Neuroprotective agents, Natural Plant Herbs & Drugs in Ischemic Stroke: A Review

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ABSTRACT

Stroke is a destructive experience which can result in permanent disability in brain. There is no permanent drug which can improve the blood flow at infracted area and also improve the neurological deficit. Due to the lack of treatments available for stroke, many researchers will investigate the suitable plants or drugs for the treatment of this disease. Numerous medicinal plants and herbal drugs are available to treat stroke, some of the plants are Ginkgo biloba, Fructus Chebulae, Pomegranate, Rosa laevigata, Garlic, Leonurus heterophyllus, Olive, Grape, Allium cepa, drugs such as Pravastatin, Senkyunolide I, Phloretin, Mgso4, HAMI 3379, Oleoylethanolamie, scopolamine and mecamylamine, Nitric Oxide, N-nitro-L-arginine methyl ester (L-NAME), 3,5,6,7,8,3',4'-Heptamethoxy flavones, Rosiglitazone, Puerarin, the activity was estimated by parameters like superoxide dismutase (SOD) activity, Hemispheric swelling index (cerebral edema), H2O2 induced cell injury, OGD-R induced cell injury, superoxide dismutase and glutathione peroxidises, mitochondrial membrane potential, Western blotting assay, ROS scavenging assays, Superoxide anion scavenging assay, Hydroxyl radical scavenging assay, H2O2 scavenging assay, Singlet oxygen scavenging assay, Peroxyl radical scavenging assay, Peroxynitrite anion scavenging assay, myeloperoxidase (MPO) activity, blood–brain barrier integrity, cerebral infarct size, in Situ Apoptosis Detection, Western blotting, SOD, GSH, glutathione peroxidase, and MDA levels, Reverse transcription polymerase chain reaction (RT-PCR), Lactate dehydrogenase activity assay, Determination of caspase activity, acetylcholinesterase (AChE) activity, Determination of choline acetyltransferase activity (ChAT), Cell viability, Oxygen glucose deprivation/reperfusion assay, Flow cytometry, Immunohistochemistry. The present review focused on different medicinal plants and drugs that have been tested in Stroke in animal models.

Keywords: Dose, BCCAO, MCAO, Nitric Oxide, Neurological, Stroke.

INTRODUCTION

Stroke, the major cause of death and disability, is regarded as the important problem in developing countries [1]. Frequent incidences of cerebral ischemia are seen in age-related disorders, hypoxic–ischemic brain injury, carotid artery pathologies, asphyxiation and shock etc. It is a devastating event that is associated with great morbidity (Madl and Holzer, 2004). In certain clinical situations such as transient global cerebral ischemia anticipates or even induced iatrogenically during cardiac or thoracic surgery. Permanent ligation of bilateral common carotid arteries is a well known model used to study cerebral ischemia (Choe et al., 2001). Bilateral common carotid artery occlusion (BCCAO) causes moderate and most likely permanent reduction of cortical and cerebral blood flow in diverse areas of brain (Jeon et al., 2004).Despite the importance of stroke and the advances of technologies nowadays. The prophylactic protection against stroke with neuroprotective agents has gained much attention. Cerebral ischemia is characterized by a rapid onset of neurological injury due to interruption of blood flow to the brain [2]. This injury has been reported to be associated with the action and interaction of many factors such as excitatory amino acids, calcium overloading, and oxidative stress damage, periphery depolarization of infarction, neuroinflammation, and apoptosis [3–5]. However, accumulative lines of evidence in this decade point out to the crucial role of oxidative stress. It has been reported that the reduction of cerebral blood flow and the reperfusion period induce the elevation of oxidative stress and lipid peroxidation [6–9]. Interestingly, both in vitro and in vivo data have demonstrated that this injury can be

