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The Potential Role of Selected Nutraceuticals (Melatonin, Isoflavones, Vitamin E, Valeriana Officinalis, Withania somnifera) in Mitigating Sleep Disturbances Among Menopausal Women: A Literature Review

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***Abstract*— Sleep disturbances represent one of the most common complaints among menopausal women, affecting up to 60% of this population. They arise from a complex interplay of declining ovarian function, reduced estrogen and progesterone levels, dysregulation of the hypothalamic–pituitary–adrenal axis, and vasomotor symptoms such as hot flushes. Conventional management strategies include cognitive behavioural therapy and hormone replacement therapy; however, concerns regarding safety, particularly in women with elevated cardiovascular or thromboembolic risk, have prompted increasing interest in non-hormonal alternatives. This narrative review evaluates the potential role of selected nutraceuticals—melatonin, isoflavones, vitamin E, Valeriana officinalis, and Withania somnifera—in alleviating sleep disturbances among menopausal women. Evidence suggests that melatonin supplementation may improve sleep onset and maintenance, although dosing requires personalization due to pharmacokinetic variability. Isoflavones, through estrogen-receptor modulation, reduce vasomotor symptoms and indirectly enhance sleep quality. Vitamin E demonstrates antioxidant and vasomotor-stabilizing properties, yet data remain inconsistent. Valeriana officinalis shows direct sedative effects mediated via GABAergic and serotonergic pathways, with clinical studies confirming its efficacy. Withania somnifera exhibits anxiolytic and neuroregulatory actions, partly through modulation of the HPA axis and cortisol reduction, representing a promising but still underexplored intervention. Current evidence supports the potential of these nutraceuticals as adjunctive therapies; however, heterogeneity of study designs, dosing regimens, and methodological limitations preclude definitive recommendations. High-quality randomized controlled trials are essential to establish safety, efficacy, and clinical applicability.**

***Keywords*— menopause, insomnia, sleep disorder, nutraceuticals, Melatonin, Isoflavones, vitamin E, Valeriana officinalis, Withania somnifera**

1.INTRODUCTION

Sleep disturbances are among the most frequently reported complaints in menopausal women, with epidemiological studies indicating that 40–60% of women in this group experience insomnia or impaired sleep quality. [41] These problems are not only associated with reduced quality of life but also contribute to the development of metabolic and cardiovascular diseases. [42] The menopausal transition is therefore considered a critical period for the onset or exacerbation of sleep difficulties. They include difficulty getting to sleep and staying asleep (awakening during the night), early morning wakening, less total sleep time, overall quality of sleep, problems with sense of well-being, overall functioning, fatigue during the day. [43] The mechanisms underlying this process involve the decline in ovarian function, leading to a subsequent decrease in the levels of sex hormones—estradiol and progesterone. [44] Furthermore, the decline in estrogen levels observed in menopausal women has been associated with dysregulation of

circadian cortisol secretion, characterized by elevated evening (27%) and reduced morning cortisol (57%) concentrations. Alterations in the hypothalamic–pituitary–adrenal (HPA) axis linked to these hormonal changes have been implicated in disturbances of sleep architecture within this population. [45] The course of sleep disturbances is also influenced by structural and enzymatic changes within the pineal gland. [1] Bioactive estrogens exert a protective role on the cardiovascular system, and their decline contributes to an increased occurrence of vasomotor symptoms. Particular attention has been directed toward hot flush episodes, which, according to research, are most strongly linked to abrupt decreases in estrogen levels. [46] The presence of hot flushes has been observed to significantly influence the course of sleep disturbances. [16] Current recommendations indicate that cognitive behavioural therapy (CBT) is the standard treatment for sleep disorders among women in the menopausal age. [47] An important aspect also includes maintaining a healthy lifestyle, diet, and smoking cessation. [48] The primary pharmacological treatment is the use of hormone replacement therapy (HRT), particularly in cases where sleep disturbances are associated with severe vasomotor symptoms. [48] However, studies suggest that such therapy is not recommended for women with an increased cardiovascular risk or an elevated risk of thromboembolic disease. [49] Some publications report beneficial effects of selective serotonin reuptake inhibitors (SSRIs), selective noradrenaline reuptake inhibitors (SNRIs), and gabapentin in reducing vasomotor symptoms. Consequently, women are seeking alternatives that are more accessible and safer.

