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Targeting cortisol dysregulation through bioactive compounds: implications for stress, sleep, and mental wellness

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ABSTRACT

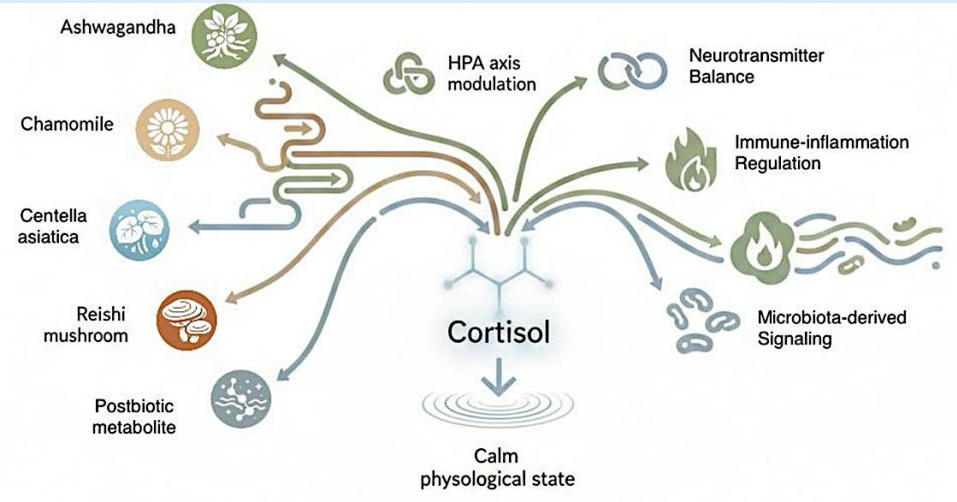
Stress and sleep disturbances have emerged as significant global health challenges, intricately linked through the hypothalamic–pituitary–adrenal (HPA) axis. Cortisol, the primary stress hormone, serves as a key biomarker of HPA axis activity, influencing metabolism, immune response, and sleep regulation. Chronic elevation of cortisol disrupts circadian rhythm, inhibits melatonin synthesis, and contributes to insomnia, anxiety, and fatigue. Therefore, identifying bioactive compounds capable of modulating cortisol and restoring HPA axis balance offers a natural strategy for improving stress resilience and sleep quality. This review consolidates scientific evidence on several plant-derived and microbial bioactive compounds with cortisol-lowering and sleep-promoting effects. Bioactive compounds that modulate the HPA axis, therefore, represent a multidimensional therapeutic opportunity, acting not only on endocrine regulation but also on neurochemical balance and immune modulation. Integrating these compounds into dietary or nutraceutical interventions could provide a preventive and restorative approach for individuals experiencing chronic stress or sleep disorders. *Withania somnifera* (ashwagandha) exhibits adaptogenic properties via withanolides that downregulate cortisol and improve sleep onset. *Panax ginseng* contains ginsenosides that modulate stress hormone release and enhance neural adaptability. *Ganoderma lucidum* (reishi mushroom) triterpenoids exert anxiolytic and sedative effects, promoting restorative sleep. *Centella asiatica* triterpenes, including asiaticoside and madecassoside, contribute to cortisol regulation and neuroprotection, improving REM sleep architecture. *Matricaria chamomilla* flavonoids, notably

apigenin, interact with GABAergic receptors and reduce HPA hyperactivation. Emerging evidence also highlights postbiotics, such as those from *Limosilactobacillus fermentum* PS150 and *Bifidobacterium breve* BB091109, which influence the gut–brain axis by enhancing neurotransmitter balance, reducing systemic inflammation, and lowering cortisol.

The novelty of this study lies in presenting an integrated linkage between plant-derived bioactive compounds and postbiotics in the regulation of stress and sleep through modulation of the HPA axis. This framework highlights their potential influence on cortisol dynamics, providing valuable insights for the future development of functional products aimed at stress reduction and the promotion of mental wellness.

Future research should focus on clinical validation, pharmacokinetic profiling, and formulation optimization to translate these natural agents into evidence-based functional foods and nutraceuticals capable of safely supporting stress regulation and sleep health.

Keyword: Cortisol modulation, Sleep quality, Hypothalamic-pituitary-adrenal (HPA) axis regulation, Adaptogenic bioactive compounds, Gut-brain axis, Neuroendocrine regulation



Graphical Abstract: Targeting cortisol dysregulation through bioactive compounds: implications for stress, sleep and mental wellness.

