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Phytotherapeutic role of medicinal compounds in treating cerebral ischemia

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----------ABSTRACT----------

The Cerebral ischemia is one of the most important causes of mortality and morbidity in the world. Prevention and effective treatment of stroke is of the utmost importance. Cerebral ischemia is characterized by decrease in adequate blood supply to the brain to fulfill metabolic demand. Limitation in number of medicines and their conventional target approach of mode of action in treating ischemic patients, led us to the search for novel therapeutic approaches. Higher extent of research in the field of drug discovery and development has focused on the possible capacity of natural compounds extracted from medicinal plants, to prevent cerebral ischemia. A series of cellular and molecular mechanisms operates during ischemic process including oxidative phosphorylation, membrane function, neurotransmitter release, and free radical generation and compounds from herbal medicine is a promising treatment for cerebral ischemia. Natural compounds with the effects of anti-oxidation, anti-inflammation, calcium antagonization, anti-apoptosis, and anti-excitotoxicity exhibit preventive or therapeutic effects on experimental ischemic brain injury. In this review, we will discuss some plants and their constituents that may protect brain ischemia or delay the neurological disorders following a stroke.importance.

Keywords *- stroke, cerebral hypoxia, natural compounds, anti-oxidation, anti-apoptosis*

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I. INTRODUCTION

Cerebral ischemia is a condition in which there is insufficient blood supply to the brain to meet required energy demand which subjects brain to hypoxia and ends in death of neuronal cells or stroke. As per the World Health Organization (WHO) stroke is characterized by rapidly progressing focal or global disturbance affecting brain functions, and symptoms lasts more than 24 h or patient succumb to ischemia, with no evident excepting vascular origin [1]. Recent survey reveals that stroke is the third largest cause of mortality after cancer and coronary heart disease and apparently the second largest cause of physiological impairment in adults [2]. The occurrence of stroke is 1 per 1000 people [3] although; this incidence varies with age and sex. In developed countries arteriovascular diseases is one of the leading causes of mortality and morbidity [4] and this widespread disabling condition leads to neurorehabilitation [5]. Multitude of *in-vitro* and *in-vivo* models of cerebral ischemia has been reported over the years. The *in-vitro* models include cultured neurons with or without synaptic formation, glia and cultured brain slice that could only suggest the level of cytotoxicity of the therapy. While *in-vivo* animal model of stroke should be suffice to reproduce the etiology, anatomical, functional and metabolic consequences of human pathology and allow the study of anti-ischemic drugs clinically proving therapeutic actions [6]. Animal models for stroke available

for screening of drugs has been broadly classified into three subgroups as global ischemia, focal ischemia and forebrain ischemia (Table1). Transient or permanent reduction of cerebral blood flow by thrombolic or thromboemblic occlusion of artery has focused on thrombolytic therapy and considered as the main rational therapeutic strategy for ischemic brain injury [7]. Reperfusion after thrombolytic therapy results in a series of cellular, biochemical and metabolic changes including intracellular reactive oxygen species (ROS) generation, calcium overload, excitotoxic cell injury and inflammation and finally contributes to irreversible brain injury. Tissue plasminogen activator, a clot-dissolving medication, is being widely used in treating early phase of cerebral ischemia [8].

