RESEARCH PAPER

Neuroprotective Potential Of Herbal Phytochemicals In Stroke Management: From Pathophysiology To Therapeutic Applications

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Abstract
Stroke continues to be one of the most significant global health burdens, as a major cause of death and disability with an enormous socioeconomic burden. Broadly, it is classified into ischemic stroke which occurs due to obstruction in the cerebral blood flow and haemorrhagic stroke caused due to rupture of vessels. Although we have made tremendous strides in acute treatments like thrombolysis and mechanical thrombectomy, their actual clinical utility is often limited due to a narrow therapeutic window inherent to these techniques and high chance of adverse haemorrhagic events. Thus, there is an immediate demand to develop new neuroprotective strategies that can blunt the intricate "ischemic cascade." Herbal phytochemicals are attractive multi-target drugs with potential neuroprotective effects, discussed in this review. In this review we attempt to throw light on intricate pathophysiological mechanisms incorporated in stroke, encompassing glutamatergic neurotoxicity, imbalance in redox homeostasis, BBB impairment and glial activation. Unlike conventional drugs pharmacologically active entities such as ginsenosides, vitexin, curcumin, resveratrol have the capability to alter neuronic injury through multiple mechanisms. These compounds effectively neutralizes ROS, impede inflammatory cytokines along with augmentation of neuronal programmed cell death. Furthermore, this review covers substantial clinical constraints related to the utilization of Phyto herbals, predominantly low aqueous solubility and imperviousness towards BBB.

Keywords: Thrombolysis, thrombectomy, stroke, ROS, haemorrhagic stroke, NF-κB

How to cite this article: Chandel S, Arora D, Sriharsh P, Naman S, Paliwal S, Patil S, Sharma S. Neuroprotective Potential Of Herbal Phytochemicals In Stroke Management: From Pathophysiology To Therapeutic Applications. Int J Drug Deliv Technol. 2026;16(33s):177-192. DOI: 10.25258/ijddt.16.33s.22

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1. INTRODUCTION

Stroke is one of the first leading causes of death and long-term disability worldwide placing a huge socioeconomic burden on health care in both developed and developing countries. It is generally divided into two large categories: ischemic and haemorrhagic stroke, which exhibit different aetiologies, pathophysiologic mechanisms, clinical features and prognosis. Ischemic stroke, which accounts for approximately 80–85% of cases, is caused by the interruption of cerebral blood flow due to thrombotic or embolic occlusion with subsequent cerebral ischemia, energy failure and neuronal injury [1]. Haemorrhagic stroke, i.e., intracerebral and subarachnoid haemorrhage results from rupture of cerebral blood vessels with direct neuronal injury, raised intracranial pressure and secondary ischemic damage in addition. Notwithstanding pooled clinical benefit from thrombolysis and mechanical thrombectomy, acute stroke treatment efficacy is restricted by the small therapeutic window of opportunity, potential for haemorrhagic events, and delayed intervention. In addition, the incidence of stroke is increasing in younger populations and low- to middle-income countries most likely due to the increased prevalence of hypertension, diabetes, obesity, and sedentary living. The heterogeneity of stroke Patho physiologies emphasizes the need for increased diagnostic accuracy, early intervention plans, and selective treatment strategies. Knowledge of the worldwide severity and mechanisms that distinguish ischemic from haemorrhagic stroke are critical in executing new technologies, like nanotheranostic systems, to enhance early stroke diagnosis and treatment with better patients outcome [2,3]. As a prominent global health problem of non-communicable diseases, and according to the latest GBD 2021 estimates it is currently considered as second cause of death globally, leading to 7 million deaths and third cause of death and

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disability together burden with more than 160 million DALYs are lost worldwide. This is the largest assessment of stroke epidemiology to date and shows a marked global rise in stroke numbers between 1990 and 2021. Over this period, the absolute number of strokes increased by 70%, stroke-related deaths by 44% and DALYs by 32%. Most importantly, burden of stroke is disproportionately distributed with low- and lower-middle-income countries contributing 87.2% of deaths and 89.4% DALYs, worldwide. Stroke is not only devastating in terms of its health consequences but also has significant economic ramifications; global annual costs are recently estimated to exceed USD 890 billion (approximately 0.66% global gross domestic product [GDP]) and on the rise, projected to almost double by 2050 [4].

1.1 Limitations of the Current Stroke Therapeutics

Current stroke treatment has several major bottlenecks and its clinical efficacy is limited. Thrombolytic treatment especially tissue plasminogen activator is limited by a short therapeutic window such that only a few patients are candidates for the treatment. Moreover, the risk of intracerebral haemorrhage and other bleeding complications restricts its use to a greater extent. Although mechanical thrombectomy is effective in certain cases, the infrastructure and skill set required is limited and not available to all. Furthermore, present treatment modalities are nonspecific and provide limited neural protection but have low effectiveness in patients with advanced disease or delayed admission, resulting in suboptimal functional recovery [5,6]. Table 1 enlists various conventional therapies along with their uses, mechanism and limitations.