INTRODUCTION

Stress has long been recognized as a major health concern. When stress occurs, it commonly disrupts sleep, and difficulty sleeping often follows as part of a frequent "paired package." When stress persists over time and cannot be effectively managed, it can negatively affect health and is considered one of the factors that increases the risk of various non-communicable diseases (NCDs)

[1]. Within the domains of wellness and longevity, including lifestyle medicine, stress and sleep are repeatedly emphasized as critical targets for health maintenance and healthy aging [2].

However, stress is difficult to measure directly because stress tolerance and perception vary considerably among individuals. Consequently, widely discussed biomarkers are often used to support stress assessment [3], among which cortisol is one of the most frequently referenced. Beyond stress, cortisol also plays a key role in circadian regulation, exhibiting characteristic secretion patterns across the sleep–wake cycle. For this reason, cortisol is frequently discussed not only in relation to stress but also in relation to sleep.

Cortisol is a stress-responsive hormone regulated by the HPA axis and is commonly measured at specific time points as a biomarker reflecting physiological stress responses. Although cortisol cannot be used to diagnose disease due to its diurnal variability, it provides an informative signal: values that are excessively high or abnormally low may indicate dysregulation that can adversely affect health, warranting appropriate management.

In addition to stress management interventions, many reports have described the use of bioactive compounds beyond conventional nutrition modification to help regulate cortisol levels. One of the most frequently cited compounds is ashwagandha, often categorized as an adaptogen and widely discussed for cortisol modulation [4]. As interest in longevity and stress/sleep wellness grows, research on herbs and bioactive compounds that regulate stress and support sleep has expanded substantially. Nonetheless, synthesizing evidence on bioactive compounds that regulate stress through the HPA axis—particularly those targeting cortisol—remains highly valuable. Therefore, this article presents existing evidence on bioactive compounds with documented effects on cortisol, aiming to expand perspectives relevant to future development and knowledge advancement in this area.

This review aims to present comprehensive evidence on bioactive compounds that influence stress regulation and sleep modulation through cortisol-related mechanisms. The article highlights the key active constituents present in specific plant sources, discusses dosage ranges reported in clinical and experimental studies, and addresses considerations related to bioavailability. In addition, it summarizes the reported effective concentrations and mechanistic pathways described in the literature. By integrating mechanistic insights, dose standardization, and bioavailability considerations, this review seeks to provide a scientific foundation for the development of evidence-based functional foods and nutraceuticals designed to support stress reduction and sleep health.

Physiology of cortisol in stress: Cortisol is secreted from the adrenal cortex and synthesized from cholesterol. Its secretion is regulated by the hypothalamus and pituitary gland, which release corticotropin-releasing hormone (CRH) and adrenocorticotropic hormone (ACTH). These hormones signal the adrenal glands to produce cortisol in response to stress signals. This regulatory system is known as the hypothalamic–pituitary–adrenal axis (HPA axis) [5]. The HPA axis functions as an integrated system that coordinates stress responses to maintain physiological homeostasis.

Once secreted, cortisol binds to glucocorticoid receptors found across most tissues. In metabolic regulation, cortisol promotes glucose production, elevates blood glucose, stimulates gluconeogenesis, and enhances protein catabolism, thereby accelerating

muscle breakdown to generate energy [6-7]. Cortisol also reduces insulin activity, further increasing blood glucose levels [8]. Additionally, cortisol can increase blood pressure through cross-reactivity with mineralocorticoid receptors, leading to sodium retention and potassium loss [9-10]. In the immune system, elevated cortisol suppresses immune function, increasing susceptibility to infection, and also affects multiple other tissues and systems [11].

When stress occurs, the HPA axis is activated and cortisol secretion increases. If cortisol rises only briefly, it may enhance hippocampal-dependent memory, particularly memory associated with positive emotional content. However, prolonged cortisol elevation, often due to chronic stress or poorly managed stress [5], can have detrimental effects on the brain. The hippocampus—critical for memory and learning—is particularly sensitive to sustained high cortisol levels [12]. Chronic exposure may lead to dendritic retraction, inhibition of neurogenesis, and impaired retrieval and formation of new memories [13].