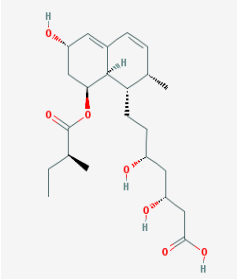
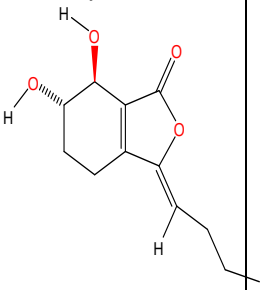
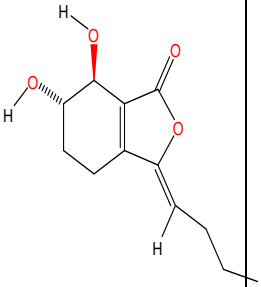
protected by polyphenolics including flavonoids [7, 8, 10–13]. ***Ginkgo biloba*** belonging to the family **Ginkgoaceae** which can improve cerebral oxygen supply, decrease cerebral oxygen extraction rate and consumption, and reduce cerebral oxygen metabolic rate[14].***Fructus Chebulae*** decreases the cerebral infarct volume and extent of hemisphere swelling[15]. **Pomegranate** decrease brain levels of NF-κB p65, TNF-α, caspase-3 and increased brain levels of IL-10, and cerebral ATP roduction[16]. **Pravastatin** drug which used for the proportion of viable neuronal cells after ischemia was greater in the pravastatin vs. control group, with greater expression of apoptotic cells in the control vs. pravastatin group. Bax protein expression was significantly decreased; Bcl-2 expression was increased, but not significantly [17]. **Puerarin** is a drug which is used for treatment significantly improved the phosphorylation level of AKT in dose-dependent, reduced the infarct volume, the number of Nissl body, and cleaved caspase-3 and GFAP positive cells increased [18].

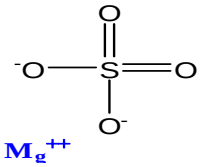
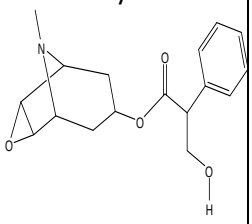
2. Natural plants Herbs & drug used as a neuroprotection in ischemic stroke

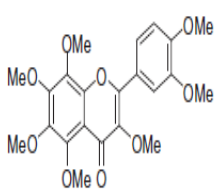
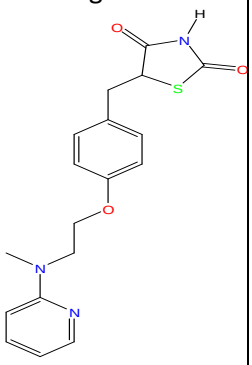
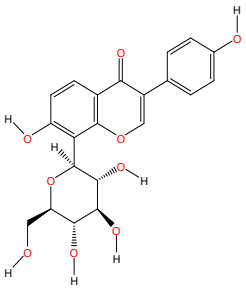
Name of plant Herbs	Dose	Model	Parameters	Result
Ginkgo biloba 	1 mg/kg	Hypoperfusin in elderly patients	CaO2, SjvO2 and CEO2, Glua, Laca, superoxide dismutase (SOD) activity.	*Ginkgo biloba* extract can improve cerebral oxygen supply, decrease cerebral oxygen extraction rate and consumption, and reduce cerebral oxygen metabolic rate [14].
Fructus Chebulae 	300, 500 mg/kg.	MCAO, 90min, reperfusion 24hr	Hemispheric swelling index (cerebral edema), H2O2 induced cell injury, OGD-R induced cell injury.	Fructus Chebulae extract increases the PC12 cell survival against OGD-R and H2O2. Fructus Chebulae also decreases the cerebral infarct volume and extent of hemisphere swelling [15].
Pomegranate 	250, 500 mg/kg.	BCCAO, 60 min, Reperfusion 60 min	Determination of brain nitric oxide, superoxide dismutase and glutathione peroxidises, glutathione reductase, brain cytokines.	Reduction in brain contents of MDA, and NO, in addition to enhancement of SOD, GPX, and GRD. Pomegranate extract decreased brain levels of NF-κB p65, TNF-α, caspase-3 and increased brain levels of IL-10, and cerebral ATP roduction. Comet assay showed less brain DNA damage [16].
Rosa laevigata 	50, 100 and 200 mg/kg	MCAO reperfusion 24hr	DAPI staining, TUNEL assay, Determination of mitochondrial membrane potential, Western blotting assay, Immunohistochemisty	Prevented I/R-induced disability and histological damage, significantly decreased DNA fragmentation, up-regulated the expression of Bcl-2, and down-

