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The Sleep-Promoting Efficacy of GABA and Its Oral Delivery Strategies: A Review

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Abstract

γ-Aminobutyric acid (GABA) is a major inhibitory neurotransmitter in the central nervous system, and exogenous supplementation shows potential value in improving sleep disorders. However, oral GABA is limited by insufficient gastrointestinal absorption, first-pass metabolism, and low permeability across the blood-brain barrier, and existing clinical results remain inconsistent. This review summarizes the sleep-promoting mechanisms of GABA, human study evidence, oral delivery technologies, and fermentation enrichment processes. Current research suggests that GABA may improve sleep through GABA receptor-mediated neural inhibition, modulation of the hypothalamic–pituitary–adrenal (HPA) axis, anti-inflammatory effects, and effects on the gut–brain axis. Evidence for shortening sleep latency is relatively consistent, whereas effects on sleep maintenance and subjective sleep quality remain unstable. Nanoliposomes, microcapsules, lipid nanocarriers, and engineered probiotics can enhance stability or regulate release, but most evidence remains at the in vitro or animal experimental stage. Lactic acid bacterial fermentation can effectively increase GABA content in functional foods, yet raw material enrichment does not necessarily translate into improved human bioavailability. Future research should conduct adequately powered randomized controlled trials with unified outcome measures and combine pharmacokinetic and gut–brain axis indicators to verify the actual sleep-promoting effects of delivery systems.

Keywords

γ-aminobutyric acid (GABA), sleep promotion, oral bioavailability, delivery systems, lactic acid bacteria fermentation

1. Introduction

Insomnia is a common sleep disorder characterized primarily by difficulty falling asleep, difficulty maintaining sleep, or early-morning awakening, often accompanied by daytime fatigue, decreased attention, and emotional disturbances. Persistent insomnia not only reduces quality of life but is also closely associated with anxiety, depression, and risks to cardiovascular, metabolic, and cognitive health [1]. Its occurrence involves the interaction of predisposing factors, precipitating events, and perpetuating factors. It is also related to hypothalamic–pituitary–adrenal (HPA) axis dysfunction, abnormal melatonin rhythms, and imbalances in multiple neurotransmitter networks [2].

Cognitive behavioral therapy for insomnia (CBT-I) is considered an important non-pharmacological intervention, but it remains limited by insufficient professional availability, treatment costs, adherence, and

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public awareness [3, 4]. Although commonly used sedative-hypnotics act relatively quickly, long-term use may be accompanied by tolerance, dependence, cognitive impairment, and daytime residual effects. Consequently, functional ingredients with higher safety profiles suitable for long-term use have gradually attracted attention.

GABA is the primary inhibitory neurotransmitter in the central nervous system. Fermented foods rich in GABA and related supplements have been reported to alleviate anxiety and improve sleep [5]. However, the efficacy of oral GABA is not stable, as its intestinal absorption, hepatic first-pass metabolism, systemic clearance, and blood–brain barrier permeability may all limit effective exposure [6]. Moreover, studies differ greatly in GABA sources, doses, intervention durations, and sleep assessment tools, adding uncertainty to their conclusions.

Addressing these issues, existing research has mainly developed along two paths: first, using liposomes, microcapsules, lipid nanocarriers, and engineered probiotics to improve stability and release behavior; second, increasing GABA content in foods or raw materials through lactic acid bacteria fermentation. This review evaluates evidence for oral GABA in sleep promotion, controversies over its mechanisms of action, and major delivery strategies, while also discussing the value of its application, industrialization conditions, and current limitations of fermentation enrichment.

2. Biological Basis of GABA-Mediated Sleep Promotion

2.1 Receptor-Mediated Neural Inhibition and Related Pathways

GABA is a four-carbon non-protein amino acid produced from L-glutamate via glutamate decarboxylase, and it plays an important role in maintaining the excitation–inhibition balance in the central nervous system. $GABA_A$ and $GABA_C$ receptors are ligand-gated chloride ion channels; upon activation, they promote chloride influx and neuronal hyperpolarization, generating fast inhibitory postsynaptic potentials. $GABA_B$ receptors, via G-protein-coupled mechanisms, inhibit Ca^{2+} influx and promote K^+ efflux, producing slower and more sustained neural inhibition. These receptors collectively regulate sleep initiation, sleep architecture, anxiety levels, and neural network stability [7, 5].

