Therapeutic role of phytoconstituents in treatment of cerebral ischemia/reperfusion injury

Prashant Kumar Dhakad, Pramod Kumar Sharma, Sokindra Kumar, Nitin Kumar, Rupesh Dudhe, Raghav Mishra

Abstract

Stroke is important cause of mortality and morbidity in the world. Prevention and effective treatment of stroke is of utmost importance. Stroke involves reduce blood supply in brain to fulfill metabolic demand. Limit in number of medicines and their conventional target approach of action in treating stroke, led us to the search for novel therapeutic approaches. Higher extent of research in field of drug discovery focus on the possible ability of natural compounds extracted from medicinal plants, to prevent ischemia. Natural compounds are promising in treating stroke involving cell process like oxidative phosphorylation, membrane functioning, neurotransmitter release, and free radical generation. Herbal compounds show preventive effect in following sequence - calcium antagonism, anti-excitotoxicity, anti-oxidation, anti-apoptosis and anti-inflammation on experimental induced ischemic brain injury. In this review, we discussed cascade pathway of stroke, role medicinal compounds and novel medical pathway and hypothesis protecting brain ischemia or delay the neurological disorders following a stroke.

Keywords: stroke, anti-oxidation, anti-apoptosis, anti-excitotoxicity, anti-inflammation

Introduction

Stroke is a condition of lacking blood supply to the brain to meet needed energy demand which subjects brain to hypoxia and results to death of neurons or stroke. WHO characterizes stroke as rapidly progressing focal or global disturbance affecting brain roles, and symptoms lasts more than 24 h [1]. Recent survey suggests stroke as third largest cause of mortality after cancer and coronary heart disease and second largest cause of path physiological injury in adults [2]. The case of stroke is 1 per 1000 people [3] although; this incidence varies with age and sex. Arteriovascular diseases is one of the leading causes of death in developed countries [4] leading to neurorehabilitation [5]. Several in-vitro and in-vivo models of brain ischemia 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 cytotoxicity of the therapy. The in-vivo animal model of stroke reproduce the etiology, anatomical, and metabolic results of human pathology and allow the study of anti-ischemic drugs clinically proving therapeutic actions [6]. Animal models for stroke meant for screening of drugs classify in three subgroups as global ischemia, focal ischemia and forebrain ischemia (Table 1). Transient or permanent decrease of cerebral blood flow by thromboembolic or thromboembolic occlusion of artery focuses on thrombolytic therapy and is 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 preferred in treating early phase of cerebral ischemia [8].

Cascade pathway of cerebral ischemia

Various cell changes weaken the energetic actions that preserve ion gradients [9, 10]. Because of vascular occlusion brain tissue deprivies of glucose and oxygen causing build-up of acidic by-products in cell [11, 12]. Decrease in glucose and pH level, lead to end of the electron transport chain within mitochondria causing sharp downfall of ATP and thus failure of energy homeostasis occurs [13, 14]. Deprivation of ATP causes disruption of ion pump systems like Na⁺-K⁺-ATPase, Ca²⁺-H⁺ ATPase, Na⁺-Ca²⁺ transporter resulting in intracellular increase of 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 receptors like NMDA, AMPA and metabotropic causes increase in Ca\(^{2+}\) ion in nerve cells which trigger path physiological changes like necrosis and apoptosis \[^{[19, 20]}\]. Changes include Ca\(^{2+}\) overload of mitochondria, generation of ROS, activation of enzymes like lipases, proteases, kinases that lead to necrosis. NO synthase activation, activation of caspases-9, 3, 8, bad, bax, & calpains result in oxidative stress, lipid peroxidation, inflammation and apoptosis \[^{[21, 22]}\]. Ca\(^{2+}\)-dependent activation of nNOS, increases NO production and formation of toxic ONOO\(^{-}\) contributes to oxidative stress and excitotoxicity \[^{[23-25]}\] (Chan PH 2001; Jordán J \textit{et al.} 2008; Sharma SS 2003). Control of many enzyme like lipase, phosphatase, kinase, protease and endonuclease activate various inflammatory molecules like cytokine and interleukins (ILs) \[^{[26, 27]}\] such as TNF-\(\alpha\), NF-\(\kappa\)B causing neuroinflammation \[^{[28]}\]. Accumulation of fluid occurs due to excessive influx of Na\(^{+}\), Ca\(^{2+}\) ions and efflux of K\(^{+}\) ions as well as action of inflammatory mediators like leukocytes \[^{[29, 30]}\], adhesion molecule causing edema at site of injury \[^{[31, 32]}\]. All above factors finally result in death of neuron cells and irreversible loss of neural role including cognitive roles \[^{[33, 34]}\].