II. CASCADE PATHWAY OF CEREBRAL ISCHEMIA

Cerebral ischemia is characterized by reduction in blood and nutrients supply to brain because of variety of cellular and molecular mechanisms that impairs the energetic processes necessary to maintain ionic gradients [9,10]. As soon as the vascular occlusion is brought about, brain tissue gets deprived of glucose and oxygen and thus acidic by-products start accumulating [11,12]. Due to gradual decline of nutrients and decrease in pH level, it leads to cessation of the electron transport chain activity within mitochondria resulting in a sharp downfall of ATP concentration [13, 14] and thus failure of energy homeostasis take place. Deprivation of ATP causes disruption of ionic pump systems like Na+-K+-ATPase, Ca2+-H+ ATPase, reversal of Na+-Ca2+ transporter resulting in increase in intracellular Na+, Ca2+, Cl- concentration and efflux of K+ [15, 16]. Redistribution of ions across plasma membrane causes neuronal depolarization, resulting in excess release of neurotransmitters, especially glutamate that causes neuronal excitotoxicity [17,18]. Hyperactivation of glutamate on its receptors like NMDA, AMPA and metabotropic causes excessive increase in Ca2+ concentration within nerve cells which then triggers a variety of processes that leads to pathophysiological changes like necrosis and apoptosis [19, 20]. The processes include Ca2+ overload of mitochondria, formation of reactive oxygen species (ROS), activation of enzymes like lipases, proteases, kinases that leads to necrosis, nitric oxide (NO) synthase activation, activation of caspases-9,3,8, bad, bax, & calpains resulting in oxidative stress, lipid peroxidation, inflammation and apoptosis [21, 22]. Ca2+ dependent activation of nNOS (neuronal nitric oxide synthase), tends to increase NO production and formation of toxic peroxynitrite (ONOO-) that contributes to oxidative stress and excitotoxicity [23, 24, 25]. Upregulation of numerous enzyme systems such as lipases, phosphatases, kinases, proteases and endonucleases activate various inflammatory molecules like cytokines and interleukins (ILs) [26, 27] such as TNF-α, NF-κB that results in neuroinflammation [28]. Excessive influx of Na+ and Ca2+ ions and efflux of K+ ions as well as action of inflammatory mediators like leukocytes [29, 30] & adhesion molecules, causes fluid accumulation at injury site resulting in edema formation [31, 32]. Eventually all these detrimental factors lead to irreversible last event in cerebral ischemic stroke i.e. the death of neuron cells and moreover irreversible loss of neurological function including cognitive functions [33, 34]. Cascade events of cerebral ischemia is described in Fig. 1.

