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Review Article

Therapeutic Potential of *Withania somnifera* (L.) Dunal (Ashwagandha) in Neuronal Plasticity and Recovery after Stroke

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Abstract

The incidence and mortality of stroke are gradually increasing. In this context, post-stroke neuronal loss and the related long-term complications, along with costly treatment strategies, are significant concerns for healthcare professionals, and effective, convenient, and inexpensive therapeutic modalities are required. Natural and easily accessible herbal remedies may be the optimal option in post-stroke recovery. This narrative review aims to summarize the neuroprotective properties of *Withania somnifera* (Ashwagandha) and its therapeutic efficacy in neuronal plasticity and recovery after stroke. Original research articles, reviews, and case studies were sourced from databases such as PubMed, Web of Science, Scopus, Google Scholar, Medline, and Embase. Only full articles published in English up to July 2025 were considered. Keywords including *W. somnifera*, Ashwagandha, stroke, cerebral ischemia, neurodegeneration, neuronal loss, and post-stroke recovery were utilized for the literature search. It has been found that various plant parts of *W. somnifera* are abundant in bioactive compounds. The neuroprotective effects of *W. somnifera* are documented in numerous diseases. Nevertheless, *W. somnifera* is reported to be involved in modulating various biological pathways to mitigate neuroinflammation, apoptosis, and oxidative stress in stroke. *W. somnifera* promotes cell proliferation and enhances neurogenesis. Preclinical experiments on murine models show the effectiveness of *W. somnifera* in post-stroke recovery by enhancing neural plasticity and reducing neuronal loss in the infarct area. Furthermore, *W. somnifera* boosts neurotransmitter levels, improves motor functions, and enhances memory. It also decreases neutrophil infiltration in the infarct region and lessens neuronal loss. Therefore, the application of *W. somnifera* may prove advantageous in facilitating post-stroke recovery by enhancing neural function. However, well-designed clinical trials are needed to confirm the efficacy of *W. somnifera* in post-stroke recovery in humans.

Introduction

Acute stroke is characterized by the abrupt onset of significant impairment of the nervous system within a vascular area that affects the brain, spinal cord, and retina, stemming from underlying cerebrovascular disorders.[1] Stroke is prevalent among diverse patient populations and can result in substantial morbidity and mortality. Strokes are categorized into two primary types: ischemic and hemorrhagic. Hemorrhagic strokes can be further classified into intracerebral and subarachnoid hemorrhages. Ischemic stroke occurs due to the obstruction of blood vessels, while hemorrhagic stroke is attributed to the rupture of blood vessels or bleeding within the brain. Subarachnoid hemorrhage refers to bleeding in the area surrounding the brain, whereas intracerebral hemorrhage pertains to bleeding that occurs within the brain tissue itself. The

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incidence of stroke has significantly increased from 1990 to 2021, with a 70.0% rise in prevalence and a 44.0% increase in mortality rates.[2] Additionally, the global cost of managing stroke patients is quite high.

The risk factors for stroke include non-modifiable and modifiable factors. Gender, age, sex, and genetic factors are non-modifiable risk factors.[3] Obesity, hypertension, diabetes, improper diet, atrial fibrillation, and smoking and alcohol consumption are modifiable risk factors. The pathophysiology of ischemic and hemorrhagic stroke leads to cellular and physiological alterations, which include neuroinflammation, increased oxidative stress, excitotoxicity, and angiopathy. Post-stroke neuroinflammation causes glial cell activation, increased leukocyte infiltration, blood–brain barrier breakdown, and increased cytokine production. Oxidative stress-induced tissue damage includes mitochondrial dysfunction, increased reactive oxygen species formation and lipid peroxidation, and reduced ATP synthesis. In addition, increased cellular Ca^{2+}/Na^{+} influx, reduced glutamate uptake, and necrosis lead to excitotoxicity. Furthermore, post-stroke pathophysiology includes interrupted blood flow, cerebral edema, and elevated intracranial pressure. These cellular and physiological alterations ultimately lead to cerebral damage and neuronal death.[4]

