, it would be interesting argue, studying of effects of antioxidants and free radicals radical scavenger, to obtain protective agents of the brain against cerebral ischemia [15]. Here, we reviewed the potential role of compounds derived from plants in the reduction of cerebral ischemia and its complications.

Review Method: In this study, we reviewed papers related to the role of compounds isolated to herb to treat cerebral ischemia. For this purpose, we searched keywords such as plants and cerebral ischemia, natural compounds and cerebral ischemia in databases include a web of science, PubMed and Scopus since from 2000 to 2017.

Natural Compounds and Cerebral Ischemia: Our research group treated rats with transient global cerebral ischemia to metformin as an AMPK activator and determined vascular responses, hyperemia, blood-brain barrier disruption, and electrophysiological activity. The results showed that oral administration of metformin leads to a reduction of blood-brain barrier disruption and reactive hyperemia as well as the increase of spike rates related to electrophysiological records. Our study revealed a regulatory role for AMPK in vascular and electrophysiological responses. Also, metformin can be a useful compound to treat cerebral ischemia [16]. In another study, we investigated the effect of metformin in the regulation of inflammatory and antioxidant pathways in rats with global cerebral ischemia. Our findings showed that pretreatment with metformin leads to a reduction of cellular levels of nuclear factor-κB, Tumor Necrosis Factor-alpha, and cyclooxygenase-2; thus it had a potential anti-inflammatory effect. Also, we found that metformin increases levels of Nrf2 and heme oxygenase-1 in the hippocampus. Metformin also increased the level of glutathione and activity of catalase that indicated its anti-oxidant effect [17].

Our other study about the role of metformin to reduce damages of cerebral ischemia on rats with transient forebrain ischemia confirmed that enhancement of sensory-motor signs; anxiolytic behavior and locomotion result from administration of metformin.

Moreover, levels of autophagy factors (light chain 3B, Atg7, Atg5-12, and beclin-1) increased followed by treatment with metformin [18]. A research group was shown that metformin pretreatment improved cerebral ischemia induced by 4-vessels occlusion in rats through a reduction of apoptosis and promotion of mitochondrial biogenesis proteins [19]. Study on rats with permanent middle cerebral artery occlusion was confirmed that metformin leads to obvious activation of AMPK and induction of autophagy. Also, metformin treatment dramatically reduced infarct volume, neurological deficits and apoptosis.

This study revealed that metformin has an anti-ischemic effect by activation of AMPK in brain [20]. Given that, oxidative stress has a pivotal role in inducing damage during the pathogenesis of ischemic; therefore, its abrogation can be a logical idea to treat ischemia. Metformin is one of the compounds to solve this problem because its oral administration to rats with global cerebral ischemia and ischemia/reperfusion improved injuries related to ischemia-reperfusion through the increase of activation of glutathione peroxidase, superoxide dismutase and catalase and reduction of malondialdehyde [21].

In a study, the effect mechanism of gallic acid on cerebral ischemia/reperfusion injury was evaluated, and results showed that gallic acid has a protective effect in rats with cerebral ischemia/reperfusion injury. Also, *in-vitro* study about the effect of gallic acid on hypoxia / reoxygenation-induced mitochondrial dysfunctions was confirmed that it reduces mitochondrial dysfunction through normalization of mitochondrial membrane potential, mitochondrial permeability transition pore, and ATP level as well as reduction of cell death and ROS level [22]. According to our study on the role of gallic acid against cerebral ischemia subsequently, induction of transient global ischemia/reperfusion in rats was revealed that oral administration of gallic acid improves gait performance, sensorimotor disorders, hypoalgesia, and passive avoidance memory. Our study showed that gallic acid had potential Cerebro-protective property [23].

