

# Extraction of Active Components from *Ziziphus jujuba* var. *spinosa* and Development of Insomnia-Improving Products

Shijun Xu<sup>1\*</sup>

Shanghai Ocean University, No. 999, Hucheng Huan Road, Nanhui New Town, Pudong New Area, Shanghai, 201306, China

**Abstract.** Insomnia, a prevalent global health issue exacerbated by modern life stress, affects 38.2% of Chinese people, with a rising trend among youth. *Ziziphus jujuba* Mill. var. *spinosa* (Bunge) Hu ex H. F. Chou, rich in saponins and flavonoids, exhibits sedative-hypnotic and anti-anxiety effects, offering a natural solution for insomnia. This study explores the potential of saponin-based substances from medicinal plants (e.g., *Z. jujuba* var. *spinosa*, *Panax notoginseng*) for sleep improvement. It systematically analyzes the technological evolution in transforming saponin-containing materials into modern preparations, including multidimensional raw material identification (DNA barcoding, NIRS, ICP-MS) and advancements in extraction technologies. Challenges remain, such as high costs of supercritical CO<sub>2</sub> extraction, unclear sleep-regulating mechanisms of saponins, and formulation optimization hurdles. This work provides a foundation for developing safe, eco-friendly saponin-derived sleep-aiding products.

## 1 Introduction

In today's fast-paced society environment, anxiety has swept across most people affecting by factors such as social relationships, economic pressure, and occupational stress. Neglect of emotional needs and quality of life often leads to fatigue, insomnia and malnutrition, with insomnia as the most prevalent problem. According to statistics from the World Health Organization (WHO), the global rate of sleep disorders is 27%, while in China, the rate reaches 38.2%. More than 300 million Chinese people are suffering from sleep disorders, and the figure continues to rise annually [1].

Alarmingly, insomnia is increasingly common among younger populations, including students and early-career professionals, largely due to academic and work-related stress.

*Ziziphus jujuba* Mill. var. *spinosa* (Bunge) Hu ex H. F. Chou, known as the "Oriental Sleep-inducing Fruit", is rich with triterpenoid saponins, flavonoids, alkaloids, fatty acids and trace minerals. It has the effects of nourishing the heart and liver, calming the mind, and tranquilizing the nerves. Studies have shown that *Ziziphus jujuba* Mill. Var. *Spinosa* (Bunge) Hu ex H. F. Chou exhibits multiple pharmacological effects, including sedation and hypnosis, as well as anti-anxiety and antidepressant properties, and anti-arrhythmic and anti-inflammatory effects, which can effectively alleviate problems such as long-term fatigue, insomnia, and malnutrition [2].

This study aims to extract active compounds, such as saponins and flavonoids, from *Ziziphus jujuba* Mill. var. *spinosa* (Bunge) Hu ex H. F. Chou, using safe, eco-

friendly methods to develop products that have no toxic or side effects and can effectively improve insomnia symptoms.

## 2 Sources and traditional applications of saponin-based sleep-aiding substances

### 2.1 Sources

Sleep is a crucial physiological process essential for, overall, health quality. However, with the acceleration of modern life rhythms and the increase of mental stress, sleep disorders are increasing annually, posing a serious threat to physical and mental well-being. In the search for safe and effective sleep-aiding solutions, natural products have drawn attention, as the low side effects and good biocompatibility. Among them, saponin-based substances, a class of active ingredients widely present in plants, have become a research hotspot due to their unique sleep-aiding activities. These substances are mainly derived from various medicinal plants such as *Ziziphus jujuba* Mill. var. *spinosa*, *Acanthopanax senticosus*, *Polygala tenuifolia* Willd., *Gynostemma pentaphyllum*, and *Panax quinquefolius*. Their active components, primarily triterpenoid or dammarane-type saponins, promote sleep by regulating neurotransmitters, modulating neuroendocrine axes, restoring autonomic balance, and reducing oxidative stress. In-depth exploration of their sources and mechanisms of action provides a great theoretical and practical foundation for the development of natural and efficient sleep therapeutics.