				regulated the expressions of p53, 37 Apaf1, Fas, FasL, Bax, Bid, cytochrome C and active Caspase-3. Moreover, decreased the expressions of NF-jB, iNOS, MMP-9, COX-2, TNF-a, IL-1b, IL-4, IL-6, and down-regulated the levels of p-JNK, p-ERK and in MAPK pathways [19].
Garlic 	360 mg/kg. i.p.	MCAO for 2hr	ROS scavenging assays, Superoxide anion scavenging assay, Hydroxyl radical scavenging assay, H2O2 scavenging assay, Singlet oxygen scavenging assay, Peroxyl radical scavenging assay, Peroxynitrite anion scavenging assay	Extracts decreased mRNA expression of NR1- and NR2B-NMDA-receptor subunits and prevented ischemia-induced reduction in mitochondrial potential and in ATP synthesis. Antioxidants present in garlic extracts may regulate ROS concentrations during ischemia, favour pro-survival pathways, and attenuate mitochondrial dysfunction [20].
Leonurus heterophyllus 	3.6, 7.2, 14.4 mg/kg	MCAO for 2 hr, reperfusion 24hr	Measurement of myeloperoxidase (MPO) activity, Measurement of NO metabolite in the brain, The apoptosis ratio of nerve fiber in the brains mensurate,	LHAE significantly decreasing neurological deficit scores, reducing the infarct volume and MPO content. LHAE at 14.4 mg/kg significantly decreased the NO level. In addition, LHAE significantly decreased the apoptosis ratio of nerve fiber [21].
Olive 	50, 75 and 100 mg/kg	MCAO for 30 min, reperfusion 24hr	Behavioural Parameter-Normal motor function, failure to extend forepaw; loss of righting reflex; no spontaneous motor activity. Biochemical parameters, Lipid profiles, Assessment of brain water content, blood–brain barrier integrity	Oral administration of olive leaf extract reduces infarct volume, brain edema, blood–brain barrier permeability, and improves neurologic deficit scores [22].
Grape	30 mg/ml	BCCAO for 5 min, reperfusion 4	Behavioural parameters-Assessment of locomotor	GPE resulted in hyperlocomotion,

		days	activity, Biochemical parameters- Assessment of neurons, astrocytes and microglial cells, DAPI staining to assess nuclear DNA damage, 8-OHdG immunohistochemistry to identify oxidized DNA	extensive DND, oxidative and fragmented DNA damage, and an increase in reactive astrocytes and microglial cells in the hippocampal CA1 region[23].
Allium cepa 	100 and 200 mg/kg	BCCAO for 10 min, reperfusion 24 hr	Behavioural parameters- Elevated plus maze, Inclined beam walking test, Lateral push test Biochemical parameters- Estimation of thiobarbituric acid reactive substance (TBARS), Assessment of cerebral infarct size,	A. cepa bulb markedly reduced cerebral infarct size and attenuated impairment in short-term memory and motor coordination. marked decrease in mitochondrial TBARS [24].

Drug	Dose	Model	Parameters	Result
Pravastatin 	1 mg/kg	BCCAO for 8 min.	In Situ Apoptosis Detection, Western blotting.	The proportion of viable neuronal cells after ischemia was greater in the pravastatin vs. control group, with greater expression of apoptotic cells in the control vs. pravastatin group. Bax protein expression was significantly decreased whereas, Bcl-2 expression was increased, but not significantly[17].
Senkyunolide I 	36 and 72 mg/kg	MCAO	Neurological function assessment, Measurement of brain water content, Detection of reporter gene activity	SEI administration significantly ameliorated the neurological deficit, reduced the infarct volume and brain edema, reversed the cerebralmorphologicdamage,decreasedthe levels of MDA and increased the activities of superoxide dismutase [25].
Phloretin 	20, 40, and 80 mg/kg	MCAO	Determination of SOD, GSH, glutathione peroxidase, and MDA levels, Reverse transcription polymerase chain reaction (RT-PCR), Western blot analysis	Phloretin significantly reduced infarct volume, brain edema, and ameliorated neurological scores. SOD, GSH and GSH-Px activities were greatly decreased, and MDA levels significantly increased. However, phloretin pretreatment dramatically suppressed these oxidative stress processes. Furthermore, phloretin up regulated Nrf2 mRNA and protein expression [26].