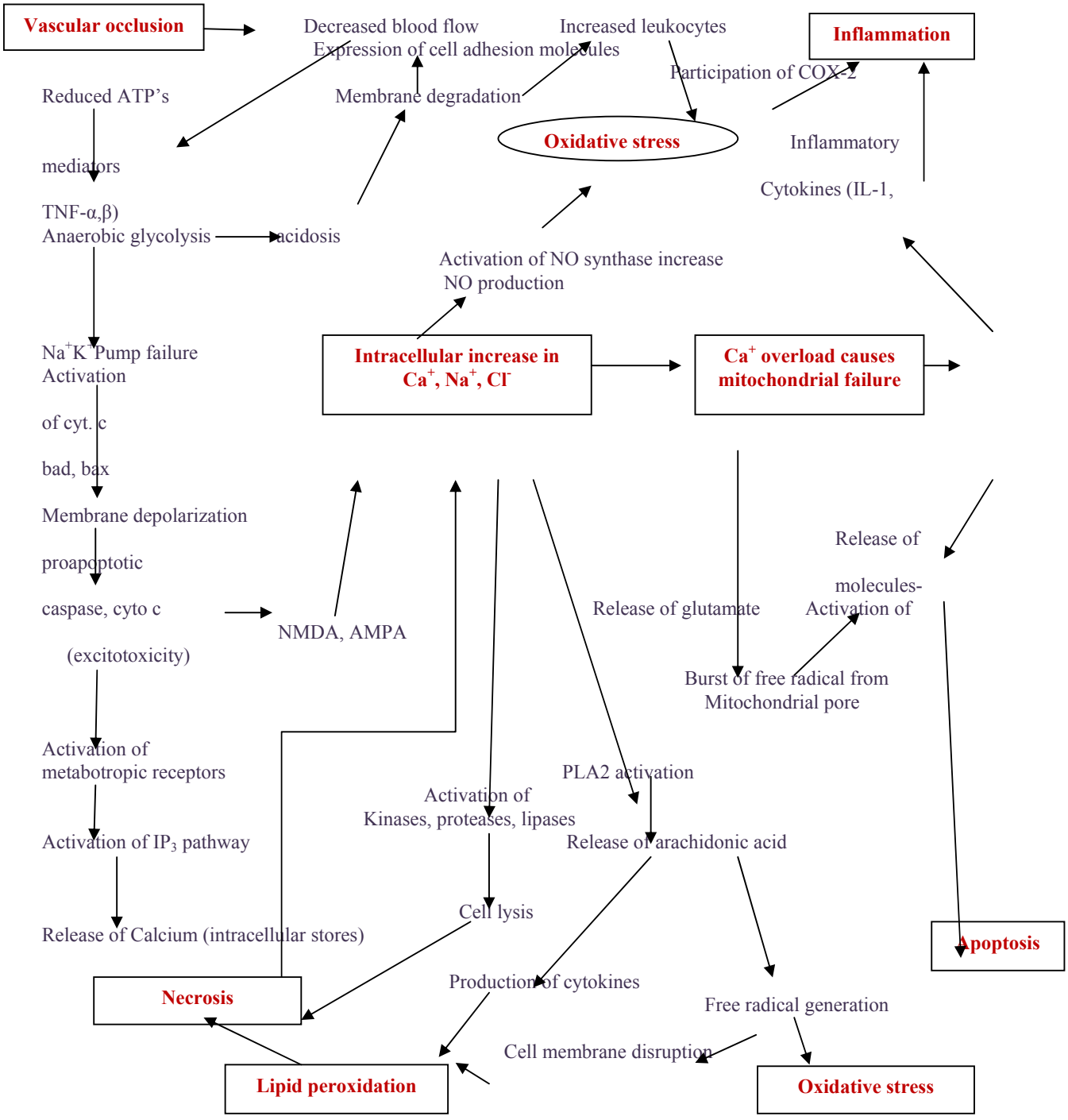

Figure 1. Cascade events of cerebral ischemia.

III. NATURAL COMPOUNDS WITH ANTIOXIDATIVE PROPERTIES

With the expansion of research it has been reported that a burst of free radical oxygen species like ROS is produced during ischemia or reperfusion, which subsequently leads to the oxidation of lipids, proteins and DNA and thus cellular damage and apoptosis [35, 18]. Natural compounds

exhibiting antioxidant abilities includes flavonoids obtained from Scutellaria baicalensis Georgi [36], Carnosic acid (CA), present in the herb rosemary obtained from Rosmarinus officinalis) [37], Curcuma Oil (isolated from powdered rhizomes of Curcuma longa) [38], Ginkgo biloba extract EGb761 [39], and Cinnamophilin (isolated from Cinnamomum philippinense) [40]. In a study pretreatment with curcuma oil, extracted from powdered rhizomes of Curcuma longa Linn, substantially reduces the levels of nitric oxide, reactive oxygen species and peroxynitrite as well as maintain the mitochondrial membrane potential [38].

Certain plant compounds like saponin and tannins extracted from root of Salvia leriifolia Benth. (Lamiaceae) and seed oil of Nigella sativa (Ranunculaceae) showed crucial antioxidative role by inhibition of lipid peroxidation, that decrease the levels of malondialdehyde (MDA) and subsequently improving the overall antioxidative mechanism by increasing the level of superoxide dismutase, catalase, glutathione peroxidase, and reduction in the levels of reactive nitrogen species (RNS) and reactive oxygen species (ROS) [41, 42]. Natural compounds have proved regulatory effects on endogenous antioxidant enzyme levels like carnosic acid (CA) obtained from Rosmarinus officinalis induces the expression of haeme oxygenase-1. Heme oxygenase (HO) is the rate-limiting enzyme for catabolism of heme, a process that gives bile pigment biliverdin(antioxidant), iron and carbon monoxide. Heme oxygenase exists in two forms- an inducible form (HO-1) and a constitutively expressed form (HO-2). HO-1 is induced in response to various noxious stimuli like hypoxia and oxidative stress and seems to protect against I/R injury [43,44,45].

