Review

Mechanistic Pathways Linking Cannabidiol, Hemp Seed Oil and Black Sesame Oil in Hyperarousal Insomnia: A Narrative Review

Piphat Kovitkanit * and Thavatchai Kamoltham

Posted Date: 6 February 2026

doi: 10.20944/preprints202602.0498.v1

Keywords: insomnia; hyperarousal; sleep–wake stability; neuroinflammation; endocannabinoid system; polyunsaturated fatty acids (PUFAs); cannabidiol (CBD); hemp seed oil; black sesame oil

 doi:10.20944/preprints202602.0498.v1

Review

Mechanistic Pathways Linking Cannabidiol, Hemp Seed Oil and Black Sesame Oil in Hyperarousal Insomnia: A Narrative Review

Piphat Kovitkanit * and Thavatchai Kamoltham

College of Health Science, Suan Sunandha Rajabhat University, Samut Songkhram 75000, Thailand

* Correspondence: piphat@kovitkanit.com

Abstract

Insomnia is increasingly recognized as a manifestation of multisystem dysregulation characterized by sustained physiological hyperarousal. This review situates insomnia within a framework of reciprocal disturbances across neuroendocrine, inflammatory, and autonomic pathways. It examines the potential roles of cannabidiol (CBD), polyunsaturated fatty acids from hemp seed oil (HSO), and lignans from black sesame oil (BSO) as modulators of upstream biological processes relevant to sleep regulation. Rather than acting as direct hypnotics, these compounds are evaluated for their capacity to influence convergent mechanisms implicated in sleep–wake stability. Preclinical evidence suggests that CBD may modulate endocannabinoid and serotonergic signaling, which could contribute to reduced hyperarousal. Concurrently, HSO-derived fatty acids are involved in mitochondrial function and inflammatory resolution. Sesame lignans further contribute through antioxidant properties plausibly linked to neurometabolic stability and modulation of neural excitability. However, the current evidence base is predominantly preclinical, and definitive conclusions regarding therapeutic efficacy or optimal dosing in humans cannot yet be drawn. Future research must prioritize integrative clinical studies that link these specific biological modulations to standardized sleep outcomes to determine their real-world applicability. Although clinical data are limited, the pathways discussed here align with biological domains repeatedly implicated across established insomnia phenotypes. By bringing these compounds together within a shared hyperarousal-based framework, this review highlights convergent upstream mechanisms that extend beyond isolated compound-specific effects.

Keywords: insomnia; hyperarousal; sleep–wake stability; neuroinflammation; endocannabinoid system; polyunsaturated fatty acids (PUFAs); cannabidiol (CBD); hemp seed oil; black sesame oil

---

Disclaimer. This preprint presents a hypothesis-generating, mechanistic narrative review that synthesizes primarily preclinical and experimental evidence. The proposed framework is intended to support conceptual integration and guide future research, rather than to establish clinical efficacy or provide therapeutic or clinical recommendations.

1. Introduction

Poor sleep has wide-ranging physiological, neurological, and psychological consequences, motivating investigation into upstream biological pathways underlying sleep dysregulation [1–3]. Extensive neurobiological and clinical research has demonstrated strong associations between sleep disruption and heightened systemic inflammation, increasing vulnerability to chronic disease [3–5]. The consequences of insufficient sleep also extend into psychological and occupational domains, where disrupted sleep is a significant risk factor for reduced emotional resilience, increased depression, and errors in high-stakes professional environments [6–8].

Insomnia, the most pervasive of these disturbances, is characterized by persistent deficits in sleep initiation, maintenance, or restorative quality [9–11]. Modern clinical frameworks increasingly

 doi:10.20944/preprints202602.0498.v1

conceptualize insomnia as a systemic disorder marked by sustained hyperarousal across neural, endocrine, and autonomic domains, promoting a self-perpetuating cycle of sleep fragmentation and heightened stress sensitivity [10,12–14]. Recent international sleep medicine guidelines continue to emphasize the clinical significance of insomnia as a prevalent and burdensome condition requiring evidence-based management [15]. Over time, these alterations impair executive functions, including memory processing and emotional regulation, further illustrating the multisystem burden of the condition [7,9,11].

Driven by the need for more targeted interventions, research attention has shifted toward identifying upstream biological pathways that precipitate sleep instability [16]. Additionally, the complex bidirectional signaling between sleep regulation and immune function suggests that modulating inflammatory and neurochemical pathways may offer significant therapeutic leverage [3–5,16].

These compounds were selected because their bioactive properties converge on upstream mechanisms implicated in hyperarousal-based insomnia [10–14]. Cannabidiol (CBD), polyunsaturated fatty acids (PUFAs) from hemp seed oil, and sesame-derived lignans do not act as direct hypnotics; instead, they influence multiple regulatory systems that shape susceptibility to sleep disruption. These include excitatory–inhibitory balance, stress responsivity, neuroimmune signaling, oxidative resilience, and circadian–metabolic coordination [3–5,16–19]. Viewed within a unified mechanistic framework, examining these agents together helps clarify how convergent biological influences may support sleep–wake stability under sustained physiological hyperarousal [12,16,19].

Public and commercial interest in these compounds has expanded in recent years. However, the underlying scientific evidence remains uneven and insufficiently integrated across studies, limiting the synthesis of how these substances might collectively interact with upstream biological drivers of sleep–wake stability.

In light of these gaps, this review brings together mechanistic evidence from neurobiological, inflammatory, metabolic, and circadian research to examine how CBD, PUFAs, and lignans interact within established sleep-regulatory networks. Situating these mechanisms within a broader sleep-science context may help inform future translational research and hypothesis-driven clinical studies.

2. Literature Search Strategy

This narrative review employed a targeted literature search to synthesize mechanistic evidence on biological pathways. These pathways describe how cannabidiol (CBD), hemp seed oil–derived polyunsaturated fatty acids (PUFAs), and black sesame oil–derived lignans may influence sleep–wake regulation. A narrative approach was selected because the relevant literature spans heterogeneous domains, including molecular pharmacology, neurobiology, immunology, metabolism, and circadian biology, which limits the suitability of formal systematic review or quantitative meta-analytic methodologies.

Accordingly, the evidence base comprised in vitro studies, animal models, mechanistic human investigations, and integrative conceptual reviews. These sources were interpreted qualitatively to elucidate biological relevance across regulatory systems rather than to aggregate effect sizes or evaluate clinical efficacy.

Literature searches were conducted using Scopus and Google Scholar, covering publications from January 2000 to October 2025. Search terms were applied in various combinations and included “cannabidiol,” “CBD,” “endocannabinoid system,” “FAAH inhibition,” “hemp seed oil,” “polyunsaturated fatty acids,” “linoleic acid,” “alpha-linolenic acid,” “black sesame oil,” “lignans,” “sesamin,” “sesamolin,” “sleep regulation,” “insomnia,” “circadian rhythms,” “inflammation,” and “oxidative stress.”