Mgso4 	1 mmol/kg	BCCAO for 10-min reperfusion 72 hr	Mitochondrial isolation and AFM measurement, Nissl staining	The MgSO4 reduced the perimeter of ischemic mitochondria. The length, width and area were significantly different. Besides, the adhesion force of isolated mitochondria from the MgSO4 group was close[27].
HAMI 3379	0.025, 0.05, 0.1, 0.2 and 0.4 mg/kg	MCAO for 60 min,24 or 72 hr reperfusion	Behavioural parameters Inclined board test Biochemical parameter-Cytokine assay	It attenuated the neurological deficits, and reduced infarct volume, brain edema, and neuronal loss and degeneration. HAMI 3379 inhibited release of the cytokines IL-1b, interferon-c (IFN-c), and tumor necrosis factor-a (TNF-a) into the serum and cerebrospinal fluid, microglial activation and neutrophil accumulation, inhibited astrocyte proliferation and reduced serum IL-4 [28].
Oleoylethanolamie	30 mg/kg	MCAO. For 120 min, 24 hr reperfusion	Behavioural parameters Morris water maze test, Electrophysiological recordings, Biochemical parameters-Immunohistochemistry and cell counting, Western blot	OEA markedly increased the expressions of brain-derived neurotrophic factor (BDNF) and peroxisome proliferator-activated receptors α(PPAR α). Chronic OEA treatment can exert functional recovery of cognitive impairments and neuroprotective effects via triggering of neurogenesis in the hippocampus [29].
scopolamine and mecamylamine 	0.1mg/kg, 0.5mg/kg	BCCAO for 45 min, reperfusion for 8 days.	Behavioural parameters Morris water maze, Biochemical parameters-Lactate dehydrogenase activity assay, Determination of caspase activity, acetylcholinesterase (AChE) activity, Determination of choline acetyltransferase activity (ChAT)	Scopolamine and mecamylamine alters memory functions following GCI/R injury substantiating the combined functional importance of both muscarinic and nicotinic receptor modulation in memory dysfunction [30].
Nitric Oxide, N-nitro-L-arginine methyl ester (L-NAME),		BCCAO for 10 min, 24 h reperfusion	Rat brain hippocampus cell dissociation, Flow cytometric analysis, infarct volume measurement, Nitric Oxide detection in vivo	Increased NO concentration, CBF significantly. Reduced infarct size and down regulated the cell death and reduced the brain injuries [31].

3,5,6,7,8,3',4'-Heptamethoxy flavones 	25 & 50 mg/kg	BCCAO for 12min reperfusion 72 hr	Y-maze test, Immunofluorescence for confocal microscopy	Protected against ischemia-induced memory dysfunction, rescued neuronal cell death in the CA1 cell layer, increased the production of BDNF, stimulated the autophosphorylation of CaMK II and suppressed microglial activation in the hippocampus [32].
Rosiglitazone 	3 mg/kg	BCCAO reperfusion 24 or 72 hr	Measurement of reduced glutathione (GSH) in brain tissue, Measurement of malondialdehyde (MDA) in brain tissue, Measurement of myeloperoxidase (MPO),	PPAR-γ agonist, demonstrated preservation of cell viability of CA1 hippocampal region and attenuation of brain edema. They also showed elevated levels of GSH and low levels of the other parameters In vitro, rosiglitazone dose-dependently inhibited ROS generation by neutrophils [33].
Puerarin 	2.62, 7.86 and 23.59 mg/kg	MCAO for 2 h	Cell viability, Oxygen glucose deprivation/reperfusion assay, Flow cytometry, Immunohistochemistry, Western blot analysis, Nissl stain	Puerarin treatment significantly improved the phosphorylation level of AKT in dose-dependent, reduced the infarct volume, The number of Nissl body, cleaved caspase-3 and GFAP positive cells increased [18].

CONCLUSION

Stroke is a destructive experience which can result in permanent disability in brain. There is no permanent drug which can improve the blood flow at infracted area and also improve the neurological deficit. Due to the lack of treatments available for stroke, many researchers will investigated the suitable plants or drugs for the treatment of this disease. Numerous medicinal plants and herbal drugs are available to treat stroke, some of the plants are *Ginkgo biloba, Fructus Chebulae,* Pomegranate, *Rosa laevigata,* Garlic, *Leonurus heterophyllus,* Olive, Grape, *Allium cepa***,** drugs.

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