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REVIEW

Pharmacological Insights and Therapeutic Applications of Leonurus in Neurological Disorders

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Abstract: Leonurus has a long history of use in traditional Chinese medicine, particularly for its therapeutic effects in gynecological disorders and its ability to promote blood circulation. Leonurus contains a variety of bioactive compounds, including alkaloids, flavonoids, and terpenoids, which demonstrate significant pharmacological activities, such as antioxidant, anti-inflammatory, and neuroprotective effects. Additionally, combining Leonurus with conventional pharmaceutical treatments may produce synergistic effects, enhancing therapeutic outcomes. This review provides a comprehensive overview of the classification, distribution, traditional uses, and recent pharmacological advancements of Leonurus, with a particular focus on its potential applications in the treatment of brain diseases. It aims to deepen understanding of Leonurus's therapeutic potential in treating neurological conditions.

Keywords: neuroprotection, traditional Chinese medicine, active components, clinical applications

Introduction

Leonurus is a herb of the Lamiaceae family, which is first published in the Shennong Classic of Materia Medica,[1] and is praised as the "holy medicine of the blood family" by the "Compendium of Materia Medica" because of its effects of invigorating blood and regulating menstruation, diuresis and swelling. Emphasizing its characteristics of "nourishing blood without harming new blood", the Huiyan of Materia Medica has become a core medicinal material for the treatment of gynecological diseases such as menstrual irregularities, postpartum lochia, edema, and sores, and is often used in the form of Leonurus decoction and Siwu decoction.[2] Modern studies have not only verified its traditional efficacy through anti-inflammatory, antioxidant, and uterine excitatory effects (promoting contraction), but also found that its alkaloids and flavonoids can inhibit apoptosis of nerve cells and regulate oxidative stress and inflammation in cerebral ischemic injury.[3,4] This discovery expands the application scenarios of Leonurus from the reproductive system to neurological diseases (such as stroke and neurodegenerative diseases), which not only continues the traditional pharmacological logic of "invigorating blood and removing blood stasis", but also provides a new direction for the development of modern neuroprotective drugs through a multi-target regulatory mechanism.

Neurological disorders, such as stroke, pose an immense global health burden, with approximately 15 million people experiencing a stroke each year. Stroke, gliomas, Parkinson's disease, Alzheimer's disease, and high-altitude cerebral edema are significant threats to human health.[5,6] Due to the blood-brain barrier, drug treatment presents considerable challenges. Although Western medicines such as Carmustine, Temozolomide, and Levodopa have shown some progress in treating certain brain disorders,[7] they still face issues such as low selectivity. Given the complexity and diversity of brain diseases, Chinese herbal medicine, with its holistic approach, plays an increasingly important role in treating neurological conditions.[8–11] As a traditional Chinese medicine, Leonurus has attracted attention for its potential in the treatment of neural injuries caused by oxidative stress.[12] This transition from traditional wisdom to modern science not only reflects the significance of the modernization of TCM but also lays a foundation for exploring the therapeutic application of Leonurus in brain diseases.

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This review analyzes and compiles the potential and mechanisms of Leonurus in treating brain disorders, aiming to provide a comprehensive overview of its potential therapeutic value and offer guidance for further research and clinical applications.

Classification and Distribution of Leonurus

Plant Species and Characteristics

Leonurus are erect, branched herbs, with nearly palmately lobed leaves. The inflorescences are cymose and appear in the axils, with the calyx typically shaped like an inverted cone or tubular bell. The corolla ranges in color from white to pink to pale purple, while the flower disk is flat-topped. This genus is primarily distributed in the temperate regions of Europe and Asia,[13] with a few species found naturally in the Americas and Africa. In China, there are approximately 12 species of Leonurus,[14] with *Leonurus* japonicus being the most common. Other species include *Leonurus* sibiricus, *Leonurus* cardiaca, *Leonurus* turkestanicus, and *Leonurus* alpinus.[15]

Leonurus is an annual, biennial, or perennial erect herb that thrives in a variety of habitats, particularly in sunny areas, with altitudes reaching up to 3400 meters.[16] Leonurus sibiricus, a perennial herb, has a woody rhizome that grows obliquely, densely covered with fine fibrous roots. Its stem is upright. This species is found in Liaoning, Jilin, and northern Hebei, growing in grassy slopes and shrublands, typically at altitudes below 400 meters.[17] Leonurus cardiaca, also a perennial herb, has a cylindrical taproot with a dense covering of fine lateral roots that generally spread horizontally. It is found in the northern regions of Hebei, growing on sunlit hillsides at an altitude of approximately 460 meters. Leonurus turkestanicus is a perennial herb with a woody rhizome, densely covered with horizontally extending lateral roots. It primarily grows at the forest edges, at altitudes around 3200 meters. Leonurus alpinus, another perennial herb, has a woody rhizome with dense fibrous roots. The taproot is conical in shape. This species is found in northern Xinjiang, commonly in moist areas such as lower mountain slopes, riverbanks, and near ditches, with an elevation range of 1000 to 2000 meters. The plant is primarily found in provinces such as Anhui, Zhejiang, Shandong, Guangdong, Henan, Jiangsu, and Xinjiang (Figure 1). Among these, the Leonurus produced in Henan, Shandong, and Xinjiang is of higher quality compared to other provinces (Table 1).[18]