Reference lists of seminal mechanistic studies and high-impact narrative or conceptual reviews were manually screened to ensure coverage of foundational work in sleep biology. Studies were included if they examined molecular, neural, endocrine, inflammatory, oxidative, metabolic, or circadian mechanisms relevant to sleep–wake regulation and involved CBD, hemp seed oil–derived

 doi:10.20944/preprints202602.0498.v1

PUFAs, or black sesame oil–derived lignans. Priority was given to studies providing mechanistic insight, cross-model consistency, or relevance to hyperarousal-based models of insomnia.

Studies focused exclusively on recreational cannabis use, anecdotal reports, or content lacking mechanistic relevance to sleep–wake physiology were excluded. In keeping with established conventions for mechanistic narrative reviews, formal risk-of-bias assessments and quantitative effect-size comparisons were not performed. The primary objective was to integrate biological plausibility across experimental models rather than to establish clinical efficacy.

This strategy enabled thematic refinement of the literature and supported synthesis of convergent mechanistic pathways relevant to sleep regulation, while also identifying priorities for future mechanistic and translational research.

3. Limitations of the Narrative Review Approach

This narrative review synthesizes mechanistic evidence across diverse biological domains relevant to sleep–wake regulation. The focus is on integrating biological plausibility from preclinical and experimental studies, not on evaluating clinical efficacy or ranking interventions by levels of evidence.

This approach supports conceptual integration of heterogeneous findings that are not suitable for systematic review, but it may introduce selection bias. To minimize this risk, studies were selected based on mechanistic relevance, consistency across models, and alignment with established frameworks of sleep regulation and hyperarousal.

The proposed framework should therefore be viewed as hypothesis-generating and not as an evidence hierarchy or clinical recommendation. Future studies that directly link these mechanisms to standardized human sleep outcomes remain necessary.

4. Foundations of Sleep Regulation

Sleep emerges from the coordinated activity of multiple biological systems that operate across different timescales. Two core processes — the homeostatic buildup of sleep pressure and the circadian system, governed by the suprachiasmatic nucleus (SCN) — work together to determine when sleep is initiated and how consolidated it becomes [16,19–22]. During wakefulness, somnogenic substances such as adenosine accumulate, increasing the drive for sleep; at the same time, circadian timing aligns sleep with environmental light–dark cues [16].

Disruptions in these systems can impair the transition into restorative non–rapid eye movement (NREM) sleep. Reduced homeostatic sleep pressure, altered adenosinergic signaling, or circadian misalignment may interact with physiological and psychological factors to fragment sleep or increase vulnerability to arousal [20,22]. These disturbances rarely occur in isolation; instead, they dynamically interact within broader neurobiological networks.

A significant determinant of stable sleep is the balance between inhibitory and excitatory neurotransmission. GABAergic activity promotes sleep initiation and NREM stability, whereas excessive glutamatergic or limbic activation can sustain cortical hyperarousal—a core feature of insomnia [10,11,13]. Recent analyses specifically highlight the GABAergic system as a key therapeutic target in insomnia [23]. Cognitive and emotional processes, including worry and conditioned arousal, further amplify neural sensitivity to internal and external cues [14].

Stress-regulatory systems intersect closely with neural pathways that govern sleep–wake regulation. Heightened activation of the hypothalamic–pituitary–adrenal (HPA) axis disrupts normal cortisol rhythms, while increased sympathetic nervous system activity interferes with the physiological downshift required for sleep initiation [12,19]. Sustained hyperarousal is further associated with elevated inflammatory activity, oxidative stress, metabolic strain, and mitochondrial dysfunction, each of which contributes to lighter and more fragmented sleep patterns [3,5,24]. Previous physiological reviews consistently document a bidirectional relationship between sleep and

 doi:10.20944/preprints202602.0498.v1

immune function, highlighting reciprocal interactions between sleep disruption and inflammatory signaling [25].

Because the biological systems governing sleep are closely interconnected, disturbances in one domain often influence others rather than occurring in isolation [3–5,12,16]. Changes in neurotransmitter balance, stress responsivity, immune signaling, metabolic regulation, or circadian timing therefore interact across broader neurobiological networks that shape sleep–wake stability [3–5,12,16,19]. From this perspective, sleep disruption reflects the combined effects of multiple regulatory systems rather than the failure of a single pathway [10,12–14].

This multisystem view provides a useful framework for examining how specific bioactive compounds may act on upstream mechanisms relevant to sleep–wake regulation, particularly within contemporary models that conceptualize insomnia as a disorder of sustained physiological hyperarousal [10,12–14]. It also allows assessment of whether proposed mechanistic actions intersect with established determinants of sleep regulation, including excitatory–inhibitory balance, stress-axis activity, neuroimmune signaling, and circadian–metabolic coordination [16,18,19,25,26]. An overview of these convergent interactions is shown in Figure 1.

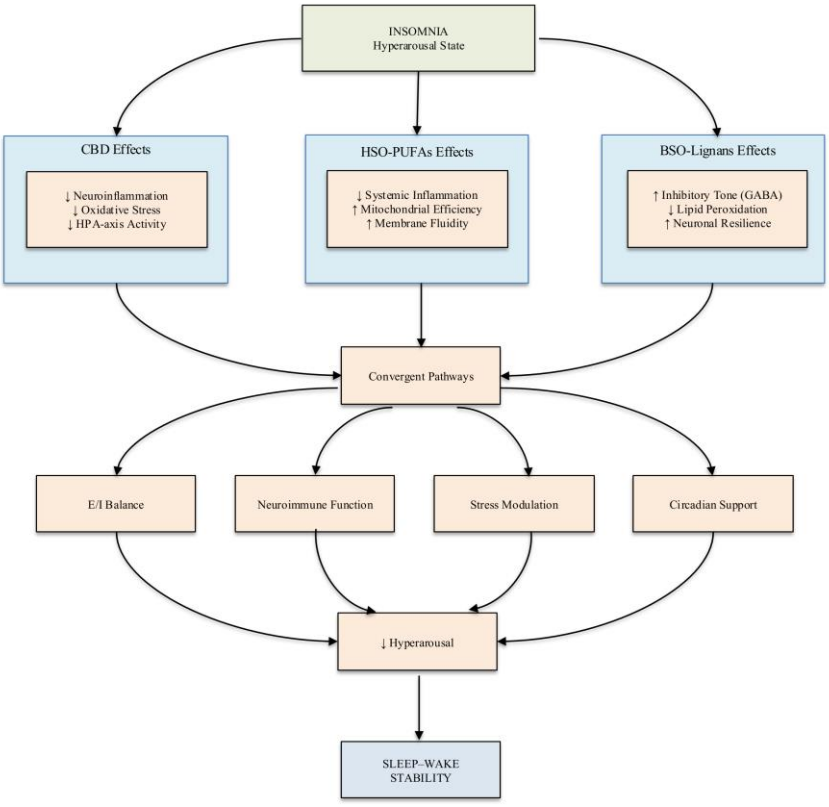

Figure 1. Convergent mechanistic pathways linking Cannabidiol (CBD), Hemp seed oil (HSO), and Black sesame Oil (BSO) to sleep–wake regulation. This figure represents a conceptual integration rather than a validated causal model.