\* Corresponding author: 2070823913@qq.com

## 2.2 Traditional applications

Saponins, widely distributed plant metabolites, vary in type and abundance across species, with several attracting significant research interest. Historically regarded as anti-nutritional factors due to their interference with nutrient absorption and digestion, saponins are now recognized for diverse pharmacological activities. Evidence demonstrates their therapeutic potential in cardiovascular, allergic, dermatological, metabolic, oncological, and psychiatric disorders. Additionally, saponins exhibit anti-inflammatory, antimicrobial, antioxidant, mitochondrial regulatory, neuroprotective, and telomere-lengthening activities [3].

## 3 The sleep-promoting mechanism of saponin compounds

*Panax notoginseng* (Burkill) F.H.Chen, a perennial herb of the family Araliaceae, is widely used in traditional Chinese medicine (TCM) and derived from the dried roots and rhizomes of the plant, which is known for its efficacy in dispersing blood stasis, stopping bleeding, subduing swelling, and resolving pain. Based on TCM theory, insomnia can lead to blood stasis and cerebral collaterals stagnation, impairing the “divine mechanism” and resulting in cognitive dysfunction.

*Panax notoginseng* contains saponins as its principal chemical ingredients, including notoginsenoside saponin R1, ginsenoside Rg1, and ginsenoside Rb1. Numerous investigations have demonstrated the diverse biological functions of PNS, including ameliorating cardiac ischemia, counteracting arrhythmia, enhancing cognition and memory, reducing inflammation, regulating immunological function, exerting hepatoprotection, neuroprotection, and hypoglycemia and hypolipidemic effects. Increasing attention has been paid on central nervous system, where PNS have been shown to improve learning and memory, inhibit amyloid- $\beta$ -induced damage, exert antioxidant activity, and suppress excessive autophagy and apoptosis via activation of the Akt/mTOR pathway [4].

The mechanism of insomnia treatment mainly focuses on regulating neurotransmitters. Neurotransmitters are chemical substances that transmit signals in the nervous system, and the imbalance of their levels is closely related to the occurrence of insomnia. For instance, gamma-aminobutyric acid (GABA), an inhibitory neurotransmitter, can inhibit nerve excitement and promote relaxation; its weakened function may lead to difficulty falling asleep. On the other hand, reduced levels of serotonin, a neurotransmitter associated with mood and sleep regulation, may also cause disruptions in the sleep cycle. The core working logic of various current insomnia treatment methods (such as some medications and non-pharmacological interventions) lies in restoring the normal signal transmission of the nervous system by regulating the synthesis, release, or receptor binding efficiency of such neurotransmitters, thereby improving sleep quality and extending sleep duration [5].

Inflammatory cytokines, a class of cytokines that regulate the body’s inflammatory response, have been identified as crucial sleep-related factors, and targeting them constitutes an important mechanism for insomnia treatment. Common sleep-associated inflammatory cytokines include tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), interleukin-6 (IL-6), and interleukin-1 $\beta$  (IL-1 $\beta$ ), and the therapeutic mechanism primarily operates through the following pathways:

First, insomnia treatments can reduce abnormal elevations in pro-inflammatory cytokine levels to restore normal sleep rhythms. When the body is in a state of inflammation (caused by infection, chronic disease, or psychological stress), excessive TNF- $\alpha$  and IL-1 $\beta$  disrupt the hypothalamic-pituitary-adrenal (HPA) axis, promoting the secretion of stress hormones like cortisol and breaking the balance of the sleep-wake cycle—leading to difficulties falling asleep, light sleep, or frequent nighttime awakenings. Therapeutic interventions (such as anti-inflammatory medications or lifestyle modifications) can inhibit the overproduction of these pro-inflammatory cytokines, weaken their inhibitory effect on inhibitory neurotransmitters (e.g., gamma-aminobutyric acid, GABA), and thus alleviate sleep disturbances.

Second, such treatments can interrupt the “poor sleep-chronic inflammation” vicious cycle. Long-term insomnia or sleep fragmentation impairs immune regulation, triggering excessive release of pro-inflammatory cytokines; in turn, sustained high levels of these cytokines further damage sleep structure, perpetuating insomnia. By modulating inflammatory cytokine levels, treatments can break this cycle: for example, non-pharmacological interventions like regular exercise or mindfulness therapy reduce IL-6 and TNF- $\alpha$  concentrations in patients with chronic insomnia, while also extending total sleep time and improving sleep continuity [6].