Traditional Uses and Ethnopharmacology of Leonurus

Leonurus has a rich history in traditional medicine, with its earliest use recorded in the Shennong Bencao Jing. The Bencao Gangmu further emphasized its therapeutic effects in promoting blood circulation, regulating menstruation, and detoxifying.[19] Traditionally, Leonurus has been widely used for gynecological issues, such as menstrual irregularities, dysmenorrhea, and postpartum bleeding. Additionally, it has been used to treat edema, abscesses, and ulcers, demonstrating its versatility in treating various conditions.[2]

In East Asia, including Japan and Korea, the use of Leonurus is similar to its application in China, focusing on regulating menstruation and postpartum care. Beyond gynecological conditions, it is also valued for its diuretic and anti-inflammatory properties, becoming a remedy for nephritis and urinary tract infections.[20] In Southeast Asia, particularly in Vietnam and Thailand, Leonurus is traditionally used to treat snakebites, fevers, and gastrointestinal disorders.[21] The common practice is to crush the fresh leaves and apply them directly to wounds, in line with the herb's cooling properties and its effect in alleviating heat-related symptoms.

In Mongolian and Tibetan traditional medicine, Leonurus is primarily used as a hemostatic agent for internal bleeding and external wounds. Tibetan medicine commonly uses this herb to treat high-altitude sickness, believing that its cooling and detoxifying properties help manage high-altitude cerebral edema and improve oxygen saturation.[22]

Traditionally, Leonurus is often used in combination with other herbs to enhance its therapeutic effects. Common combinations include Leonurus Tang (Leonurus Decoction) and Danggui Shenghua Tang (Tangkui Shenghua Decoction), both of which are used to promote blood circulation and regulate menstruation.[23] This herb is typically prepared as a decoction, pill, or topical ointment, targeting specific conditions. Decoctions are often used to alleviate menstrual pain and postpartum abdominal discomfort, typically combined with herbs such as Danggui (Angelica sinensis) and

Figure 1 Geographical Distribution of Leonurus in China.

Chuanxiong (Ligusticum chuanxiong) to enhance circulation and relieve pain.[24] At the same time, topical pastes or ointments are used to speed up wound healing and stop bleeding, reflecting the herb's traditional role in wound care.[25]

Recent ethnopharmacological studies have begun to validate the traditional applications of Leonurus, revealing its diverse pharmacological properties. Modern research has found that its active ingredients, such as leonurine, stachydrine, flavonoids, and diterpenes, possess anti-inflammatory, antioxidant, neuroprotective, and anticancer effects.[26] These findings not only support the historical uses of the herb but also expand its potential applications in treating central nervous system disorders, cardiovascular diseases, and other systemic conditions. By combining traditional knowledge

Table 1 Name and Distribution of Leonurus Species

No	Latin	Distribution
1	Leonurus *japonicus*	Henan, Shandong, Guangdong, etc.
2	Leonurus *macanthus*	Liaoning, Jilin, Hebei, etc.
3	Leonurus *sibiricus*	Inner Mongolia, Hebei, Shanxi, etc.
4	Leonurus *chaituroides*	Hubei, Anhui, etc.
5	Leonurus *glaucescens*	Inner Mongolia
6	Leonurus *pseudomacranthus*	Shandong, Hebei, Liaoning, etc
7	Leonurus *villosissimus*	Hebei
8	Leonurus *urticifolius*	Tibet
9	Leonurus *turkestanicus*	Xinjiang
10	Leonurus *deminutus*	Inner Mongolia
11	Leonurus *wutaishanicus*	Shanxi
12	Leonurus *pseudopanzerioides*	Xinjiang Uygur Autonomous Region

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with modern pharmacological insights, a scientific foundation has been provided for the continued use of Leonurus in both traditional and modern medicine.

In summary, the traditional uses and ethnopharmacology of Leonurus reflect its significance as a multifunctional medicinal herb. Its long-standing cross-cultural history, coupled with modern research support, highlights its therapeutic potential and supports its integration into current medical practices.

Synergistic Effects of Leonurus and Modern Pharmaceuticals in the Treatment of Neurological Disorders

As a traditional Chinese medicine, Leonurus has been widely used in TCM for its effects on promoting blood circulation, removing blood stasis, and detoxifying. Traditionally, it has been primarily used in the treatment of gynecological disorders.[27] However, ancient texts also mention its applications in improving blood circulation and treating blood stasis-related symptoms,[28] which lay the foundation for its adjunctive use in treating brain diseases. Recent modern pharmacological studies have shown that Leonurus possesses significant neuroprotective, antioxidant, and anti-inflammatory properties, which demonstrate its vast potential in the treatment of neurological disorders.

