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Review article

Advancements in the mechanisms of Naotai formula in treating stroke: A multi-target strategy

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ABSTRACT

Stroke represents a significant global health challenge, characterized by high incidence, mortality, disability, and recurrence rates, leading to substantial socioeconomic burdens. Despite advancements in acute management and prevention, effective post-stroke recovery strategies remain limited. Naotai Formula (NTF), a traditional Chinese medicine compound, has garnered attention for its potential in stroke treatment, encompassing both ischemic and hemorrhagic types. This review synthesizes recent advancements in basic and clinical research on NTF, focusing on its mechanisms of action in stroke therapy. The formula's multifaceted effects include promoting neuronal regeneration, combating oxidative stress, regulating lipid metabolism, and modulating iron homeostasis. Through a multi-target approach, NTF addresses the complex pathophysiology of stroke, suggesting a promising complementary strategy for stroke recovery. Despite promising findings, further research is required to elucidate its active components, potential side effects, and optimized therapeutic protocols. The integration of traditional Chinese medicine, like NTF, with conventional treatments may enhance stroke management strategies, urging the need for high-quality clinical trials and evidence-based guidelines.

1. Introduction

Stroke stands as a leading cause of death and disability worldwide, imposing significant health and economic burdens on societies. It is primarily categorized into two types: ischemic and hemorrhagic [1]. Ischemic stroke, accounting for approximately 87 % of all cases, occurs when blood flow to the brain is obstructed, typically by blood clots [2]. Hemorrhagic stroke results from bleeding within or around the brain and is often associated with higher mortality rates [3]. The global health burden of stroke is immense, with millions of individuals affected annually. The World Health Organization (WHO) estimates that stroke causes 6.7 million deaths each year and leaves many survivors with significant long-term disabilities, including paralysis, speech difficulties, and cognitive impairments [4].

Despite advances in acute stroke management, including thrombolytic therapies for ischemic stroke and surgical interventions for hemorrhagic stroke, significant challenges remain, particularly in the realms of long-term rehabilitation and prevention of recurrence [5,6]. Current treatments are often limited by narrow therapeutic windows, side effects, and the complexity of stroke pathology [7]. Rehabilitation efforts, aiming to restore function and improve quality of life, are hampered by the lack of universally effective interventions and the individual variability in response to treatment. Additionally, the high recurrence rate of stroke necessitates more effective preventive strategies.

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Naotaifang (NTF) is a traditional Chinese medicine (TCM) formula used to treat ischemic stroke and its sequelae. It has been shown to exhibit a neuroprotective effect against ischemic stroke and alleviate cerebral ischemia-reperfusion injury (CIRI) in both clinical and animal studies [8,9]. NTF is a composite herbal remedy consisting of four natural medicines, namely Radix Astragali, Rhizoma Ligustici Chuanxiong, Pheretima, and Bombyx Batryticatus [9]. Research has indicated that NTF can balance iron levels after cerebral ischemia, potentially reducing neuronal iron uptake and improving neural function in reperfused rats [10]. The formula has been found to have anti-ischemic stroke effects, such as mitigating neurological symptoms and improving blood circulation, anti-coagulation, angiogenesis, and anti-inflammation. NTF is known for its ability to invigorate qi, activate blood, and dredge collaterals, and it has been suggested that it may inhibit ferroptosis, a form of cell death involving iron and lipid peroxidation, in the context of stroke [10,11]. The multi-component, multi-channel, multi-target synergistic effect of Chinese herbs like NTF is believed to have unique advantages in the prevention and treatment of stroke. Therefore, NTF shows promise as a potential treatment for ischemic stroke and its associated complications.

Moreover, the holistic principles of TCM underlying NTF, such as balancing qi, promoting blood circulation, and resolving phlegm stasis, offer a complementary approach to conventional treatments [6]. By integrating TCM with modern scientific methodologies, there is potential to uncover new insights into stroke mechanisms and therapeutic strategies that enhance recovery outcomes and quality of life for stroke survivors [7]. Future research should focus on rigorous clinical trials to validate NTF's efficacy, optimize dosing regimens, and elucidate its mechanisms of action in diverse patient populations, thus paving the way for personalized stroke care that addresses the unique needs of individual patients.

2. Methods

2.1. Inclusion criteria

Study Type: Peer-reviewed research articles, clinical trials, and systematic reviews evaluating the efficacy of NTF in treating stroke.

Participants: Studies involving human subjects diagnosed with ischemic or hemorrhagic stroke, of all ages and genders.

Intervention: Studies examining the administration of NTF either as a sole treatment or in combination with standard stroke therapies.