Cascade events of cerebral ischemia is described in Figure 1 and list of medicinal compounds exhibiting neuroprotective role is shown in Table (2).

<table>
<thead>
<tr>
<th>Experimental animal models</th>
<th>Subtypes</th>
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</thead>
</table>
| 1. Global ischemia         | 1. Total Body Ischemia  
Decapitation  
Cardiac arrest with resuscitation  
Profound systemic hypotension |
|                            | 2. Global cerebral ischemia  
Increased intracranial pressure  
Combination of occlusion of the major arteries |
| 2. Forebrain ischemia      | 1. Bilateral common carotid occlusion in Mongolian gerbil  
hypotension.  
2. Four vessel occlusion in the rats  
4. Two vessel occlusion with hypotension in rats. |
| 3. Focal ischemia          | 1. Middle cerebral artery occlusion  
Intraluminal arterial occlusion without craniotomy  
Mechanical or electrical arterial occlusion with craniotomy and dural opening  
2. Photochemically induced focal cerebral thrombosis  
3. Cerebral embolism  
Blood clot embolization  
Microsphere embolization |

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*Table 1*

**Cerebral Ischemia Reperfusion**

- Decrease in Tissue O\(_2\), Glucose
- ATP depletion
- Membrane Depolarization
- NMDAR, AMPAR, Metabotropic receptors activation (excitotoxicity)
- Opening of Ca\(^{2+}\) channels
- Increase in intracellular Ca\(^{2+}\) levels
- Release of Inflammatory mediators, cytokines (ILs, TNF)
- Apoptotic Pathway
- Oxidative stress
- ROS, RNS
- Activation of cyt. C, bad, bax
- Release of proapoptotic molecules-caspase activation
- Cell death

**Fig 1:** Pathway of cerebral ischemia
lipase, protease, and endonuclease that may damage DNA, damage. Increased calcium levels activate enzymes such as edema and oxidative stress occur and results in cellular afterwards disturb ionic homeostasis. As a result cytotoxic and AMPA receptors that leads to influx of calcium and glutamate in synaptic cleft causes over activation of NMDA Enormous release of excitatory neurotransmitters, particularly Natural compounds with anti-excitotoxicity properties Excess concentration of Ca $^{2+}$ in neuron begins disastrous events leading to irreversible neuronal injury. Natural compounds like Guattegaumine (bisbenzylisouquinoline alkaloid obtained from Guatteria gaumeri) [46] and tetrahydroxystilbene glucoside (TSG) [47], have shown promising results by reducing ischemia induced Ca$^{2+}$ overload in neurons. VGCC blockers are significant therapeutic approach for post-ischemia neuroprotection in humans. Research studies have shown that some isouquinoline alkaloids extracted such as berberine (an alkaloid derived from Rhizoma coptidis) [50, 51]. Some medicinal plant compounds have shown neuroprotective by reducing glutamate release, inhibiting glutamate receptor stimulation, or reducing cellular Ca$^{2+}$ overload [40, 52] (Hosseinizadeh H et al. 2005; Lee JM et al. 2000). Example medicinal extracts of Opuntia ficus-indica (Cactaceae) and Alpinae oxyphyllae (Zingiberaceae) showed neuroprotective effect against NMDA-induced and KA induced neurotoxicity in cultured neuronal cells [53, 54].