S.No.	Therapy	Uses	Mechanism	Limitations	References
1.	IV Thrombolysis (tPA: Alteplase/Tenecteplase)	Acute IS within 3-4.5 hrs of onset.	Fibrinolytic: dissolves clots by converting plasminogen to plasmin.	Narrow time window; bleeding risk (sICH ~6%); exclusions (e.g., recent surgery, low platelets).	[7]
2.	Mechanical Thrombectomy (EVT)	Acute IS with large vessel occlusion (LVO), up to 6-24 hrs.	Endovascular: stent retriever/aspiration removes clot mechanically.	Requires neurointerventional expertise; access site complications; higher risk in large infarcts/low ASPECTS.	[8]
3.	Antiplatelet Therapy (Aspirin, Clopidogrel, Aspirin-Dipyridamole)	Secondary prevention post-IS/TIA; acute aspirin within 48 hrs.	Inhibits platelet aggregation (e.g., aspirin blocks COX-1; clopidogrel P2Y12).	Bleeding risk (GI); aspirin resistance; no acute benefit in severe stroke.	[9]
4.	Anticoagulation (Heparin, Warfarin, DOACs)	Secondary prevention in cardioembolic IS (e.g., AFib).	Inhibits clotting factors (e.g., DOACs target thrombin/Xa).	Contraindicated acutely (↑ICH risk); bleeding; poor adherence/dosing issues.	[9]
5.	Statins (e.g., High-dose Atorvastatin)	Secondary prevention in IS (non-cardioembolic).	Lowers LDL; plaque stabilization; anti-inflammatory effects.	Possible ICH risk in microbleeds/prior ICH; myopathy; not for acute phase.	[10]
6.	Blood Pressure Management	Acute IS (permit ↑ 185/110 pre-thrombolysis); HS (reduce to <140/90).	Antihypertensives (e.g., labetalol) lower BP to prevent extension/recurrence.	Over-lowering risks hypoperfusion/ischemia; rebound hypertension.	[11]
7.	Surgical Evacuation/Craniotomy	Large HS with deterioration; mass effect.	Open surgery drains hematoma, reduces ICP.	Invasive; no mortality benefit in trials (STICH); perioperative risks.	[12]
8.	Ventriculostomy/EVD	HS with IVH/hydrocephalus.	Drains CSF to control ICP.	Infection; haemorrhage; obstruction.	[13,14]
9.	Minimally Invasive Surgery (Endoscopy/Thrombolysis)	HS/IVH clot removal.	Stereotactic aspiration ± tPA for faster clearance.	Limited availability; rebleeding risk; trial results mixed (e.g., CLEAR III).	[15,16]

Table 1: Uses and Limitations of Current Stroke Therapies

1.2 Role of Herbal Remedies and Plant-Derived Phytochemicals in Stroke Management

Mounting evidences indicates that plant-derived phytochemicals exhibit significant neuroprotective effects in experimental models of ischemic stroke, particularly in middle cerebral artery occlusion (MCAO)–induced cerebral injury. Bioactive compounds including vitexin, eriodictyol, carveol, ferulic acid, rosmarinic acid, paeoniflorin, allicin, curcumin, ginkgolide K, 6″-O-succinylapigenin, forsythiaside A, isoquercetin, trilobatin, genistein, and tocotrienol demonstrate pleiotropic protective mechanisms encompassing antioxidant, anti-inflammatory, anti-apoptotic, and mitochondrial-protective actions. These agents have been shown to attenuate cerebral infarct volume, brain edema, oxidative stress biomarkers (ROS, MDA), and pro-inflammatory mediators (TNF-α, IL-1β, NF-κB, MPO), while simultaneously enhancing endogenous antioxidant capacity through activation of Nrf2-regulated signalling pathways.
[3,17–21]

Phytochemical	Biological Source	Class	Dose	Administration Route	Bioavailability	Animal Model	References
Vitexin	*Vitux agnus-castus*, *Vitex negundo*	Flavone C-glycoside (apigenin-8-C-β-D-glucopyranoside)	2 mg/kg	IV	Low, because of pre- systemic elimination	MCAO induced Rats stroke model	[22,23]
Eriodictyol	*Dracocephalum rupestre*	Flavonoid	1,2 and 4 mg/kg	Oral	Efficient	Male Swiss mice model and Rat model of focal cerebral ischemia	[24,25]
Carveol	Caraway seeds (*Carum carvi*), Dill seeds, Spearmint seed	p-menthane derivative	20 mg/kg	I/P	Efficient	MCAO-induced ischemic stroke model	[26,27]
Ferulic acid	*Ferula foetida* (asafoetida)	Plant phenols	80 and 100 mg/kg	IV	Inconsistent (0.4–98%)	MCAO-induced stroke model	[28,29]
Rosamirinic acid	*Salvia miltiorrhia*	Plant phenols	50 mg/kg	IV	Profoundly Low (1.57%)	Rat models of cerebral ischemia-reperfusion injury	[30,31]
Paeoniflorin	*Paeinia lactiflora* Pall.	Glycosylated monoterpenes	20 mg/kg	IV	Profoundly Low (2.32%)	MCAO ischemic stroke rat model	[32,33]
Allicin	Garlic species such as *Allium sativum*	Bioactive Sulphur Compounds (OSCs)	50 mg/kg	IP	Efficient	MCAO ischemic stroke rat model	[34,35]
Curcumin	*Curcuma longa* (turmeric)	diphenylheptanoid	300 mg/kg 50 mg/kg	IP	Profoundly Low	MCAO ischemic stroke rat model	[36–38]
Ginkgolide K	*Gingko biloba*	Isoprenoids	2.4 and 8 mg/kg	IP	Approximately 80%	Rat Ischemia model	[39]
6″-O-succinylapigenin	*Cynara cardunculus var. scolymus* L	Bioflavonoid	20, 40 and 60 mg/kg	IP	Efficient	MCAO-induced rat models	[40]
Forsythiaside A	Fruit of *Forsythia suspense.*	Phenylpropanoids	50 mg/kg	IP	Intermediate Impact	MCAO-induced rat models	[41]
Isoquercetin	Citrus fruits, apples, onions etc.	O-Glycoside	20 mg/kg	IV	Intermediate Impact	MCAO-induced rat models	[42,43]
Trilobatin	*Lithocarpus polystachyus*	Plant phenols	20 mg/kg	IV	--	MCAO-induced rat models	[44]
Genistein	Plants including lupin, fava beans etc.	7-hydroxyisoflavone	10 mg/kg	IP	Low	-	[45,46]