Combination with Other Traditional Chinese Medicines

In traditional Chinese medicine, Leonurus is considered to have the functions of promoting blood circulation, removing blood stasis, clearing heat, and detoxifying. Recent studies have explored its synergistic effects when combined with other traditional Chinese herbs, particularly in the treatment of brain diseases. For instance, Danshen (Salvia miltiorrhiza), known for its blood-activating, blood-stasis-resolving, and microcirculation-improving effects, is widely used in stroke rehabilitation and brain circulation improvement. When used in combination with Leonurus,[19,29] it may produce a synergistic effect on brain blood circulation, brain injury repair, and neural regeneration. In addition, Chuanxiong (Ligusticum chuanxiong), which promotes blood circulation and moves qi, can complement Leonurus, helping alleviate symptoms such as headaches, dizziness, and sequelae of strokes caused by blood stasis. Astragalus (Astragalus membranaceus), known for its qi-tonifying, immune-enhancing, and protective effects, when combined with Leonurus, may positively affect overall health and immune regulation in patients with brain diseases, in addition to improving blood circulation.[30] Goji berries (Lycium barbarum), which nourish the liver and kidneys and improve vision, may also support the health of the nervous system when combined with Leonurus to enhance blood circulation.

Combination with Western Pharmaceuticals

Recent studies have also explored the combination of Leonurus with modern pharmaceuticals. For example, the combination of Leonurus with antidepressants or anxiolytic drugs may produce synergistic effects. The blood-activating and stasis-removing properties of Leonurus improve blood circulation and optimize the metabolic environment of the nervous system, thereby enhancing the efficacy of antidepressant drugs.[31] Studies have shown that combining Leonurus with selective serotonin reuptake inhibitors (SSRIs) like sertraline can have an adjunctive effect on the symptoms of depression.[32,33] The mechanism may be related to the improvement of brain blood flow and oxygen supply. This combination of traditional Chinese medicine and Western pharmaceuticals provides a new direction for comprehensive treatment of brain diseases in the future, enriching the application of Leonurus in neurological disorders and offering scientific evidence for its integration with modern pharmaceuticals. The specific synergistic mechanisms and therapeutic effects of Leonurus in combination with Western drugs still require further clinical studies and mechanistic exploration to fully harness its therapeutic potential in brain diseases.

Main Bioactive Components of Leonurus and Their Potential Role in the Treatment of Neurological Disorders

Leonurus contains various bioactive components, which demonstrate different levels of research interest and potential application in the treatment of brain diseases. To clarify the key areas and impact of these components in relevant studies, we conducted a statistical analysis of the frequency of citations for different active ingredients in the literature (Figure 2).

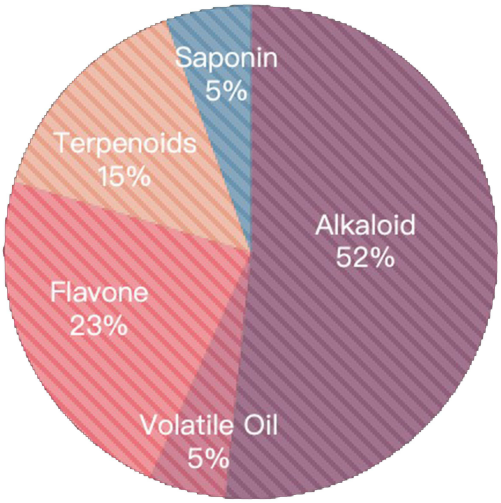

Figure 2 Distribution of Literature on Different Bioactive Components of Leonurus in Brain Disease Research.

Among them, alkaloids such as Leonurus alkaloid and stachydrine have been widely studied for their neuroprotective and anti-inflammatory effects. Flavonoids and terpenoids also exhibit significant pharmacological actions in antioxidant stress and blood-brain barrier modulation.

Alkaloids and Their Pharmacological Activity

Leonurus contains various alkaloid compounds, with alkaloid content ranging from 0.11% to 2.09%.[34] Although the content is low, these alkaloids have high pharmacological activity and are among the main therapeutic substances in Leonurus. Common alkaloids include: trigonelline, stachydrine, Leonurus ning, Leonurus alkaloid, and Leonurus din (Figure 3). Among these, Leonurus alkaloid and stachydrine are the main active alkaloid components in Leonurus,[35] showing significant potential in the treatment of brain diseases. The 2020 edition of the Chinese Pharmacopoeia specifies hydrochloride stachydrine and hydrochloride Leonurus alkaloid as important indicators for quality control of Leonurus. It requires that the content of hydrochloride stachydrine be ≥0.5%, and the content of hydrochloride Leonurus alkaloid be ≥0.05%.[19]