A variety of complications are associated with stroke patients, including post-stroke seizures, mobility disabilities, hemiplegic pain, cognitive deficits, emotional fluctuations, and depression.[5] The strategies for post-stroke treatment depend on prehospital patient care, emergency diagnostic assessments, and intravenous and intra-arterial therapies.[6] Nevertheless, extensive research is currently being conducted to investigate the effectiveness of natural and readily available herbal remedies and Ayurveda for the recovery of neural damage.[7] *W. somnifera* is a potential medicinal plant that is used traditionally in Ayurveda. It has numerous therapeutic applications to prevent inflammation, cancer, diabetes, microbial infection, etc. However, extensive research shows that *W. somnifera* is effective against neurodegenerative diseases.[8] The administration of root powder in a rat model demonstrates enhancements in post-traumatic stress disorder, as well as in memory impairments induced by post-traumatic stress disorder in the hippocampus.[9] *W. somnifera* has gained significant attention for its potential in addressing post-stroke complications due to its remarkable neuroprotective properties.[10] Additionally, *W. somnifera* extract significantly improves cognitive impairments and reaction time.[11] The present article aims to elucidate the role of *W. somnifera* in post-stroke recovery by enhancing neural functions.

Data curation

Peer-reviewed research articles, such as original research articles, reviews, and case studies, were obtained from databases including PubMed, Web of Science, Scopus, Google Scholar, Medline, and Embase. Only full-length articles published in the English language up to July 2025 were included in this study. The searching strategy included keywords such as *W. somnifera*, Ashwagandha, stroke, cerebral ischemia, neurodegeneration, neuronal loss, and post-stroke recovery, which were employed for literature searches.

Botanical and taxonomical description of *W. somnifera*

W. somnifera, commonly known as Ashwagandha, Indian ginseng, winter cherry, and suranjan, flourishes extensively in areas such as India, Africa, Sri Lanka, Pakistan, and the Mediterranean (Fig. 1).[12] This species, *W. somnifera*, is classified under the family Solanaceae and the genus *Withania*. The growth of this crop necessitates semi-tropical climates characterized by an annual rainfall of 650–750 mm and an optimal temperature range of 20°C to 35°C. Every part of the plant, including the leaves, bark, stem, seeds, and flowers, is rich in various phytochemicals that may enhance neuronal function (Table 1).[12,13–17] A recent study has reported the cytotoxic effect of a single bioactive compound, withaferin A, at a minimum concentration of 0.6 μM on SH-SY5Y cells.[18] Nevertheless, the hydroalcoholic extract of *W. somnifera* root, administered at a dosage of 2,000 mg/kg body weight per day, has been demonstrated to be safe, as evidenced in Wistar rats.[19] Thus, normalization of dose is crucial for the safe application of *W. somnifera* phytochemicals and therapeutic accuracy.

Pathophysiology of stroke

Stroke is the second leading cause of death globally and a significant contributor to disability. Considerable advancements have been made in stroke research through various *in vivo* and *in vitro* studies aimed at elucidating the underlying mechanisms of stroke pathogenesis.[20] A stroke is characterized by a sudden and unforeseen alteration in neurological function resulting from impaired blood flow to the brain. The primary blood supply to the brain is facilitated by the circle of Willis, which comprises two anterior, two middle, and two posterior cerebral arteries, in addition to the anterior and posterior communicating arteries. Ischemic stroke, which occurs due to insufficient blood and oxygen supply to the brain, accounts for 85% of strokes, in contrast to hemorrhagic stroke, which accounts for 10%–15%. The obstruction of blood vessels in the brain may result from plaque buildup or blood clots. Localized blood clot formation is referred to as thrombosis, while a movable clot is termed embolism.

In atherosclerosis, plaque accumulates on the inner walls of arteries, leading to the narrowing of blood vessels. This results in diminished blood flow, reduced oxygen supply to brain tissue, increased stress, and ultimately cell death or necrosis. Necrosis causes the leakage of cellular debris into the extracellular space, resulting in the loss of neural functions. Neuroinflammation is a significant biological response observed following a stroke. This process involves the activation of resident immune cells (microglia), which is modulated by fibroblast growth factors. These cells subsequently release proinflammatory and anti-inflammatory cytokines, leading to neural damage.[21] Furthermore, increased oxidative stress contributes to the formation of cerebral edema. Additionally, excessive influx of Ca^{2+} and Na^{+} ions into neurons may lead to cellular damage. Dysfunction of the blood–brain barrier may be observed in both ischemic and hemorrhagic strokes, serving as a major factor in the functional loss of neurons.[22] However, blood–brain barrier disruption in the case of ischemic strokes is mediated by acute hyperpermeability largely due to MMP-9,[23] while hemorrhagic strokes often exhibit delayed or subtype-specific disruption.[20]

