

Exploration of the Feasibility of Gleditsiae Fructus Abnormalis Total Saponins in Promoting Arousal in Stroke Coma Patients via the Nasal-brain Transport Pathway

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Received: 29 June 2025; Accepted: 16 July 2025; Published: 6 August 2025

Abstract:

The Pharmacopoeia records Tongguan San, with Gleditsiae Fructus Abnormalis (GFA) as the monarch drug, administered nasally to induce sneezing for unblocking orifices, restoring consciousness, and reviving the spirit. Gleditsiae Fructus Abnormalis Total Saponins (GFATS), abundant and highly purified within GFA, possess extensive pharmacological activities and can cross the blood-brain barrier (BBB), recognized as the primary active components. For stroke coma patients, conventional drug delivery routes suffer from slow absorption and limited efficacy, often failing to achieve timely arousal. Given the unique physiological and anatomical connections between the nasal mucosa and the brain, intranasal delivery of GFATS may directly target the central nervous system via brain-targeting pathways, potentially reducing neurological damage in stroke coma patients. This article focuses on GFATS as the main research subject, delving into the feasibility of its intranasal delivery via the nasal-brain transport pathway for promoting arousal in stroke coma patients.

Keywords:

Stroke Coma, Nasal-brain Pathway, Gleditsiae Fructus Abnormalis Total Saponins, Arousal Promotion, Nasal Administration

1. Introduction

With China's rapid economic growth, changes in lifestyle and living conditions, and intensifying population aging, the national disease and mortality spectrums have shifted significantly in recent years. Cerebrovascular diseases have risen to become the leading cause of death, with stroke being the single disease with the highest disability rate [1]. Sudden stroke coma is particularly common. However, the effectiveness of arousal-promoting treatments is limited, as approximately 90% of drugs struggle to cross the BBB or are diminished by the first-pass effect, leaving few viable therapeutic options [2]. We postulate that the ease with which many neurotropic viruses enter the brain to rapidly cause intracranial infections stems from specific pathways connecting the nose and brain. Intranasal drug delivery allows

direct entry into systemic circulation, bypassing hepatic first-pass metabolism. Therefore, leveraging this intricate nasal-brain relationship could potentially transform a pathogenic pathway into a therapeutic conduit. GFA, the dried sterile fruit of *Gleditsia sinensis* Lam., possesses effects including unblocking orifices and promoting defecation, and crucially, can cross the BBB [3]. GFATS, the major extracted component from GFA, is abundant and highly purified [4]. It holds promise as an advantageous intranasal drug for stroke treatment, potentially representing a breakthrough in brain-targeted drug delivery. Consequently, we designate GFATS as the primary research subject to investigate the nasal-brain transport pathway and further substantiate the possibility of its intranasal delivery for treating stroke coma.

2. Pharmacological Effects of GFATS

GFATS is the primary active component extracted from GFA, exhibiting anti-inflammatory, anti-allergic, myocardial ischemia-improving, cerebral hypoxia-alleviating, and anti-tumor effects [5-8]. Studies indicate that 75% ethanol extraction yields the highest GFATS content [9]. Deng Xianyi et al. [10], through isolating active fractions of GFA, found that GFATS significantly enhanced hypoxia tolerance and expectorant ability in mice. Ischemic stroke, the most prevalent type of cerebrovascular disease, results primarily from cerebral circulation disorders leading to local brain tissue hypoxia, ischemic necrosis, or softening, ultimately causing neurological deficits. Given that GFATS improves hypoxia tolerance in mice, it may also confer protective effects on hypoxic brain tissue in stroke. Cellular experiments demonstrate that GFATS inhibits histamine release from mast cells, showing significant therapeutic effects against acute inflammation [11]. Hu Haotian's team [12] found that persistent global brain inflammation accelerates cerebral edema and oxidative stress, potentially hindering post-stroke recovery. Thus, the anti-inflammatory properties of GFATS could contribute to more effective immunomodulatory strategies for stroke. Relevant studies [13] identified an increased stroke risk in rheumatoid arthritis (RA) patients. GFATS can reduce serum levels of type II collagen antibodies and inhibit type II collagen-induced delayed-type hypersensitivity, showing good therapeutic potential for recurrent stroke coma in RA patients. This suggests GFATS offers a new treatment option for stroke comorbid with RA. Ding Yunlu et al. [14] experimentally found that GFATS significantly improved abnormal ST-segment changes in electrocardiograms and inhibited lactate dehydrogenase (LDH) release in rats with acute myocardial ischemia. Hyperlipidemia, especially elevated low-density lipoprotein cholesterol, is a major risk factor for atherosclerosis and stroke. GFATS shows significant promise in lipid-lowering effects, potentially serving as an alternative lipid-lowering agent. Therefore, GFATS may emerge as a superior drug candidate for stroke treatment.