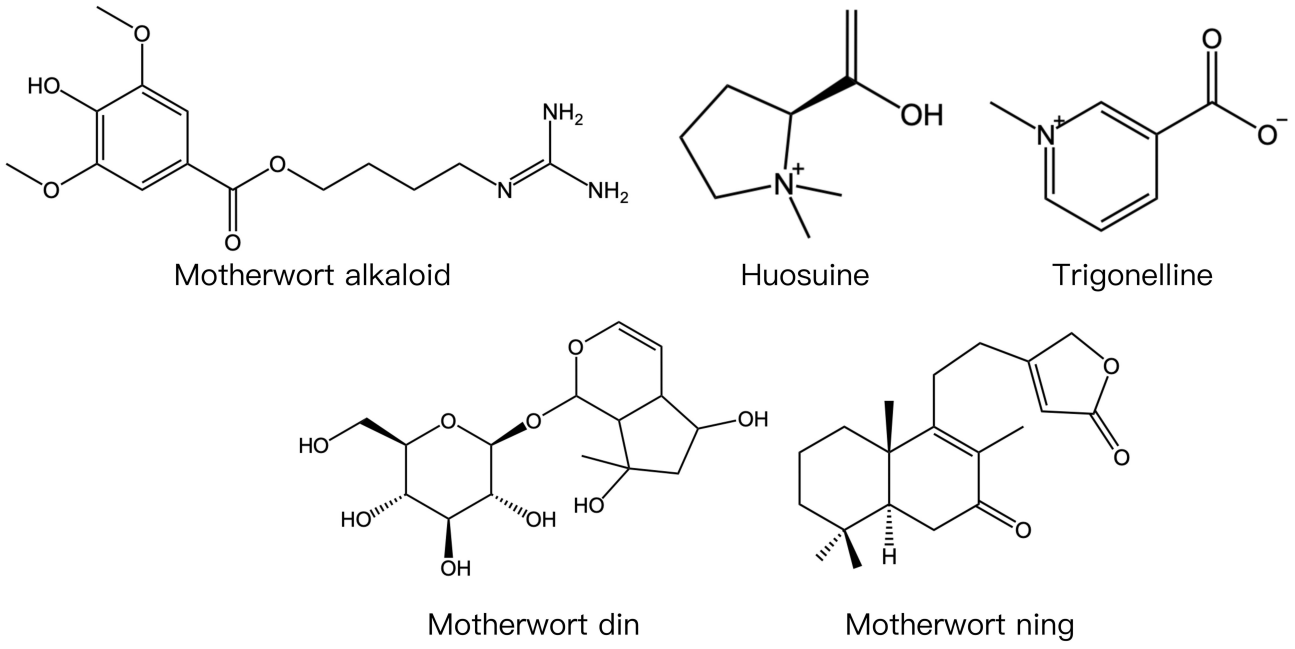

Figure 3 Common Alkaloid Structural Formulas.

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Pharmacological Properties of Leonurine Alkaloid and Its Application in Neurological Disorders

Leonurine is an alkaloid extracted from Leonurus, traditionally used in Chinese medicine to regulate female physiological functions. Modern studies have found that Leonurine not only alleviates myocardial ischemia and stroke symptoms by inhibiting vascular smooth muscle contraction through blocking Ca^{2+} influx,[36,37] but also demonstrates significant neuroprotective, anti-inflammatory, and antioxidant effects, especially its potential in brain disease treatment, which has attracted widespread attention.

The molecular structure of Leonurine, including guanidine, butyl, and cinnamate ester groups, provides a molecular basis for its pharmacological actions.[38] However, its high-polarity functional groups limit its transmembrane ability and bioavailability.[39] To overcome this, researchers have optimized its structure. For example, replacing the guanidine group with a thiomethyl group significantly improved its lipophilicity and brain permeability, showing enhanced neuroprotective effects in animal experiments. This optimized compound increased Bcl-2 expression, inhibited Bax expression, and reduced neuronal apoptosis.[40] Additionally, Leonurine, when used in combination with other compounds (such as aspirin or cysteine), shows synergistic effects, further enhancing its antioxidant and anti-inflammatory properties, thus providing new avenues for treating brain ischemia and neurodegenerative diseases.[41]

In the treatment of cerebral infarction, Leonurine exerts multiple effects. Studies show it activates the PI3K/Akt signaling pathway, effectively reducing oxidative stress, upregulating Trx and its reductase expression, significantly increasing the activities of antioxidant enzymes such as SOD, GPx, and CAT, while reducing MDA production.[42] This helps restore the balance between oxidation and antioxidation in neurons, alleviating damage caused by reactive oxygen species accumulation. Moreover, Leonurine activates eNOS phosphorylation to protect blood-brain barrier integrity, further reducing ischemic brain injury.[43]

In glioma studies, Leonurine inhibits tumor cell proliferation and induces apoptosis by modulating the Akt/MDM2/p53 signaling pathway,[44,45] and significantly reduces tumor-associated markers such as Ki67 expression.[46] These effects suggest its potential value in brain tumor treatment. Furthermore, under high-glucose conditions, Leonurine can regulate brain-derived neurotrophic factor levels, inhibit inflammatory cytokines and neuronal apoptosis,[47] thereby improving pathological changes in hippocampal neurons.[48] It can also reduce excitotoxicity by regulating glutamate transporter expression and lowering extracellular glutamate levels, thus alleviating neural damage under hyperglycemic conditions.[49]

In addition, Leonurine specifically inhibited the assembly of NLRP3 inflammatory vesicles and reduced the release of IL-1β and IL-18, a mechanism that showed significant anti-inflammatory effects in an Alzheimer's disease model.[50]

The multiple mechanisms of Leonurine in treating brain diseases not only demonstrate its broad clinical application potential but also provide important clues for the modernization of traditional Chinese medicine and the development of new drugs for brain diseases. Future studies, focusing on deeper mechanism exploration and structural optimization, are expected to further enhance its efficacy in treating brain diseases and offer more possibilities for related treatments.