Against this background, exploring the efficacy and mechanisms of non-hormonal interventions, including melatonin, phytoestrogens, vitamins, and herbal preparations, is of particular clinical and scientific interest.

2. METHODS

An in-depth literature review was performed using PubMed and Google Scholar, including keywords such as: “menopause sleep disorders”, “menopause melatonin”, “menopause isoflavones”, “menopause vitamin E”, “menopause Valeriana officinalis”, “menopause Withania somnifera”.

3. NUTRACEUTICALS

A. Melatonin

The level of melatonin secreted by the pineal gland declines with age. [1] Several factors contribute to this phenomenon, one of which is the alteration in the concentration of enzymes involved in melatonin synthesis. AANAT (arylalkylamine N-acetyltransferase) is the key rate-limiting enzyme in the synthesis of melatonin in the pineal gland. It converts serotonin into N-acetylserotonin, which is then methylated to melatonin. AANAT activity is tightly regulated by circadian signals. With aging, the expression and enzymatic activity of AANAT progressively decrease. In older individuals, the phosphorylated, stable form of AANAT is significantly reduced, and its interaction with stabilizing proteins weakens, leading to faster degradation. This decline is a major factor contributing to lower nocturnal melatonin levels and a flattened circadian rhythm in the elderly. [2] With advancing age, the suprachiasmatic nucleus (SCN), the central circadian pacemaker, undergoes a progressive decline in function. Both the number of SCN neurons and the rhythmic expression of key neuropeptides decrease, accompanied by alterations in glucose metabolism. These changes weaken the circadian signals transmitted to the pineal gland, resulting in a reduced amplitude of the melatonin rhythm. Consequently, this attenuation contributes to more frequent sleep disturbances and increased fragmentation of daily activity patterns in older individuals. [3] During the menopausal transition, melatonin supplementation may aid in sleep onset and maintenance, especially in the context of hormonal changes and circadian rhythm disruptions. However, studies show significant variability in the recommended dosages. [4] They underscore the importance of individual variability in

melatonin pharmacokinetics. Therefore, melatonin dosing should be personalized. [5] Among the group of women starting with poor quality of sleep, the supplementation of small doses of melatonin trended towards improving the quality. [6] Starting with low doses (e.g., 0.3–1 mg) and adjusted as needed. In some cases, the endogenous melatonin may already be elevated due to drug interactions, making supplementation unnecessary or requiring lower doses to avoid supraphysiological levels. [5] Side effects of melatonin include daytime sleepiness, headache, nausea, and dizziness. [37]

B. Isoflavones

Isoflavones are a group of substances of plant and animal origin. Under the influence of intestinal enzymes, they are broken down into precursors such as genistein and daidzein. They exhibit estrogen-like effects due to their structural similarity to 17-β-estradiol (E2). [15] They act on two types of estrogen receptors, ERα and ERβ. They have a higher affinity for ERβ receptors, which are found in the cardiovascular, genitourinary systems, and bones. According to in vitro studies, the activity of genistein and daidzein compared to estrogen is as follows: estrogen - 100, genistein – 0.084, and daidzein – 0.013. [14] It is believed that estrogen affects the temperature-regulating centers located in the brain. Therefore, fluctuations occurring during the menopausal period result in disturbances of this mechanism, presenting as hot flushes and night sweats. [16] Women in menopausal age presenting with insomnia should be routinely assessed for the occurrence of hot flushes, as their management may enhance sleep quality and help reduce the adverse effects associated with chronic insomnia. [25] A meta-analysis of eight clinical trials demonstrated that administering isoflavones at a dose of 80 mg/day for 12 weeks in postmenopausal women experiencing five or more hot flushes daily resulted in a statistically significant reduction in symptom frequency compared with the placebo. The weighted mean difference (WMD) was −1.73 hot flushes per day, with a 95% confidence interval (CI) ranging from −3.28 to −0.18 ($p = 0.0292$). [17] In another publication, a meta-analysis of 10 randomized controlled trials, based on data available up to 2013, assessed the effect of phytoestrogens on hot flushes in midlife women. The mean age ranged from 49 to 58.3 years in the placebo group and from 48 to 60.1 years in the phytoestrogen group. The number of participants ranged from 30 to 252, and the intervention periods varied between 3 and 12 months. The pooled analysis demonstrated that phytoestrogens were associated with a significantly greater reduction in the frequency of hot flushes compared to placebo (pooled mean difference = 0.89; $p < 0.005$). [18] Based on a meta-analysis of five studies, the incidence of adverse effects was assessed in both the intervention and placebo groups. The analysis revealed no statistically significant difference between the groups ($p = 0.175$). [18] In a randomized controlled trial, the direct impact of isoflavone supplementation on sleep quality and the occurrence of insomnia among menopausal women was investigated. Participants in the intervention group received 80 mg/day of isoflavones for a period of four months. This group demonstrated a reduction in the incidence of hot flushes and in the frequency of sleep disturbances. Polysomnographic assessments revealed an improvement in sleep efficiency in the isoflavone group (from 77.9% to 83.9%) compared with the placebo group (from 77.6% to 81.2%). [33]