In the amygdala, which regulates emotions, anxiety, fear responses, and threat detection, cortisol is a key modulator [14]. Elevated cortisol can heighten amygdala reactivity, causing exaggerated responses to stimuli and persistent perceptions of threat [15-16], thereby increasing the risk of anxiety [17]. Chronic stress may also increase dendritic arborization in the amygdala, further sensitizing the brain to fear and stress. In the prefrontal cortex, chronic stress reduces synaptic plasticity, impairing emotional regulation, decision-making, and attention, which may worsen anxiety-related symptoms [17-18].

Under normal conditions, cortisol exhibits a diurnal pattern. Cortisol levels typically rise about 30–45 minutes upon waking (the cortisol awakening response), influenced by sleep quality and psychological stress. This morning rise supports alertness and daily functioning, after which cortisol gradually declines and reaches low levels at night, preparing the body for rest [19]. This decline supports pineal gland melatonin secretion, facilitating deeper sleep.

When stress activates the HPA axis, ACTH stimulates increased cortisol production. In acute stress, this response is adaptive: it promotes vigilance, mobilizes energy (via increased blood glucose), raises blood pressure to enhance perfusion, and suppresses inflammation—supporting short-term survival (Figure 1). After the stressor ends, physiological systems typically return to baseline. However, in chronic stress, persistent HPA activation maintains elevated cortisol levels [5], disrupts normal circadian rhythms, and may cause cortisol secretion to rise again at night [20]. As a result, the brain fails to enter restorative sleep and remains in a state of hypervigilance, contributing to nighttime rumination and anxiety. This dysregulated pattern can impair daytime cortisol normalization, reducing overall physiological efficiency and creating a persistent cycle that damages homeostasis and sleep balance [21].

Chronic stress also disrupts astrocyte and microglial activity, promoting neuroinflammation and oxidative stress, interfering with synaptic connectivity and sleep homeostasis. One major pathway involves chronic cortisol exposure via the HPA axis, which can increase pro-inflammatory cytokines such as interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), and interleukin-1β (IL-1β). These cytokines may disrupt sleep homeostasis by interfering with the balance of γ-aminobutyric acid (GABA) and glutamate neurotransmission [21].