Neuroprotective functions of *W. somnifera*

Extensive studies have been conducted to investigate the neuroprotective properties of *W. somnifera*. It has been observed that *W. somnifera* facilitates the recovery of neurons by reducing inflammation, oxidative stress, and apoptosis, while also promoting cell proliferation and neurogenesis. Furthermore, *W. somnifera* mitigates oxidative stress by reducing the production of free radi-

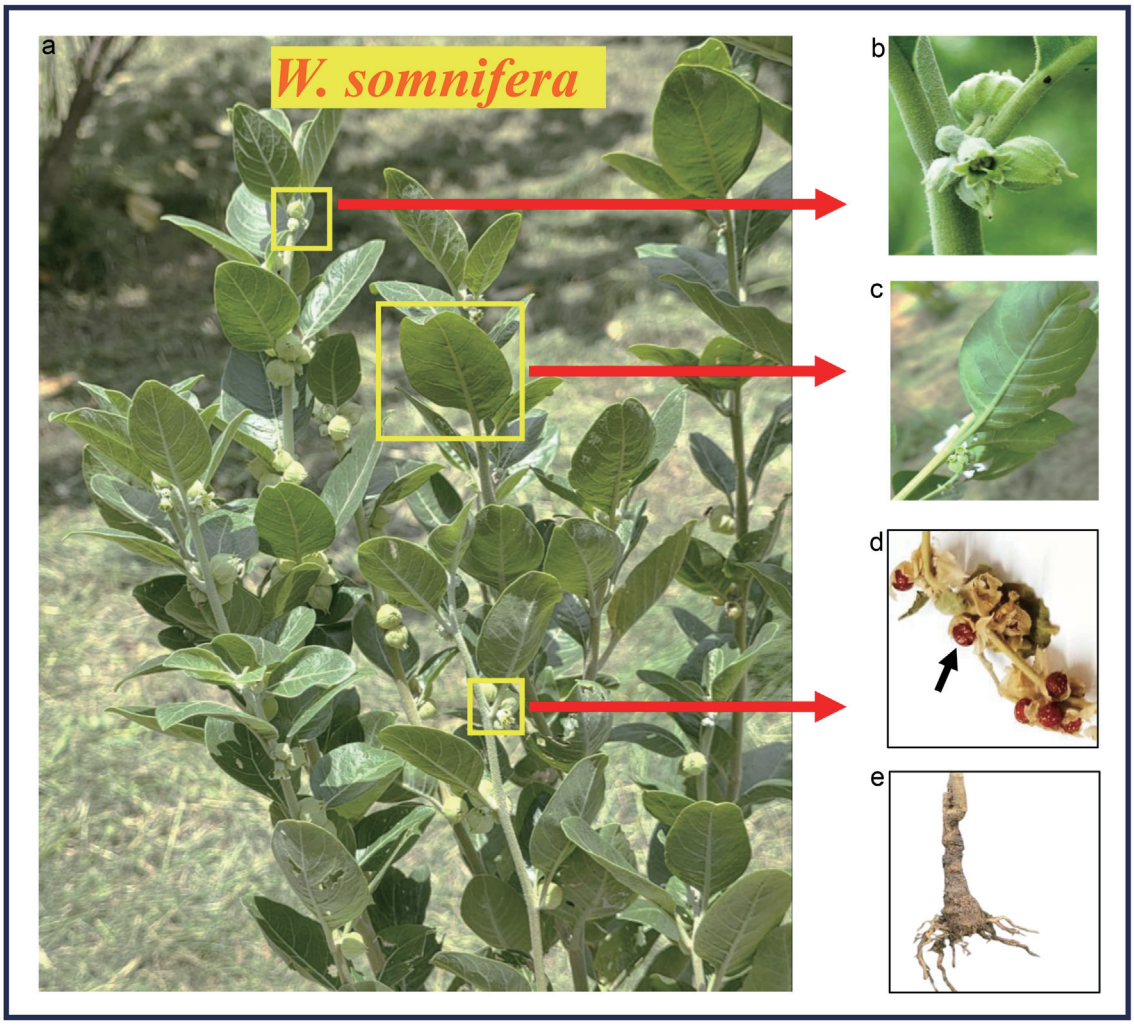

Fig. 1. Different plant parts of *W. somnifera*. (a) whole plant, (b) flower, (c) leaf, (d) fruit, and (e) root.