This conceptual framework illustrates how three plant-derived compounds—CBD, polyunsaturated fatty acids (PUFAs) from hemp seed oil, and lignans from black sesame oil—modulate overlapping biological systems implicated in the pathophysiology of insomnia. Rather than acting as direct sedatives, these agents exert upstream modulatory effects: CBD primarily engages endocannabinoid and serotonergic (5-HT1A) signaling, HSO-derived PUFAs support inflammatory resolution and membrane homeostasis, and BSO-derived lignans provide antioxidant and GABAergic support. By acting on excitatory–inhibitory balance, neuroimmune signaling, stress-response circuitry, and circadian–metabolic coordination, these mechanisms reduce physiological hyperarousal and support stable sleep–wake regulation. The diagram highlights the multisystem

 doi:10.20944/preprints202602.0498.v1

nature of sleep regulation and potential mechanistic synergies relevant to integrative therapeutic strategies.

5. The Multifaceted Neurobiological Pathways Linking CBD and Sleep Regulation

Cannabidiol (CBD) influences endocannabinoid signaling through CB1-related pathways within brain networks that regulate mood, alertness, and circadian rhythms [27,28]. Systematic reviews have consolidated evidence supporting cannabinoid-mediated modulation of sleep, detailing interactions with endocannabinoid signaling, GABAergic transmission, and stress-responsive neural circuits [29–32]. This neuromodulatory influence extends to non-canonical targets, including TRPV1 and GPR55, which collectively regulate nociception, the excitatory–inhibitory balance, and neuroendocrine stress signaling [27,33]. While these secondary mechanisms remain subjects of ongoing investigation, they highlight CBD's capacity to influence multiple layers of neural regulatory control relevant to sleep regulation [27].

The potential relevance of CBD to sleep architecture is further supported by its anti-inflammatory and antioxidative properties [17,34]. Persistent brain inflammation and overactive immune cells are linked to heightened brain arousal and poor sleep quality [3,4,17]. In this context, CBD's ability to moderate proinflammatory cytokine activity, reduce oxidative stress, and normalize neuroimmune signaling provides a plausible pathway for stabilizing sleep–wake regulation [17,22,24]. These immune-related effects are indirect but may help establish physiological conditions that support improved sleep over time [34,35].

Central to this sleep-supportive profile is modulation of stress-sensitive neural circuitry, particularly within the amygdala, hippocampus, and hypothalamic–pituitary–adrenal (HPA) axis [19,28,36]. Experimental and neuroimaging evidence indicate that CBD can dampen amygdala reactivity and support more adaptive HPA-axis feedback, thereby reducing persistent stress signaling that sustains insomnia through heightened physiological arousal [12,19,37]. Such attenuation of stress-related arousal is especially relevant for counteracting threat-based cognitive patterns that interfere with sleep initiation and maintenance in individuals characterized by chronic hyperarousal [37,38].

When considered together, this mechanistic profile positions CBD as a potential adjunctive strategy rather than a conventional, direct-acting hypnotic, with the most significant relevance for individuals whose sleep disturbances are driven by emotional or physiological hyperactivation rather than purely circadian or structural sleep abnormalities [38–41]. Dedicated reviews further support these observations by consolidating evidence on cannabinoids, endocannabinoid signaling, and sleep regulation [29–32].

Table 1. Key bioactive components of HSO, CBD, and BSO and their major biological roles.

Source / Component	Major Molecules	Primary Biological Activities	Sleep-Relevant Implications
Hemp Seed Oil (HSO)	Linoleic acid (LA), alpha-linolenic acid (ALA), gamma-linolenic acid (GLA), tocopherols, phytosterols	Anti-inflammatory; membrane stabilization	Supports ECS homeostasis and reduces inflammatory sleep disruption
Cannabidiol (CBD)	CBD, terpenophenolics	ECS modulation; 5-HT1A receptor involvement	Reduces physiological hyperarousal; may support sleep initiation

 doi:10.20944/preprints202602.0498.v1

Black Sesame Oil (BSO)	Sesamin, sesamolin, sesamol	Antioxidant; GABAergic support	Enhances inhibitory tone; mitigates oxidative stress

6. Mechanistic Contributions of Polyunsaturated Fatty Acids in Hemp Seed Oil

Hemp seed oil (HSO) contains polyunsaturated fatty acids (PUFAs), primarily linoleic acid (LA) and alpha-linolenic acid (ALA). These fatty acids help regulate neural, metabolic, and inflammatory processes that influence sleep [42,43]. HSO does not act as a primary hypnotic. Its lipid constituents refine physiological domains essential to sleep quality, including systemic inflammatory tone, neuroimmune signaling, and mitochondrial efficiency [3,4,17]. Analyzing these mechanisms establishes a functional framework for evaluating how HSO-derived PUFAs mitigate upstream biological stressors that precipitate sleep–wake disturbances [42].

A fundamental driver of PUFA activity lies in the optimization of lipid metabolism and systemic homeostasis. Data from structurally similar PUFA-rich oils indicate that these lipids enhance lipid handling and alleviate metabolic strain, thereby modifying cardiometabolic risk factors that exacerbate inflammatory tone [43,44]. Such systemic stabilization is highly relevant to insomnia, where chronic low-grade inflammation and metabolic dysregulation are consistently linked to diminished sleep depth and increased fragmentation [12,14,20].

Beyond metabolic support, PUFAs directly orchestrate inflammatory resolution. Experimental evidence suggests that omega-3 and omega-6 fatty acids engage with neuroinflammatory pathways to modulate cytokine production and glial cell reactivity [28,42]. This is particularly critical because neuroinflammation fundamentally disrupts the neural circuits governing sleep initiation and maintenance [3,4]. Gamma-linolenic acid (GLA), a prominent omega-6 PUFA present in hemp seed oil, demonstrates specific anti-inflammatory properties in metabolic and inflammatory contexts, including modulation of proinflammatory mediators [45]. In addition, structurally related antioxidant compounds present in these oils provide protective effects for neuronal and vascular tissues by reducing oxidative stress and lipid peroxidation [18,43]. These antioxidant properties are vital for maintaining mitochondrial resilience — a factor essential for meeting the brain's high metabolic demands during sleep [38].