Beyond directly inhibiting neuronal excitability, GABA may improve sleep through multiple indirect pathways. Inflammation and oxidative stress can disrupt sleep–wake rhythms and enhance central hyperarousal. GABA may reduce neuroinflammation by inhibiting inflammatory signals such as NF-κB and p38 MAPK, and may interact with melatonin secretion and circadian rhythm regulation. GABAergic signaling can also influence HPA axis activity, reducing cortisol-related responses under stress. Therefore, the potential sleep-promoting effects of exogenous GABA may simultaneously involve neural inhibition, stress relief, and rhythm regulation, rather than being limited to a single receptor pathway.

2.2 Blood–Brain Barrier Limitations and the Gut–Brain Axis Hypothesis

A central controversy regarding the mechanism of oral GABA is its low permeability across the blood–brain barrier. The tight junctions of the blood–brain barrier restrict the entry of polar small molecules into the brain parenchyma; animal studies show that GABA efflux from the brain is markedly more efficient than influx [8]. A few experiments suggest that GABA entry into brain tissue may increase when the blood–brain barrier is immature, locally damaged, or affected by factors such as nitric oxide [9]. However, these special models differ substantially from the general healthy population and are insufficient to demonstrate that conventional oral GABA doses can achieve stable, physiologically meaningful brain exposure.

The gut–brain axis has thus become an important hypothesis for explaining the effects of oral GABA. Dietary- or microbial-derived GABA may act on the enteric nervous system and vagal afferent fibers, alter peripheral hormone release, or indirectly influence central nervous system activity by modulating the gut microbiota and other metabolites [10]. Some lactic acid bacteria and bifidobacteria can also synthesize GABA from glutamate, providing a biological basis for an "in situ intestinal production–peripheral signal transduction" pathway [11]. Nevertheless, existing human studies rarely measure gut microbiota, plasma GABA, vagal nerve-related indicators, and sleep outcomes simultaneously; therefore, this mechanism remains largely speculative.

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3. Evidence for Oral GABA in Sleep Promotion

3.1 Effects on Sleep Onset and Sleep Architecture

Overall, clinical studies suggest that oral GABA has relatively consistent effects on improving sleep onset, but its effects on sleep maintenance, total sleep time, sleep efficiency, and subjective sleep quality are unstable. A randomized crossover trial by Yamatsu et al. (2015) found that healthy subjects who consumed 100 mg GABA before bedtime for one week showed shortened sleep latency and increased non-rapid eye movement (NREM) sleep time [12]. A four-week randomized double-blind placebo-controlled trial by Byun et al. (2018) also observed improvements in sleep latency and total PSQI scores, but no significant changes in sleep efficiency, REM sleep, or nocturnal awakening frequency [13]. Collectively, GABA may be more beneficial for sleep initiation, and its effects on nocturnal sleep continuity and sleep architecture require further confirmation.

Functional food studies provide supplementary evidence for practical application. One study enrolling 267 subjects with sleep disorders compared low-dose GABA, high-dose GABA, GABA combined with theanine, and a control group using functional biscuits. After one week of intervention, effective sleep duration and deep sleep time increased to varying degrees across groups, but sleep onset time, deep sleep proportion, and nocturnal awakenings did not show consistent improvements [14]. Although this study had a relatively large sample size and approximated real consumption scenarios, it employed an open-label design, a short intervention period, and the control group also showed improvement. Thus, the results may have been influenced by placebo effects, measurement errors in wearable devices, and short-term behavioral changes among subjects.

3.2 Dose and Safety

There is currently no consensus on the optimal dose. Studies using low-dose natural GABA have shown that 75 mg can shorten objective sleep latency, increase N3 sleep, and reduce the arousal index, but effects on sleep maintenance, insomnia, and some subjective scales are limited [15]. A systematic review noted that common effective doses of naturally sourced GABA are lower than those of some biosynthetic preparations, possibly due to synergistic effects with theanine, polyphenols, or other active components in the food matrix [16]. However, different studies vary considerably in raw material sources, purity, subject baseline status, and dosing regimens. Therefore, it is not possible to conclude that natural sources have a definite dose advantage, nor can effects observed in different foods be fully attributed to GABA itself.

Regarding safety, most short-term studies have not reported serious adverse events; occasional mild events include abdominal discomfort, headache, mood fluctuations, and transient reductions in blood pressure. A USP safety review concluded that existing data generally support good short-term tolerability of GABA at common supplemental doses [17]. However, long-term studies with safety as the primary endpoint are currently lacking. Existing trials have paid insufficient attention to liver and kidney function, neurocognitive effects, and post-discontinuation changes. Data for pregnant and lactating women, children, older adults, and those concurrently using antihypertensive, sedative, or anxiolytic drugs are also very limited.