cals, reactive oxygen species, and lipid peroxidation. Additionally, it enhances the activity of superoxide dismutase and catalase. *W. somnifera* also bolsters antioxidant defense by elevating levels of vitamins A, C, and E, as well as essential metal ions such as Cu^{2+}, Fe^{2+}, and Zn^{2+}.[13]

Various parts of the *W. somnifera* plant, including the root, leaf, fruit, shoots, and bark, are abundant in active constituents and secondary metabolites such as alkaloids, flavonoids, phenolics, saponins, steroids, and glycosides (Table 1).[24] It possesses a diverse array of withanolide alkaloids that are potentially associated with the activation of the cytoprotective PI3K/mTOR pathway, as well as the reduction of inflammation and oxidative stress.[12] *W. somnifera* counteracts the effects of β-amyloid$_{1-42}$ and modulates acetylcholine and acetylcholinesterase (AChE), thereby decreasing neurotoxicity.[25] The bioactive compounds found in *W. somnifera*, including stigmasterol, withaferin A, withanolide G, and withanolide B, exhibit a strong binding affinity for PARP-1. In this context, the inhibition of PARP-1 is associated with a decrease in neuronal cell death.[26] The advantageous effects of *W. somnifera* against various neurological disorders, such as schizophrenia, Huntington's disease, Parkinson's disease, and Alzheimer's disease, have already been documented.[27]

Roles of *W. somnifera* in post-stroke pathophysiology

Various studies have already been conducted demonstrating the beneficial effects of *W. somnifera* in the recovery of stroke outcomes (Fig. 2). Mice subjected to middle cerebral artery occlusion (MCAO) exhibit significant recovery in the infarct region when treated with an aqueous extract of *W. somnifera*.[28] This research indicates that *W. somnifera* can modulate the expression of key proteins associated with the ischemic–apoptotic cascade. The administration of a root extract of *W. somnifera* (200 mg/kg body weight) in C57BL/6 mice following permanent distal MCAO in the contralateral cortex demonstrates a significantly reduced infarct volume in the *W. somnifera* pre-treatment group compared to the vehicle group (23.1 ± 3.4% versus 35.5 ± 2.5%). Furthermore, the *W. somnifera*-pretreated mice exhibit enhanced locomotor activity after 24 h and one week, indicating a potential for functional recovery following MCAO.[28] *W. somnifera* enhances the expression of HO-1 while reducing levels of PARP-1 and Sema3A. HO-1 plays a crucial role in ischemic stroke through its antioxidant, anti-inflammatory, and antiapoptotic properties.[29] Among the downstream products of HO-1, previous studies have reported a reciprocal relationship between serum bilirubin levels

Table 1. List of phytochemicals reported in different plant parts of *W. somnifera*

Plant parts	Name of phytochemicals	Reference
Root	Basic alkaloids: anahygrine, cuscohygrine, pseudotropine, tropine, anaferine, isopelletierine, pseudo-withanine, withananinine, withananine somnine, somniferine, somniferinine. Neutral alkaloids: 3-tropyltigloate. Other alkaloids: Withasomnine, withanine, and visamine. Free amino acids: Glycine, alanine, tyrosine, proline, cystine, glutamic acid, tryptophan, and aspartic acid	13
Leaf	Withanolides, alkaloids, free amino acids, chlorogenic acid, glycosides, glucose, condensed tannins, and flavonoids, withaferin A	13
Fruit	Condensed tannins, proteolytic enzymes, and flavonoids. Alanine, glycine, proline, valine, glutamic acid, cystine, tyrosine, hydroxyproline, aspartic acid, and cysteine	13
Shoots	Crude protein, calcium and phosphorous, Coumarin: scopoletin	13
Stem	Condensed tannins and flavonoids	13
Bark	Free amino acids	13
Root	Steroids, Terpenoids, Alkaloids, Flavonoids, Tannins, Phenol, Anthraquinone, Catechin	14
Root	withanolide A, 12-deoxywithastromonolide and withaferin A	15
Leaf and root	Withanolide-A, withanone, withaferin A, withastramonolide, 27-hydroxywithanone, withanoside, physagulin	16
Root	Phenolic compounds, flavonoids, coumarins tannins, saponins, protein, steroid glycosides, alkaloids, reducing sugars	17