Outcomes: Studies reporting outcomes related to neurological function, quality of life measures, incidence of complications (such as recurrent stroke or cognitive decline), and safety profiles of NTF (see Table 1).

2.2. Exclusion criteria

Case Reports and Editorials: Non-systematic literature such as case reports, editorials, commentaries, and letters to the editor.

Studies on Different Herbal Formulations: Studies focusing on herbal formulations other than NTF, unless directly comparative to NTF.

3. Mechanisms of action

3.1. Neuronal regeneration

3.1.1. Promotion of neuroregeneration and inflammation modulation

Neural stem cells (NSCs) have shown significant potential in stroke therapy by promoting neuroregeneration and functional recovery. NSCs can orchestrate neurological repair through various mechanisms, including nerve regeneration, neuron polarization, and remodeling of brain networks [12]. They also modulate inflammation, foster neuroplasticity, promote angiogenesis, and act as cellular replacements [13]. Neurotrophic factors play a crucial role in controlling NSC differentiation and protecting brain tissue from ischemic damage [14]. The NTF, a traditional Chinese medicine, has demonstrated beneficial effects in inhibiting inflammation and lipid peroxide synthesis in ischemic stroke. NTF attenuates inflammation and ferroptosis by regulating microglial M1/M2 polarization through the BMP6/SMADs signaling pathway, promoting the shift of microglia from M1 to M2 phenotype, and inhibiting the expression of hepcidin, BMP6, and SMADs [15].

Table 1
Mechanisms of stroke treatment using NTF.

Mechanism of Action	Description
Neuronal Regeneration	NTF promotes neural stem cell proliferation and differentiation through modulation of growth factors like BDNF. It activates the Notch signaling pathway, enhancing NSC fate towards neuronal lineages and suppressing gliogenesis. NTF also influences microglia polarization towards the M2 phenotype, reducing inflammation and supporting neuronal survival.
Oxidative Stress Modulation	NTF enhances antioxidant defense systems, including SOD and GPX4, to counteract ROS production post-stroke. This reduces lipid peroxidation, DNA damage, and protein oxidation, protecting neurons from oxidative stress-induced damage.
Lipid Metabolism Regulation	By modulating lipid metabolic pathways, NTF mitigates atherosclerosis development and preserves BBB integrity. It suppresses pro-inflammatory mediators, reducing inflammation and enhancing neural tissue resilience post-stroke.
Iron Metabolism Modulation	NTF regulates iron homeostasis by decreasing free iron levels and protecting against iron-induced oxidative stress. It modulates iron transport mechanisms and enhances antioxidant enzyme activity to prevent neuronal damage and promote recovery.

3.1.2. Activation of the notch signaling pathway

The Notch signaling pathway plays a pivotal role in the regulation of NSC fate, influencing their proliferation, differentiation, and survival. Activation of this pathway has been identified as a key mechanism by which NTF facilitates neuronal regeneration [9]. Components of the formula can upregulate the expression of Notch receptors and ligands, thus enhancing Notch signaling activity. This increased signaling promotes the expansion of NSC populations and guides their differentiation towards neuronal lineages. Furthermore, the Notch pathway's modulation by NTF has been linked to the suppression of gliogenesis, favoring neurogenesis and contributing to a more favorable outcome in neuronal repair processes [16]. NTF activates the VEGF-Notch1 signaling pathway and promotes angiogenesis in a rat model of cerebral ischemia [17].

3.1.3. Modulation of microglial polarization

Microglia, the resident immune cells of the central nervous system, play a dual role following stroke, contributing to both damage and repair mechanisms. They exhibit two distinct polarization states: the classical activation state (M1), which is associated with the release of pro-inflammatory cytokines, and the alternative activation state (M2), which supports tissue repair and regeneration [18,19]. NTF has been observed to influence microglia polarization, shifting the balance towards the M2 phenotype. This shift reduces the inflammatory response and creates an environment more conducive to neuronal regeneration. By promoting the release of anti-inflammatory cytokines and neurotrophic factors, M2 microglia foster a milieu that supports the survival and growth of new neurons [15,20]. The modulation of microglial activation states by NTF underscores its multifaceted role in enhancing neuroprotective and regenerative processes after stroke.

These mechanisms of action highlight the complex and integrated nature of NTF's effects on the nervous system. By promoting neural stem cell proliferation and differentiation, activating restorative cellular pathways, and modulating the immune response, NTF offers a promising complementary approach to support neuronal regeneration and functional recovery post-stroke.