In summary, existing clinical studies provide preliminary support for GABA's role in improving sleep onset, but the quality of the evidence is limited by sample size, blinding, intervention duration, and outcome heterogeneity. Future trials need to distinguish among healthy populations, patients with subclinical sleep disorders, and those meeting diagnostic criteria for insomnia, and should combine subjective scales, polysomnography (PSG), actigraphy, and daytime function indicators.

4. Delivery Strategies to Improve Oral Bioavailability

Oral GABA faces multiple limitations, including the gastrointestinal environment, hepatic first-pass metabolism, rapid systemic clearance, and low permeability across the blood–brain barrier. Existing delivery technologies primarily aim to protect GABA from degradation, improve gastrointestinal stability, regulate the release site, and prolong local action time. It should be noted that improved formulation parameters do not necessarily mean increased brain exposure or sleep-promoting efficacy; therefore, evaluation of delivery

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systems should simultaneously consider encapsulation efficiency, digestive release, plasma exposure, and actual sleep outcomes.

4.1 Nanoliposomes and Microcapsules

Nanoliposomes consist of phospholipid bilayers encapsulating a hydrophilic core, providing a certain degree of protection for GABA in the gastrointestinal environment. Zhang et al. prepared GABA nanoliposomes with an average particle size of 172 nm and an encapsulation efficiency of nearly 90%. These showed minimal release in simulated gastric fluid but markedly increased release in intestinal fluid, and improved in vivo effective content and sleep-related phenotypes in a *C. elegans* model [18]. These results demonstrate the protective and sustained-release potential of liposomes, but nematodes differ substantially from humans in digestive physiology, metabolism, and blood–brain barrier structure; thus, these findings require validation through mammalian pharmacokinetic and human trials. Oxidative stability, cold-chain storage, and scalable production are also issues to be addressed during industrialization.

Spray-dried microcapsules offer advantages such as mature technology, relatively controllable costs, and ease of food processing. Pandey et al. (2021a) co-encapsulated GABA and Lactobacillus plantarum using inulin, dextran, and maltodextrin, achieving approximately 84% GABA encapsulation efficiency and maintaining high stability during long-term low-temperature storage [19]. Further use of multilayered wall materials can enable different materials to assume gastric-protection or intestinal-release functions, thereby regulating GABA release and probiotic survival [20]. However, microcapsule release behavior is highly dependent on wall material ratio, particle size, digestive environment, and food matrix; in vitro simulation results cannot fully substitute for real human digestive processes.

4.2 Lipid Nanocarriers and Engineered Probiotics

Solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs) can improve the oral bioavailability of certain drugs through lipid protection, mucoadhesion, and potential lymphatic transport [21]. NLC reduces lattice integrity by mixing solid and liquid lipids, theoretically increasing drug loading and storage stability. However, GABA is a small, hydrophilic molecule, and its loading efficiency in lipid matrices may be limited; it may also migrate to the external phase during storage. Direct research on GABA is currently scarce, so the applicability of results from other drugs cannot be inferred.

Engineered probiotics provide another approach by continuously synthesizing GABA in the intestinal tract. Escherichia coli Nissle 1917 overexpressing gadB and gadC can achieve high GABA production [22], thereby theoretically reducing the need for repeated supplementation and prolonging the duration of local action. However, its sleep-promoting effects have not been adequately validated. Issues requiring systematic evaluation include whether the strain can stably colonize, whether individual gut environments affect production, and the safety risks of exogenous genes and resistance markers. For food or live biotherapeutic applications, regulatory acceptability may be more critical than production yield itself.

Table 1: Comparison of Major Oral GABA Delivery Strategies

Delivery Strategy	Main Advantages	Main Limitations	Potential Applications
Nanoliposomes	High encapsulation efficiency; can protect GABA and achieve sustained release	High preparation and storage requirements; insufficient human evidence	Functional beverages, oral liquid preparations
Spray-dried microcapsules	Mature technology; easy to scale up; can co-encapsulate probiotics	Release affected by wall materials and food matrix	Solid beverages, functional food powders
Double emulsion microcapsules	Can regulate GABA release location and protect probiotics	Multiple steps; system stability needs optimization	Composite functional food ingredients
SLN/NLC	Lipid protection, mucoadhesion, and potential lymphatic transport advantages	Lack of direct evidence for hydrophilic GABA loading and in vivo effects	Oral solid preparations, soft capsules
Engineered probiotics	Can continuously synthesize GABA in the gut	Genetic safety, colonization stability, and regulatory issues prominent	Experimental live biotherapeutics, fermented foods

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5. Fermentation Enrichment and Food Applications of GABA

GABA can be obtained through chemical synthesis, plant enrichment, and microbial fermentation. Chemical synthesis offers high yield but may involve organic solvents, chemical residues, and environmental concerns. Plant enrichment is relatively simple but is often limited by the availability of raw materials and growth cycles. Lactic acid bacteria fermentation offers advantages such as high safety, mild reaction conditions, and direct applicability to functional food production, making it the most widely used natural enrichment method [23, 24].