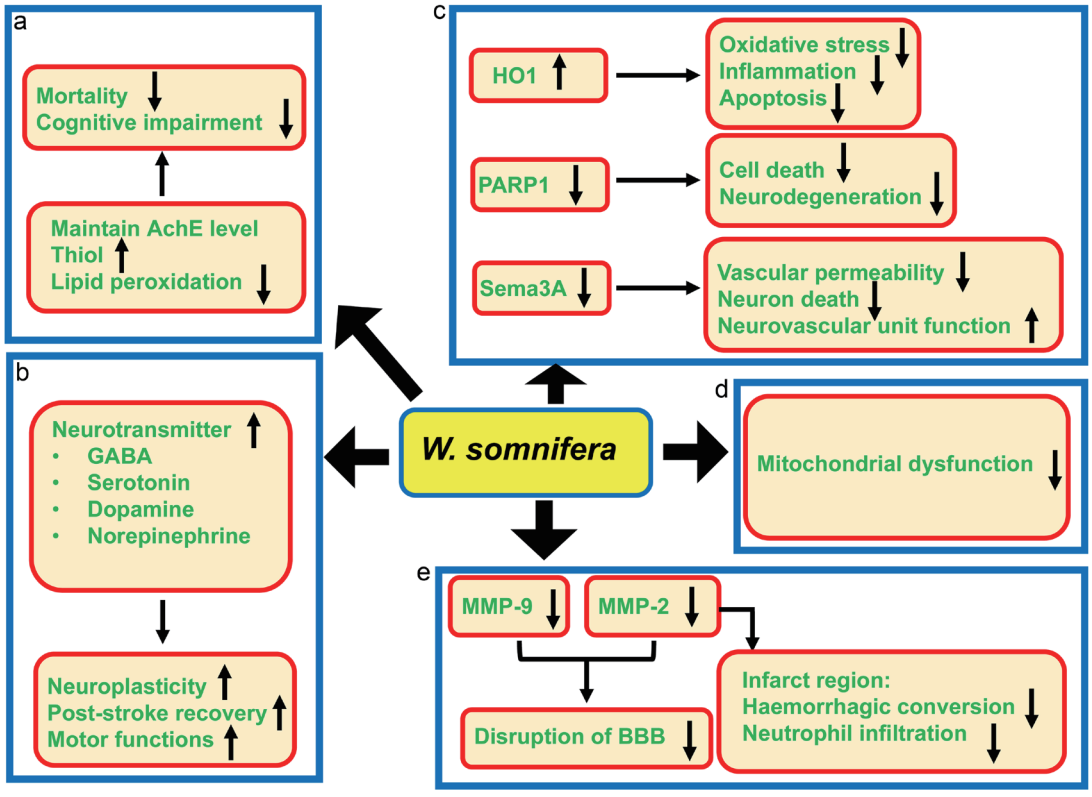

Fig. 2. The neuroprotective functions of *W. somnifera* in regulating different molecular events in stroke. Regulation of different biomolecules by *W. somnifera* in stroke leads to (a) a reduction in mortality and cognitive impairment, (b) an increase in neuroplasticity, post-stroke recovery, and motor functions, (c) a reduction in oxidative stress, inflammation, apoptosis, neuronal cell death, and vascular permeability, and improved neurovascular unit functions, (d) a reduction in mitochondrial dysfunction, and (e) restricted hemorrhagic conversion and neutrophil infiltration in the infarct region. The symbols "↑" and "↓" represent "high" and "low," respectively. AChE, acetylcholinesterase; BBB, blood–brain barrier; GABA, gamma-aminobutyric acid; HO-1, heme oxygenase 1; MMP, matrix metalloproteinase; PARP-1, poly(ADP-ribose) polymerase-1; Sema3A, semaphorin-3A.