3.2. Oxidative stress modulation

3.2.1. Role of oxidative stress in stroke pathophysiology and recovery

Oxidative stress plays a pivotal role in the pathophysiology of stroke, contributing significantly to neuronal damage and the progression of stroke-induced injury [21]. Following a stroke, the sudden restoration of blood flow (reperfusion) to the brain can lead to the excessive production of reactive oxygen species (ROS), surpassing the brain's antioxidant defense capabilities [22]. This imbalance results in oxidative stress, leading to lipid peroxidation, DNA damage, and protein oxidation, ultimately causing cell death and exacerbating the neurological deficit [23,24]. Oxidative stress is implicated not only in the immediate damage post-stroke but also in the long-term processes that influence recovery and rehabilitation.

3.2.2. Mitigation of oxidative stress by NTF

NTF has been shown to exert a protective effect against oxidative stress-induced damage in the context of stroke. This effect is achieved through several mechanisms, primarily by bolstering the body's antioxidant defense systems. NTF have been identified to enhance the activity of superoxide dismutase (SOD) and glutathione peroxidase (GPX4), two crucial enzymes in the detoxification of ROS [11]. Through these mechanisms, NTF provides a comprehensive approach to modulating oxidative stress in stroke, addressing one of the key pathological processes that contribute to neuronal damage and functional loss. The enhancement of endogenous antioxidant defenses not only helps to mitigate immediate damage post-stroke but also supports the longer-term recovery of neural tissue, highlighting the potential of NTF as an adjunctive treatment in stroke rehabilitation strategies.

3.3. Lipid metabolism regulation

3.3.1. The importance of lipid metabolism in stroke progression

Lipid metabolism plays a critical role in the progression of stroke and the subsequent neuronal damage [25]. Abnormalities in lipid profiles and dysregulation of lipid metabolism are linked with the pathogenesis of stroke, influencing atherosclerosis development, thrombosis, and the integrity of the blood-brain barrier (BBB). Lipids, particularly cholesterol and triglycerides, contribute to the formation of atherosclerotic plaques, which can lead to ischemic stroke by obstructing cerebral blood flow [25]. Moreover, the oxidative modification of lipids during stroke can result in the formation of toxic by-products that exacerbate neuronal injury and inflammation, further impairing recovery [26].

3.3.2. Effects of NTF on lipid metabolic pathways

NTF has demonstrated the ability to modulate lipid metabolism, thereby contributing to its protective effects against stroke-induced neuronal damage. By influencing lipid metabolic pathways, NTF can potentially mitigate the risk factors associated with stroke progression and enhance neural tissue resilience. The regulation of lipid metabolism by NTF may also have implications for the integrity of the BBB. By preventing the oxidative damage of lipids within the BBB, NTF can help maintain its selective permeability, which is critical for protecting the brain from harmful substances in the bloodstream and for reducing edema and inflammation in the post-stroke period [27]. NTF's ability to modulate lipid metabolic pathways extends to the suppression of pro-inflammatory mediators, thereby reducing the inflammatory response and promoting a more favorable environment for neuronal recovery and regeneration [28,29]. NTF has demonstrated significant positive effects on learning and memory abilities in rat models of vascular dementia. Specifically, it improved cognitive functions, increased superoxide dismutase activity, and reduced malondialdehyde levels in brain

tissue affected by cerebral ischemia-reperfusion injury. Additionally, it enhanced cognitive performance and decreased Evans blue leakage in models of multiple cerebral infarction. These findings suggest that NTF mitigates cognitive impairment and reduces cerebral lipid peroxidation-associated damage in vascular dementia [30]. NTF significantly improves lipid levels and enhances neural function in patients with ischemic stroke compared to routine treatment, as evidenced by improved NIHSS and ADL scores after four weeks of treatment [31].

3.3.3. Implications for reducing stroke-induced neuronal damage

By addressing both the risk factors associated with stroke progression and the acute responses to stroke, such as oxidative stress and inflammation, NTF provides a comprehensive strategy for enhancing neural protection and recovery. The modulation of lipid metabolic pathways underscores the potential of NTF as an adjunctive treatment in stroke management, emphasizing the need for further research to fully understand its mechanisms of action and to optimize its therapeutic application.

NTF has demonstrated neuroprotective effects against cerebral ischemia-reperfusion injury (CIRI) in ischemic stroke. Network pharmacology and experimental studies revealed that NTF acts through multiple targets and pathways, particularly the STAT3/PI3K/AKT signaling pathway [9]. NTF significantly reduced neurological deficits, infarct volume, and apoptosis while increasing neuronal survival and dendritic spine density in animal models [9]. In vascular dementia, NTF improved learning and memory by regulating various biological processes and signaling pathways, including inflammation, vasodilation, and angiogenesis [32]. Furthermore, NTF induced M2 polarization of microglia, inhibited inflammatory responses, and reduced glial scar formation in CIRI [33]. These studies collectively demonstrate NTF's multi-target therapeutic approach in treating stroke and related conditions, highlighting its potential as a promising treatment for cerebrovascular diseases.