PUFAs may also affect sleep circuits indirectly by modulating endocannabinoid signaling. Given that the ECS regulates stress, mood, and arousal, its dysregulation is a primary contributor to the heightened vigilance observed in insomnia [33,37]. While cannabidiol (CBD) provides more direct receptor-level modulation, PUFAs appear to support ECS-related homeostasis and cardiovascular health [46]. These lipids also safeguard the neural environment by maintaining microglial function and reducing the concentration of neurotoxic mediators [42]. Such actions help counteract the cortical instability and hyperarousal that characterize chronic insomnia [26].

At the cellular level, PUFAs enhance mitochondrial performance, neuronal energy production, and synaptic stability [47]. These mitochondrial effects are intrinsically linked to circadian regulation, as circadian oscillators coordinate metabolic cycles that rely heavily on mitochondrial integrity [38]. Emerging evidence indicates that dietary PUFAs can modulate circadian clock gene expression and metabolic cycles, suggesting a direct role in circadian entrainment and metabolic homeostasis [48,49]. Research connecting circadian misalignment to neurodegeneration further underscores how compromised neuronal resilience increases susceptibility to oxidative stress and functional decline [35]. Especially in the context of aging, where circadian efficiency and stress responsivity naturally deteriorate, adequate PUFA availability may be necessary to preserve the biological terrain required for healthy sleep [44,47].

From this mechanistic perspective, these pathways indicate that HSO-derived fatty acids function as systemic stabilizers rather than direct sedatives. By reducing chronic inflammation and supporting metabolic and mitochondrial stability, PUFAs contribute to a neurobiological milieu associated with lower arousal and more consolidated sleep–wake patterns [14,38,42]. This positions

 doi:10.20944/preprints202602.0498.v1

PUFAs as upstream modulators within the multisystem framework underlying the pathophysiology of insomnia.

7. Mechanistic Contributions of Black Sesame Oil and Lignans

The sleep-related potential of black sesame oil (BSO) stems from its unique lignan content, including sesamin and sesamolin. These compounds exhibit antioxidant, anti-inflammatory, and neuroprotective properties that may support sleep–wake physiology [16,43]. Preliminary clinical evidence from an elderly Thai population suggests that black sesame seed consumption is associated with measurable improvements in subjective sleep quality [50]. The bioactive compounds in BSO do not induce sleep directly. Their effects involve modulation of biological systems that shape vulnerability to insomnia, including neuroinflammation, oxidative stress, synaptic stability, and circadian timing [14,38,44].

A cornerstone of sesame lignan activity is the mitigation of oxidative stress within neural and vascular tissues. Experimental evidence indicates that sesamin and sesamolin reduce lipid peroxidation and protect mitochondrial membranes, thereby enhancing cellular resilience under oxidative load [16,18]. Beyond antioxidant effects, sesamin specifically exhibits anxiolytic and neuroprotective properties in experimental models, modulating behavioral responses and protecting against neuronal excitotoxicity [51,52]. This protection is vital for stabilizing neuronal energy demands during the transition from wakefulness to sleep, a phase that is highly sensitive to redox imbalance and mitochondrial strain [38].

Lignans also interact with inflammatory pathways that are increasingly recognized as contributors to sleep disruption. Inflammation-driven alterations in neural excitability and synaptic signaling can heighten arousal and fragment sleep continuity [4,14]. By shaping inflammatory tone, BSO-derived lignans may help attenuate physiological drivers of hyperarousal, thereby supporting sleep initiation and maintenance [16].

These lignans do not directly engage cannabinoid receptors, but their influence on lipid metabolism and oxidative balance overlaps conceptually with domains regulated by the endocannabinoid system. The ECS plays a central role in stress regulation, emotional processing, and neural homeostasis — functions that strongly shape sleep behavior [19,27]. Dysregulation of ECS signaling has been linked to stress-related arousal states [36]. The metabolic and antioxidant effects of BSO may therefore indirectly contribute to ECS-mediated resilience without requiring direct receptor-level interactions [16].

The functional efficacy of sesame lignans also varies across cultivars, reflecting natural differences in seed composition and lipid profiles. Such variability may result in subtle differences in antioxidant potency or metabolic effects among BSO preparations, underscoring the importance of source-specific considerations when evaluating mechanistic or translational relevance [43].

Beyond their antioxidant and anti-inflammatory actions, lignans intersect with broader lipid-mediated signaling pathways implicated in sleep regulation. Research on N-acylethanolamine metabolism highlights the role of lipid-derived mediators in nociception, inflammation, and sleep-related neurobiology [27]. Although lignans do not directly regulate these pathways, their capacity to shape oxidative and metabolic environments may influence overlapping neurobiological domains relevant to sleep stability [16].

These mechanistic properties also carry implications for how sleep-related outcomes are assessed. Improvements in inflammatory or metabolic balance may be reflected differently depending on whether sleep is measured using polysomnography or actigraphy, consistent with contemporary frameworks that conceptualize insomnia as a multidimensional, transdiagnostic condition [8,10].

At a systemic level, the endothelial-protective and lipid-modulating effects of lignans contribute to the broader relationship between sleep and overall health. Sleep quality both influences and reflects systemic physiological stability, and lignans may support this bidirectional relationship by modulating oxidative burden and metabolic efficiency [1,44]. As with other lipid-derived bioactive

 doi:10.20944/preprints202602.0498.v1

compounds, potential interactions with metabolic pathways and drug metabolism warrant consideration in translational contexts [26].

On this basis, the mechanistic actions of black sesame lignans position BSO as an upstream modulator of biological processes relevant to sleep regulation. Rather than inducing sleep directly, these compounds contribute to physiological conditions characterized by reduced hyperarousal, enhanced neuronal resilience, and improved inflammatory and metabolic balance—conditions that support more consolidated and restorative sleep–wake patterns [14,38,44].

Table 2. Mechanistic domains associated with cannabidiol (CBD), hemp seed oil (HSO), and black sesame oil (BSO) based on preclinical evidence.

Mechanistic domain	HSO (PUFAs)	CBD	BSO (Lignans)	Evidence base
GABA-related signaling	Indirect membrane-mediated effects	Context-dependent modulation	Association with inhibitory signaling	In vitro, animal
Serotonin-related pathways	—	5-HT1A receptor involvement	Indirect stress-related effects	Animal
Endocannabinoid-related pathways	Precursor availability	FAAH inhibition; ECS modulation	Indirect metabolic support	In vitro, animal
Inflammatory signaling	Lipid-mediated modulation	Anti-inflammatory activity	Lignan-associated effects	In vitro, animal
Oxidative stress pathways	Reduced lipid peroxidation	Antioxidant-associated effects	Antioxidant activity	In vitro, animal
Stress-related pathways	Metabolic support	Stress-responsive circuitry modulation	Endocrine buffering	Animal
Cellular membrane stability	Enhanced membrane fluidity	Indirect effects	Indirect effects	In vitro

Note: This table summarizes mechanistic associations derived primarily from preclinical and experimental studies. These pathways indicate biological plausibility and do not imply direct effects on sleep outcomes or clinical efficacy.