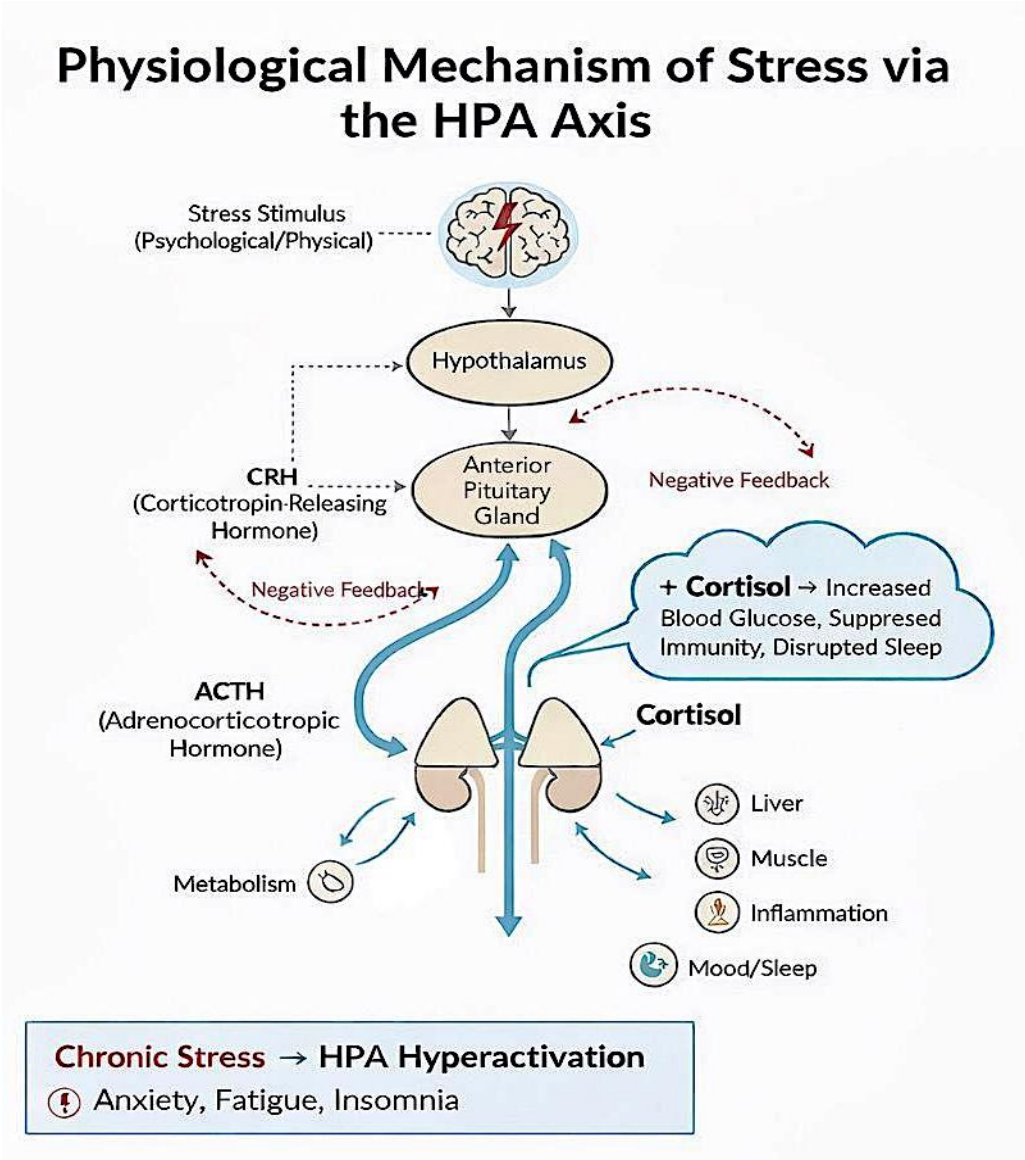


Figure 1. Physiological Mechanism of Stress via the HPA Axis.

Bioactive compounds targeting cortisol pathways: mechanistic insights into stress reduction and sleep regulation: The relationship between nutrition and cortisol has been discussed since the 1970s. Cortisol levels have been reported to rise after food intake, peaking at approximately one hour and returning to baseline within two hours. Late-night meals may elevate nighttime cortisol and disturb sleep. Skipping breakfast may reduce morning cortisol but increase cortisol later in the day, potentially increasing the risk of HPA axis dysfunction. In contrast, skipping dinner may reduce nighttime cortisol and improve sleep [22]. These observations suggest that nutrition itself influences cortisol regulation.

In addition, many herbal and plant-derived bioactive compounds studied for stress and cortisol modulation are classified as adaptogens, as they may act on the HPA axis and adrenal function to help normalize cortisol levels [23]. This review highlights bioactive compounds with evidence supporting beneficial effects on cortisol, stress, sleep, longevity, and mental wellness.

Ashwagandha: Ashwagandha (*Withania somnifera*), commonly known in Thailand as Indian ginseng, has a

long history of traditional use in multiple countries. Reported pharmacological activities include immune enhancement, anti-inflammatory effects, glycemic regulation, cardioprotective properties, and more. Notably, the Latin term *somnifera* means "sleep inducer" [24], consistent with scientific findings describing its sleep-supportive effects.

Ashwagandha is well known for reducing cortisol and stress [25-26]. The root is the primary part used, and it is formulated into nutraceuticals in both crude and standardized extract forms. Bioactive constituents include alkaloids (e.g., withanine), flavonoids (e.g., quercetin), and nitrogen-containing compounds, among others. The most frequently cited quality-control markers are withanolides, a class of steroidal lactones [27].

Clinical evidence includes a study using an ashwagandha extract standardized to 5% withanolides (300 mg per capsule, twice daily), which reduced stress and cortisol levels by over 20% on average [28]. Mishra DN et al. tested a different extract derived from both roots and leaves standardized to 35% withanolides in adults with high stress and anxiety. Participants consumed 60 or 120 mg with breakfast for 60 days, resulting in a 66–67% reduction in morning cortisol in each group and an increase in testosterone levels [29]. Another study by Pandit S et al. used a root-and-leaf extract standardized to 0.4–1% withanolides and flavonoid glycosides, testing 125 mg, 250 mg, and 500 mg daily for 8 weeks. All doses reduced cortisol, increased ACTH, and improved sleep performance [30].

Mechanistically, ashwagandha appears to act via the HPA axis to reduce cortisol and may also influence sleep through GABA receptors, serotonin receptors, and histamine H3 receptors [31-32]. However, variability in extracts and standardization remains a key consideration, since ashwagandha is not a single-compound intervention and contains multiple active constituents within the same dose.