5.1 Fermentation Mechanism and Key Influencing Factors

Lactic acid bacteria primarily use glutamate decarboxylase (GAD) to convert L-glutamate to GABA. This reaction requires pyridoxal phosphate as a cofactor and is usually coupled with glutamate/GABA antiporter activity. Yield is mainly influenced by strain, pH, temperature, substrate concentration, cofactors, and fermentation time. Acidic environments generally favor GAD system activation, but excessively low pH inhibits cell growth. Appropriate amounts of monosodium glutamate (MSG) provide a glutamate precursor, but excessive concentrations may inhibit proliferation due to osmotic pressure. Excessively long fermentation times may also lead to decreased yield due to substrate depletion or degradation by GABA transaminase. Therefore, simply increasing a single parameter does not necessarily increase production; joint optimization of strain and the food matrix is required.

Table 2: Key Factors Influencing GABA Production by Lactic Acid Bacteria Fermentation

Factor	General Trend	Key Considerations
pH	Acidic environments generally favor GAD system activation	Excessively low pH may inhibit cell growth
Temperature	Optimal temperature varies by strain; most studies focus on 30–45°C	Must balance enzyme activity and cell proliferation
Substrate (MSG)	Provides glutamate precursor for GABA synthesis	Excessive concentration may cause osmotic inhibition
Cofactor (PLP)	Promotes conversion as GAD cofactor	Addition amount must balance cost and food regulations
Fermentation time	Yield usually rises first then stabilizes or declines	Avoid substrate depletion and GABA degradation

5.2 Strain Optimization and Food Applications

Lactobacillus brevis and Lactobacillus plantarum are among the most studied GABA-producing bacteria. Significant differences in yield across strains and culture conditions indicate that strain screening remains key to improving efficiency. Engineering strategies mainly include enhancing the expression of gadA/gadB and glutamate/GABA transporters, reducing competitive degradation, and increasing the supply of glutamate precursors. Co-culture can utilize metabolic complementarity among different strains to increase yield. For example, acid-producing strains can improve system pH, proteolytically active strains can release amino acids, and glutamate-producing strains can continuously provide precursors. Compared with genetically engineered strains, co-culture is more readily applicable to traditional food production, but bacterial ratios and long-term stability still require optimization [23, 24].

Lactic acid bacteria fermentation has been applied to various matrices, including cereals, dairy products, fruit and vegetable juices, and soybean products. Existing studies generally report increased GABA content after fermentation, but differences in raw materials, strains, fermentation scale, and measurement units make direct cross-study comparison of yields inappropriate. Zhu et al. (2024) used L. brevis and Streptococcus thermophilus co-fermentation to prepare GABA yogurt; after optimization, GABA content reached 75.3 mg/100 g, with stable viable counts, texture, and sensory quality, indicating that dairy products can simultaneously provide fermentation substrate, live bacteria carrier, and consumption scenarios, showing good industrialization potential [25].

Practical application of fermentation enrichment also requires careful consideration of strain safety, substrate cost, scalable production, and product stability. Strains with GRAS/QPS safety status that do not produce excessive tyramine, histamine, or other biogenic amines should be prioritized. Co-culture, utilization of agricultural by-products, and process control can help reduce the cost of the glutamate substrate. Spray-

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dried microencapsulation can improve the storage stability of bacteria and GABA, but high temperature, oxygen, and moisture may still affect product quality. Furthermore, enrichment processes must balance flavor, texture, nutritional composition, and consumer acceptability; maximum yield alone should not be the sole criterion for evaluation.

Increasing GABA content in foods can raise intake doses but cannot automatically solve limitations in intestinal absorption and blood–brain barrier permeability. High-content products may also produce different effects due to the food matrix, coexisting components, and single-dose intake amounts. Therefore, evaluation of fermented products should shift from "yield-oriented" to a combination of "intake dose–in vivo exposure–sleep outcome," and actual benefits should be verified through standardized human trials.