Natural compounds with anti-oxidative properties A research has reported that a burst of free radical oxygen species like ROS produce during ischemia or reperfusion, which later leads to the lipid oxidation, damage to proteins and DNA and apoptosis [55, 56]. Natural compounds showing antioxidant effect includes flavonoids obtained from Scutellaria baicalensis Georgi [57], CA present in the herb rosemary obtained from Rosmarinus officinalis [58] Curcuma Oil (isolated from powdered rhizomes of Curcuma longa) [59], Ginkgo biloba extract EGb761 [60], and Cinnamophilin (isolated from Cinnamomum philippinense) [61]. In a scientific 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 and regulates the mitochondrial membrane potential [59]. Certain plant compounds like saponin and tannins extracted from root of Salvia terifolia Benih (Lamiaceae) and seed oil of Nigella sativa (Ranunculaceae) has shown important anti-oxidative role by inhibiting lipid peroxidation. Hence reducing the levels of MDA and later improving the overall anti-oxidative mechanism by increasing the levels of superoxide dismutase, catalase, glutathione (Lamiaceae) and palmatine (a flavonoid in Rhizome bioactive component of Curcuma longa Linn.) [47] and tetrahydroxystilbene glucoside (TSG) [47], have shown promising results by reducing ischemia induced Ca$^{2+}$ overload in neurons. VGCC blockers are significant therapeutic approach for post-ischemia neuroprotection in humans. Research studies have shown that some isouquinoline alkaloids extracted such as berberine (an alkaloid derived from Rhizoma coptidis) [50, 51]. Some medicinal plant compounds have shown neuroprotective by reducing glutamate release, inhibiting glutamate receptor stimulation, or reducing cellular Ca$^{2+}$ overload [40, 52] (Hosseinizadeh H et al. 2005; Lee JM et al. 2000). Example medicinal extracts of Opuntia ficus-indica (Cactaceae) and Alpinae oxyphyllae (Zingiberaceae) showed neuroprotective effect against NMDA-induced and KA induced neurotoxicity in cultured neuronal cells [53, 54].