A human pharmacokinetic report tested 400 mg ashwagandha containing total withanolides 10.76 mg (including withanoside IV 2.42 mg, withaferin A 3.04 mg, 12-deoxy-withastramonolide 0.82 mg, and withanolide A 1.42 mg). Blood measurements of withanoside IV, withaferin A, 12-deoxy-withastramonolide, and withanolide A showed no reported toxicity. Observed Cmax values were: withanoside IV 0.673 ng/mL, withaferin A 1.4071 ng/mL, 12-deoxy-withastramonolide 3.214 ng/mL, and withanolide A 1.927 ng/mL. Half-life (T1/2) values were: withanoside IV 0.377 h, withaferin A 3.782 h, 12-deoxy-withastramonolide 2.086 h, and withanolide A 1.696 h [33]. These findings suggest absorption occurs, but the active profile is complex and varies by constituent.

Another report compared conventional ashwagandha root extract with a sustained-release formulation, both standardized to 30 mg withanolides. Measurements of total withanolides, withanolide A, and 12-deoxy-withastramonolide showed higher Cmax in the sustained-release form: total withanolides 0.648 vs 3.07 ng/mL, withanolide A 0.085 vs 0.491 ng/mL, and 12-deoxy-withastramonolide 0.606 vs 2.667 ng/mL [34]. Therefore, when developing nutraceuticals for a targeted effect, it is essential to standardize bioactive compounds and consider dosage form and absorption-enhancing technologies, as formulation can substantially influence systemic exposure.

Ginseng: Korean ginseng (*Panax ginseng*) has a long history of use throughout Asia and is a major medicinal plant used in herbal medicine, functional foods, and nutraceuticals. Its key active compounds are ginsenosides, a broad group of saponins generally categorized into two major classes: protopanaxadiol (PPD) and protopanaxatriol (PPT) [35]. PPD derivatives include Rb1, Rb2, Rc, Rd, and compound K, while PPT derivatives include Re, Rf, Rg1, Rg2, among others [35-

36]. Because ginsenosides exist as multiple structurally distinct derivatives, they can interact with diverse targets and pathways [36]. Ginseng preparations commonly contain mixtures of ginsenosides rather than isolated single derivatives [37].

After ingestion, most ginsenosides resist gastric acid and are metabolized by gut microbiota. The intestinal microbiome is a major determinant of conversion, absorption, and bioactivity [38]. In particular, ginsenoside compound K (GC-K) is produced via breakdown of protopanaxadiol complexes and is more stable and better absorbed [39]. GC-K has been reported to support glycemic control, exert anti-cancer activity, reduce intestinal inflammation, and more [40].

Ginseng has repeatedly been reported to reduce stress and exhibit adaptogenic properties. A study in working-age men found that ginseng extract reduced stress and fatigue by week 8, affecting neurotransmitters and stress-related hormones, including reductions in epinephrine and norepinephrine and changes in DHEA. Although cortisol increased with stress, the rise was smaller in the ginseng group than in the control group. Transcriptomic analyses also suggested modulation of choline metabolism and pathways related to adrenaline and monoamines, supporting stress reduction mechanisms [41].

At the mechanistic level, chronic stress elevates cortisol and can damage the hippocampus, contributing to reduced stress regulation and memory decline due to hippocampal atrophy. In vitro evidence suggests ginseng may enhance neuroplasticity and neuronal survival under stress and may support memory function [42]. Ginseng may also regulate stress through maintenance of gut microbiome balance, supporting beneficial probiotic populations and reducing intestinal inflammation [43].

In physically active individuals, ginseng extract has been reported to reduce acute exercise-induced cortisol. Proposed mechanisms include antioxidant effects during exercise, central nervous system modulation, reduced inflammation, reduced fatigue, and decreased muscle injury via anti-inflammatory actions—collectively contributing to reduced stress and cortisol responses through HPA axis modulation and related pathways [44]. Conversely, a study in healthy Japanese volunteers assessing fatigue using a visual analogue scale over 3 weeks found reduced fatigue scores in the ginseng group but no significant reduction in cortisol [45]. A limitation was the lack of reported standardization of ginsenoside content.

Overall, evidence supports a trend toward benefits of ginseng for stress reduction, though results are not fully consistent. Future work should standardize ginsenoside content, identify ginsenosides most relevant to stress and cortisol regulation, address stability, and account for microbiome-dependent metabolism. Additionally, ginseng use should consider potential herb–drug interactions in individuals taking medications or other supplements.