The central nervous system (CNS) serves as the core hub for regulating the sleep-wake cycle, and the integrity of its structure and stability of its function directly determine sleep quality. Chronic insomnia can lead to structural abnormalities in key brain regions of the CNS, and improving these structural damages through therapeutic interventions is a crucial mechanism to break the “insomnia-neural structural damage” vicious cycle and achieve long-term sleep improvement. As the “high-level control center” of the CNS, the prefrontal cortex is responsible for emotion management, stress response, and the integrated regulation of sleep rhythms. Chronic insomnia can cause a reduction in gray matter volume and a decrease in neuronal synaptic density in this region; for example, the gray matter density of the dorsolateral prefrontal cortex in patients with chronic insomnia is 8%-12% lower than that in healthy individuals. This impairs their ability to regulate emotions, making them more prone to exacerbated insomnia due to stress responses. Effective insomnia treatments can reverse this damage: Cognitive Behavioral Therapy for Insomnia (CBT-I) reduces the long-term stress-induced damage to the prefrontal cortex through “sleep restriction + cognitive restructuring”, promotes the secretion of neurotrophic

factors (such as brain-derived neurotrophic factor, BDNF), and increases the number of synaptic connections in the prefrontal cortex. Additionally, certain natural ingredients with neuroprotective effects (such as saponins in *Ziziphus jujuba* var. *spinosa*) can inhibit the apoptosis of prefrontal neurons, repair the gray matter structure, thereby enhancing its ability to regulate sleep rhythms and reducing sleep disruptions caused by emotional fluctuations [7].

## 4 The transformation process from traditional medicinal materials to modern preparations

With advances in medical technology, saponin research has shifted from experience-driven to science-driven approaches. Innovations in quality control, efficient extraction, precise purification, and formulation innovation have enabled the shift from crude extracts to high-purity monomers and from traditional dosage forms to modern preparations. We hope to examine this transformation pathway and systematically analyse the technological evolution and practical applications at each stage [8].

### 4.1 Importance of raw material quality

Raw materials control is the foundation of saponin transformation. The authenticity of the variety and the stability of the saponin content directly determine the process efficiency and product quality. Traditional pretreatment relies on experience, while modern technology achieves standardized control through origin identification, process optimization, and pretreatment enhancement.

### 4.2 Identification of medical materials

Historically, medicinal materials were identified by morphological traits, such as rhizome head, transverse stripes, and fibrous root points. However, these features are subjective and often insufficient for distinguishing closely related species or detecting adulterants such as American ginseng (*Panax quinquefolius*) or *Platycodon grandiflorum*.

Modern technology has established a multidimensional identification system: first, Molecular Identification using DNA barcoding of core gene fragments, such as ITS2 and *matK*, enables accurate species differentiation. For example, the ITS2 sequence difference rate between ginseng (*Panax ginseng*) and American ginseng (*Panax quinquefolius*) is 8.3%, and it can be quickly identified by electrophoresis or sequencing [9]; second Fast Spectral Detection with near-infrared spectroscopy (NIRS) quantifies total saponin content within 30 seconds. Combined with the partial least squares regression (PLSR), the error rate is less than 5%, enabling rapid elimination of substandard materials, such as ginseng with < 2.0 % saponins [10]; third Origin traceability using inductively coupled plasma mass spectrometry (ICP-MS) of trace elements, such as Ge and So, combined with principal component

analysis (PCA), distinguishes sources such as Jilin Changbai Mountain versus Korean ginseng, ensuring saponin content stability.

Traditional processing techniques in Chinese medicine aim to reduce toxicity and enhance efficacy. For example, honey-frying licorice converts glycyrrhizin into glycyrrhetic acid, thereby strengthening its spleen-invigorating and qi-replenishing effects. When ginseng is processed into red ginseng by steaming, low-activity ginsenosides (Rg1 and Re) are hydrolyzed into high-activity forms (Rg3 and Rb1), enhancing anti-tumor potential. However, outcomes remain inconsistent: reliance on empirical parameters such as heat intensity and processing time often results in variability, with Rg3 content in red ginseng differing by as much as 1.5-3-fold.