8. Convergent Mechanisms Linking CBD, PUFAs, and Lignan Pathways to Sleep Regulation

Rather than functioning as direct sedatives, these agents exert upstream modulatory effects on physiological systems. Cannabidiol (CBD) primarily engages endocannabinoid and serotonergic (5-HT1A) signaling, while hemp seed oil–derived PUFAs promote inflammatory resolution and membrane homeostasis, and black sesame oil–derived lignans provide antioxidant and GABAergic support [22,43]. This convergence reinforces the view that sleep regulation arises from integrated neurobiological and systemic mechanisms rather than from isolated receptor-specific effects [43].

A critical junction of this convergence lies in the maintenance of excitatory–inhibitory (E/I) balance within central neural circuits. Within the hyperarousal model of insomnia, characterized by excessive cortical excitability and heightened autonomic activation, CBD's modulation of serotonergic and endocannabinoid signaling may help attenuate neural hyperexcitability [10,13–16]. In parallel, the membrane-stabilizing effects of PUFAs and GABAergic support from sesame lignans may further dampen activity within wake-promoting neural networks [10,13–16].

 doi:10.20944/preprints202602.0498.v1

The bidirectional relationship between sleep and immune function represents another shared mechanistic domain. Neuroinflammatory signaling can precipitate arousal and fragment sleep, while sleep disruption reciprocally amplifies inflammatory activity [3–5,28]. Through complementary actions — CBD's anti-inflammatory effects, PUFA-derived pro-resolving lipid mediators, and the antioxidant and anti-inflammatory properties of lignans — these compounds may help restore immune–sleep homeostasis and promote more consolidated sleep patterns [3,17,24].

Stress-regulatory systems constitute a further axis of convergence. Heightened hypothalamic–pituitary–adrenal (HPA) axis activity and sympathetic nervous system activation are central drivers of physiological hyperarousal, which interferes with sleep initiation and maintenance [12,20,27]. Evidence indicates that CBD can attenuate stress-induced neuroendocrine responses. In parallel, PUFAs and lignans support metabolic, vascular, and endocrine resilience, collectively reducing stress-related physiological load and improving sleep continuity [19,27,28].

Coordination between circadian and metabolic regulation represents an additional pathway through which sleep may be indirectly supported. Disruptions in circadian signaling and metabolic homeostasis contribute to sleep fragmentation and impaired sleep quality, particularly in aging populations [26,44]. Although cannabidiol (CBD), polyunsaturated fatty acids (PUFAs), and sesame lignans do not act as melatonin agonists [21], their combined effects on metabolic efficiency, oxidative balance, and vascular function may help stabilize circadian rhythms and support sleep regulation [38,39,44].

Within this framework, CBD, PUFAs, and sesame lignans appear to influence sleep by modulating interconnected brain and body systems associated with insomnia risk. Their complementary actions highlight the importance of mechanism-informed investigation to clarify how these pathways interact across physiological and clinical contexts and to identify convergent processes with the most significant translational relevance for human sleep regulation [43].

Table 3. Systems-level integration of cannabidiol (CBD), hemp seed oil (HSO), and black sesame oil (BSO) within the hyperarousal model of insomnia.

Functional system	CBD	HSO	BSO	Integrated interpretation
Arousal regulation	Attenuation of stress-related neural activity	Indirect metabolic stabilization	Indirect anxiolytic support	Reduced physiological hyperarousal
Excitatory–inhibitory balance	Context-dependent inhibitory modulation	Synaptic membrane support	Inhibitory-associated effects	Lower cortical excitability
Stress-responsive neurocircuitry	Modulation of limbic and HPA-axis signaling	Metabolic and vascular support	Endocrine buffering	Dampened stress–arousal loops
Neuroimmune regulation	Anti-inflammatory signaling	Inflammatory resolution	Antioxidant and anti-inflammatory effects	Improved immune–arousal balance
Oxidative and mitochondrial resilience	Reduced oxidative burden	Mitochondrial support	Protection from lipid peroxidation	Enhanced neurometabolic stability

 doi:10.20944/preprints202602.0498.v1

Circadian–metabolic coordination	Indirect ECS–SCN interactions	Circadian-related metabolic modulation	Redox-related circadian support	Improved system alignment

Note: This table presents a conceptual systems-level synthesis of convergent mechanisms relevant to hyperarousal-based insomnia. The framework does not represent validated causal effects on sleep architecture or clinical outcomes.

9. Research Gaps and Directions for Future Mechanistic Inquiry

Work on cannabidiol (CBD), hemp seed oil (HSO), and black sesame oil (BSO) has grown quickly, but the mechanistic picture remains patchy. Many findings derive from narrowly focused experiments conducted under heterogeneous conditions, limiting cross-study comparability and synthesis. As a result, it remains uncertain how molecular or cellular changes translate into measurable alterations in sleep itself. *In particular, links between these compounds and vulnerability to insomnia remain only partially resolved. These effects may be mediated through inflammation, oxidative stress, altered arousal, metabolic disruption, or circadian instability.*

A recurring weakness in the literature is that sleep is frequently treated as a secondary outcome or not measured directly at all. Although several biologically plausible pathways have been proposed based on laboratory data, relatively few studies evaluate sleep architecture, continuity, or arousal thresholds using standardized methodologies. This complicates interpretation, as improvements in upstream physiology do not necessarily translate into improved sleep, and observed effects may vary across insomnia phenotypes rather than reflect generalizable mechanisms.

Another unresolved issue concerns how these compounds might interact across shared biological systems. Cannabidiol (CBD), polyunsaturated fatty acids (PUFAs), and lignans each influence immune signaling, oxidative balance, metabolic regulation, and stress responsiveness, yet most studies consider these effects in isolation. Whether their actions converge, counteract one another, or depend on physiological context remains largely unknown. Integrated mechanistic models have been proposed to illustrate these potential synergies, as summarized in Tables 2 and 3. However, empirical evidence at the integrated-system level—including limbic arousal circuitry, mitochondrial energetics, and circadian–metabolic coupling—remains fragmentary.