Table 2. This table incorporates various Phytochemicals, their route of administration, dose, animal model used along with bioavailability

2. Pathophysiology of Stroke

Amongst all reasons stroke is the widespread cause of disability in humans worldwide. When an embolism appears in the cerebral blood vessel it leads to occlusion and causes ischemic stroke, Which ultimately leads to oxygen and other important nutrients deficiency. Furthermore, there is a swift attenuation in ATP, electrolyte disbalance, glutamate mediated toxicity and evolution of cellular swelling, which cause irreparable neuronal damage. In contrast, haemorrhagic stroke is caused by rupture of cerebral vessels, commonly associated with hypertension or aneurysms, leading to extravasation of blood into the brain parenchyma or subarachnoid space. The resulting hematoma exerts mechanical compression and mass effect, disrupts normal cerebral architecture, and triggers secondary inflammatory and neurotoxic processes that exacerbate brain damage.[47,48]

2.1 Pathogenic pathways of ischemic stroke

Ischemic stroke is a condition that interrupts cerebral blood flow producing a complex series of pathologic changes that ultimately culminate in neuronal injury and death. Energy depletion accompanying hypoxia ischemia leads to decreased ATP with alterations in ionic homeostasis and impairment of calcium balance, which trigger massive glutamate release and overstimulation of NMDA receptor (via glutamatergic excitotoxicity), leading to oxidative damage, impaired mitochondrial function, and ultimately neuronal death. At the same time, oxidative stress is increased by overproduction of reactive oxygen species from dysfunctioning mitochondria as well as enzymes such as xanthine oxidase and NADPH oxidase leading to more damage to lipids, proteins, and DNA. These events trigger a neuroinflammatory response via microglia and the infiltrating immune cells, resulting in the opening of BBB and secondary damage. Neuronal death can result from various types of regulated cell death, such as apoptosis, ferroptosis, necroptosis, pyroptosis, and parthanatos as well as phagoptosis; in contrast, uncontrolled autophagy might exert an adaptive or toxic influence on neurons based on the level of activation and duration. [49,50] Figure 1.

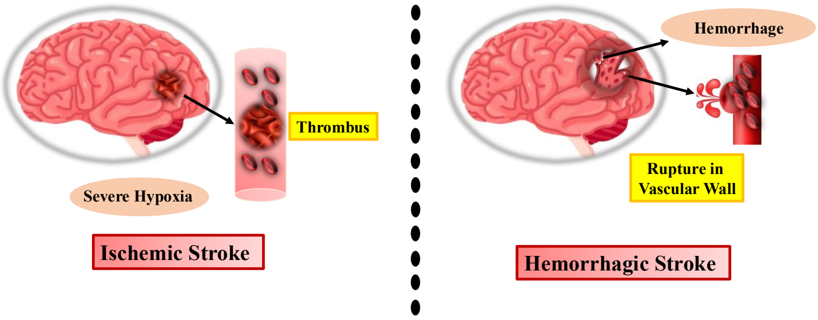


Figure 1: Figure depicts the Ischemic and Haemorrhagic Stroke

2.2 Pathophysiology of haemorrhagic stroke

Although less frequent than ischaemic stroke, haemorrhagic stroke has significant morbidity and mortality from cerebral vessel rupture resulting in intracerebral or subarachnoid bleeding, often secondary to hypertension, anticoagulant therapy, trauma or aneurysm rupture. After intracerebral haemorrhage, hematoma is quickly formed and directly damages the structure of the brain, but secondary injuries also result from it (hematoma expansion and oedema) or form toxic blood components such as thrombin, haemoglobin, and iron. These events induce oxidative stress via over-generation of reactive oxygen species and lead to mitochondrial dysfunction, apoptosis, and blood–brain barrier damage. At the same time, vigorous neuroinflammatory action is triggered involving microglial and astrocyte activation, inflammasome signalling and emerging of pro-inflammatory mediators including TNF-α, IL-1β and HMGB1 that collectively aggravate neuronal injury and neurological dysfunction [51]. Figure 1

2.3 Therapeutic targets influenced by herbal phytochemicals

Herbal phytochemicals regulate the pathophysiology of ischemic and haemorrhagic stroke by impacting interconnected mechanisms viz. oxidative stress, neurological inflammation, apoptosis, vascular dysfunction, and blood-brain barrier destruction which provides a multitargeted neuroprotective approach. Curcumin, resveratrol and quercetin are known bioactive compounds that increase endogenous antioxidant defence mechanisms like Nrf2/HO-1 pathway, whereas ginsenosides, apigenin and curcumin dampen inflammatory signal cascades (NF-κB, MAPK JAK/STAT) and influence microglial phenotype. Its anti-apoptotic effects are related to the up-regulation of Bax/Bcl-2 ratio and suppression of caspase triggering. Moreover, phytochemicals have antithrombotic and vasodilatory effects, enhance cerebral blood flow, maintain the stability of the blood–brain barrier and facilitate neurogenesis along with synaptic plasticity [52].