3. Nasal-Brain Pathway Hypothesis

3.1. Neural Pathways for Intranasal Delivery

Neural pathways primarily include the trigeminal, facial, and olfactory nerve pathways [15]. Laboratory studies confirmed these pathways by detecting strong radioactivity in the trigeminal nerve, trigeminal ganglia, pons, and olfactory bulb after intranasal administration of fluorescently labeled proteins [16]. The facial nerve, a mixed cranial nerve predominantly motor, contains four fiber components. Its general visceral motor fibers, originating from the superior salivatory nucleus in the pons,

innervate nasal mucosal glands. Thus, intranasal drugs can stimulate nasal nerves, influencing brain and other functions via reflex regulation. The olfactory nerve, a special visceral sensory nerve, originates from olfactory cells in the nasal mucosa. Its axons traverse the cribriform plate and dura mater to reach the anterior cranial fossa, terminating in the olfactory bulb. Fibers from olfactory bulb neurons then travel via the olfactory tract to olfactory centers, with some fibers crossing through the medial olfactory stria and intermediate olfactory stria to terminate in the subcallosal area and anterior perforated substance [17]. Therefore, intranasally administered GFATS can potentially access the brain via the trigeminal nerve branches, facial nerve branches, and the olfactory nerve pathway. (Figure 1)

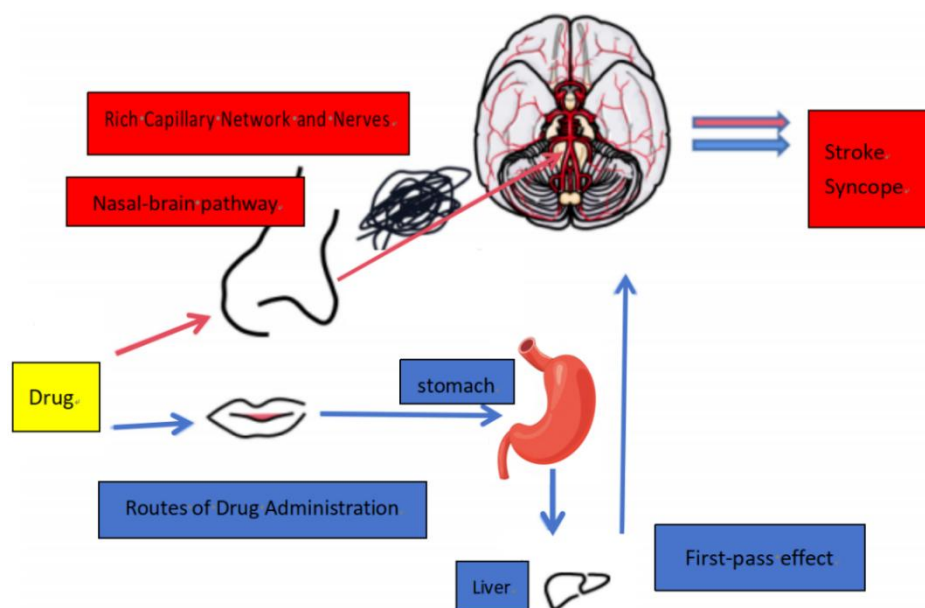


Figure 1. Nasal-brain pathway.