Dose, timing, and duration of exposure add further uncertainty. The biological effects of these compounds are unlikely to be uniform over time or across conditions and may vary according to circadian phase, metabolic state, stress reactivity, or dietary background. PUFA-related effects may depend on circadian lipid metabolism, whereas CBD appears particularly sensitive to baseline stress responsivity. In the absence of standardized dosing strategies or temporal profiling, optimal dose–response relationships in humans remain to be determined, making it difficult to define when these interventions are most likely to influence sleep-related physiology in a meaningful way.

The translation of mechanistic findings into clinically relevant outcomes also remains underdeveloped. Only a limited number of studies combine objective sleep measures with biological markers such as inflammatory profiles, electrophysiological indices of arousal, or indicators of metabolic timing. Individual variability—including genetic differences in endocannabinoid signaling, fatty-acid metabolism, antioxidant capacity, and stress sensitivity—is rarely addressed, despite the well-recognized heterogeneity of insomnia. *Uniform responses across individuals should therefore not be assumed. Different insomnia phenotypes—such as those driven primarily by neuroinflammation versus those characterized by autonomic hyperarousal—may respond uniquely to the neuroimmune or GABAergic pathways targeted by these compounds.*

Advancing this field will require research designs that move beyond compartmentalized approaches. Integrative studies that combine molecular, metabolic, immune, and electrophysiological measures with direct assessments of sleep may help clarify which biological changes are most relevant to sleep–wake regulation. Such approaches will be essential for identifying

 doi:10.20944/preprints202602.0498.v1

when, and for whom, compounds such as CBD, PUFAs, and lignans are most likely to provide meaningful translational benefit.

10. Conclusions

This narrative review integrates mechanistic evidence across neurobiological, inflammatory, metabolic, and circadian domains to examine how cannabidiol (CBD), hemp seed oil (HSO), and black sesame oil (BSO) may influence upstream processes that shape sleep–wake regulation. Although these compounds have traditionally been examined within separate disciplinary frameworks, their bioactive components converge on several interconnected systems increasingly recognized as central to the pathophysiology of insomnia. These systems include excitatory–inhibitory balance within arousal circuitry, endocannabinoid tone, neuroimmune signaling, oxidative resilience, mitochondrial efficiency, and the coordination of circadian and metabolic rhythms.

Across these domains, a coherent mechanistic pattern emerges. CBD appears to modulate stress- and arousal-related neural systems, particularly through serotonergic and GABAergic mechanisms. In contrast, PUFAs derived from HSO primarily influence inflammatory resolution and metabolic processes relevant to sleep pressure and neural stability. Sesame-derived lignans from BSO contribute antioxidant and inhibitory support that may help preserve neurometabolic integrity.

Although each compound influences distinct biological processes, their effects converge on shared regulatory systems. These convergent actions may reduce physiological hyperarousal and support more consolidated and restorative sleep.

At the same time, substantial uncertainties remain. Much of the evidence arises from molecular and preclinical work, with limited studies directly connecting these upstream processes to measurable changes in human sleep architecture. At present, dose–response relationships in humans remain to be determined. Furthermore, current findings do not establish definitive clinical efficacy or standardized therapeutic protocols.

Interactions among CBD, PUFAs, and lignans remain largely unexplored, and the influence of timing, metabolic state, and individual variability has not been adequately characterized. These gaps underscore the need for research approaches that integrate molecular mechanisms with translational biomarkers and clinically relevant sleep measures.

Within this mechanistic context, this review *offers a conceptual basis for considering* natural compounds such as CBD, HSO, and BSO for modulating biological systems implicated in insomnia. Rather than suppressing symptoms, these agents may influence multiple regulatory pathways involved in sleep–wake control. Clarifying how these compounds interact across shared physiological systems may inform the development of targeted strategies—whether as standalone or adjunctive approaches—that support sleep–wake stability and long-term physiological resilience.

Author Contributions: Conceptualization, P.K.; methodology, P.K. and T.K.; investigation, P.K.; formal analysis, P.K.; writing—original draft preparation, P.K.; writing—review and editing, T.K.; visualization, P.K.; supervision, T.K. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding. The APC was not funded by any external source.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: No new data were created or analyzed in this study. Data sharing is not applicable to this article.

Acknowledgments: The authors would like to express their sincere appreciation to Dr. Thavatchai Kamoltham, MD, Dr.PH, for his academic supervision, critical review, and constructive guidance throughout the preparation of this manuscript.

 doi:10.20944/preprints202602.0498.v1

Conflicts of Interest: The authors declare no conflicts of interest.