3. Pharmacology-Based Mechanism of Herbal Drugs on Stroke

The phytomedicines mitigate and remediate stroke pathways utilizing composite and poly-pharmacological mechanisms. The key targets of some common phytochemicals involve amelioration of microcirculation via scavenging free radicals, preventing inflammatory response, impeding platelet aggregation, modulating phosphatidylinositol 3-kinase/Protein Kinase B signaling pathways, stabilizing ras signaling networks, stimulating vascular endothelial growth factor A and hypoxia-inducible factor-1 alpha [53],[54], [55],[56]. In contrast to modern medicines the phytochemicals bear lesser side effects and safe for use.

3.1 Indigenous Knowledge Systems and Historical Use

Traditional medicine (TM) or Traditional systems of medicine, including Traditional Chinese Medicine (TCM), Ayurveda and indigenous systems, perceive health and disease from a different point of view to Western biomedicine, often denigrated as parochial in scope [57]. Over the generations, traditional healers have developed large pools of empirical knowledge and an extensive repertoire of drug resources that constitute a *materia medica* of indigenous medical systems [58]. The use of traditional Chinese medicine (TCM) for stroke treatment dates back thousands of years in China, and the scientific context even though it has had meagre records during early ages has developed constantly with ancient empirical evidence laying a base for modern domain like those ethno-pharmacology [53]. The long-standing practice of complex multi-herb combinations in TCM has traditionally challenged the simplistic approach inherent in reductionist science, but is now being reinterpreted within systems biology and network pharmacology models that embrace poly-pharmacology or the concomitant interaction of multiple compounds with multiple targets [58],[59].

3.2 Widely Utilized Medicinal Plants for Cerebral Ischemia

Diverse phytochemicals have demonstrated potential against cerebral ischemia and brain related disorders. For instance, studies have reported *Artemisia absinthium* prevalently known as absinthe, significantly curtailed ischemia and reperfusion mediated augmented concentrations of thiobarbituric acid reactive elements [60]. *Ocimum basilicum* is another herbal drug that bears cerebral-protective effects along with decrement in infarct magnitude and oxidative degeneration of lipids, additionally restoration of intrinsic antioxidant defence systems [61]. There are many other plants including *Ginkgo biloba* L, *Ocimum tenuiflorum*, *Gastrodia elata*, green tea, olive leaves, *Lavandula officinalis* etc., have shown promising potential against cerebral ischemia in various in-vitro and in-vivo studies. These all herbal drugs utilizes copious mechanisms to show their neuroprotective effects incorporating suppression of active iNOS, generation of NO, impediment of HIF-1A, actuation of TNF-α, attenuation of intercellular glutamate, and endo-cellular calcium. [62] [63] [64] [65] [66] [67][68] [69] [70] [71].

3.3 Cross-Cultural Similarities and Regional Practices

The conventional remediation modalities have acted as rudimentary determinant for therapeutic interventions, mirroring millennia of evidence-based knowledge and cultural transmission globally. Incorporating a broad spectrum of traditional knowledge systems viz. traditional Chinese medicine, Ayurveda, Siddha, Unani, European herbalism and other ethnopharmacological practices make this system more versatile [72]. From centenaries these remediation modalities are essential part of clinical practices across Africa, Asia, USA and Europe [73][74][75]. Ingrained in provincial conceptual, aesthetic and intervention strategies conventional remediation modalities underscore integrated well-being and stability of physiological components [76]. Over the past decade multidisciplinary approach incorporating amalgamation of conventional and allopathic remediation have attained elevated utilization Globally. This paradigm focusses on fostering validated and evidence-based utilization of herbal remediation [77].

4. Various Extraction Techniques for Phytochemicals

There are copious processes to extract phytochemicals from medicinal plants such as Microwave-Assisted Extraction (MAE), a sophisticated and productive extraction method that utilizes microwaves for heating dissolvent and sample leading to accelerated perforation and liberation of required phytoconstituents. Another method incorporates Ultrasound-assisted extraction (UAE) a productive, and ecologically sound process, which utilizes ultrasonic waves to generate vibrational cavitation to disrupt semi permeable membrane, augmenting molecular diffusion and dissolvent perforation [78,79].

4.1 Selection of Plant Material and Herbal Preparation Forms

First step for recovering phytochemical, is stringent selection of suitable herbal constituent as it crucially affects bioactive plant compounds and constancy of the yielded extract [24]. The fundamental factors involve precise taxonomical determination, provenance, crop season and particular component harnessed viz. leaves, fruits etc. [23] [25]. Furthermore, the herbal formulation development contributes pivotally to regulate stability and isolability of phytoconstituents [26][27]. Therefore, it is crucial to select a proper and apt extraction process for the phytoconstituents in order to preserve their structure and desired pharmacological action [28].

4.2 Conventional Extraction Methods Used in Herbal Medicine Research

Several conventional methods incorporating maceration, decoction, infusion, soxhlation etc. have been used for extraction of phytochemicals from medicinal plants utilizing apt solvent system since ancient times [29]. The selection of extraction process governed by structure of plant components, solvent utilized, solvent pH, temperature and ratio of solvent and sample.[30,32]; Commonly used solvents for the phytochemical extraction process are water, alcohol, chloroform, ether, and green solvent, which are used for extracting secondary metabolites, flavonoids, fats, wax, gums terpenoids, fatty acids etc. [22,33] Various factors are to be kept in mind while selecting solvent such as safety, selectivity, reactivity and viscosity etc. [30,34][35].