The cytoplasmic enzyme NADPH oxidase is responsible for ROS production in cerebral ischemia and has gained a lot of focus in recent years. Over activation of the neuronal N-methyl-D-aspartate receptor (NMDAR) causes superoxide generation and boosts neuronal death. A recent study has suggested that activation of NADPH oxidase is required for NMDAR-mediated superoxide generation [46]. As a matter of fact, certain natural compounds shows inhibition of NADPH oxidase like sinomenine, an alkaloid extracted from Sinomenium acutum, inhibits the activation of microglial NADPH oxidase [47].

IV. NATURAL COMPOUNDS WITH ANTI-INFLAMMATORY EFFECTS

Within the few hours of ischemia/reperfusion injury, inflammation begins and is contributed by injury caused by the microglial activation, perivascular and parenchymal macrophages and infiltration of peripheral inflammatory cells and expression of cytokines, adhesion molecules, chemokines, and leukocytes. It is evident by research studies that neutrophils plays a prominent role in inducing the ischemic cerebral damage while reduction and decreased infiltration of neutrophils ameliorates the ischemic brain injury [48]. There are many biologically active moieties that shows significant antiinflammatory and neuroprotective effects against ischemia e.g. *Uncaria rhynchophylla (Rubiaceae)* extract exhibits neuroprotective effect by inhibiting cyclooxygenase-2 within hippocampus and *in-vitro* inhibition of proinflammatory process like microglial activation [49].

V. NATURAL COMPOUNDS WITH CALCIUM ANTAGONIZATION EFFECTS

ROS bursts and excitatory glutamate toxicity because of ischemia/ reperfusion results in intracellular Ca^{2+} overload. Excessive accumulation of Ca^{2+} in neurons is a significant factor for initiation of catastrophic events leading to irreversible neuronal injury. Natural compounds like Guattegaumerine (bisbenzylisoquinoline alkaloid obtained from *Guatteria gaumeri*) [50] and tetrahydroxystilbene glucoside (TSG) [51], have shown promising results by reducing ischemia induced Ca^{2+} overload in neurons. Voltage gated calcium channels (VGCC) blockers is a significant therapeutic approach for post-ischemia neuroprotection in humans. Research studies have proved that some isoquinoline alkaloids extracted such as berberine (an alkaloid derived from *Rhizoma coptidis*) and palmatine (a flavonoid in propolis) exhibit rapid inhibition of voltage-gated calcium entry in many native cells [52, 53].

VI. NATURAL COMPOUNDS WITH ANTI-EXCITOTOXICITY PROPERTIES

Exorbitant release of excitatory neurotransmitters, particularly glutamate in synaptic cleft causes overactivation of N-methyl-D-aspartate (NMDA) and α-Amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors that leads to influx of calcium and subsequent disturbance of ionic homeostasis. Consequently occurrence of cytotoxic oedema and oxidative stress results in cellular damage. Increased calcium levels activate enzymes such as lipases, proteases, and endonucleases that may damage DNA, cell proteins, and lipids thus leading to cellular necrosis [54, 55]. Some medicinal plant compounds have shown neuroprotective effects through reduction of glutamate release, inhibition of glutamate receptor stimulation, or reduction of cellular Ca^{2+} overload [56, 13] e.g. medicinal extracts of *Opuntia ficus-indica (Cactaceae)* and *Alpinae oxyphyllae (Zingiberaceae)* exhibited neuroprotective effect against NMDA-induced and kainic acid (KA) induced neurotoxicity in cultured neuronal cells [57, 48].