Due to their estrogen-like structure, the potential relationship between isoflavones and the risk of developing hormone-dependent cancers may be a subject of discussion. According to meta-analyses published in recent years (2020–2024), isoflavone supplementation may contribute to a reduced risk of breast ([20][21][22][24]), ovarian, and endometrial cancers [19], as well as exert potential antiangiogenic effects [23] However, an increased risk of thyroid cancer has been observed (OR = 1.24, 95% CI: 1.03-1.50)[19]

C. Vitamin E

Vitamin E is a lipid-soluble compound of plant origin. [26] Two main isoforms of vitamin E are tocopherol and tocotrienol. [27] It is abundant in seeds, fruits, and green leafy vegetables, though supplements often provide much higher doses than food sources. Its roles include antioxidant activity (neutralizing free radicals), maintaining membrane stability, regulating enzyme activity and gene expression, inhibiting platelet aggregation, and supporting the prevention of certain diseases such as cardiovascular and neurodegenerative disorders, eye and skin aging, and infertility. Tocotrienols, a form of vitamin E, may offer additional benefits, such as enhancing immune function and reducing cholesterol levels. [26] The primary mechanism attributed to vitamin E in potentially improving sleep quality is its ability to reduce oxidative stress. Supplementation with vitamin E helps maintain adequate blood levels of glutathione peroxidase while suppressing malondialdehyde concentrations. [32]

In a literature review of 16 studies, the effects of vitamin E supplementation in menopausal women were analyzed. The research examined its impact on postmenopausal vasomotor symptoms, plasma lipid profile, vascular, psychiatric, neurological, and vaginal changes. However, due to variations in dosage and inconsistencies in the data, definitive conclusions cannot be drawn at this time. [28] A double-blinded, randomized, placebo-controlled trial conducted by Wirun Thongchumnum in 2023 evaluated the effect of oral administration of mixed tocopherols on postmenopausal women with chronic insomnia disorder. Participants who received 400 IU of mixed tocopherols daily for one month demonstrated significant improvements in sleep quality compared to the placebo group. [29] In a triple-blind, randomized controlled trial conducted in 2020 (Khatereh Ataei-Almanghadim), a cohort of postmenopausal women received vitamin E supplementation at a dose of 200 IU per day for a period of eight weeks. The primary outcome was the frequency of hot flushes, which are known to adversely affect sleep quality in this stage of life. [25] No statistically significant differences were observed between the intervention and control groups after four weeks of supplementation. However, by the end of the eight-week intervention, a significant reduction in hot flush frequency was recorded among participants in the vitamin E group. [30] At present, the available data are very limited, and vitamin E supplementation cannot be unequivocally recommended for postmenopausal women. Further well-designed studies are required to clearly confirm its beneficial effects on sleep. Regarding safety, particular attention has been given to an increase in the risk of haemorrhagic stroke in administration of high dosage, [31] likely due to its antiplatelet properties.