4.3 Advanced and Green Extraction Technologies

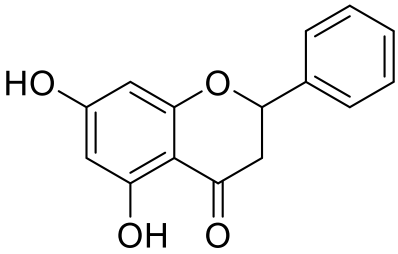
The green chemistry techniques are beneficent over traditional extraction methods as they ameliorate and strengthen process of extraction, conserve ecological conditions and focused on consumer product safety management [36]. Such techniques involve utilization of sophisticated extraction processes viz. microwave-assisted extraction (MAE), supercritical fluid extraction (SFE), ultrasound-assisted extraction (UAE), and pressurised liquid extraction (PLE), amalgamated with generally recognized as safe solvents like sustainable, microbially degradable and non-toxic dissolvents [30,37]. As a sophisticated method for extraction MAE uses microwaves, to extract phytoconstituents from various plants. The process is based on coupling amongst microwave radiations, that induce electromagnetic radiations bearing a frequency spanning between 300 MHz to 300 GHz and sample to potentiate mechanism of extraction from food and agronomic Industrial residues [35,38]. The constituents absorbs microwaves which leads to a sudden shift in polar components generating dipolar rotation, causing molecular transport synchronised with already existed electric field that further, induces internal energy in the form of heat causing bond cleavage and expedite the extraction mechanism. Furthermore, UAE utilizes ultrasonic waves of >20 kHz to cleave the extracellular matrix and liberate phytoconstituents within solvents. In contrast to others, supercritical fluid extraction (SFE) is an optimized technique that utilizes compounds, such as carbon dioxide at supercritical conditions to extract target phytoconstituents, attributable to its comparatively low critical temperature and pressure it is innocuous and efficacious for numerous employments [39][40,41]. Another pivotal extraction method involve pressurised liquid extraction method (PLE) which is also termed as accelerated solvent extraction (ASE) utilizes dissolvents at high temperature i.e. between 40^0C to 200^0C and elevated pressure between 3.3 MPa to 20 MPa, swiftly extract analyte by solidified and quasi-solid media. All these sophisticated extraction methods have demonstrated sturdy capabilities for extracting phytochemicals from plant sources along with mitigating the limitations of traditional extraction methods. [42][43].

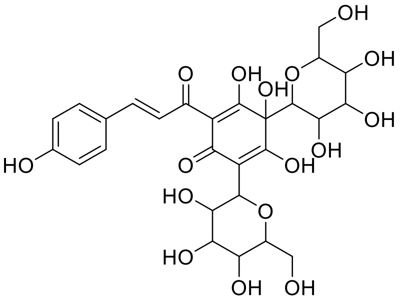
4.4 Factors Influencing Phytochemical Yield and Reproducibility

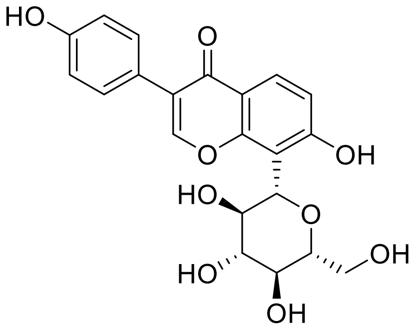
There are multifarious factors that affects medicinal plants attributes during their operational phases including cultivation to post harvesting phase inevitably impacting their pharmacological efficaciousness [25,44]. These determinants involve environmental parameters, asymmetrical dissemination of phytoconstituents throughout the plant, causing divergence in the terminal medicinal attributes, drying operation, that affect moisture level, neutralize constituents, and elongate stability period leading to impacting attributes of medicinal plant. Segregation and storing methods are identically pivotal because they ascertain the quality of end product by limiting impurities and attenuating the frequency of degeneration [26]. Another pivotal determinant is age of the plant, diverse experimental studies have revealed the ontogenetic deviations in the composition of phytochemicals and their biological effects, for instance an undeveloped fruit extract of black raspberry demonstrated better antiallodynic impact then a completely developed fruit [23,30]. Furthermore, extracts of *Iphiona aucheri* during flowering season bears maximum concentrations of phytochemicals incorporating phenols, tannins, anthocyanins and flavonoids which ultimately leads to optimum free-radical scavenging, antimycotic and antimicrobial properties [24,45].

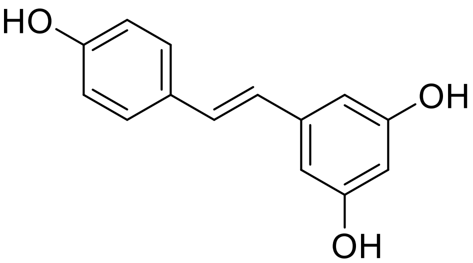
5. Primary categories of phytochemicals for Stroke management

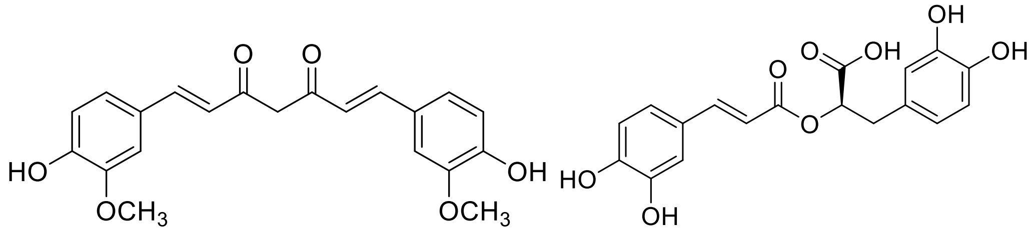
Copious naturally occurring pharmacologically active constituents, extracted from medicinal plants are thoroughly examined for their efficaciousness against stroke. They exert their action by preventing deterioration of brain cells from impairment and heals them too. These categories predominantly incorporates polyphenols, isoprenoids, alkaloids, and organosulfides. [46].Table-2 enlists various phytochemicals along with their categories.