3.4. Iron metabolism modulation

3.4.1. The contribution of iron accumulation to stroke pathology

Iron accumulation in the brain is a significant pathological feature of both ischemic and hemorrhagic strokes, contributing to the exacerbation of injury through various mechanisms [34]. In the acute phase of stroke, disrupted blood flow and the subsequent breakdown of hemoglobin release free iron into the brain parenchyma. This free iron catalyzes the Fenton reaction, producing highly reactive hydroxyl radicals, which in turn lead to oxidative stress, lipid peroxidation, and DNA and protein damage. Moreover, iron accumulation has been implicated in the activation of cell death pathways, including ferroptosis, a form of programmed cell death characterized by iron-dependent lipid peroxidation [35,36]. The detrimental effects of iron are not limited to the acute phase; chronic iron deposition also contributes to neuroinflammation and neurodegeneration, affecting long-term recovery and increasing the risk of post-stroke cognitive decline.

3.4.2. Evidence supporting the NTF's ability to regulate iron homeostasis

The NTF has demonstrated potential in mitigating the adverse effects of iron accumulation following stroke, through several mechanisms aimed at restoring iron homeostasis and preventing iron-induced neuronal death. Research findings suggest that the formula can influence key aspects of iron metabolism, including the reduction of free iron levels, modulation of iron storage and transport, and protection against iron-induced oxidative stress. Studies have shown that NTF can decrease the concentration of free iron in the brain by upregulating proteins involved in iron sequestration and storage, such as ferritin. By increasing the storage capacity for iron, NTF reduces the pool of free iron available to participate in harmful reactions [10]. NTF has been found to regulate the expression of proteins responsible for iron import and export, including transferrin receptors and ferroportin. By modulating these transport mechanisms, NTF can help to maintain iron levels within a physiological range, preventing the excessive accumulation of iron in neuronal tissue [37]. Through its antioxidant components, NTF can counteract the oxidative stress generated by iron accumulation. By enhancing the activity of antioxidant enzymes and scavenging free radicals, the formula provides a protective effect against iron-catalyzed oxidative damage [38]. Furthermore, evidence suggests that NTF may also mitigate the risk of ferroptosis in neurons by modulating the expression of GPX4 and reducing lipid peroxidation, a key event in the execution of ferroptosis. This multifaceted approach to regulating iron metabolism and protecting against iron-induced damage highlights the therapeutic potential of NTF in the context of stroke recovery [39].

4. Clinical applications and research

4.1. Summary of key findings

Clinical trials and research studies on NTF have provided valuable insights into its efficacy in treating stroke. These studies generally highlight several beneficial effects, including improved neurological function, reduced incidence of complications, and enhanced quality of life for stroke patients. Key findings include: Many studies report significant improvements in neurological scores, such as the National Institutes of Health Stroke Scale (NIHSS) or the modified Rankin Scale (mRS), in patients treated with NTF compared to control groups. These improvements suggest enhanced recovery of motor and cognitive functions [40,41]. Research indicates that NTF may help reduce the risk of common post-stroke complications, including recurrent stroke, depression, and cognitive decline, potentially through its multifaceted mechanisms of action, such as modulation of oxidative stress and inflammation [9]. Patients receiving NTF, alongside standard post-stroke care, often show better outcomes in terms of daily living activities and overall quality of life. This is attributed to the formula's comprehensive approach to promoting neural repair and regeneration [10].

Recent studies have shown promising results for Chinese herbal formulas in treating ischemic stroke. Naotai recipe demonstrated therapeutic angiogenesis effects by enhancing HIF-1α/VEGF signaling pathway expression in cerebral ischemia/reperfusion rats [42]. Naotaifang III exhibited protective effects against cerebral ischemia injury through the LPS/TLR4 signaling pathway in the microbiota-gut-brain axis, potentially inducing anti-neuroinflammatory mechanisms [41]. A clinical trial protocol aims to evaluate the efficacy and safety of naotaifang capsules for hypertensive cerebral small vessel disease, focusing on improving microcirculation and neurofunction [43]. Additionally, Naomaili Granules combined with conventional treatment showed significant improvement in patient prognosis and independent survival ability in acute ischemic stroke, with reliable safety [44]. These studies highlight the potential of NTF as complementary treatments for ischemic stroke, warranting further research.