Pharmacological Properties of Housuine and Its Application in Neurological Disorders

As one of the key active components of Leonurus, housuine's potential in treating brain diseases is primarily related to its molecular structure,[51,52] where its nitrogen-containing heterocyclic and ester group features play important roles in neuroprotection, anti-inflammation, and cognitive function improvement,[53] Studies show that housuine possesses cholinergic-like properties, which may enhance neurotransmission through modulating the cholinergic system, thereby improving cognitive function.[54] In addition, housuine can reduce the release of inflammatory cytokines such as TNF-α and IL-1β by modulating PI3K/Akt and NF-κB signaling pathways,[55] while inhibiting pyroptosis, thereby alleviating brain damage and neuronal injury.[56] Its protective effects on the cardiovascular system are closely related to the treatment of cerebrovascular diseases, as brain diseases often involve vascular dysfunction. Although housuine is not a typical monoamine oxidase inhibitor, its unique nitrogen-containing heterocyclic structure offers possibilities for further pharmacological exploration and optimization.[57] Modern technologies such as computer-aided drug design can help reveal the relationship between its molecular structure and bioactivity, optimizing its neuroprotective and cognitive function-improving effects, further promoting its application in treating brain diseases.

In pharmacological effects, housuine demonstrates significant anti-inflammatory and anti-apoptotic actions in ischemic brain injury, especially in inhibiting pyroptosis.[51] Studies show that housuine can effectively reduce neuronal pyroptosis and the release of inflammatory cytokines such as TNF-α and IL-1β induced by oxygen-glucose deprivation/reoxygenation, through regulating the PI3K/Akt/NF-κB signaling pathway.[58] Housuine significantly downregulates the ratio of p-PI3K/PI3K and p-Akt/Akt while inhibiting NF-κB signaling,[59] thus reducing the inflammatory response and alleviating the severity of ischemic brain injury. Additionally, housuine protects neurons through its anti-inflammatory action and reduces pathological changes by inhibiting programmed cell death mechanisms.[60] These findings suggest that housuine has great potential in the treatment of brain diseases, and future in-depth mechanism studies and structural optimization may lead to the development of novel brain disease therapeutics based on housuine.

Other Leonurus Alkaloids

Trigonelline is a natural alkaloid derived in Leonurus, Fenugreek, and other plants. It has been studied for its potential antidiabetic effects. Research indicates that it can help reduce blood sugar by promoting insulin secretion and enhancing insulin action.[61] Furthermore, trigonelline has neuroprotective effects,[62] which can alleviate neural damage and promote nerve repair.[63] Current research suggests that trigonelline in Leonurus can significantly promote angiogenesis in zebrafish models by upregulating the expression of Tie-2, VEGFR2, and VEGF.[64] However, apart from this study, the pharmacological activity of other Leonurus alkaloids in cerebrovascular-related diseases remains relatively underexplored. Current literature does not provide sufficient experimental data to support further application, but future research may uncover these compounds' potential mechanisms and clinical value.

Flavonoid Compounds in Neurological Disorders

Flavonoid compounds are one of the main chemical components of Leonurus. Several flavonoid compounds have been isolated from Leonurus, including Isoorientin A, baicalein, genistein, swertisin, rutin, and others—approximately 20 compounds in total (Figure 4).[65] Among them, rutin and quercetin are the primary active flavonoid components in Leonurus, which have also shown significant effects in the treatment of brain diseases.[66]