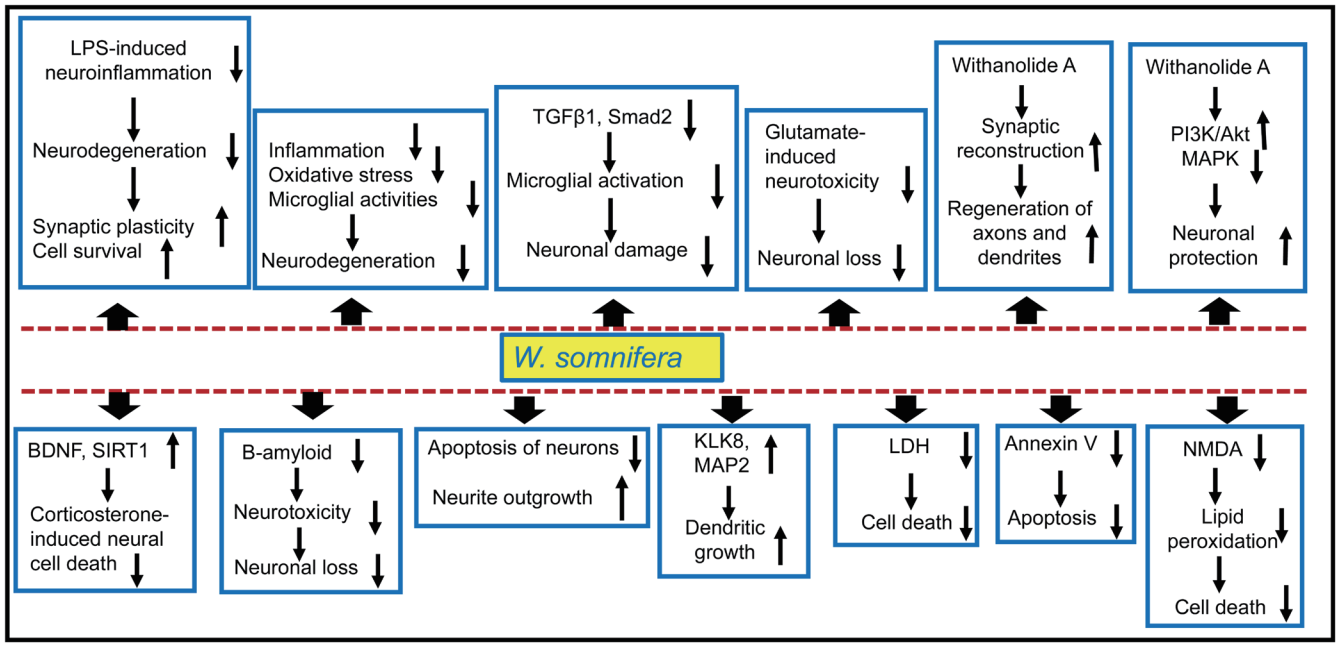

Fig. 3. Regulation of different molecular mechanisms by *W. somnifera* to decrease neuronal loss and increase neural plasticity. The symbols "↑" and "↓" represent "high" and "low," respectively. BDNF, brain-derived neurotrophic factor; KLK8, kallikrein 8; LDH, lactate dehydrogenase; LPS, lipopolysaccharide; MAP2, microtubule-associated protein 2; MAPK, mitogen-activated protein kinase; NMDA, N-methyl-D-aspartate; PI3K/Akt, phosphoinositide 3-kinase/protein kinase B; Smad2, mothers against decapentaplegic homolog 2; SIRT1, sirtuin 1; TGF-β1, transforming growth factor beta 1.