Table 2: Isolated medicinal compounds treating cerebral ischemia

<table>
<thead>
<tr>
<th>Compounds</th>
<th>Origin</th>
<th>Dosage and route of exposure</th>
<th>In vivo and in vitro studies</th>
<th>Mechanism of action</th>
<th>Form of ischemia</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Curcumin</td>
<td>Rhizome bioactive component of Curcuma longa Linn.</td>
<td>30 mg/kg (i.p)</td>
<td>Mongolian gerbils</td>
<td>Inhibition of mitochondrial mediated apoptosis</td>
<td>MCAO and BCAO</td>
<td>[55]</td>
</tr>
<tr>
<td>Scutellarin</td>
<td>Extracted from Erigeron brevicaudus</td>
<td>50 and 75mg/kg (p.o.)</td>
<td>Male Sprague Dawley rats</td>
<td>Upregulation of eNOS and downregulation iNOS</td>
<td>MCAO</td>
<td>[56]</td>
</tr>
<tr>
<td>Ginkolide B</td>
<td>Terpenic lactones present in Ginkgo biloba</td>
<td>5 mg/kg (i.v.)</td>
<td>Male and female tree shrews</td>
<td>Inhibiting pathological manifestation of PAF, such as inducing calcium overload, brain edema, and secondary brain damage in penumbra</td>
<td>Photochemically induced thrombotic cerebral ischemia</td>
<td>[57]</td>
</tr>
<tr>
<td>Crataegus flavonoids</td>
<td>Extracted from Crataegus pinnatifida</td>
<td>0.5 and 2.5 mg/ml orally</td>
<td>Male Mongolian gerbils</td>
<td>Scavenging effect on superoxide anion</td>
<td>MCAO and BCAO</td>
<td>[58]</td>
</tr>
<tr>
<td>Ascovertin</td>
<td>Complex of dihydroquercetin and ascorbic acid</td>
<td>70 mg/kg (p.o.)</td>
<td>Male and female wistar rats</td>
<td>Protection of brain Na$^{+}$ K$^{+}$ ATPase activity</td>
<td>LCAO</td>
<td>[59]</td>
</tr>
<tr>
<td>Safranal</td>
<td>Crocus sativus L. stigmas</td>
<td>72.5 mg/kg (i.p.)</td>
<td>Male NMRI rats</td>
<td>Antioxidant</td>
<td>Four vessel occlusion</td>
<td>[60]</td>
</tr>
<tr>
<td>SSF</td>
<td>A flavonoid isolated from aerial parts of Scutellaria baicalensis Georgi</td>
<td>35 mg/kg (p.o.)</td>
<td>SD rats</td>
<td>Block the pathogenic process in vascular dementia ameliorating cognitive deficit protecting neuronal injury and modulating abnormal changes in energy metabolites</td>
<td>BCAO</td>
<td>[61]</td>
</tr>
<tr>
<td>Lecithin and α tocopherol</td>
<td>Structural elements of biological membrane</td>
<td>Lecithin 300 mg/kg, and tocopherol 200 mg/kg(p.o.)</td>
<td>Male wistar rats</td>
<td>Antioxidant</td>
<td>BCAO</td>
<td>[62]</td>
</tr>
<tr>
<td>Thymoquinone</td>
<td>Nigella sativa seeds oil</td>
<td>10 mg/kg and 2.5, 5, and 10 mg/kg (i.p.)</td>
<td>NMRI rats</td>
<td>Inhibition of lipids peroxidation</td>
<td>Four vessel occlusion method</td>
<td>[63, 64]</td>
</tr>
<tr>
<td>Buckwheat polyphenol</td>
<td>Polyphenolic compounds such as catechin, epicatechin, quercetin, and epicatechin from Fagopyrum esculentum</td>
<td>600 mg/kg (p.o.)</td>
<td>Male wistar rats</td>
<td>Inhibition of excess release of glutamate Inhibition of delayed generation of NO$^{2-}$</td>
<td>Repeated cerebral ischemia(10 min., two times occlusion, 1 h interval)</td>
<td>[65]</td>
</tr>
</tbody>
</table>
peroxidase, and decreasing the level of reactive nitrogen species and reactive oxygen species [43, 62].

Natural compounds showed therapeutic effects on endogenous antioxidant enzyme levels like carnosic acid obtained from Rosmarinus officinalis induces 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 induces cytoplastic 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 causes neuronal death. Recent study suggests activation of NADPH oxidase for NMDAR-mediated superoxide generation (Brennan AM 2009). Certain natural compounds like simoninene extracted from Sinomenium acutum inhibit activation of microglial NADPH oxidase [60,61].

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 resulting 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 damage deoxyribonucleic acid and cause apoptosis [67, 68]. In extrinsic pathway, the extracellular Fas ligand binds to Fas death receptors and strengthens caspase-8 activation which leads to apoptotic cascade [69]. The death receptor Fas belongs to the tumor necrosis factor (TNF) receptor superfamily, and regulates death and survival of cells, as well as growth and differentiation [69, 14]. Fas ligand (Fas-L) activates Fas in an autocrine or paracrine pattern, which causes trimerization of Fas with Fas-associating proteins with death domain (FADD) and procaspase-8. Fas stimulation contributes to cascade of actions contribute to apoptosis of neuronal cells [70-72]. Certain herbal compounds have inhibitory effect on intrinsic or extrinsic pathways of apoptosis. Curcumin isolated from the rhizome of Curcuma longa (Zingiberaceae) inhibit mitochondrial-mediated apoptotic signaling pathway [38].