References

1. Luyster, F.S.; Strollo, P.J.; Zee, P.C.; Walsh, J.K. Sleep: A Health Imperative. *Sleep* **2012**, *35*, 727–734, doi:10.5665/sleep.1846.
2. Grandner, M.A. Sleep, Health, and Society. *Sleep Med. Clin.* **2017**, *12*, 1–22, doi:10.1016/j.jsmc.2016.10.012.
3. Irwin, M.R. Sleep and Inflammation: Partners in Sickness and in Health. *Nat. Rev. Immunol.* **2019**, *19*, 702–715, doi:10.1038/s41577-019-0190-z.
4. Irwin, M.R.; Olmstead, R.; Carroll, J.E. Sleep Disturbance, Sleep Duration, and Inflammation: A Systematic Review and Meta-Analysis of Cohort Studies and Experimental Sleep Deprivation. *Biol. Psychiatry* **2016**, *80*, 40–52, doi:10.1016/j.biopsych.2015.05.014.
5. Besedovsky, L.; Lange, T.; Born, J. Sleep and Immune Function. *Pflüg. Arch. - Eur. J. Physiol.* **2012**, *463*, 121–137, doi:10.1007/s00424-011-1044-0.
6. Kalmbach, D.A.; Arnedt, J.T.; Song, P.X.; Guille, C.; Sen, S. Sleep Disturbance and Short Sleep as Risk Factors for Depression and Perceived Medical Errors in First-Year Residents. *Sleep* **2017**, *40*, doi:10.1093/sleep/zsw073.
7. Walker, M.P.; Van Der Helm, E. Overnight Therapy? The Role of Sleep in Emotional Brain Processing. *Psychol. Bull.* **2009**, *135*, 731–748, doi:10.1037/a0016570.
8. Hertenstein, E.; Feige, B.; Gmeiner, T.; Kienzler, C.; Spiegelhalder, K.; Johann, A.; Jansson-Fröjmark, M.; Palagini, L.; Rücker, G.; Riemann, D.; et al. Insomnia as a Predictor of Mental Disorders: A Systematic Review and Meta-Analysis. *Sleep Med. Rev.* **2019**, *43*, 96–105, doi:10.1016/j.smrv.2018.10.006.
9. Morin, C.M.; Benca, R. Chronic Insomnia. *The Lancet* **2012**, *379*, 1129–1141, doi:10.1016/S0140-6736(11)60750-2.
10. Riemann, D.; Spiegelhalder, K.; Espie, C.; Pollmächer, T.; Léger, D.; Bassetti, C.; Van Someren, E. Chronic Insomnia: Clinical and Research Challenges - An Agenda. *Pharmacopsychiatry* **2010**, s-0030-1267978, doi:10.1055/s-0030-1267978.
11. Brown, R.E.; Basheer, R.; McKenna, J.T.; Strecker, R.E.; McCarley, R.W. Control of Sleep and Wakefulness. *Physiol. Rev.* **2012**, *92*, 1087–1187, doi:10.1152/physrev.00032.2011.
12. Meerlo, P.; Sgoifo, A.; Suchecki, D. Restricted and Disrupted Sleep: Effects on Autonomic Function, Neuroendocrine Stress Systems and Stress Responsivity. *Sleep Med. Rev.* **2008**, *12*, 197–210, doi:10.1016/j.smrv.2007.07.007.
13. Van Someren, E.J.W. Brain Mechanisms of Insomnia: New Perspectives on Causes and Consequences. *Physiol. Rev.* **2021**, *101*, 995–1046, doi:10.1152/physrev.00046.2019.
14. Harvey, A.G. A Cognitive Model of Insomnia. *Behav. Res. Ther.* **2002**, *40*, 869–893, doi:10.1016/S0005-7967(01)00061-4.
15. Morin, C.M.; Bei, B.; Bjorvatn, B.; Poyares, D.; Spiegelhalder, K.; Wing, Y.K. World Sleep Society International Sleep Medicine Guidelines Position Statement Endorsement of "Behavioral and Psychological Treatments for Chronic Insomnia Disorder in Adults: An American Academy of Sleep Medicine Clinical Practice Guidelines." *Sleep Med.* **2023**, *109*, 164–169, doi:10.1016/j.sleep.2023.07.001.
16. Borb, A.A.; Achermann, P. Sleep Homeostasis and Models of Sleep Regulation. *J. Biol. Rhythms* **1999**, *14*, 559–570, doi:10.1177/074873099129000894.
17. Burstein, S. Cannabidiol (CBD) and Its Analogs: A Review of Their Effects on Inflammation. *Bioorg. Med. Chem.* **2015**, *23*, 1377–1385, doi:10.1016/j.bmc.2015.01.059.
18. Kamal-Eldin, A.; Pettersson, D.; Appelqvist, L. Sesamin (a Compound from Sesame Oil) Increases Tocopherol Levels in Rats Fed *Ad Libitum*. *Lipids* **1995**, *30*, 499–505, doi:10.1007/BF02537023.
19. Buckley, T.M.; Schatzberg, A.F. On the Interactions of the Hypothalamic-Pituitary-Adrenal (HPA) Axis and Sleep: Normal HPA Axis Activity and Circadian Rhythm, Exemplary Sleep Disorders. *J. Clin. Endocrinol. Metab.* **2005**, *90*, 3106–3114, doi:10.1210/jc.2004-1056.
20. Fernandez-Mendoza, J.; Vgontzas, A.N. Insomnia and Its Impact on Physical and Mental Health. *Curr. Psychiatry Rep.* **2013**, *15*, 418, doi:10.1007/s11920-013-0418-8.

 doi:10.20944/preprints202602.0498.v1

21. Pandi-Perumal, S.R.; Zisapel, N.; Srinivasan, V.; Cardinali, D.P. Melatonin and Sleep in Aging Population. *Exp. Gerontol.* **2005**, *40*, 911–925, doi:10.1016/j.exger.2005.08.009.
22. Bonnet, M.H.; Arand, D.L. Hyperarousal and Insomnia: State of the Science. *Sleep Med. Rev.* **2010**, *14*, 9–15, doi:10.1016/j.smrv.2009.05.002.
23. Varinthra, P.; Anwar, S.N.M.N.; Shih, S.-C.; Liu, I.Y. The Role of the GABAergic System on Insomnia. *Tzu Chi Med. J.* **2024**, *36*, 103–109, doi:10.4103/tcmj.tcmj_243_23.
24. Krueger, J.M.; Frank, M.G.; Wisor, J.P.; Roy, S. Sleep Function: Toward Elucidating an Enigma. *Sleep Med. Rev.* **2016**, *28*, 46–54, doi:10.1016/j.smrv.2015.08.005.
25. Besedovsky, L.; Lange, T.; Haack, M. The Sleep-Immune Crosstalk in Health and Disease. *Physiol. Rev.* **2019**, *99*, 1325–1380, doi:10.1152/physrev.00010.2018.
26. Zendulka, O.; Dovrtělová, G.; Nosková, K.; Turjap, M.; Šulcová, A.; Hanuš, L.; Juřica, J. Cannabinoids and Cytochrome P450 Interactions. *Curr. Drug Metab.* **2016**, *17*, 206–226, doi:10.2174/1389200217666151210142051.
27. Borgwardt, S.J.; Allen, P.; Bhattacharyya, S.; Fusar-Poli, P.; Crippa, J.A.; Seal, M.L.; Fraccaro, V.; Atakan, Z.; Martin-Santos, R.; O'Carroll, C.; et al. Neural Basis of Δ-9-Tetrahydrocannabinol and Cannabidiol: Effects During Response Inhibition. *Biol. Psychiatry* **2008**, *64*, 966–973, doi:10.1016/j.biopsych.2008.05.011.
28. Campos, A.C.; Moreira, F.A.; Gomes, F.V.; Del Bel, E.A.; Guimarães, F.S. Multiple Mechanisms Involved in the Large-Spectrum Therapeutic Potential of Cannabidiol in Psychiatric Disorders. *Philos. Trans. R. Soc. B Biol. Sci.* **2012**, *367*, 3364–3378, doi:10.1098/rstb.2011.0389.
29. Babson, K.A.; Sottile, J.; Morabito, D. Cannabis, Cannabinoids, and Sleep: A Review of the Literature. *Curr. Psychiatry Rep.* **2017**, *19*, 23, doi:10.1007/s11920-017-0775-9.
30. Kaul, M.; Zee, P.C.; Sahni, A.S. Effects of Cannabinoids on Sleep and Their Therapeutic Potential for Sleep Disorders. *Neurother. J. Am. Soc. Exp. Neurother.* **2021**, *18*, 217–227, doi:10.1007/s13311-021-01013-w.
31. Kesner, A.J.; Lovinger, D.M. Cannabinoids, Endocannabinoids and Sleep. *Front. Mol. Neurosci.* **2020**, *13*, 125, doi:10.3389/fnmol.2020.00125.
32. D'Angelo, M.; Steardo, L. Cannabinoids and Sleep: Exploring Biological Mechanisms and Therapeutic Potentials. *Int. J. Mol. Sci.* **2024**, *25*, 3603, doi:10.3390/ijms25073603.
33. Zou, S.; Kumar, U. Cannabinoid Receptors and the Endocannabinoid System: Signaling and Function in the Central Nervous System. *Int. J. Mol. Sci.* **2018**, *19*, 833, doi:10.3390/ijms19030833.
34. Zurier, R.B.; Burstein, S.H. Cannabinoids, Inflammation, and Fibrosis. *FASEB J.* **2016**, *30*, 3682–3689, doi:10.1096/fj.201600646R.
35. Russo, E.; Guy, G.W. A Tale of Two Cannabinoids: The Therapeutic Rationale for Combining Tetrahydrocannabinol and Cannabidiol. *Med. Hypotheses* **2006**, *66*, 234–246, doi:10.1016/j.mehy.2005.08.026.
36. Campos, A.C.; Ferreira, F.R.; Guimarães, F.S. Cannabidiol Blocks Long-Lasting Behavioral Consequences of Predator Threat Stress: Possible Involvement of 5HT1A Receptors. *J. Psychiatr. Res.* **2012**, *46*, 1501–1510, doi:10.1016/j.jpsychires.2012.08.012.
37. Zanelati, T.; Biojone, C.; Moreira, F.; Guimarães, F.; Joca, S. Antidepressant-like Effects of Cannabidiol in Mice: Possible Involvement of 5-HT$_{1A}$ Receptors. *Br. J. Pharmacol.* **2010**, *159*, 122–128, doi:10.1111/j.1476-5381.2009.00521.x.
38. Zuardi, A.W.; Rodrigues, N.P.; Silva, A.L.; Bernardo, S.A.; Hallak, J.E.C.; Guimarães, F.S.; Crippa, J.A.S. Inverted U-Shaped Dose-Response Curve of the Anxiolytic Effect of Cannabidiol during Public Speaking in Real Life. *Front. Pharmacol.* **2017**, *8*, 259, doi:10.3389/fphar.2017.00259.
39. Moltke, J.; Hindocha, C. Reasons for Cannabidiol Use: A Cross-Sectional Study of CBD Users, Focusing on Self-Perceived Stress, Anxiety, and Sleep Problems. *J. Cannabis Res.* **2021**, *3*, 5, doi:10.1186/s42238-021-00061-5.
40. Carrier, E.J.; Auchampach, J.A.; Hillard, C.J. Inhibition of an Equilibrative Nucleoside Transporter by Cannabidiol: A Mechanism of Cannabinoid Immunosuppression. *Proc. Natl. Acad. Sci.* **2006**, *103*, 7895–7900, doi:10.1073/pnas.0511232103.
41. Bazinet, R.P.; Layé, S. Polyunsaturated Fatty Acids and Their Metabolites in Brain Function and Disease. *Nat. Rev. Neurosci.* **2014**, *15*, 771–785, doi:10.1038/nrn3820.