and carotid atherosclerosis.[30] Conversely, PARP-1 is significant in the progression of ischemic stroke and cell death, suggesting that targeting PARP-1 could be a promising therapeutic approach for post-stroke neurodegeneration.[31] Furthermore, the vascular permeability factor Sema3A is vital for neuroprotection by regulating immune responses and angiogenesis following ischemic stroke.[32] Mice pre-supplemented with the root extract of *W. somnifera* demonstrate a reduction in tissue inflammation and an increase in neurotransmitters such as serotonin, dopamine, norepinephrine, and GABA after MCAO.[33] In this context, the modulation of inhibitory neurotransmitters such as GABA is essential for neuronal plasticity and post-stroke recovery.[34] Additionally, serotonergic and dopaminergic medications are utilized to enhance motor functions following a stroke.[35] Pretreatment with a hydroalcoholic extract of *W. somnifera* in Wistar rats over a period of 30 days results in significant improvements in motor function and a decrease in malondialdehyde levels two hours after MCAO.[36] Reports indicate that rats pre-supplemented with *W. somnifera* (300 mg/kg body weight) maintain normal AChE levels, increase thiols, alleviate neurobehavioral deficits, and reduce lipid peroxidation following MCAO.[37] In this context, elevated levels of AChE correlate with increased mortality rates in stroke patients and those experiencing post-stroke cognitive decline.[38] Thiols serve as cellular antioxidant defense molecules. A decrease in thiol levels leads to heightened oxidative stress, which is linked to the severity of post-stroke conditions.[39] Neurobehavioral deficits refer to dysfunctions in locomotor abilities typically observed following cerebral ischemia–reperfusion injury (hereinafter referred to as I/R injury). Likewise, an increase in lipid peroxidation has been documented in both the ipsilateral and contralateral hemispheres of the brain after MCAO.[40] Sood *et al*.[41] have shown that pre-supplementation with *W. somnifera* in MCAO models may alleviate mitochondrial dysfunction, apoptosis, oxidative stress, and cognitive deficits. The liposomal delivery of the ethanolic root extract from the *W. somnifera* chemotype variety NMITLI-118 exhibits neuroprotective properties against I/R injury following MCAO.[42] An *in silico* study conducted by Kumar *et al*.[43] shows that 28 out of 36 phytochemicals derived from *W. somnifera* inhibit binding to the catalytic domain of matrix metalloproteinases, specifically MMP-2 and MMP-9. However, this needs to be validated using *in vivo* experiments. In rodent models, it has been reported that MMP-9 expression peaks during the acute phase of stroke, while MMP-2 expression is elevated in the later stages post-stroke. The heightened levels of MMP-2 and MMP-9 are associated with disruption of the blood–brain barrier.[44] Furthermore, MMP-9 is linked to hemorrhagic transformation and neutrophil infiltration within the infarct area.[23]

W. somnifera and functional recovery of neurons

Cerebral ischemia results in immediate tissue loss in the area affected by stroke, a phenomenon known as infarction. Furthermore, secondary neurodegeneration develops over time due to the ongoing tissue loss in regions connected to the infarct area. Following a stroke, neurons experience stress from inflammation, ischemia, and excitotoxicity. The pathophysiology of stroke onset involves the release of molecules such as ATP and phosphatidylserine, and the binding of complement components (C1q and C3b), along with microglia, to stressed neurons. Consequently, microglial phagocytosis is linked to neuronal loss following a stroke.[45] In this context, *W. somnifera* has been reported to be advantageous in protecting neurons and mitigating neuronal loss (Fig. 3). Research conducted on human neuroblastoma cells (SH-SY5Y) indicates that the root extract of *W. somnifera* (20 µg/mL) is effective in reducing apoptotic markers (annexin V), terminal cell death parameters such as lactate dehydrogenase, and cell death markers such as Bax (Bcl-2-like protein 4).[46] A study performed on the brains of rats