1. Pinocembrin (123)


2. Hydroxysafflor yellow A (HSYA) (124)

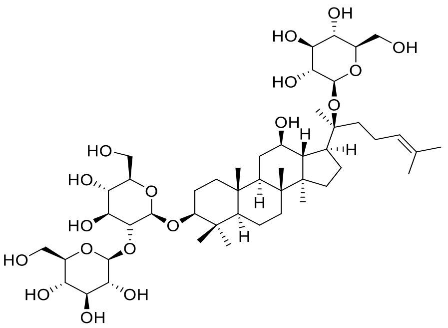

3. Puerarin (131)


4. Resveratrol (126)

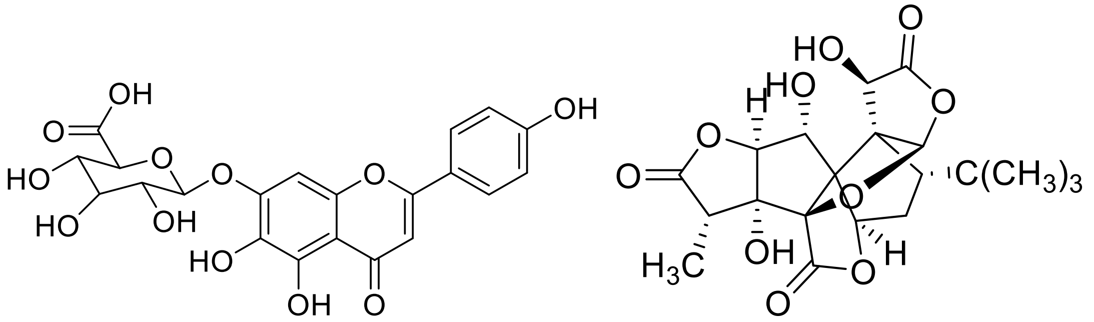


5. Curcumin (130)

6. Rosmarinic acid (132)

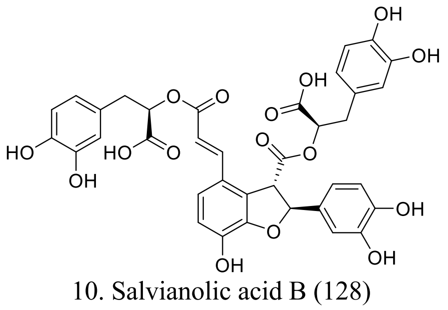


7. Ginsenoside Rd (125)



8. Scutellarin (127)

9. Ginkgolide B (129)



10. Salvianolic acid B (128)

Figure 2: Chemical Structures of Commonly Used Phytochemicals

5.1 Flavonoids

An epochal subgroup of polyphenols, flavonoids are widely recognized for their high free radical scavenging and anti-inflammatory potential [81]. For instance, studies on *Ziziphora clinopodioides* have highlighted the role of its flavonoid constituents in the management of neurodegenerative disorders and brain injuries [82]. Furthermore, luteolin-7-*O*-β-*d*-glucuronide (LGU), a flavonoid glycoside isolated from *Ixeris sonchifolia*, has demonstrated significant protective effects against cerebral ischemic injury through modulation of the RIP3/MLKL signalling pathway, as evidenced in both in vitro oxygen–glucose deprivation models and in vivo middle cerebral artery occlusion models [83].

5.2 Terpenoids

Terpenoids, including triterpenoid glycosides such as saponins, exhibit significant therapeutic potential against various neurological disorders, including stroke and atherosclerosis [84]. These compounds commonly exert their neuroprotective effects through anti-inflammatory and antioxidant mechanisms [85]. For example, thymoquinone (TQ), a monoterpene quinone, has demonstrated protective effects against *D*-galactose–induced memory impairment in rats by modulating MAPK signaling, oxidative stress, and neuroinflammatory pathways [86] . Similarly, vialinin A, a terpenoid isolated from a Chinese edible mushroom, has been shown to attenuate oxidative stress and neuronal injury following ischemic stroke by promoting Keap1 degradation through the inhibition of USP4-mediated deubiquitination [87].

5.3 Alkaloids

Alkaloids are a complex group of nitrogen-containing phytochemicals, which exhibit wide pharmacological activities; many have shown anti-stroke effects probably by their neuroprotective effects in the manner such as antioxidant and anti-inflammatory agents or through modulation of neurotransmitter systems but the exact mechanisms contributing to the action of individual alkaloid remains not fully clarified [88]. Tetramethylpyrazine (TMP), a bioactive ingredient derived from ligustrazine in the Traditional Chinese Medicine Ligusticum chuanxiong, is widely studied for its cerebroprotective effects on cerebral microcirculation enhancement, platelet aggregation attenuation, oxidative stress suppression and inflammatory response inhibition that affect multiple phases of the ischemic cascade at once [89]. Another prominent alkaloid, huperzine A derived from Huperzia serrata, is commonly known as an acetylcholinesterase (AChE) inhibitor used to treat Alzheimer's disease, and also shares stroke-related neuroprotective features including anti-apoptosis, reduction of oxidative stress and suppression of neuroinflammation to maintain the neuronal integrity in ischemic insult [46,59]. Berberine, an isoquinoline alkaloid from natural herbs such as *Coptis chinensis* Franch and *Phellodendron amurense*, has also been suggested to exert neuroprotection by regulating inflammation, oxidative stress pathway, mitochondrial function and consequently attenuating additional brain injury after ischemia–reperfusion injury [46]. Also, other alkaloids and plant extracts rich in alkaloids like those from Uncaria rhynchophylla (Gouteng) which has long been used for the treatment of neurological disorders including stroke in TCM are actively being investigated, with their beneficial effects suggested to be mediated through anti-inflammatory actions, modulation of neurotransmitter systems and regulation of cerebral blood flow [89].