3.2. Non-Neural Pathways for Intranasal Delivery

Non-neural pathways primarily involve circulatory and cellular pathways [18]. The human nasal mucosa covers approximately 150 cm², is extremely thin, and separated from underlying blood vessels by only a single epithelial cell layer. Apart from neural routes, drugs entering the brain via other paths must first traverse this epithelial layer. Due to the large intercellular gaps in the epithelium, drugs readily permeate this layer to enter the submucosal capillary network and lymphatic vessels. Furthermore, venous sinuses within the nasal capillary network anastomose with cerebral blood vessels, and veins from the upper nasal cavity drain via the anterior and posterior ethmoidal veins into the cavernous sinus. This means GFATS entering the nasal cavity can easily permeate the epithelium, enter the capillary network and lymphatics, directly access systemic circulation bypassing hepatic first-pass metabolism, and reach the brain with maximum speed and efficacy.

3.3. TCM Concept: “Receiving through the Nose Connects the Twelve Meridians”

Yilin Gaicuo states: “The nose connects to the brain, and the perception of scents belongs to the brain.” Liyue Pianwen records: “Receiving through the nose connects the twelve meridians.” Chuangyang Jingyan Quanshu states: “The nose is the clear orifice of the lung; its qi ascends to the brain and descends to the lung.” These affirm the close relationship between the nose, heart, lung, and brain. Drugs absorbed

through the nasal orifices can be distributed via the heart and lung to act on the whole body, treating systemic diseases. Nasal-brain transport drug delivery, known as nasal therapy in TCM, boasts a long history and broad efficacy [19]. Nasal therapy first appeared in the Wushi'er Bingfang (Prescriptions for Fifty-Two Ailments) unearthed from the Mawangdui Han Tomb No. 3. Zhang Zhongjing in the Eastern Han Dynasty pioneered its use in TCM emergencies. Ancient texts like the Dunhuang medical manuscript Fuxingjue Zangfu Yongyao Fayao state: "Open the orifices to rescue sudden death and evil strike; blow into the nose to unblock the lung pores; treat all cases of sudden death with breath stoppage, this method can revive them." Jingui Yaolue contains three formulas for nasal administration to treat "sudden death." Qianjin Yaofang, Juan 25 Beiji lists over ten nasal therapy formulas for sudden death. Ge Hong's Zhouhou Beiji Fang records using Gleditsia, scallion, leek juice, realgar, etc., administered by blowing, stuffing, pricking, or pouring into the nose to treat various emergencies. Shiyi Dexiao Fang uses Tongguan San blown into the nose to treat "sudden violent stroke, unconscious blockage, and locked jaw." This evidence demonstrates that intranasal drugs can effectively treat brain orifice disorders.

4. Conclusions

In summary, acute stroke coma is clinically common. Patients exhibit no conscious response to external stimuli, and prolonged coma is highly detrimental. "Blockage syndrome must be opened; failure to open leads to death" – treatment at this stage is critical. Proper treatment can loosen the locked jaw, restore consciousness, and improve the condition; improper treatment may lead to separation of Yin and Yang, failure of Qi to return, and death. "The nose connects to the brain, and the perception of scents belongs to the brain." Ancient renowned TCM physicians frequently used nasal therapy for emergencies with marked efficacy. Intranasal drug delivery acts rapidly on the central nervous system via neural and non-neural pathways, bypassing gastric mucosal and hepatic first-pass effects. This enables the most effective drug dose to reach the brain orifices quickly, safely, effectively, and conveniently, offering significant advantages for stroke coma patients. GFATS, the primary component extracted from GFA, possesses broad pharmacological effects closely related to cerebral hypoxia, inflammation, and immunity, and shows clear efficacy in lipid-lowering, potentially forming an effective immunomodulatory strategy for stroke. We posit that the extensive pharmacological profile of GFATS could become a new focus in TCM treatment for brain disorders, and its intranasal administration holds substantial promise for arousing comatose patients. However, current research on nasal delivery relies mainly on animal experiments, with insufficient study on brain diseases and limited understanding of the toxic side effects of TCM intranasal administration. Therefore, future research should delve deeper into the mechanisms of intranasal delivery, enhance the bioavailability of TCM nasal formulations, and provide a new therapeutic option for TCM emergency treatment of stroke.

Conflicts of Interest

The authors declare that there is no conflict of interest regarding the publication of this article.

Funding

This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

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