6. Discussion and Comprehensive Analysis

6.1 Sources of Heterogeneity in Clinical Evidence

Heterogeneity in GABA sleep-promoting research mainly stems from subject populations, raw material sources, doses, intervention durations, and outcome measures. Healthy individuals, those with mild sleep disorders, and clinically diagnosed insomnia patients have different baseline states and may respond differently to exogenous GABA. Existing trials span wide ranges of dose and duration and often fail to control for dietary GABA intake, caffeine, alcohol, exercise, and other sleep-promoting factors, making direct comparisons of results across studies difficult. Natural fermentation, chemical synthesis, and biosynthetic products may also differ in purity, accompanying components, and food matrix, further complicating the attribution of efficacy.

The timing of administration is also an easily overlooked variable. If GABA primarily affects sleep initiation, short-term pre-bedtime administration may be more likely to show effects; if its action depends on modulation of the gut microbiota or the HPA axis, longer intervention periods may be required. Some studies juxtapose single-dose and multi-week supplementation results without distinguishing acute effects from chronic adaptation processes. Future trials should pre-specify primary mechanistic hypotheses and correspondingly set sampling times and follow-up periods.

Inconsistency between subjective questionnaires and objective sleep monitoring is another important issue. Some studies observed improvements in PSG sleep latency, N3 sleep, or the arousal index, but subjective scores such as the PSQI and ISI showed no significant differences from placebo. This may mean that short-term changes in sleep architecture have not yet translated into perceptible quality-of-life improvements, or may be related to insufficient sample size, first-night effects, wearable device accuracy, and placebo responses. Therefore, subsequent studies should simultaneously employ PSG or actigraphy, standardized scales, sleep diaries, and daytime function indicators, with pre-specified primary outcomes to reduce selective reporting.

6.2 Comparison and Evaluation of Delivery Strategies

Different delivery strategies vary markedly in maturity. Spray-dried microcapsules are closest to large-scale functional food applications. Liposomes offer high encapsulation efficiency and good in vitro sustained-release performance, but scaled-up production and storage stability still require optimization. The applicability of SLN/NLC to hydrophilic GABA has not been directly validated. Engineered probiotics are at an even earlier stage. Many current studies report only particle size, encapsulation efficiency, and in vitro release, lacking correlations among plasma concentration, tissue distribution, and sleep behavior. Future research should compare different carriers using unified models and equivalent doses to assess gastrointestinal release, plasma exposure, duration, and sleep-improvement effects, and avoid inferring clinical advantages based solely on formulation parameters.

6.3 Current Limitations and Future Directions

Existing research has four main limitations. First, most RCTs have small sample sizes and intervention periods of no more than several weeks; some studies are industry-sponsored or involve author conflicts of interest, and the risk of publication bias is non-negligible. Second, direct causal evidence for GABA crossing the blood–brain barrier and gut–brain axis-mediated effects in humans is lacking; existing mechanistic explanations are often extrapolated from animal studies. Third, delivery system research mostly remains at the

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in vitro, nematode, or other animal model stage; long-term safety and release behavior in real food environments remain unclear. Fourth, the stability, biogenic amine risk, and regulatory compliance of high-yield fermentation strains in different food matrices still require validation.

Future clinical studies should increase sample sizes, standardize GABA sources, purity, and doses, use consistent evaluation indicators, and conduct stratified analyses by insomnia type. Studies should also combine plasma GABA, related metabolites, gut microbiome, vagal nerve function, cortisol, and melatonin indicators to attempt establishing an "intake–exposure–mechanism–efficacy" evidence chain. Delivery system development should prioritize addressing the challenges of stable loading, controlled release, storage stability, and scalable production for hydrophilic GABA, and confirm through human pharmacokinetic studies and randomized controlled trials whether they are truly superior to conventional preparations.

7. Conclusion

Existing evidence suggests that oral GABA may shorten sleep latency and improve some NREM sleep indicators, but its effects on sleep maintenance and subjective sleep quality remain unstable. Because most trials have small sample sizes, short durations, and marked differences in product sources, doses, and outcome measures, it is currently insufficient to determine the optimal dose and most suitable population.

The ability of GABA to directly cross the blood–brain barrier is limited, and its sleep-promoting effects may be partially mediated by the gut–brain axis. Nanoliposomes and microcapsules can improve stability and regulate release; SLN/NLC and engineered probiotics have potential applications, but relevant evidence is derived mainly from in vitro or animal studies. Lactic acid bacteria fermentation can increase GABA content in functional foods, but raw material enrichment cannot substitute for validation of human absorption and clinical efficacy.

Future research should conduct rigorously designed, adequately powered randomized controlled trials; integrate pharmacokinetics, objective sleep monitoring, and gut–brain axis indicators to validate mechanisms of action; and compare in vivo exposure, safety, and actual sleep-promoting effects of different delivery systems under uniform conditions.

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Conflicts of Interest

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