5.4 Phenolic Acids

It is one of the pivotal categories of secondary metabolites bearing a phenolic ring along with carboxyl group attached to it. These metabolites profusely located in fruits, plants, and vegetables and bears sturdy antioxidant potential that safeguard from various infections [90]. An essential hydro soluble and biologically active phytochemical Hydroxysafflor Yellow A have been extensively exploited for remediating ischemic stroke in copious experimental studies, and have shown potential in treating the condition which make it a promising compound for mitigating stroke and related conditions [91].

5.5 Lignans

A polyphenolic phytochemical lignan located in linseed, benniseed, legumes and kernels substantiated to bear free radical scavenging and anti-inflammatory attributes [88]. This phytochemical exert its action by triggering cytological immune signalling cascades, they curtail disbalance among oxidative species by supressing ROIs, and safeguarding against peroxidative degradation [92].

5.6 Organosulfur Compounds

This class of phytochemicals, bearing Sulphur moiety, extensively located in genus allium and brassicaceous viz. *Allium sativum*, *Allium cepa*, and *Brassica oleracea* L. etc. These phytochemicals are recognized for their antioxidant, anti-inflammatory, biocidal and antineoplastic attributes. These compounds also bear a sturdy capability of mitigating crucial processes involved in neuronal dysfunction and death [93].

5.7 Stilbenes

Stilbenes are the bunch of polyphenolic compounds located in *Vitis vinifera*, *Arachis hypogaea* and bacca acts as biocidal agent safeguarding against ailments and lesions. A crucial phytochemical resveratrol of this class potentially exert cerebroprotective effect by targeting auxiliary cerebral damage [80,94].

S.No.	Plant-Derived Bioactive Compounds	Biological Source	Mechanism	References
1	Pinocembrin	*Eucalyptus*, *Pinus* heartwood, Poplar	Regulation of Ca^{2+} channels, Prevent Nerve Cell Death and Impede Programmed Cell Death	[95]
2	Hydroxysafflor yellow A (HSYA)	*Carthamus tinctorius L.*	Impede Inflammation by acting as SIRT1 activator, Neurotrophic Factor Modulation	[96,97]
3	Ginsenoside Rd	*Panax ginseng*	Impede Inflammation by acting on NF-κB and Equilibration of Mitochondria	[98]
4	Resveratrol	*Vitis vinifera*	Activation of SIRT1, Free Radical Scavenger and Prevent Inflammation	[99,100]
5	Scutellarin	*Erigeron breviscapus*	Free Radical Scavenger by targeting Nuclear factor erythroid 2-related factor 2, Prevent Inflammation and maintain the integrity of blood brain barrier	[101,102]
6	Salvianolic acid B	*Salvia miltiorrhiza*	Act as Free Radical Scavenger, Prevent programmed Cell Death, Alterations in Phagocytosis Mechanism	[103,104]

7	Ginkgolide B	*Ginkgo biloba*	Impede Platelet actuation factor, and Prevent programmed Cell Death	[105,106]
8	Curcumin	*Curcuma longa*	Actuation of Nrf2, and Alleviate excitotoxicity	[107,108]
9	Puerarin	*Pueraria lobata*	Attenuate Reactive Oxygen Species, and Shield Mitochondria	[109,110]
10	Rosmarinic acid	*Rosmarinus officinalis*	Impede NOX and attenuate Inflammatory Process	[111]

Table 3: Characterized Phytochemicals and Their Reported Mechanisms of Action in Stroke Pathophysiology

6. Mechanism of Action of Herbal Phytochemicals

Various phytochemicals act through polypharmacological framework to manage stroke, that revolves around deterioration of intricate mechanisms involved in ischemia [46]. The core mechanism incorporates free radical scavenging, where phytochemicals act upon ROS pathway, which further stimulates NFE2L2 pathway that ultimately leads to antioxidant action. Another mechanism involves protection from inflammation, where phytochemicals potentially impede proinflammatory signaling cascade. [57,112]. Moreover, they also act through regulating calcium channels by impeding neuronal overload of calcium [113]. Further, safeguarding mitochondria and blood brain barrier are also involved in the pivotal mechanisms of phytochemicals against stroke [114][115]. Table 3 and table 4 incorporates various phytochemicals and their mechanisms for stroke management.

Class of the Phytochemical	**Name**	**Biological Target**	**Therapeutic Outcomes**	**References**
Phenolics	Salvianolic acid B, Ferulic acid, Curcumin	NF-κB/MMP-9, NLRP3, impediment of Lysine Deacetylase (KDAC)	Coherence in blood brain barrier and attenuation of Inflammasome	[116]
Stilbenoids & Alkaloids	Resveratrol, vinpocetine	NAD-dependent protein deacetylase sirtuin-1, Liberation of Neurotrophic Factors.	Modulation of auto phagocytosis, Inter neuronal Remediation	[46]
Terpenoids	Ginkgolides, bilobalide, borneol	Thrombocyte Conglomeration and Ca^{2+} channels	Preclusion of Intravascular Coagulation and Attenuation of Programmed Cell Death	[46]
Flavonoids	Puerarin, Pinocembrin, Baicalin	Nrf2/HO-1, BDNF, mitophagy (PINK1/Parkin)	Diminution of Infarct and Neural cell generation	[46]