D. Valeriana officinalis

Valeriana officinalis is an herb that has been used for centuries in medicine. Among its benefits are sedative, spasmolytic, tranquilizing, as well as anti-inflammatory and antioxidant effects. [37] The primary compound responsible for these actions is valerenic acid. [38] It has a pivotal role in its hypnotic mechanism by acting as a positive allosteric modulator of GABA A. [39] Furthermore, extracts of Valeriana officinalis demonstrate high binding affinity to serotonergic receptors within the suprachiasmatic nucleus (SCN), a key regulatory centre of the circadian sleep–wake cycle. [40] In a randomized controlled trial conducted by Simin Taavoni et al. (2011), postmenopausal women aged 50–60 years experiencing insomnia were enrolled. Participants in the intervention group received 530 mg of valerian extract twice daily for four weeks. At the end of the intervention, a 30% improvement in sleep quality was observed in the treatment group compared with a 4% improvement in the placebo group. [34] In another randomized trial by Ensiyeh Jenabi et al. (2023), postmenopausal women were randomly assigned to receive either 500 mg fennel–valerian extract capsules twice daily for eight weeks or placebo. After two months, assessment with the Pittsburgh Sleep Quality Index (PSQI) demonstrated a reduction in hot flush frequency as well as an improvement in overall sleep quality in the intervention group compared with placebo. [35] Furthermore, in a double-blind clinical trial conducted by Parvaneh Mirabi and Faraz Mojab (2013), menopausal women experiencing hot flushes were administered 255 mg valerian capsules three times daily for eight weeks. The analysis showed a significant reduction in hot flush severity in the intervention group, whereas no statistically significant changes were observed in the placebo group. [36]

E. Withania somnifera

In recent years, *Withania somnifera*, also known as Ashwaghanda, has become more well-known for its anxiolytic and neuroregulatory properties. [7], which may be beneficial in addressing sleep disturbances in menopausal women. The menopausal period is characterized by hormonal changes, specifically related to a decrease in estrogen levels, resulting in many symptoms like mood swings, anxiety, and stress. [8] Due to its documented effect on the hypothalamic–pituitary–adrenal (HPA) axis and reducing cortisol levels, ashwagandha may help improve sleep quality and continuity. [9] In a randomized, double-blind, placebo-controlled study, after 60 days of 240mg of a standardized ashwagandha extract intake once daily, a statistically significant 23% reduction in cortisol was observed over time. [12] It is also thought to induce sleep through GABAergic activity. [10] The mechanism is the promotion of expression of the $GABA_A$, $GABA_B$ receptors and their proteins. It significantly increased after four weeks of oral administration of Withania somnifera [11]. The present experimental study demonstrated that supplementation with Withania somnifera significantly increased estrogen levels and induced a slight elevation in progesterone levels in rats [13]. Due to the inherent limitations of the study, including the use of an animal model, these findings cannot be directly extrapolated to the human population. Further well-designed clinical trials

involving peri- and postmenopausal women are warranted to verify the potential application of Withania somnifera as a dietary supplement for alleviating sleep disturbances in this demographic.

4. CONCLUSIONS

Sleep disturbances are highly prevalent among menopausal women, largely due to hormonal fluctuations, circadian rhythm dysregulation, and the presence of vasomotor symptoms. A range of pharmacological and non-pharmacological interventions have been explored to address this issue. Among supplements, melatonin, phytoestrogens (isoflavones), vitamin E, Valeriana officinalis, and Withania somnifera demonstrate potential benefits in improving sleep quality in this population. Melatonin supplementation may support sleep onset and maintenance, although inter-individual variability and potential interactions necessitate a personalized dosing strategy. Isoflavones, through their estrogen-like effects, can reduce vasomotor symptoms such as hot flushes, indirectly improving sleep continuity. Vitamin E shows promising antioxidant and vasomotor-stabilizing properties, but current evidence is limited and inconsistent. Valeriana officinalis exerts direct sedative and sleep-enhancing effects via GABAergic modulation and serotonergic receptor activity in the suprachiasmatic nucleus, with clinical studies confirming its efficacy in postmenopausal women. Withania somnifera acts through modulation of the HPA axis, cortisol reduction, and possible GABAergic mechanisms, representing a novel and promising approach. Although these findings indicate therapeutic potential, the heterogeneity of available studies, variations in dosage, and methodological limitations restrict the possibility of drawing firm recommendations. Further high-quality, randomized controlled trials are required to determine optimal dosing, long-term safety, and clinical applicability of these supplements in the management of menopausal insomnia.

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