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Therapeutic Implication of Herbal Phytoconstituents in Stroke

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ABSTRACT

Introduction: Ischemic stroke is a prominent global cause of death and disability. Other than employingischemic stroke treatment with recombinant tissue plasminogen activator, which must be administered within 3 hours of an acute incident and carries a high risk of hemorrhagic complications, there is currentlya few effective stroke treatment should be done. Herbal medicines, mainly derived from plants, are an excellent source for developing novel therapeutic agents for a wide range of human illnesses. In additionally, the multifaceted influence of herbal medicine and its active ingredients on stroke aetiology may indicate a bright future for natural medicine in stroke therapy.

Objective: Herbal medications are effective in stroke therapy because of their anti apoptotic, neuroprotective, anti inflammatory, and vascular protecting effects. Although herbal remedies are often thought of as safe and effective, there is a frequent misconception that if a treatment is effective, it must have side effects. As a result, herbal remedies are either useless or have undesirable side effects as medications. A sizeable portion of the populations in many developed countries relies on traditional healers and their supply of medicinal plants to suit their medical needs.

Conclusion: Even after due to historical and cultural factors, herbal medicines have typically retained their popularity despite the advent of modern medicine alongside such ancient therapies. Additionally, herbal remedies are more advantageous for chronic health issues like stroke. This review looks at the possible mechanism of Action for the Valuable Effects of Herbal Medicines in stroke patients.

1. Introduction

Stroke is one of the main factors contributing to death and disability in India. In the US, there are more than 795,000 stroke victims annually. Stroke is an abrupt loss of brain function that is a primary caused of death and disability. It is primarily brought on by a blockage in blood flow to the brain or by bursting of blood vessels or capillaries in the brain(that is, hemorrhagic stroke) (Khan et al., 2020; Andersen et al., 2009). Neurons of the impacted brain regiondie due to blood supply interruption or blood vessel rupture. Despite the fact that there are numerous medical treatments for restoring cerebral blood flow, including thrombolytic and endovascular therapy, the majority of stroke patients continue to be largely incapacitated (Iadecola & Anrather, 2011). When a vascular obstruction causes an ischemic stroke, the cerebral blood flow is disrupted, resulting in a multistage, complex pathophysiologic process known as an ischemic cascade at the cellular and tissue levels. In addition to chemical medications, herbal compounds that are relatively safe could be employed to treat complex illnesses like stroke. Additionally, these herbal remedies enhance brain microcirculation and shield cells from harm and apoptosis (Andersen et al., 2009). Cerebral ischemia, a vascular-induced neurological disorder in which a series of pathophysiological events, known as the 'ischemic cascade, because neuronal cell death. These events include energy failure, oxidative stress, inflammation, apoptosis, etc. reduced/blocked blood flow causes these adverse effects (Grewal et al., 2020; Iadecola & Anrather, 2011).

For the brain to operate normally, it requires a constant source of glucose and oxygen via blood flow, which can be disrupted, resulting in irretrievable brain injury. Ischemic brain injury occurs due to a series of molecular and cellular changes initiated by a rapid blood loss followed by reperfusion of the ischemic area. Brain damage occurs faster and more severely in the epicenter of the ischemic zone, where blood flow is the lowest, in ischemia caused by obstruction of the cerebral arteries, primarily the most typical type of stroke is caused by the middle cerebral arteries. (Tuo et al., 2022;

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Moskowitz et al., 2010). A severely ischemic core focus and an ischemic penumbra zone make up ischemia. Any investigation into the aetiology of ischemia lesions must focus on energy depletion. In the ischemic core area, neuronal cell death frequently results from energy loss. This is because neurons cannot manufacture adenosine triphosphate (ATP) without oxygen and glucose, which is required to supply energy to the ionic pumps that keep the membrane's ionic gradient of the neuron, primarily the Na+-K+ ATPase. As a result of the large Na^{+} and Ca^{2+} cytoplasmic buildup, brain edema and neurodegeneration develop (necrotic cell death) (Zhang et al., 2022; Iadecola & Anrather, 2011).Thus, some herbal medicines can lessen the intracellular Ca2+ overload brought on oxidation.