Reishi mushroom (*Ganoderma lucidum*): Reishi mushroom (*Ganoderma lucidum*) has been used in Asian traditional medicine for a long time and is regarded as an adaptogenic agent. Reported activities include immune modulation, anti-cancer effects, and glycemic regulation. Its bioactive compounds include triterpenoids such as ganoderic acids, lucidenic acids, and more than 100 additional triterpenoid variants; polysaccharides such as β-glucans and ganoderan; as well as peptides and sterols such as ergosterol [46].

Regarding stress, human studies using reishi extracts standardized to polysaccharides have reported improvements in fatigue and well-being. Reishi spores have also been investigated for anxiety and depression in cancer patients. However, some clinical reports have found no significant effects on anxiety or stress outcomes [47]. Mechanistically, evidence suggests reishi may

influence the HPA axis and cortisol production. For example, endurance cyclists receiving reishi combined with cordyceps showed improved cortisol responses compared with placebo, where cortisol increased markedly post-exercise.

For sleep, animal studies report that mice receiving reishi extract for 4 weeks demonstrated reduced sleep latency and increased total sleep time compared with controls. Increased serotonin levels were observed, alongside gut microbiome changes including increases in *Bifidobacterium sp* and *Bifidobacterium animalis* and elevated metabolites such as indole-3-carboxylic acid and acetylphosphate. These findings suggest reishi may support sleep through microbiome-mediated mechanisms and serotonin modulation [49]. Additional studies report reduced neuroinflammation, which may improve sleep-related brain mechanisms [50]. Sedative effects via GABA receptor modulation have been attributed to specific reishi triterpenes such as ganoderic acid and ganoderenic acid, potentially reducing hypervigilance mediated by the amygdala [51].

***Centella asiatica* (gotu kola):** *Centella asiatica* is a widely used medicinal plant in Asia and is described in Ayurvedic records as neuroprotective [52]. Several countries have also recognized health claims related to cognitive support and memory enhancement [52-53]. Major bioactive compounds include asiatic acid, asiaticoside, madecassic acid, and madecassoside. These constituents vary depending on cultivation conditions, including geographic location and light exposure.

In zebrafish experiments assessing cortisol, asiaticoside and madecassoside showed cortisol-lowering effects, suggesting these compounds reduce stress sensitivity through HPA axis modulation in a chronic unpredictable stress zebrafish model [53]. In zebrafish sleep models, Centella extract improved sleep quality by reducing orexin and p38 protein expression, thereby supporting sleep regulation [54]. In rodent stress models, Centella leaf extract containing asiaticoside and madecassoside reduced aggressive behaviors and lowered cortisol compared with controls [55]. In aged mice, Centella mixed into the diet increased REM sleep duration in males and reduced sleep fragmentation in females. These findings support further investigation of Centella in the areas of sleep, mental wellness, and neuroprotection [56]. However, as with other botanicals, standardized bioactive compound control is essential for deeper research progress.

Chamomile: The most widely consumed and recognized chamomile is German chamomile (*Matricaria chamomilla*). It is commonly used as herbal tea and as an extract in dietary supplements. Chamomile is well known for its calming properties and is often used to promote sleep. Its bioactive compounds include flavonoids—most notably apigenin—as well as coumarins, phenolic acids, and volatile oils such as azulenes, alpha-bisabolol, and spathulenol [57-58].

Human studies have reported that chamomile may reduce anxiety in women during menstruation, in menopausal women, and in individuals with insomnia. Daily chamomile use has improved symptoms without notable adverse effects. Although mechanisms are not fully established, apigenin is hypothesized to exert sedative effects through GABA receptor modulation and to support sleep. Chamomile may also regulate cortisol through HPA axis modulation [59].

In one study, chamomile tea made from 1 g of chamomile flowers daily for 8 weeks reduced stress and cortisol levels. This effect differed from passion flower tea, as cortisol reduction was observed specifically with chamomile. Importantly, 1 g/day chamomile tea also improved sleep quality in those with primary insomnia [60]. Another study combining chamomile and lavender (1.2 g each; total 2.4 g/day) for 8 weeks reduced cortisol

and lowered both systolic and diastolic blood pressure in the intervention group [61]. This suggests chamomile–lavender combinations may reduce HPA axis-driven stress via cortisol reduction, contributing to improved blood pressure outcomes.