There lies a physical balance between anti-apoptotic and pro-apoptotic members of the Bcl-2 family, imbalance of which controls the survival and death of developing and mature cells. The pro-apoptotic members of Bcl-2 family include Bax, Bel-xs, Bak, Bad, Bid and these plays an important role in ischemic neuronal death [73]. Anti-apoptotic members of Bcl-2 family include Bel-xl, and Bel-w. Excessive expression of Bel-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. Therefore in recent researches Bel-xl has become a promising target for drugs to reduce cell apoptosis [74]. Administration of 4-hydroxybenzyl alcohol (an active phenol constituents of Gastrodia elata) Blume) 30 min. before ischemia antagonize cerebral ischemia by increasing Bcl-2 expression and inhibiting caspase-3 activity, ameliorate cell apoptosis in ischemic regions [75].

Natural compounds with anti-inflammatory effects

Microglial activation, perivascular and parenchymal macrophages, infiltration of peripheral inflammatory cells and expression of cytokines, adhesion molecules, chemokines, and leukocytes occurs few hours of ischemia or reperfusion injury. Research studies suggest the role of neutrophils in inducing the ischemic cerebral damage; reduction and decreased infiltration of neutrophils ameliorate the ischemic brain injury [76]. There are many biologically active moieties that prove 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 [77].

Novel pathways regulating neuroprotection

A major polyphenol component of green tea EGCG, improve age-related cognitive decline and protect against cerebral ischemia or reperfusion injuries [78, 79] and brain inflammation and neuronal damage in experimental autoimmune encephalomyelitis [80]. Several evidences suggest the biological action of green tea catechins is not only because of their antioxidant or radical-scavenging potential but also because of modulating various protein kinase signaling pathways. In vitro cell-signaling studies on the neuroprotective action of EGCG revealed a specific involvement of protein kinase C [81, 82] a family of serine/threonine kinases consisting of 11 isoforms, and divided into subclass: conventional (α, β1, β2, γ), novel (δ, ε, ζ, η, θ) [83]. Induced PKC in neurons is neuroprotective against several exogenous insults. Indeed, PKCe activation after ischemic preconditioning or pharmacological preconditioning (with either PKCe, NMDA, or AIAR agonists) showed necessary for neuroprotection against oxygen/glucose deprivation in organotypic slice cultures [84]. Activation of EGCG by PKC prevents apoptosis and mitochondrial membrane collapse. Rapid phosphorylative activation of PKC by EGCG accounts for its neuroprotective activity against several neurotoxins such as Aβ [28], 6-OHDA [81].

A novel pathway in the neuroprotective mechanism of action of EGCG involves a rapid PKC mediated degradation of the Bad protein by the ubiquitin proteasome system and pronounced reduction after 24 h in cell culture [85]. Bad protein is responsible for opening of the mitochondrial mega channel permeability transition pore by its heterodimerization with the mitochondrial death suppressor proteins Bcl-2 and Bcl-xL, thus neutralizing their anti-apoptotic role [85]. Administration of EGCG for 30 min prevented scattering the mitochondrial membrane potential, induced by short-term (4 h) exposure to 6-OHDA. Apart from PKC, other cell signaling pathways have been implicated in the action of green tea catechins, such as the mitogen-activated protein kinases (MAPK), phosphatidylinositide 3'-OH kinase/AKT and protein kinase A signaling cascades, and cell calcium influx regulation [86]. These cascades have shown central roles in neuronal protection against various extracellular insults [87, 88].

Novel medical hypothesis

It is imperative that ischemia or reperfusion cascade begins
with disruption of cerebral blood flow that deprives brain cells of glucose and oxygen supply, resulting in decrease in energy production and accumulation of toxic substances like glutamate, inflammatory mediators, and free radicals that could eventually result in neurodegeneration [89]. Oxidative damage plays a key role during ischemia. Neuroprotective role of Nrf2 can be highlighted by up-regulating a series of ARE driven anti-oxidative and cytoprotective genes to defend against oxidative stress [90]. Hence, agents that interfere with the Nrf2 pathway show a neuroprotective potential. AKBA, a novel Nrf2 activator, enhance the protective defense mechanisms through the HO-1 neuroprotective pathway. Nrf2 is a key regulator of endogenous antioxidant defense. Nrf2 remained bound to its cytosolic inhibitor, Kelch-like ECH-associated protein 1 (Keap1), and remains in the cytoplasm before targeted for proteosomal degradation [89]. Activation and nuclear accumulation of Nrf2 influences endogenous antioxidant defenses to restore cellular redox homeostasis by inducting phase II defense enzymes.