Our study on the effect of ellagic acid against global cerebral ischemia showed that ellagic acid could be a potential compound for management and control cerebral ischemia due to the enhancement of electrocardiogram waves and blood pressure and reduction of MDA level in rats with global cerebral ischemia induced by bilateral vertebral and common carotid arteries occlusion [24]. Also, in another study, it has been reported that ellagic acid leads to improvement of neurological deficit and brain weight to body weight ratio. Ellagic acid also normalized lactate dehydrogenase activity and malondialdehyde level in serum while reduced superoxide dismutase activity in rats with focal cerebral ischemia [25]. A research group was induced by transient focal cerebral ischemia in rats by middle cerebral artery occlusion, and then animals were treated by crosin.

The results showed that this compound leads to the reduction of infarct volume and brain edema. Also, it had an antioxidant effect so that normalized activity of superoxide dismutase and glutathione peroxidase and reduced malondialdehyde level [26]. It has also been reported that oral administration of crosin results increase of activity of superoxide dismutase and glutathione peroxidase and reduction of nitric oxide and malondialdehyde levels and nitric oxide synthase activity in rats with transient focal cerebral ischemia. In addition, crosin abrogated serous edema, vacuolation, membrane damage and mitochondrial damages in cortical microvascular endothelial cells. Evaluation in molecular level revealed that crosin leads to improvement of phosphorylation of extracellular signal-regulated kinase ½ (ERK1/2) and reduction of expression of matrix metalloproteinase-9, oxidizing reactions, and inhibition of GRK2 translocation from the cytosol to the membrane [27].

Study on safranal as an herb active compound was confirmed its anti-ischemic effect against cerebral ischemia-reperfusion-induced by four-vessel occlusion method rats. Indeed, safranal administration leads to increase of total SH contents and antioxidant capacity as well as reduction of TBARS and MDA levels in hippocampus so that these events had a prominent effect of reducing oxidative damage in brain [28]. Given that quercetin significantly reduced up-regulation of matrix metalloproteinase-9, blood-brain barrier permeability, and brain edema in rats with focal ischemia induced by photo thrombosis;

therefore it is a useful compound for the treatment of cerebral ischemia [29].

Also, it has been reported that quercetin reduces cerebral ischemia neuronal damage in rats with transient focal cerebral ischemia through reduction of infarct size, TBARS level, neuronal loss, and p53 expression, inhibition of the activity of poly (ADP-ribose) polymerase (PARP) and caspase-3 as well as improvement of behaviors deficits [30]. Treatment of rats with cerebral ischemic induced by middle cerebral artery occlusion with quercetin leads to the promotion of neurological function and reduction of infarct volume and cell apoptosis. These effects caused by reduction of the number of TdT mediated dUTP nick end labeling positive cells and cleaved caspase-3 protein as well as the increase of expression of BDNF, TrkB and p-Akt [31]. Moreover, oral administration of quercetin to rats with chronic cerebral ischemia by bilateral occlusion of the carotid arteries results in promotion of learning and memory performance as well as normalization of long-term potentiation and amplitude of voltage-dependent sodium currents [32].

In a study, the effect of curcumin against cerebral ischemia caused by middle cerebral artery occlusion in rats was evaluated, and results revealed the anti-ischemic effect of curcumin due to the reduction of stress oxidative. Administration of curcumin led to reduction of lipid peroxidation and reduced peroxynitrite formation as well as the increase of activity of superoxide dismutase and glutathione peroxidase in the ipsilateral and contralateral hemisphere. Also, reductions in infarct volume and brain edema were observed [33].

Also, the anti-ischemic effect of curcumin can be related to its antiapoptotic effect because the administration of curcumin to rats with focal cerebral ischemia-reperfusion results in a reduction of cytochrome c releasing and cleaved caspase 3 expression and increase of mitochondrial Bcl-2 expression as well as reduction of malondialdehyde level in the brain. These events had a potential effect of reducing infarct volume and neurological damage [34]. In another study, about the role of curcumin in abrogation of damages caused by focal cerebral ischemia in rats was confirmed that curcumin administration leads to up-regulation of Nrf2 and HO-1 as well as reduction of infarct volume, brain water content and behavioral deficits. It seems that to target Nrf2 and HO-1 can be a promising idea to treat cerebral ischemia [35].