In contrast, aromatherapy use of chamomile essential oil (e.g., in shampoo or body cleansing products) and inhalation of chamomile oil rich in bisabolol reduced stress, anxiety, and improved sleep quality, but did not significantly change cortisol levels [62]. Overall, chamomile bioactive compounds appear to work through multiple mechanisms, often including cortisol regulation. Because chamomile can be consumed in multiple forms (tea, powder, extracts, essential oils), standardized quality control is necessary for development of chamomile-based interventions targeting stress, cortisol reduction, and sleep support.

Postbiotics: Interest in the microbiome has grown significantly in functional food and nutraceutical fields. Research initially focused on probiotics—live microorganisms that confer health benefits—then expanded toward related concepts, including postbiotics. Unlike probiotics, postbiotics refer to bioactive preparations derived after microbial activity and may include metabolites, post-metabolites, and non-living microbial components (including dead microbial cells) [63].

Thus, postbiotics can encompass enzymes, peptides, short-chain fatty acids (SCFAs), and microbial fractions such as cell surface proteins and peptidoglycans. These bioactive compounds may still provide health benefits, including antioxidant activity, immunomodulation, and restoration of gut ecological balance [63-65]. In 2019, the International Scientific Association for Probiotics and Prebiotics (ISAPP) convened an expert panel and defined postbiotics as a "preparation of inanimate microorganisms and/or their components that confers a health benefit on the host" [65]. Since then, research on postbiotics has expanded, revealing diverse mechanisms depending on postbiotic type.

This article focuses specifically on postbiotics related to cortisol, stress, and sleep. For example, a heat-killed postbiotic *Lactobacillus gasseri* improved sleep quality in students, particularly male students, increasing sleep latency and duration and increasing NREM sleep after consumption. SCFAs such as acetate, propionate, and butyrate have also been reported to reduce stress-induced cortisol responses. Individuals with healthier microbiomes tend to produce more SCFAs and show lower cortisol responses under stress compared with individuals with poorer microbiome profiles. Higher SCFA production is also associated with better sleep, supporting an HPA axis–gut microbiome pathway [66].

A study in healthy women reported that postbiotic *Bifidobacterium breve* BB091109 reduced inflammatory mediators such as CRP and IL-6 and, importantly, lowered cortisol levels compared with placebo [68]. Another animal study examined postbiotics derived from selected lactic acid bacteria in chronically stressed mice with chronic sleep problems. Postbiotics restored microbiome diversity and composition, improved sleep, reduced corticosterone, and decreased inflammatory cytokines. In the brain, glutamate and GABA levels increased in the prefrontal cortex and hypothalamus, and higher fecal GABA levels were detected. These results support the concept that postbiotics can reduce stress and improve sleep via the HPA axis and gut microbiome through neurotransmitter rebalancing [68].

In a working adult trial of heat-treated *Limosilactobacillus fermentum* PS150, overall sleep quality did not differ significantly from placebo. However, cortisol decreased during nighttime, melatonin secretion increased, and daytime plasma orexin improved. Sleep symptom scale outcomes did not significantly change.

[69] This suggests postbiotic effects may vary by source, type, and dosage, and their efficacy may not be equivalent across preparations. Nevertheless, the evidence indicates postbiotics may modulate stress, cortisol, and sleep through multiple pathways including the HPA axis, gut–brain signaling, inflammatory regulation, and neurotransmitter balance. More data are needed to identify optimal postbiotic types and effective doses in relevant populations. Another interesting study has demonstrated the potential of postbiotics derived from a traditional food source, natto. In this work, researchers selected a Bacillus strain naturally present in fermented natto beans and administered an inactivated preparation of natto-derived Bacillus (heat-inactivated *Bacillus subtilis* subsp. *natto* strain QOL) at a dose of 100 mg. The findings showed significant benefits for mental health, including reductions in stress levels and negative mood, as well as an overall decrease in psychological stress among healthy adults. [70] These results highlight the role of natto-derived postbiotics in stress regulation through modulation of the gut–brain axis, supporting their potential as functional ingredients for mental wellness. Importantly, this example illustrates how naturally occurring functional food components, originally recognized as probiotic microorganisms, can be further developed into postbiotic-based interventions with clinically relevant effects on stress reduction. Moreover, it is noteworthy that even when natto is consumed after heating, beneficial microbial components may remain in the form of postbiotics. This raises the possibility that traditional dietary practices could serve as a foundation for the development of functional foods aimed at reducing stress and promoting mental health wellness. Overall, this study confirms that postbiotics derived from everyday foods can be translated into functional food strategies targeting stress modulation via the gut–brain axis.