## 5 Innovation and Application of Modern Extraction Technologies

### 5.1 Optimized Solvent Extraction Method

Based on the dissolution characteristics of saponins, screen the "optimal solvent concentration": For example, the optimal extraction solvent for ginsenosides is 70% ethanol (if the ethanol concentration is too low, the dissolution of polysaccharides increases; if it is too high, the fat - soluble impurities increase). Using heat - reflux extraction (80°C, 2h), the total saponin yield is increased by 30% - 50% compared with the decoction method, and the impurity content is reduced by 20%.

### 5.2 Physical Field - Enhanced Extraction Technologies

Ultrasound - assisted Extraction (UAE): Using the "cavitation effect" of ultrasonic waves (shock waves generated by the rupture of bubbles in the solvent to break the cell wall), extracting at room temperature for 30 - 60 minutes. The saponin yield is increased by 20% - 25% compared with the traditional decoction method, and the degradation rate of thermosensitive saponins is < 5% (avoiding high temperature). It is suitable for rhizome - type medicinal materials (such as *Panax notoginseng* and ginseng) and has been applied on a large scale in industrial production.

Microwave-assisted Extraction (MAE): Microwaves have strong penetration (able to reach deep inside medicinal herbs), rapidly heat the solvent (reaching the extraction temperature within 1 - 2 minutes), and are suitable for hard-textured medicinal herbs (such as *Dioscorea*). Research shows that the yield of dioscin extracted by microwave (with a power of 600W, an ethanol concentration of 80%, and a time of 15 minutes) is 15% - 25% higher than that of the traditional method, and the energy consumption is reduced by 40%.

Supercritical CO<sub>2</sub> Extraction (SFE-CO<sub>2</sub>): Using supercritical CO<sub>2</sub> (non-toxic and easy to recycle) as the solvent, it is suitable for lipophilic saponins (such as dioscin and saikosaponin). By adding ethanol as an "entrainer" (to improve the dissolution of water-soluble saponins), the target saponins can be directionally

extracted, and the content of impurities (such as polysaccharides and proteins) is less than 5%. However, the equipment cost is relatively high, and it is suitable for the extraction of high-value-added saponins (such as ginsenoside Rg3).

## 6 Conclusion

This study systematically explored the potential of saponin-based natural active substances, particularly those derived from *Ziziphus jujuba* Mill. var. *spinosa* (Bunge) Hu ex H. F. Chou, in addressing global sleep disorder challenges, while analysing the technological evolution and practical bottlenecks in the transformation of saponin-containing medicinal materials into modern sleep-aiding products.

First, the research confirmed the value of saponin compounds as safe and effective sleep-aiding candidates. With the global sleep disorder rate remaining high—especially the worrying upward trend among young people in China—natural products with saponins as core active components (e.g., *Ziziphus jujuba* var. *spinosa*, *Panax notoginseng*) have demonstrated multiple pharmacological effects such as sedation, hypnosis, and anti-anxiety. Their low toxicity and good biocompatibility address the limitations of conventional sleep aids, providing a promising direction for developing natural sleep-improving solutions.

Second, the analysis of saponin-based medicinal materials' transformation process revealed a clear shift from traditional empirical operations to modern standardized and precise production. In raw material pretreatment, molecular identification (e.g., DNA barcoding), rapid spectral detection (e.g., NIRS), and origin traceability (e.g., ICP-MS) have replaced subjective morphological identification, ensuring the authenticity and stability of saponin sources. In processing, although traditional methods (e.g., steaming, honey-frying) can enhance saponin activity, modern technologies enable precise regulation of saponin transformation, overcoming the variability of empirical processes.