Moreover, it has been reported that curcumin protects blood-brain barrier integrity and reduces infarct volume, mortality, water content and extravasation of Evans blue dye in the ipsilateral hemisphere as well as improves in rat's brain with focal cerebral ischemia/reperfusion.

Also, the study on cultured astrocytes was confirmed inhibition of inducible nitric oxide synthase expression and nitrites/nitrates contents after their increase by lipopolysaccharide/tumor necrosis factor α induction. Another effect of curcumin was an abrogation of $ONOO^-$ donor SIN-1-induced cerebral capillaries endothelial cells damage [36]. A research group was induced focal cerebral ischemia-reperfusion damage by middle cerebral artery occlusion in rats and then evaluated the effect of curcumin administration. The results showed that curcumin reduces apoptotic by abrogation of expression of caspase-3 protein and followed by TUNEL-positive cells [37]. It has been reported that the reason for curcumin anti-ischemic property is its agonist effect on PPARγ.

This property of curcumin leads to the reduction of infarct volume and neuronal damage, suppression of neuroinflammatory response by reduction of IL-1β, TNF-α, PGE2, NO, COX-2, and iNOS in rats with middle cerebral artery occlusion model. Given that, curcumin is a potent PPARγ agonist and subsequently reduced inflammatory response related to cerebral ischemia, therefore, it could be considered as a therapeutic strategy for the treatment of cerebral ischemia damages [38]. Experiment on Mongolian gerbils with global cerebral ischemia caused by transient occlusion of the common carotid arteries was showed that curcumin administration reduced neuronal death, glial activation, lipid peroxidation, mitochondrial dysfunction, apoptosis induction and locomotor disability [39].

CONCLUSION: During ischemia, lack of oxygen creates a situation in which bloodstream back leads to the induction of inflammation and oxidative damage rather than normalization of tissue function. Increase of oxygen after the

reestablishment of cerebral blood flow has a pivotal role in the formation of free radicals and ultimately deleterious of cell function by cell necrosis and apoptosis. Basic and clinical studies have been indicated that the production of free radicals is one of the most important factors, which leads to cerebral damage, so that oxidative and inflammatory factors significantly increase after cerebral ischemia. Plants are an important source of antioxidants, and natural antioxidants increase plasma antioxidant potency and improvement of diseases such as cancer, heart disease, and stroke. Due to their toxicity and the aberrant effects of synthesized antioxidants, it can be a dire need to reliable sources of antioxidant such herbs because they have properties such as less toxic and more effective.

In conclusion, it can be stated that plant compounds protect the brain against ischemia potential antioxidant activity. Their antioxidant and anti-apoptotic properties may be involved in the protection of neuron during injury induced by cerebral ischemic. Therefore, plants can be ideal candidates to treat cerebral ischemia whether single or co-administration intervention. However, there are still many questions in this area so that their revealing depended on future studies.

ACKNOWLEDGEMENT: Us acknowledgment and gratefulness at the beginning and at last is to God who gave us the gift of the mind. The authors thank Young Researchers and Elite Club, Yasooj Branch, Islamic Azad University due to cooperation in this study.

CONFLICT OF INTEREST: The authors declare that there is no conflict of interest regarding this study.

FINANCIAL SUPPORT AND SPONSORSHIP: This study was supported by the authors named in this article.

ETHICAL APPROVAL: This research did not contain any studies with human participants or animals and was performed by the authors alone.

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How to cite this article:
Hassanpour SH and Karami SZ: The role of herbal compounds in the treatment of cerebral ischemia. Int J Pharmacognosy 2018; 5(3): 117-22. doi link: http://dx.doi.org/10.13040/IJPSR.0975-8232.IJP.5(3).117-22.