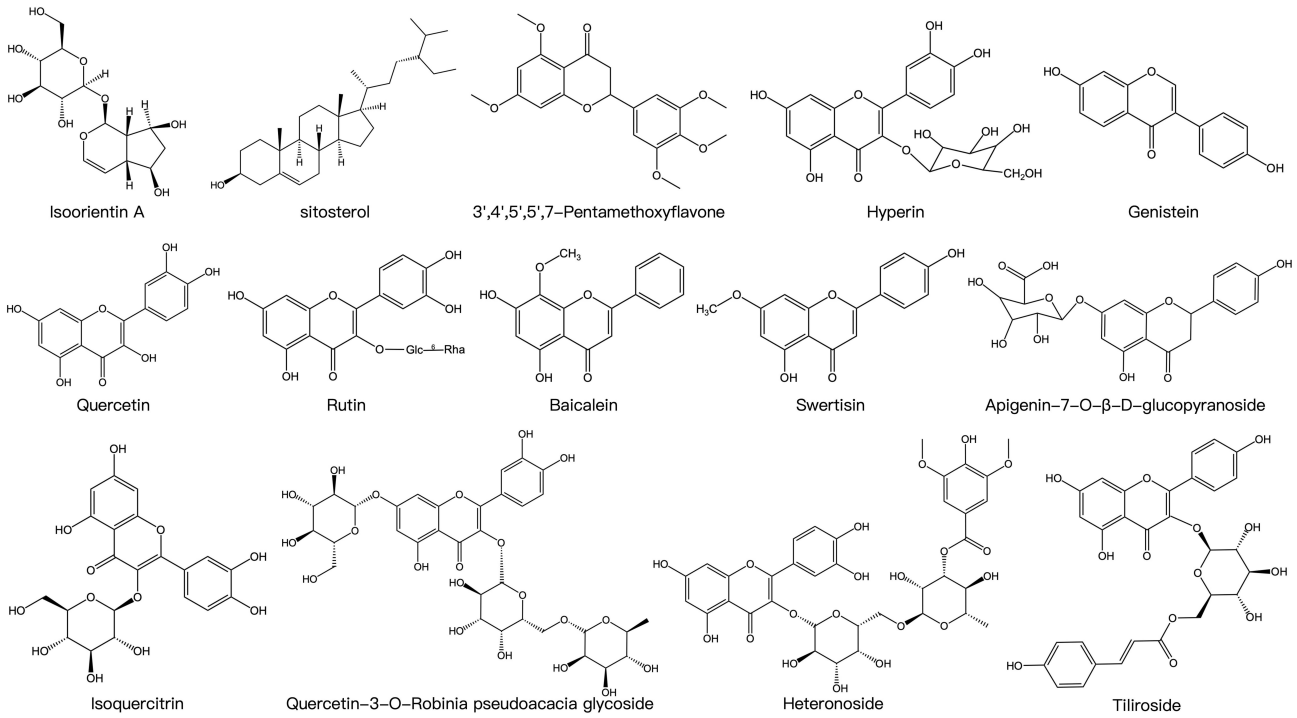

Figure 4 Chemical structures of some flavonoid compounds from Leonurus.

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Neuroprotective Effects of Luteolin

Luteolin is a naturally occurring flavonoid compound widely found in plants such as chrysanthemums, asparagus, chili peppers, thyme, chamomile, and orange peel.[67] Known for its remarkable antioxidant, anti-inflammatory, and anti-allergic properties, luteolin has been confirmed in numerous studies to have beneficial effects on human health.[68] Due to its extensive biological activities, luteolin occupies an important position in traditional medicine and has shown promising potential in modern pharmaceutical research.[69] Currently, luteolin has been developed as a dietary supplement and health product, particularly in areas such as antioxidant effects,[70] anti-inflammatory properties, diabetes treatment,[71] and cardiovascular health.

The antioxidant effect of luteolin correlates with its ability to directly bind Keap1 protein. By stabilizing Nrf2 and promoting its nuclear translocation, luteolin activates the expression of downstream antioxidant enzymes (eg SOD, CAT) and scavenges free radicals.[70] In terms of blood-brain barrier protection, luteolin reduces the degradation of tight junction proteins by inhibiting matrix metalloproteinase-9 activity, thereby maintaining barrier integrity. Animal experiments showed that the infarct volume after cerebral ischemia was reduced by about 40% in the luteolin treatment group.[72] The molecular structure of luteolin consists of quercetin and a rhamnose moiety connected by a glycosidic bond, and this unique structure-activity relationship underpins its diverse pharmacological activities.[73] The glycoside portion (rhamnose) enhances the water solubility and bio-stability of luteolin, while the conjugated double bond system in the molecule plays a critical role in the antioxidant process, effectively scavenging free radicals to protect cells from oxidative stress damage.[74] Additionally, the spatial structure of luteolin is closely related to its ability to bind to targets, which significantly affects its pharmacological effects.[75]

In the treatment of brain diseases, luteolin demonstrates significant neuroprotective effects.[74] Studies show that luteolin, as a potent antioxidant, can effectively scavenge free radicals and protect neural cells from oxidative stress damage.[76] Furthermore, luteolin reduces the production of inflammatory factors by inhibiting the NF-κB signaling pathway, thus alleviating neuroinflammation.[77] More importantly, luteolin enhances the integrity of the blood-brain barrier, reducing the entry of harmful substances into the brain.[78] These actions make luteolin a promising candidate for neuroprotection in stroke and Alzheimer's disease prevention, offering new therapeutic possibilities for these conditions.