VII. NATURAL COMPOUNDS WITH ANTI-APOPTOTIC EFFECTS

Two general pathways in general regulate the cerebral ischemia- intrinsic and extrinsic pathways. Intrinsic pathway originates from mitochondrial release of cytochrome c and subsequent stimulation of caspase-3. Increased intracellular calcium activates Bid (tBid) which interacts with apoptotic proteins such as Bad and Bax, on the mitochondrial membrane that leads to release of cytochrome c (Cytc) which further binds to apoptotic protein-activating factor-1(APAF) and procaspase-9 that activates caspase-9 and caspase-3. Activated caspase3 results in DNA damage and apoptosis [58, 59]. In extrinsic pathway, the extracellular Fas ligand binds to Fas death receptors and enhances caspase-8 activation which leads to apoptotic cascade [58]. The death receptor Fas belongs to the tumor necrosis factor (TNF) receptor superfamily, and regulates death and survival of cells, as well as proliferation and differentiation [60, 14]. Fas ligand (Fas-L) activates Fas in an autocrine or paracrine pattern, which causes the trimerization of Fas with Fas-associating proteins with death domain (FADD) and procaspase-8. Fas activation corresponds to the cascade of actions contributing to apoptosis of neuronal cells [61,62,63]. Certain herbal compounds have inhibitory effect on intrinsic

or extrinsic pathways of apoptosis. Curcumin isolated from the rhizome of *Curcuma longa Linn. (Zingiberaceae)* proved to inhibit mitochondrial-mediated apoptotic signaling pathway [64]**.** There lies a physical balance between anti-apoptotic and pro-apoptotic members of the Bcl-2 family, imbalance of which determines the survival and death of developing and mature cells. The pro-apoptotic members of Bcl-2 family include Bax, Bcl-xs, Bak, Bad, Bid and these plays an important role in ischemic neuronal death [65]. Anti-apoptotic members of Bcl-2 family include Bcl-xL, and Bcl-w. Excessive expression of Bcl-xL protein in the adult brain suppresses activation of procaspase 9 by forming a complex with Apaf1 and thus prevents the release of cytochrome c from mitochondria, and maintains cell viability. A number of herbal drugs have shown their action on anti-apoptotic pathways, such as Bcl-2 family proteins. Hence in recent researches Bcl-xL has become a promising target for drugs to reduce cell apoptosis [66]**.** Administration of 4-hydroxybenzyl alcohol (an active phenolic constituents of *Gastrodia elata Blume)* 30 min before ischemia could antagonize cerebral ischemia by increasing Bcl-2 expression and inhibiting caspase-3 activity, leading to the amelioration of cell apoptosis in ischemic regions [67]**.**

VIII. CONCLUSION

Herbal compounds have got immense therapeutic potential and used as a treatment modality in cerebral ischemia. Due to availability, lower cost, and less adverse effects of herbal compounds in comparison to synthetic makes them as an excellent choice in the treatment of stroke. Cerebral ischemia involves multifactorial progressive pathophysiological processes which suggest that drugs binding to multiple targets or combinations of drugs that act on single target would be more effective in curing cerebral ischemia. Therapeutic combination of herbal medicines and neurochemical agents could be a better blend in ameliorating cerebral ischemia in patients. Preclinical and clinical trials will ensure the combination therapy as a good option for treating cerebral ischemia in humans. Despite many research findings of neuroprotective effect of herbal compounds it is a big question that how herbal medicines enter the CNS. Blood brain barrier is made of brain endothelial cells that forms tight junction and possess a number of specific uptake and efflux transport systems and metabolic enzymes, which regulates the passage of flavonoids and flavonoid glucosides to the CNS. Recent studies showed that the citrus flavonoids (hesperetin, naringenin) and their relevant *in vivo* metabolites (cyanidin-3-rutinoside and pelargonidin-3-glucoside) can be taken up by two kinds of brain endothelial cell lines from mice (b.END5) and rats (RBE4), demonstrating that flavonoids and some metabolites are able to traverse the BBB [68]. In the future, more and more attention has to be paid to natural compounds that can transverse the blood brain barrier and show broad therapeutic dimension, clear pharmacological targets and fewer side effects.

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