2. Herbal Phytoconstituents and Stroke

Scientists are becoming more and more interested in conventional and alternate remedies, primarily of plant origin, which have amassed a large number of observational and anecdotal experiences over thousands of years, due to the lack of adequate and widely applicable pharmacological strategies for treating ischemic stroke (Wu et al., 2021; Gong & Sucher, 1999). Herbal remedies are tailored and precise medicines, whereas western medicine is a therapy with a single objective. Western medicine is a therapy with a single goal, whereas herbal remedies are specialised and precise therapies. Depending on the patient's symptoms, herbal treatments might have several formulations for the same ailment; as a result, they can be thought of as a form of precision medicine. On the other hand, Western medicineis frequently delivered in fixed doses of particular medications, such as a tablet or capsule, and is not designed for individualised or exact therapy. (Roy & Datta, 2021; Bai & Zhang, 2021; Gaire et al., 2014; Wing et al., 2012).

In various forms, such as spices, herbs, and meals, plants provide an inexhaustible supply of promised compounds that can be used to improve human health. The ethnobiological strategy is a popular method for finding new neuroactive natural compounds in plants using as medicinal herbs, spices, or cuisines by various cultural groups (Rehman et al., 2019; Joshee et al., 2019). Some herbal remedies or derivatives have been shown to increase microcirculation in ischemic stroke patients is justified by the fact that it reduces ischemia/reperfusion injury, has neuroprotective properties, and prevents apoptosis. (He & Wang, 2021; Khan et al., 2021; Green 2008) (Figure 1). However, unlike the active (potent) components of industrially produced pharmacological drugs used in Western medicine, herbal medicines' active (potent) components are frequently not specified and comprehensively described, despite recent attempts by some governments to regulating dosages and use of these medications. Several potent phytochemicals generated from traditional medicinal herbs work on various pathways and direct targets (Saklani et al., 2022; Thapa et al., 2021; Wu et al., 2010). Given the complex and cumulative pathophysiological events in cerebral ischemia, medicines that bind to numerous targets or combination of medications that primarily operate on a single target may be more successful in treating ischemia and associated neurological diseases. Many herbal treatments have recently been tested for their potential neuroprotective effectiveness.

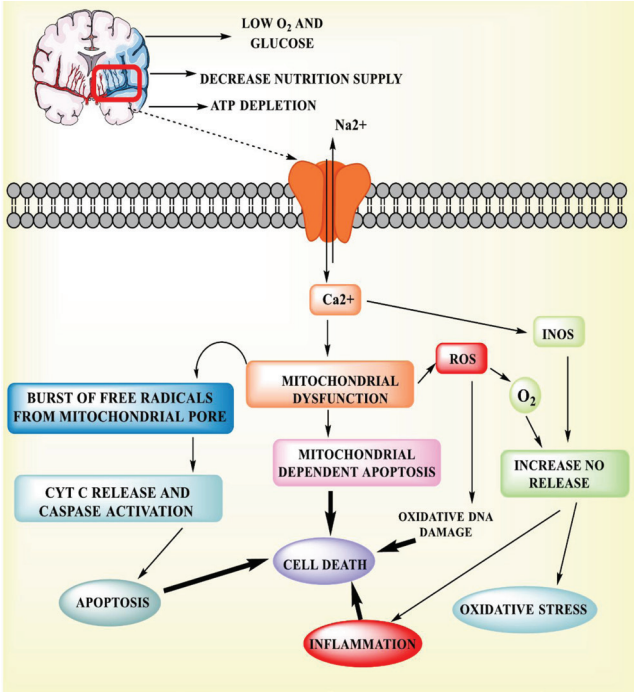

Figure 1: Pathophysiology of Cerebral Ischemic Injury.