In addition to postbiotics, several plant-derived bioactive compounds have also been reported to influence stress regulation through the modulation of the HPA axis. For example, anthocyanin-rich fruits such as blueberries and raspberries have been shown to affect HPA axis activity in association with gut microbiome modulation. These compounds may act through multiple targets involved in neuroendocrine regulation, ultimately influencing cortisol levels.[71] The development of functional foods aimed at stress reduction and sleep improvement is therefore not limited to mechanisms involving cortisol alone. For instance, functional foods derived from asparagus have been investigated for their potential to improve sleep quality through the regulation of heat shock protein 70, which has been associated with improved sleep outcomes.[72]

These findings highlight that bioactive compounds involved in stress reduction and sleep regulation may operate through diverse molecular pathways and biological targets. Such mechanistic diversity provides promising opportunities for further research and development of functional foods targeting stress management and sleep health.

CONCLUSION

Research on bioactive compounds related to stress, cortisol, and sleep has increased, including plant-derived adaptogens, flavonoid-rich botanicals, and microbiome-derived postbiotics. These agents may influence stress and sleep via the HPA axis, gut–brain connections, and neurotransmitter modulation. Overall, bioactive compounds demonstrate potential to regulate stress through HPA axis modulation, reduce cortisol levels, and support sleep quality. The evidence presented in this review on bioactive compounds with stress-reducing and sleep-promoting effects primarily focuses on one major regulatory mechanism, namely modulation of the hypothalamic–pituitary–adrenal (HPA) axis and the

reduction of cortisol levels. However, it is important to acknowledge that other bioactive compounds capable of improving stress resilience and sleep quality may exert their effects through additional pathways that were not addressed within the scope of this manuscript. Therefore, further mechanistic perspectives remain to be explored. A key issue highlighted by the findings summarized in this article is the necessity of controlling and standardizing the dosage of bioactive compounds if they are to be translated into clinical applications. In particular, future development requires greater attention to the stability of these compounds when formulated into nutraceuticals and functional foods. Moreover, more comprehensive pharmacokinetic investigations are needed to clarify absorption, bioavailability, metabolism, and effective dosing strategies. Such evidence will provide an essential foundation for optimizing the design and formulation of nutraceutical products in various delivery forms. In addition, future research should examine the potential benefits of combining multiple bioactive compounds with complementary mechanisms, as certain combinations may produce synergistic effects in stress reduction and sleep enhancement, thereby improving clinical efficacy.

This review highlights a promising direction for the development of functional foods and nutraceuticals targeting stress reduction and sleep support within the broader framework of mental wellness—an increasingly significant and high-impact health concern in the modern working population. By integrating mechanistic evidence on plant-derived bioactive compounds and postbiotic interventions, the article provides a translational foundation for researchers, functional food developers, and nutrition professionals seeking to advance evidence-based strategies for stress resilience and sleep health. Nevertheless, further research is required to ensure rigorous standardization of bioactive compounds in both botanical extracts and postbiotic preparations, including stability assessment, bioavailability evaluation, dose optimization, and formulation refinement. Additionally, careful consideration of potential herb–drug interactions is essential when these compounds are used alongside medications or other supplements. Addressing these scientific and translational challenges will be critical for advancing bioactive compounds from mechanistic insights to clinically relevant and safe functional food applications.

List of abbreviation: ACTH: Adrenocorticotropic Hormone; AMY: Amygdala; CRH: Corticotropin-Releasing Hormone; CRP: C-Reactive Protein; CNS: Central Nervous System; Cmax: Maximum Plasma Concentration; DHEA: Dehydroepiandrosterone; GABA: Gamma-Aminobutyric Acid; GC-K: Ginsenoside Compound K; HPA axis: Hypothalamic–Pituitary–Adrenal Axis; IL-1β: Interleukin-1 Beta; IL-6: Interleukin-6; ISAPP: International Scientific Association for Probiotics and Prebiotics; NCDs: Non-Communicable Diseases; NREM: Non-Rapid Eye Movement; PPD: Protopanaxadiol; PPT: Protopanaxatriol; REM: Rapid Eye Movement; SCFAs: Short-Chain Fatty Acids; TNF-α: Tumor Necrosis Factor-Alpha; T1/2: Half-Life; VAS: Visual Analogue Scale.

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