Various defense mechanisms activate Nrf2 and increases expression of antioxidative genes. AKBA is a potent antioxidant in treating oxidative injuries [95]. In a study AKBA showed protective effect against cerebral I/R injury in MCAO model proved by improved neurologic condition, reduced infarct volume and ameliorated neuronal apoptosis. The mechanism involved is by activating Nrf2/HO-1 pathway. Recently, triterpenoids such as maslinic acid and oleanolic acid being structurally similar to AKBA, reported significant increase in Nrf2, promising neuroprotection [90, 94]. The mitochondrial presence of nearly 1,000 different proteins, two different membranes, many transporters for metabolites, proteins, and ions provide target for both injury and cytoprotection. Similar to injured cells, damaged mitochondria can destroy their immediate environment, leading to the death of the host cells where they remain. Various tactics for protecting cells against pathologic mitochondrial injury includes (1) optimization of mitochondrial dynamics through mitophagic disposal of abnormal mitochondria and biogenesis of new, healthy mitochondria. (2) Use of ischemic-preconditioning mechanisms like mitochondrial protein phosphorylation and sirtuin activation that improve mitochondrial bioenergetics. (3) Inhibition of mitochondrial oxidative stress by inhibition of mitochondrial superoxide production, by mitochondrial targeted antioxidants, and by stimulation of antioxidant gene expression that increases endogenous mitochondrial antioxidant defense mechanisms. Medicinal compounds or conditions that activate all three pathways show neuroprotection [95].

**Abbreviations**

<table>
<thead>
<tr>
<th>1.</th>
<th>A1AR</th>
<th>A 1 Adenosine Receptor</th>
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<tbody>
<tr>
<td>2.</td>
<td>AMPA</td>
<td>α-Amino 3 Hydroxy 5 Methyl 4 Isoxazolepropionic Acid</td>
</tr>
<tr>
<td>3.</td>
<td>AKBA</td>
<td>Acetyl 11 Keto Beta Boswellic Acid</td>
</tr>
<tr>
<td>4.</td>
<td>APAF</td>
<td>Apoptotic Protein Activating Factor 1</td>
</tr>
<tr>
<td>5.</td>
<td>ARE</td>
<td>Antioxidant Response Element</td>
</tr>
<tr>
<td>6.</td>
<td>ATP</td>
<td>Adenosine Triphosphate</td>
</tr>
<tr>
<td>7.</td>
<td>BHB</td>
<td>Blood Brain Barrier</td>
</tr>
<tr>
<td>8.</td>
<td>CA</td>
<td>Carnosic Acid</td>
</tr>
<tr>
<td>9.</td>
<td>Cytc</td>
<td>Cytochrome C</td>
</tr>
<tr>
<td>10.</td>
<td>DNA</td>
<td>Deoxy Ribose Nucleic Acid</td>
</tr>
<tr>
<td>11.</td>
<td>EGCg</td>
<td>Epigallocatechin 3 Gallate</td>
</tr>
<tr>
<td>12.</td>
<td>FADD</td>
<td>Fas Associated Proteins With Death Domain</td>
</tr>
<tr>
<td>13.</td>
<td>HO</td>
<td>Heme Oxygenase</td>
</tr>
<tr>
<td>14.</td>
<td>ILs</td>
<td>Interleukins</td>
</tr>
</tbody>
</table>

**References**


**Conclusion**

Herbal compounds have vast therapeutic potential and used as a treatment measure in cerebral ischemia. Because of availability, lower cost, and fewer adverse effects of herbal compounds in comparison to synthetic makes them as an excellent choice in treating stroke. Cerebral ischemia involves multifactorial progressive path physiological events which suggest designing cocktail drugs that target different signaling events entering cerebral ischemic damage. 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 alternative for treating cerebral ischemia in humans.

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