3. Herbal Phytoconstituents Used for the Treatment of Stroke

The following table provides a summary of the various plants, their active ingredients, and their mechanisms of action (Table 1).The plants listed below have hepatoprotective, analgesic, anti-inflammatory, antioxidant, antithrombotic, detoxifying, anti-aging, antidepressant, and memory-stabilizing characteristics. The research listed above evaluated the beneficial effects of herbal remedies in minimising brain damage through several mechanisms, including antiplatelet and anti-inflammatory actions, and enhancing brain perfusion. (Figure 2).

Table 1: List of various plants and its constituents with their mechanism of action.

S.NO.	PLANT NAME	ACTIVE CONSTITUENTS	MOA	REFERENCE
1.	*Boerhaaviadiffusa*	b-sutosterol, hexacosonoic, Ester of b-sitosterol, Tetracosanoic, palmitic acid, stearic, Arachidic acid, Urosolic acid, b-ecdysone and tricontanol, Hentriacontane	Antioxidant activities, Anti-inflammatory, Immunomodulatory, Immunosuppressive, Hepatoprotective, Analgesic	(Tilak et al., 2004)
2.	*Bacopa monnieri*	Bacosides, cucurbitacin and plantainoside B.	Total adenine nucleotides, ATP content, energy charge, nitric oxide level, Na^+K^+ATPase, and $Ca^{2+}Mg^{2+}$ATPase activity were all measured in the brain	(Ghasemi et al., 2013)
3.	*Nardostachys jatamansi*	Angelicin, beta-eudesemol, Alpha-patchoulenese, beta-patchoulenese, betasitosterol, calarenol, calarene	Prevent lipid peroxidation and suppresses oxidative stress.	(Dwivedi et al., 2018)
4.	*Allium sativum*	Alliin, S-methyl cysteine and S-allyl cysteine),sulfur-containing amino acids (Leucine, methionine)	Suppression of free radical burst caused by reperfusion antioxidant enzyme preservation, Blood pressure reduction and platelet aggregation inhibition.	(Wattanathorn et al., 2011; Farhana et al., 2014)
5.	*Curcuma longa*	Diarylheptanoids, Curcuminoids, Curcumin, Demethoxycurcumin and Bisdemethoxycurcumin	Anti-inflammatory, antithrombotic and anti-oxidative	(Banjare et al., 2012)
6.	*Withaniasomnifera*	Withanine, pseudowithanine, tropin, pseudotropin, hygrin, isopellederine, anaferine, anahygrine and steroid lactones (withanolides), somniferine	Inhibiting Platelet Activating Factor (PAF) pathogenic manifestations, such as calcium overload and subsequent brain injury in the penumbra	(Balkrishna et al., 2017)
7.	*Rauwolfia serpentine*	Ajmaline, ajmalicine, reserpine, and serpentine	Antioxidant	(Ayyappan et al., 2016)
8.	*Hygrophilia ariculata*	Oleic acid, elaidic acid, isopropylester, 5-(hydroxymethyl), 5-(hydroxymethyl)-2 (dimethoxymethyl) furan and methyl, 2-furancarboxaldehyde, 2,6-difluorobenzoate	Neuroprotective and antioxidant	(Sahu et al., 2016)
9.	*Ocimum sanctum*	Cirsilineol, circimaritin, eugenol, methyl eugenol	Anti-stress, Detoxification antidepressant, memory stabilizer, anti-aging and cognitive activities	(Laird et al., 2010)
10.	*Plumbago zeylanica*	3-chloroplumbagin, 3'-biplumbagin, Chitranone, zeylinone, isozeylinone, elliptinone, droserone, Plumbagin	It regulated the expression of transcription factor Nrf2 in neuroblastoma cells.	(Bhanumathy et al., 2010)
11.	*Celastruspaniculatus*	Triterpene (lupeol), sesquiterpenepolyol ester and angulatueoid C	Antioxidant properties by decreasing the lipid peroxidation	(Ulpulwar et al., 2013)