 doi:10.20944/preprints202602.0498.v1

42. Comini, E.; Rubiales, D.; Reveglia, P. Variability of Fatty Acid Composition and Lignan Content in Sesame Germplasm, and Effect of Roasting. *ACS Food Sci. Technol.* **2023**, *3*, 1747–1758, doi:10.1021/acsfoodscitech.3c00304.
43. Hood, S.; Amir, S. The Aging Clock: Circadian Rhythms and Later Life. *J. Clin. Invest.* **2017**, *127*, 437–446, doi:10.1172/JCI90328.
44. O'Sullivan, S.E. Endocannabinoids and the Cardiovascular System in Health and Disease. In *Endocannabinoids*; Pertwee, R.G., Ed.; Handbook of Experimental Pharmacology; Springer International Publishing: Cham, 2015; Vol. 231, pp. 393–422 ISBN 978-3-319-20824-4.
45. Kim, D.-H.; Yoo, T.-H.; Lee, S.H.; Kang, H.Y.; Nam, B.Y.; Kwak, S.J.; Kim, J.-K.; Park, J.T.; Han, S.H.; Kang, S.-W. Gamma Linolenic Acid Exerts Anti-Inflammatory and Anti-Fibrotic Effects in Diabetic Nephropathy. *Yonsei Med. J.* **2012**, *53*, 1165–1175, doi:10.3349/ymj.2012.53.6.1165.
46. Luchtman, D.W.; Song, C. Cognitive Enhancement by Omega-3 Fatty Acids from Child-Hood to Old Age: Findings from Animal and Clinical Studies. *Neuropharmacology* **2013**, *64*, 550–565, doi:10.1016/j.neuropharm.2012.07.019.
47. Yao, J.; Zhang, Y.; Jiao, J. Rewiring Marine N-3 Polyunsaturated Fatty Acids as Circadian Rhythm Regulators for Manipulating Glycolipid Metabolism: Emerging Insights into Molecular Mechanism and Potential Targets. *Curr. Opin. Food Sci.* **2024**, *60*, 101228, doi:10.1016/j.cofs.2024.101228.
48. Liu, H.-Y.; Gu, H.; Li, Y.; Hu, P.; Yang, Y.; Li, K.; Li, H.; Zhang, K.; Zhou, B.; Wu, H.; et al. Dietary Conjugated Linoleic Acid Modulates the Hepatic Circadian Clock Program via PPARα/REV-ERBα-Mediated Chromatin Modification in Mice. *Front. Nutr.* **2021**, *8*, 711398, doi:10.3389/fnut.2021.711398.
49. Saisum, S.; Hudthagosol, C.; Srisorrachatr, S. Effect of Black Sesame Seeds (Sesamum Indicum L.) Consumption on Sleep Quality among Thai Elderly. *Food Appl. Biosci. J.* **2020**, *8*, 68–75.
50. Malekinia, F.; Farbood, Y.; Sarkaki, A.; Khoshnam, S.E.; Navabi, S.P. Sesamin Alleviates Defects in Seizure Behavioral Symptoms and Hippocampus Electroencephalogram in a Pentylenetetrazol Rat Model. *Iran. J. Basic Med. Sci.* **2023**, *26*, doi:10.22038/ijbms.2023.69565.15151.
51. Guo, H.; Xiao, Y.; Tian, Z.; Li, X.; Wang, D.; Wang, X.; Zhang, Z.; Zhao, M.; Liu, S. Anxiolytic Effects of Sesamin in Mice with Chronic Inflammatory Pain. *Nutr. Neurosci.* **2016**, *19*, 231–236, doi:10.1179/1476830515Y.0000000015.
52. Wagner, H.; Ulrich-Merzenich, G. Synergy Research: Approaching a New Generation of Phytopharmaceuticals. *Phytomedicine Int. J. Phytother. Phytopharm.* **2009**, *16*, 97–110, doi:10.1016/j.phymed.2008.12.018.