with Parkinson's disease demonstrates that the root extract of *W. somnifera* leads to a decrease in inflammation, oxidative stress, and microglial activity, ultimately resulting in reduced neuronal degeneration in the cerebral cortex.[47] The excessive production of glutamate, an excitatory neurotransmitter, in the brain leads to glutamate excitotoxicity following a stroke, which significantly contributes to neuronal damage and cell death.[48] In this context, a study performed on a rat model of Alzheimer's disease indicates that the aqueous extract of *W. somnifera* root may offer protection against neurotoxicity induced by glutamate and prevent neuronal loss in the cerebral cortex and hippocampal regions.[49] It has been reported that the aqueous extract of *W. somnifera* leaf, along with its active fractions, is advantageous for synaptic plasticity and the survival of neuronal cells against neuroinflammation and neurodegeneration caused by bacterial lipopolysaccharide. Furthermore, it mitigates apoptotic cell death in neurons and promotes the restoration of neurite outgrowth.[50] However, a nanoemulsion could be developed to enhance the delivery of the leaf extract across the blood–brain barrier. TGF-β1 and Smad2 are crucial in the pathogenesis of acute and post-stroke conditions, as these molecules are essential for regulating neuroinflammation, microglial activation, and angiogenesis.[51] In this context, the nanoemulsion of *W. somnifera* leaf extract may be vital in downregulating the TGF-β1 and Smad2 signaling pathways to safeguard against neuronal damage and apoptosis.[52] The accumulation of β-amyloid in the brain is regarded as neurotoxic, leading to neuronal loss.[53] It is hypothesized that cerebral ischemia contributes to the buildup of β-amyloid in the brain.[54] In this context, the methanol:chloroform (3:1) root extract of *W. somnifera* has been reported to counteract β-amyloid-induced neurotoxicity in human neuronal SK-N-MC cells.[25] Corticosterone is known to induce neuronal cell death during cerebral ischemia.[55] Reports indicate that the root extract of *W. somnifera* is effective in protecting against corticosterone-induced neuronal cell death by upregulating the expression of brain-derived neurotrophic factor (hereinafter referred to as BDNF) and SIRT1, which leads to mitochondrial biogenesis and enhances neuroenergetics.[56] It has been demonstrated in a mouse model that withanolide A, isolated from *W. somnifera*, promotes synaptic reconstruction in neurons and facilitates the regeneration of axons and dendrites.[57] The leaf extract of *W. somnifera* has been reported to play a role in neuroregeneration and memory recovery in a mouse model. Research indicates that the *W. somnifera* leaf extract enhances KLK8 and MAP2 levels, thereby promoting dendritic growth, which is crucial for receiving signals from other neurons.[58] The inhibition of the PI3K/Akt pathway is linked to neuronal cell death. In this context, withanolide A activates the PI3K/Akt pathway while inhibiting mitogen-activated protein kinases, leading to neuroprotection.[59] Under normal physiological conditions, glutamate plays a crucial role in neural development and synaptic plasticity. However, excessive release and accumulation of glutamate can activate the N-methyl-D-aspartate (NMDA) receptor. NMDA is a postsynaptic receptor that induces excitotoxicity through lipid peroxidation, ultimately resulting in neuronal cell death. In this regard, withanone has been reported to mitigate NMDA-induced excitotoxicity in neuron-like cells.[60]

Limitations and future research directions

Extensive research indicates that phytochemicals derived from various parts of *W. somnifera* are effective in reducing neuronal death and promoting neuroprotection by modifying various cellular and physiological processes. However, these investigations have primarily been carried out through *in vitro*, *in silico*, and *in vivo* methodologies. Consequently, the effects of *W. somnifera* phytochemicals must be experimentally validated in humans to improve therapeutic efficacy. Therefore, it is essential to conduct clinical trials with large cohorts to establish a safe dosage of *W. somnifera* phytochemicals for human use. Additionally, *in vivo* studies and behavioral experiments must be performed to elucidate functional recovery metrics, disability, quality of life, recurrent stroke, mortality, and other related factors. Furthermore, future research is necessary to investigate the physiological pathways targeted by *W. somnifera* to enhance the understanding of post-stroke recovery.

Conclusions

The rising mortality rates associated with stroke and the subsequent neuronal loss are significant concerns for healthcare professionals. This study illustrates how the neuroprotective properties of *W. somnifera* can facilitate recovery after a stroke. A thorough review of the literature and analysis indicates that *W. somnifera* is instrumental in enhancing post-stroke recovery. Extracts from various parts of the plant, including fruits, flowers, roots, and leaves, are rich in diverse bioactive compounds. The neuroprotective effects of *W. somnifera* may aid in post-stroke recovery by mitigating neuroinflammation, apoptosis, and oxidative stress. Furthermore, *W. somnifera* may enhance post-stroke recovery by reducing mitochondrial dysfunction and neuronal loss, and by promoting neuronal plasticity. Additionally, it may contribute to increased neurotransmitter levels and improved motor functions. The plant also protects the infarct area from neutrophilic infiltration. Utilizing *W. somnifera* may enhance memory and functional recovery following a stroke. *W. somnifera* may play a significant role in mitochondrial biogenesis and neuroregeneration. Therefore, it is essential to determine the target-specific effects of *W. somnifera* on HO-1, BDNF, SIRT1, KLK8, and MAP2. Additionally, future research at the molecular level and clinical trials are recommended to investigate the biological pathways influenced by the active compounds in *W. somnifera*.

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Conflict of interest

No potential conflict of interest was reported by the authors.

Author contributions

Conceptualization, data curation, study design, data compilation, interpretation, original draft writing, formatting, editing and review (SS, AD, MS), original draft editing and review (RPS, SC, AS, SKS). All authors have approved the final version and publication of the manuscript.

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