Table 4: Classes of Phytochemicals and their biological targets

7. Evidence and Safety in Pre-Clinical Practice of Herbal Medicines

In a preclinical study, researchers subjected male C57BL/6 mice to distal middle cerebral artery occlusion, followed by intraperitoneal curcumin administration (150 mg/kg) at 0 and 24 h post-ischemia. Infarct volume was quantified via TTC staining at 72 h, sensorimotor deficits via adhesive removal and modified Garcia tests at days 3–10, and microglial polarization via RT-PCR (M1 markers: TNF-α/IL-12/CD16; M2: CD206/Arg1) and immunofluorescence ($CD16^+$/$CD206^+$/$Iba1^+$ cells) at days 3/10. Parallel in vitro experiments stimulated BV2 microglia with LPS/IFN-γ ± curcumin (12.5–25 µM) for 48 h, evaluating mRNA/cytokine expression by RT-PCR/ELISA. Curcumin markedly reduced infarct volumes, enhanced neurological recovery, suppressed M1 polarization (↓TNF-α/IL-12/CD16) while promoting M2 shift (↑CD206/Arg1), and attenuated pro-inflammatory cytokines (TNF-α/IL-6/IL-12p70) in both models, underscoring its role in microglial repolarization and neuroprotection post-stroke [117]. In another study, researchers experimented on male Sprague-Dawley rats (250–300 g) unsystematically allotted to control, sham, MCAO, or MCAO+vitexin groups, administering vitexin (2 mg/kg) intravenously 60 minutes antecedent to central cerebral artery occlusion (MCAO), and revealed that brain infarction (assessed via TTC staining), apoptosis (Caspase-3/Bax/Ki-67/Bcl-2 levels), oxidative injury (LDH/MDA/NO), inflammation (TNF-α/IL-6↓, IL-10↑), along with autophagy (mTOR/PPARγ/p62↑; Ulk1/Beclin1/LC3II/I↓ via mTOR/Ulk1 pathway) were significantly ameliorated by vitexin—effects reversed by rapamycin—thus confirming vitexin's neuroprotective role in suppressing MCAO-induced cerebral ischemic stroke through anti-apoptotic, antioxidant, anti-inflammatory, and autophagy-regulatory mechanisms [118]. *Atef et al.,* after performing preclinical studies on natural compounds containing a sulfur moiety that exhibit diverse biological activities beneficial in CNS disorders, examined the curative potential of allicin, in a mouse model of intracerebral hemorrhage (ICH) induced by intrastriatal collagenase injection. Allicin (50 mg/kg, intraperitoneally) was administered starting 3 h post-ICH and continued daily. The treatment significantly attenuated ICH-induced neuropathology, as evidenced by increased neuronal survival within contusion, preservation of axonal transport and structural integrity, and marked reductions in microglial/macrophage activation and neutrophil infiltration. [119].

8. CHALLENGES WITH HERBAL REMEDIES

The herbal remedies though considered safe and reliable for managing stroke yet face substantial constraints during evidence-based assessment. Major challenges involve pre-clinical & clinical gaps, risk mitigation & analytical validation, narrow therapeutic index, pharmacological synergy, blood brain barrier conductance, methodological deviations, molecular pathways, and polypharmacology etc. Greater emphasis on clinically relevant experimental models, synergistic herbal combinations, real-world evidence generation, and integrative treatment approaches that combine herbal therapies with standard stroke care may help expand therapeutic windows and support the development of personalized, evidence-based interventions validated through rigorous clinical trials [55].

9. CONCLUSION

Stroke is declared as a worldwide epidemic by WHO with escalating incidence, high mortality, persistent disability and an emerging economic burden predominantly in poor and median-income countries. Despite advances in available conventional therapies for acute stroke, such as thrombolysis and mechanical disruption of the clot via endovascular therapy, they have had limited clinical applicability because of a restricted therapeutic time window, haemostatic dysfunction, lack of infrastructure, and inadequate neuroprotection - leading to poor outcome in many patients. The complicated and disparate pathological mechanism for ischemic stroke (IS) and haemorrhagic stroke (HS), necessitates the development of new targeted drugs. In this context, mounting preclinical evidence supports that herbal drugs and plant-derived phytochemicals offer considerable potential for versatile neuroprotection given their multi-faceted intervention in the key pathological pathways associated with AD viz. oxidative stress, neuro-inflammation, excitotoxicity, programmed cell death, autophagy, mitochondriopathy and blood–brain barrier (BBB) disruption. A diverse array of phytochemical categories, like flavonoids, terpenoids, alkaloids, polyphenols, stilbenes along with organosulfur compounds show pleiotropic mechanisms of action that fit the multi-faced properties of stroke pathogenesis. However, in spite of promising preclinical results, translation to clinic remains a formidable challenge due to the low bioavailability of many herbal compounds, lack of standardized preclinical and clinical research methodologies, insufficient pharmacokinetic (PK) and safety data from toxicological studies in animals/healthy volunteers and limited large scale/methodologically sound human trials. The combination of green extraction techniques, novel phytochemical characterization methods, system pharmacology and nanotechnology based delivery systems is seen as a potential strategy to circumvent these constraints. Further advances will rely on scholarly translation research, better methodological strategies for clinical trials and community based studies, successful merging of ancient wisdom with modern biomedical science, in addition to modes of treatment that integrate the available individualistic models. In sum, herbal phytochemicals have significant potentials to be adjunctive or alternative agents for conventional stroke care that say fresh leaves or open new frontiers in prevention, treatment and rehabilitation of disease in the context of integrative healthcare.

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