12.	*Catharanthus roseus*	Actineoplastidemeric, Vinblastine, Vincristine, Vindesine, Vindeline and Tabersonine	Enhancing cerebral blood circulation, Increasing mental productivity, supporting brain metabolism, reducing memory and concentration issues, improving memory and thinking abilities, and preventing early brain cell aging	(Viswanatha et al., 2019)
13.	*Punica granatum*	Icosanoic, Linolenic, Oleic, Palmitic, Punicic, Stearic, Citric and Malic acid	Inhibit the generation of nitrite, ROS, and TNF-α	(Girdhar et al., 2015)
14.	*Zingiber officinalis*	linoleic, linolenic, palmitic, oleic, β-besabolene and zingiberene	Antiplatelet aggregation (inhibition of thromboxane synthesis), inhibiting HMGCoA reductase	(Sakina &Dandiya, 1990)
15.	*Centella asiatica*	Polyacetylenes, triterpenoids, asiaticosides, centellin, asiaticin and centellicin	Reduce permeability of the blood-brain barrier and mitochondrial damage to protect against glutamate or beta-amyloid-induced neurotoxicity	(Winkler et al., 1995)
16.	*Nicotiana tobacum*	Palmitic, oleic, and linoleic acids),triglycerides, sterol esters, and free sterols (Sitosterol).	Protect against neurodegeneration by inhibiting neuronal nitric oxide synthase.	(Schulz et al., 2001)

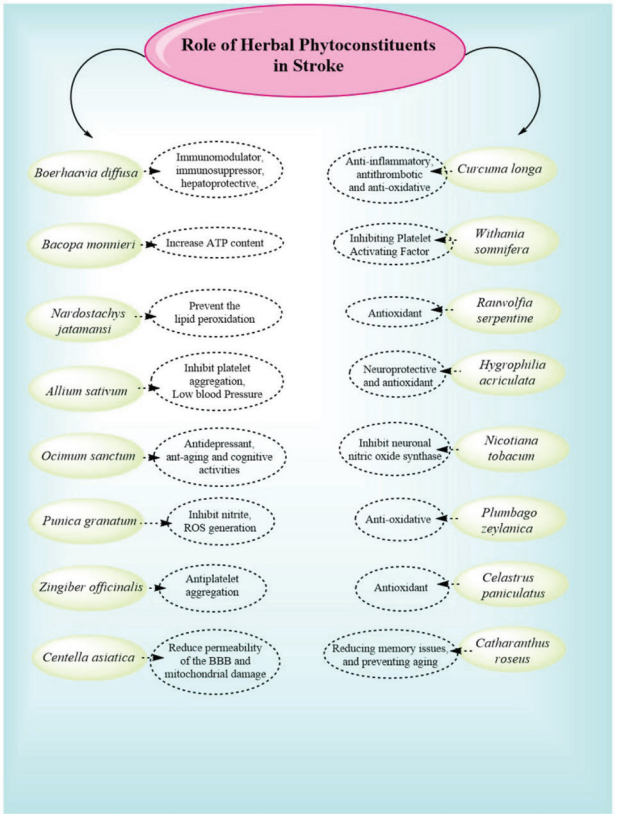

Figure 2: Summarization of the role of Herbal Phytoconstituents in Stroke.

4. Merit and Demerits of Herbal Phytoconstituents in Stroke

The stroke patient tolerates most herbal medicines/ preparations well, significantly fewer unwanted side effects compared to medication treatments. Herbs, on the whole, have fewer adverse effects than allopathic treatment and may be harmless to take over time. Herbal medicine also have the advantage of being less expensive and more readily available (Tewari et al., 2018; Iriti et al., 2010; Ernst, 2007; Wachtel-Galor et al., 2011). However, to properly evaluate their bioactivity, interpret laboratory results, and devise novel techniques, a greater understanding how bioavailable dietary phytochemicals is required, mostly in the central nervous system (CNS). Pharmacokinetic evidence to support their absorption, distribution, metabolism, and excretion (ADME) in the human body is still absent contempt several investigations on their bioactivities in experimental reports (Singh et al., 2021; Garg et al., 2021; Grewal et al., 2019).