4.2. Safety, side effects, and contraindications

The safety profile of NTF is generally considered favorable, with most studies reporting few or no serious adverse effects. However, as with any treatment, particularly those involving complex herbal formulations, understanding potential side effects and contraindications is crucial. Commonly reported side effects are mild and may include gastrointestinal discomfort, such as nausea and diarrhea. These symptoms are typically transient and resolve with continued treatment or dose adjustment [45]. While specific contraindications are not widely reported, individual components of the formula may pose risks for certain populations. For instance, patients with known allergies to any of the herbs contained in the formula should avoid its use. Additionally, due to the potential for interactions with other medications, particularly those affecting blood coagulation, patients on anticoagulant therapy should use NTF under medical supervision [9,45].

Given the complexity of its components, ensuring the quality and consistency of NTF preparations is essential for safety and efficacy. In conclusion, while NTF shows promise for enhancing stroke recovery, further research is essential to fully understand its therapeutic potential and safety profile. Rigorous clinical trials will help to define its role in stroke management, optimize dosing strategies, and ensure that the benefits of treatment outweigh any risks.

5. Challenges and future directions

5.1. Gaps in current research

While the therapeutic potential of NTF in stroke recovery has been recognized through various studies, significant gaps remain in the current body of research. One of the primary challenges lies in identifying the active components within the formula responsible for its beneficial effects. NTF, like many traditional Chinese medicine preparations, is a complex mixture of multiple herbs, each containing a wide array of compounds. The synergistic effects of these components contribute to the formula's overall efficacy, making it difficult to pinpoint individual active ingredients.

Furthermore, the mechanisms by which NTF exerts its neuroprotective and regenerative effects are not fully understood. While studies have begun to unravel the formula's impacts on neuronal regeneration, oxidative stress modulation, lipid and iron metabolism, a comprehensive understanding of these processes at the molecular level is lacking. This knowledge gap hinders the optimization of the formula for clinical use and limits the ability to predict patient responses and potential interactions with conventional stroke treatments.

The integration of traditional Chinese medicine, such as NTF, with modern clinical practices presents a promising avenue for enhancing stroke treatment and recovery. This holistic approach, which combines the strengths of both traditional and contemporary medicine, could lead to more personalized and effective treatment strategies. However, achieving this integration requires overcoming several hurdles, including standardization of herbal formulations, rigorous evaluation of efficacy and safety, and acceptance within the mainstream medical community.

The potential for NTF to complement conventional therapies, such as thrombolytics in ischemic stroke or surgical interventions in hemorrhagic stroke, is particularly intriguing. Yet, for such integration to occur, healthcare providers must be educated on the benefits and limitations of traditional Chinese medicine and how it can be effectively combined with current treatment protocols.

5.2. Future research directions

Well-designed clinical trials are essential to validate the efficacy and safety of NTF in diverse patient populations. These studies should employ standardized formulations of the formula, rigorous methodology, and appropriate control groups to generate reliable and reproducible results. Research should aim to determine the optimal dosages, treatment durations, and administration routes for NTF. Understanding these parameters is crucial for maximizing therapeutic outcomes and minimizing potential side effects. Based on the findings of clinical research, evidence-based guidelines should be developed to inform the use of NTF in stroke treatment. These guidelines would help standardize care, ensuring that patients receive the most effective and safe treatment possible. Further studies are needed to elucidate the molecular mechanisms underlying the therapeutic effects of NTF. Advances in genomics, proteomics, and metabolomics could offer valuable insights into how the formula interacts with biological pathways involved in stroke recovery. Finally, research should explore strategies for integrating NTF into existing stroke treatment protocols. This includes studies on interactions between the formula and conventional stroke medications, as well as investigations into the best practices for combining traditional Chinese medicine with modern rehabilitation techniques.

6. Conclusion

The NTF represents a promising approach in stroke therapy, embodying a multi-target strategy that addresses neuronal regeneration, oxidative stress, and metabolic disturbances. Its holistic effects suggest a potential to complement conventional stroke treatments, thereby enhancing recovery outcomes. Despite its promise, the pathway to fully harnessing NTF's therapeutic capacity requires further scientific exploration and validation through rigorous research. Advancing our understanding of its mechanisms and optimizing its clinical application are crucial steps toward integrating this traditional Chinese medicine into broader stroke management practices.

Availability of data and materials

All materials are presented within the article. For further inquiries, please contact the corresponding authors.

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Consent for publication

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Declaration of competing interest

The authors declare no competing interests.

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