Third, the comparison of extraction technologies highlighted the superiority of modern methods in efficiency, safety, and eco-friendliness. Traditional extraction methods such as decoction and alcohol soaking suffer from high thermosensitive saponin degradation, low yield, and high impurity content. In contrast, optimized solvent extraction, ultrasound-assisted extraction (UAE), and microwave-assisted extraction (MAE) significantly improve saponin yield (by 15 - 50%) and reduce impurity levels, while supercritical CO<sub>2</sub> extraction (SFE-CO<sub>2</sub>) enables directional extraction of high-value saponins, aligning with the study's goal of "safe and eco-friendly extraction."

However, several limitations remain in the current research and application of saponin-based sleep-aiding products. On the technical front, supercritical CO<sub>2</sub> extraction's high equipment costs restrict its large-scale application; meanwhile, the mechanisms by which saponins regulate sleep—such as their interactions with

neurotransmitters and neuroendocrine axes—require further in-depth exploration at the molecular level. On the product development front, the transformation from purified saponin monomers to stable, bioavailable modern preparations (e.g., microcapsules, oral solutions) still faces challenges in formulation optimization.

Looking forward, future research should focus on three key areas: 1) Developing low-cost, scalable extraction technologies (e.g., combining UAE with SFE-CO<sub>2</sub>) to balance efficiency and economic feasibility; 2) Conducting in vivo and clinical studies to clarify the structure-activity relationship and sleep-regulating mechanisms of saponins from *Ziziphus jujuba* var. *spinosa*, laying a solid foundation for targeted product development; 3) Integrating multidisciplinary technologies (e.g., nanotechnology, pharmaceuticals) to optimize product formulations, improving saponin bioavailability and patient compliance.

In summary, saponin-based natural active substances, represented by those from *Ziziphus jujuba* var. *spinosa*, hold great potential for addressing sleep disorders. The advancement of modern extraction, purification, and preparation technologies will accelerate the transformation of these natural resources into safe, effective, and eco-friendly sleep-aiding products, contributing to improving public sleep health.

## References

1. Chinese Medicine for Sleep Disorders: Dominance of a Single Player vs. Fierce Multi-Party Competition. *China Pharmacy*. **13**,12 (2015)
2. H. Li, Analysis of Saponin Components in Semen *Ziziphi Spinosae* and Research on Its Antidepressant Mechanism. *Changchun University of Chinese Medicine*. (2023).
3. J. Wang, X. Tang, F. Liu, B.Y. Mao, Q.X. Zhang, J.X. Zhao, W. Chen, S.M. Cui, Sources, metabolism, health benefits and future development of saponins from plants, *Food Research International*. **197**, 1 (2024).
4. M.Y. Zhang, C. Yin, L. Ding, L. Cheng, L.V. Qing, P. Wang, S.-B. Zhang, Q.Y. You, Mechanism of *Panax notoginseng* saponins in improving cognitive impairment induced by chronic sleep deprivation based on the integrative analysis of serum metabolomics and network pharmacology, *Journal of Ethnopharmacology*. **337**, 3 (2025)
5. Xu, H., Wang, Z., Zhu, L., Sui, Z., Bi, W., Liu, R., et al. (2018). Targeted Neurotransmitters Profiling Identifies Metabolic Signatures in Rat Brain by LC-MS/MS: Application in Insomnia, Depression and Alzheimer's Disease. *Molecules* **23** (9), 2375
6. Irwin, M. R., Olmstead, R., and Carroll, J. E. (2016). Sleep Disturbance, Sleep Duration, and Inflammation: A Systematic Review and Meta-Analysis of Cohort Studies and Experimental Sleep Deprivation. *Biol. Psychiatry* **80** (1), 40–52.

7. Morin, C. M. (2012). Chronic Insomnia (Vol 379, Pg 1129, 2012). *Lancet* 379 (9825), 1488.
8. S.H. Kim, J.H. Kim, J.H. Park, Pharmacokinetics of ginsenoside Rg3 after oral administration of Panax ginseng extract in healthy volunteers. *Journal of Ethnopharmacology*, **174**, 403-408 (2015)
9. S.L. Chen, H. Yao, J.P. Han, DNA barcoding for the identification of Panax species. *Planta Medica*, **76**, 1721-1727 (2010)
10. Y. Li, X. Wang, H. Zhang, Rapid determination of total saponins in Panax notoginseng by near-infrared spectroscopy. *Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy*. **190**, 563-568 (2018)