The Application Prospects of Quercetin

Quercetin is another important natural flavonoid compound widely found in plants such as apples, onions, grapefruits, green tea, cherries, citrus fruits, and red wine.[79,80] Due to its strong antioxidant, anti-inflammatory, anti-allergic,[81] and antiviral activities, quercetin has garnered significant attention.[82] It has now been developed as a dietary supplement, particularly in the fields of immune modulation, anti-aging, and anti-allergy, showing broad market potential.[83]

The molecular structure of quercetin consists of three benzene rings (A, B, and C) and a ketone group,[84] and its structure-activity relationship is mainly reflected in the following aspects. The hydroxyl groups on the A ring significantly enhance its free radical scavenging ability, thereby improving its antioxidant effects.[85,86] Animal experiments further showed that quercetin inhibited histone deacetylase activity and increased histone H3 acetylation level, thereby improving learning memory function, which is important for the treatment of neurodegenerative diseases.[73] In addition, the glycoside structure of quercetin increases its water solubility and bioavailability, improving its absorption and distribution in the body.[87]

In the treatment of brain diseases, quercetin also shows great potential. Studies suggest that quercetin activates the Nrf2 signaling pathway, enhancing the antioxidant capacity of neurons, thus protecting them from oxidative damage.[88,89] Furthermore, quercetin inhibits the aggregation of β-amyloid proteins, a hallmark feature of Alzheimer's disease, offering new insights into the prevention and treatment of this condition.[90,91] Animal studies have shown that quercetin significantly improves learning and memory, which is of great significance for the treatment of neurodegenerative diseases.[92] These findings suggest that quercetin is a promising candidate drug with great potential in neuroprotection and cognitive function improvement, warranting further research and development.

Terpenoid Compounds in Neurological Disorder

Terpenoid compounds are a class of naturally occurring organic compounds with diverse structures and significant biological activities. They are typically derived from isoprene (C_5) as a basic unit, forming through various ring formation, rearrangement, and oxidation reactions. Based on the length of their carbon chains, terpenoids can be classified as monoterpenes (C_{10}), sesquiterpenes (C_{15}), diterpenes (C_{20}), and triterpenes (C_{25}).[93]

The cyclic structure and the number of rings in terpenoid compounds determine the rigidity, lipophilicity, and binding ability to targets, influencing their biological activities. The type and position of substituents, such as hydroxyl, methyl, and ester groups, significantly affect the solubility, lipophilicity, and receptor interactions of the molecules. The presence and position of double bonds can increase the reactivity of the molecule, enhance its free radical scavenging ability, or increase its affinity for targets. Oxidation functional groups influence the electrophilicity, reactivity, and binding strength with target proteins.

The diterpenoid compounds in Leonurus, primarily leonurine, have shown significant pharmacological potential in the treatment of brain diseases, including antioxidant, anti-inflammatory, neuroprotective, and cognitive-enhancing effects.[94] These compounds exert their effects primarily through two mechanisms: first, they demonstrate notable neuroprotective effects by potentially protecting neurons from damage via antioxidant and anti-inflammatory mechanisms.[95] Second, some studies suggest that leonurine may improve cerebral blood flow and promote circulation, which holds potential therapeutic value for ischemic brain diseases.[96] These findings not only expand our understanding of the pharmacological actions of Leonurus, but also provide valuable directions for developing new strategies for the treatment of brain diseases.

Other Active Ingredients

Saponins and volatile oils in Leonurus are also important active components.[61] Saponin components often exhibit certain toxicity to the human body. For example, ginsenosides and phytolaccosides are known to have some degree of toxicity.[97,98] Saponins and volatile oils in Leonurus have demonstrated protective effects in brain diseases. Studies have shown that the antioxidant components in the volatile oils of Leonurus may help alleviate oxidative damage and reduce brain lesions.[68] Additionally, saponins in Leonurus can significantly reduce neuroinflammation by inhibiting microglial activation and reducing the release of pro-inflammatory cytokines in a cerebral ischemia-reperfusion model. These results suggest that saponins may have the potential to combat post-stroke inflammatory responses.[69] However, research on their specific mechanisms and clinical efficacy remains relatively limited. Further clinical and basic studies are required to confirm their practical applications and effectiveness in the prevention and treatment of brain diseases.

Toxicity and Safety of Leonurus

Toxicity studies on Leonurus have revealed some concerns in early case reports, which indicated that high doses of the herb might cause adverse reactions such as kidney damage.[99] However, these incidents are typically associated with excessive use or individual-specific responses. More recent toxicity studies have focused on animal experiments, with systematic observations conducted using mouse and rat models. Research by Chen Hongbin et al found that the toxicity of Leonurus is related to the extraction method and type of compounds used.[100] Luo Yi et al demonstrated that high doses of Leonurus decoction might cause mild liver and kidney inflammatory lesions.[101] In contrast, a study by Lü Lili et al showed that large doses of Leonurus extract administered over a short period did not cause significant liver or kidney damage, suggesting a high safety profile when used within reasonable doses.[102] Further analysis identified alkaloid compounds in Leonurus as the primary source of its toxicity.[103] Luo Yi et al extracted and analyzed the petroleum ether extract of Leonurus, finding that these compounds could contribute to toxicity.[101] However, at regular doses, these harmful compounds do not pose significant risks.

The toxicity mechanism of Leonurus is primarily associated with its potential effects on the liver and kidneys. Research by Huang Wei et al indicated that the nephrotoxicity of Leonurus ethanol extract may be linked to oxidative stress.[104] Further cell experiments showed that the petroleum ether extract of Leonurus might cause renal damage by increasing cell apoptosis.[105] Although these studies suggest some potential mechanisms at high doses, no significant

toxicity has been observed at reasonable doses. Therefore, these findings provide valuable dosage guidelines for clinical use but do not raise concerns about the herb's overall safety.