Many herbal medicines have been shown to be effective; however, this is not true of many others due to a dearth of adequate scientific trials. Furthermore, because herbal remedies are natural, many individuals believe that they are risk-free. On the other hand, several natural treatments have been linked to severe toxicity. Another safety concern is the sometimes-unregulated quality of herbal medicines (Ernst, 2007). Furthermore, contamination of herbal remedies is possible, resulting in negative consequences.

Dietary phytochemicals/nutraceuticals, contrasted with, dietary phytochemicals/nutraceuticals must be absorbed to exhibit their pharmacological effects, and several human investigations have shown clear proof that these chemicals are absorbed and eliminated by the urine following delivery.

Furthermore, one of the essential properties of phytochemicals as a neuroprotective agent is their capacity to cross the blood-brain barrier (BBB) and influence CNS target areas. Even though various phytochemicals have been shown to have good benefits on neuroprotection after stroke insult in laboratory models, few exhibit the same effects in humans (Mantz et al., 2010). Because several drugs are difficult to transfer over the BBB, determining their actual neuroprotective effects is problematic. More consideration must be given to phytochemicals' therapeutic time windows. The majority of researchers continue to focus on "preconditioning" or preventive care for ischemic disorders rather than actual treatment, which has a concise therapeutic time window. Post-ischemic therapy has greater significance for ischemic stroke patients, as it is tempting to explore the therapeutic properties of desirable phytochemicals. Phytochemicals may also have remarkable therapeutic effects in the treatment of ischemia; nevertheless, therapeutic concentrations may cause cellular toxicity, resulting in serious side effects. Finally, The precise procedures and target are still described, based on the properties of various multi-component herb resource agents. As a result, determining whether the single- or coordination-compound technique is more compelling is complex (Wu et al., 2010). Lack of availability, expiration dates, regulatory requirements, lack of dose instructions, lack of quality control, poison risk connected with wild herbs, and combinations with other pharmaceuticals are some of the major downsides of herbal medicine, ambiguous health efficacy claims, self-medication, and so on (Ernst & Pittler, 2002; Capasso et al., 2000; Pinn, 2001). Animal research enabled most medicinal breakthroughs in stroke care in the previous century. Animal models of cerebral ischemia are widely used in toxicity testing and experimental/biomedical research to identify therapies for human disorders based on the notion that they are reasonably predicting of human outcomes. It is not easy to extrapolate findings from animal studies to human conditions due to evident and subtle variations in physiology, anatomy, and metabolism between people and animals. As a result, changes in gene regulation, gene expression, genes/alleles present, proteins and protein activity, proteins and protein activity, environmental revelations, evolutionary history, and other factors may be present. Furthermore, the complexity of brain vascularity and BBB (blood-brain barrier)penetrability restricts herbal medicine's therapeutic potential for various CNS illnesses, including stroke.

Conclusion

Herbal chemicals have much medicinal potential and are used to cure strokes. Several herbs used to prevent strokes and treat typical post-stroke symptoms are included in the review Natural medicine may have a promising future in the treatment of strokes given the extensive effects of herbal medicine and its active constituents on stroke pathophysiology. However, regulating the safety of herbal remedies for human use has greatly benefited from the translation of laboratory animal studies into clinical trials. Phytochemicals/natural compound that can cross the BBB (blood-brain barrier) and has been long therapeutic time windows, specific pharmacological targets and common adverse effects should be given more consideration. Yes, herbal medicine has a bright future as a therapy for stroke.

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Conflict of Interest

There is no conflict of interest.

Authorship Contribution

Conceived and Designed the Experiments: Thakur Gurjeet Singh, Heena Khan.
Analyzed the Data: Heena Khan, Thakur Gurjeet Singh.
Wrote the Manuscript: Vivek Rihal, Heena Khan.
Editing of the Manuscript: Thakur Gurjeet Singh.
Critically Reviewed the Article: Amarjot Kaur Grewal, Thakur Gurjeet Singh.
Supervision: Thakur Gurjeet Singh.

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