In summary, studies indicate that Leonurus demonstrates a high level of safety when used at standard doses. Toxic reactions are generally only observed at extremely high doses or under special conditions. In clinical practice, Leonurus has shown good tolerance in the treatment of various diseases, with no reports of serious adverse reactions. While there is a potential risk of liver and kidney issues in extreme cases, these are typically associated with doses beyond the normal range. Therefore, when used within standard doses, Leonurus is a safe and effective therapeutic agent, with toxicity risks being mitigated through proper dose control.

Clinical Applications and Future Development of Leonurus

Common Preparations and Indications

Leonurus is commonly used in clinical practice and is frequently included in traditional Chinese medicine formulations. Studies on its chemical composition have shown that alkaloids are its main active ingredients.[106] The predominant alkaloids in Leonurus japonicus are leonurine and stachydrine. The bioavailability of these active constituents varies significantly depending on the pharmaceutical formulation employed. Oral administration demonstrates the highest bioavailability among various delivery routes for Leonurus alkaloids. Specifically, the oral bioavailability is approximately 15–20% for leonurine and 25–30% for stachydrine.[107,108] Well-known preparations include the Compound Leonurus Syrup from Beijing Tongrentang, Compound Leonurus Capsules from Jiangxi Bosda, and Compound Leonurus Tincture from Zhejiang Tianyi Tang, primarily used for regulating menstruation, invigorating blood circulation, and aiding postpartum uterine recovery, with a focus on gynecological diseases.[109] The "2024–2029 China Leonurus Industry Market In-Depth Discussion and Investment Feasibility Report" indicates that the market for Leonurus has been growing at an annual rate of approximately 10%, with an increasing demand for Leonurus syrup.

In addition, the active components of Leonurus have shown numerous pharmacological effects. Zhang Zigang et al found that the total alkaloids of Leonurus significantly reduced the expression of Bcl-2 in a prostate hyperplasia rat model, suggesting its potential use in treating prostate hyperplasia.[110] Huang Hui et al used Leonurus alkaloid to treat db/db mice, confirming that it could alleviate diabetic symptoms by inhibiting the NF-κB/IKK pathway.[111] Furthermore, experiments revealed that Leonurus alkaloid could act as a glycation inhibitor, preventing the formation of advanced glycation end-products, thus preventing diabetes and its complications.[112] Leonurus alkaloids also demonstrate cardiovascular protective effects. Liang Zhaowen et al found that Leonurus alkaloid reduced serum levels of brain natriuretic peptide and angiotensin II, inhibiting myocardial remodeling in chronic heart failure rats.[113] Moreover, Leonurus alkaloid has shown protective effects on the kidneys. Xu Daliang et al discovered that it improved kidney function, significantly inhibited the TNF-α signaling pathway and inflammatory factors, reducing kidney pathological damage and offering protection against septic kidney injury.[114]

The Translational Application of Leonurus Alkaloids: From Lipid-Lowering to Neurological Disorders Treatment Potential

With the successful completion of Phase I clinical trials, Professor Zhu's team has transitioned the Leonurus alkaloid from laboratory research to clinical application, backed by investment.[115] This milestone signifies that Leonurus alkaloid has the potential to become one of the few original drugs from China, with its lipid-lowering effects now recognized, demonstrating its significant market potential as a lipid-lowering drug. However, the application prospects of Leonurus alkaloid extend far beyond this. Extensive research has unveiled its considerable neuroprotective potential and efficacy in the treatment of brain diseases, opening new doors for its application in neurological disorders.

We believe that with further research and clinical trials, Leonurus alkaloid will shine in future medical applications, providing new therapeutic options for patients with brain diseases. Through this translational application, Leonurus alkaloid not only enriches its pharmacological application range but also offers new insights and directions for the modernization and internationalization of traditional Chinese medicine. However, the clinical validation of Leonurus in neurological diseases is centered on the treatment of stroke, and the preclinical research data of its active ingredient SCM-198 are solid, but human clinical trials have not yet been fully carried out. In the future, it is necessary to further

promote its transition to Phase II/III clinical trials and explore its potential applications in other neurological diseases (eg, neurodegenerative diseases, spinal cord injury). Existing studies have provided a scientific basis for the leap from traditional gynecological drugs to neuroprotective agents, but the clinical application still needs to be carefully verified.

Conclusion

Leonurus exemplifies the successful integration of traditional Chinese medicine with modern pharmacology. Its bioactive components, such as alkaloids and flavonoids, provide a scientific basis for its traditional uses and reveal new therapeutic potentials, particularly in neurological and cardiovascular diseases. With its established safety profile and growing clinical applications, Leonurus represents a promising bridge between ancient wisdom and contemporary medicine, paving the way for further advancements in global healthcare.

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Disclosure

The authors report no conflicts of interest in this work.

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