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Rosmarinic Acid - A Potential Therapeutic Agent for Sleep Disorders

Review Article

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Abstract

Rosmarinic acid (RA) is a naturally occurring polyphenolic compound found in numerous plants, such as rosemary, salvia, lemon balm, mint, and oregano. It has various pharmacological effects, including antioxidant, anti-inflammatory, anti-aging, antiviral, antibacterial, antidepressant, and sleep-inducing properties. Rosmarinic acid is used in the food industry as a natural preservative and flavour enhancer, in addition to its potential health benefits. The oral bioavailability of RA ranges between 0.91 and 1.61 percent. After oral administration, rosmarinic acid is rapidly absorbed, with peak plasma concentrations occurring within 1-2 hours. The half-life reported for RA is relatively short ranging from 0.75 to 1 hour. Phase II enzymes, such as glucuronidation and sulfation, predominantly metabolise RA in the liver following absorption. These metabolic pathways lead to the formation of numerous conjugated metabolites, which are excreted in the urine and faeces. The bioavailability of RA can vary based on its source, formulation, as well as individual differences in metabolism and other factors. Several studies suggest that RA may have a positive impact on sleep quality, as RA administration has been shown to improve sleep quality, decrease sleep latency, and increase the duration of deep sleep via its effect on the GABAergic system. Moreover, RA has also been shown to have anti-anxiety and calming effects, which may contribute to its sleep-inducing properties. Additional research is necessary to fully comprehend the effects of RA on sleep, including its optimal dose, duration of use, and potential side effects.

Introduction

Rosmarinic acid (RA) is a phenylpropanoid compound formed from the dimer of caffeic acid and 3,4-dihydroxyphenyl lactic acid, bound by an ester linkage [1]. Rosmarinic acid is found in several plants of the Lamiaceae family like rosemary, salvia, lemon balm, mint, oregano, etc. Rosmarinic acid was isolated for the first time in 1958 from the rosemary plant (Rosmarinus officinalis L.). Rosmarinic acid has been reported to possess several biological properties like antioxidant, anti-inflammatory, anti-aging, antiviral, antibacterial and antidepressant effects[1]. Additionally, RA has been shown to have a positive impact on sleep quality and reduce the severity of insomnia [2] [Figure1].

Rosmarinic acid is a reddish-orange powder that is well soluble in the majority of organic solvents but largely insoluble in water [1]. For thousands of years, people have used plants with high levels of RA in food and medicine. There are many dietary supplements on the market that are concentrated with the active component of RA, such as Melissa officinalis (lemon balm), Perilla frutescens (perilla extract), and Salvia rosmarinus (rosemary extract) [3-5].

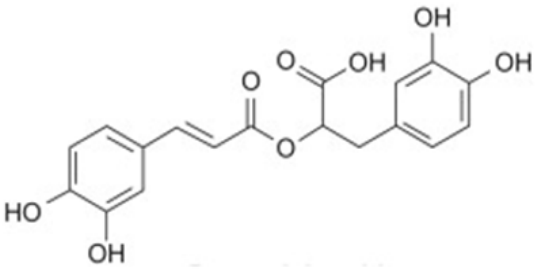

Figure 1: Structure of Rosmarinic acid

Materials and Methods

Search Results: Overall 154 research papers were extracted based on

a thorough search from Pubmed. The search was done using keywords like (rosmarinic acid) AND (pharmacokinetics) which gave 137 papers, whereas the keywords (rosmarinic acid) AND (sleep) gave 17 papers. One Hundred Thirty-Seven (137) papers were screened thoroughly to write the review section on pharmacokinetics of rosmarinic acid. From the list of 17 papers on (rosmarinic acid) AND (sleep), this systematic review contained 7 appropriate study papers.

Characteristics of the Included Studies: All 7 studies were included in this review. The main topic of most of these studies was the effect of rosmarinic acid on sleep. Four studies were done in rodents to show mechanistic evidence of rosmarinic acid on sleep, while 3 were clinical studies done in human subjects. The clinical studies samples ranged in size from 20 to 89 subjects. These three clinical studies were conducted in Italy, USA and Iran.

Pharmacokinetics of Rosmarinic acid

Absorption: Rosmarinic acid can be administered by oral, topical, pulmonary and intranasal routes. Studies of RA absorption conducted in vitro and in vivo reveal that its intestinal permeability was substantially lower than that of the administered dose, at about 1% [6, 7] and it was absorbed by enterocytes by paracellular transport in tight junctions [8].

The absolute oral bioavailability of RA was observed in the range from 0.91% to 1.69% [9]. The maximum serum concentration was seen as 72.22 ± 12.01nmol/ L with 250mg dose of RA and 162.20 ± 40.20nmol/ L with 500mg dose of RA at 1 hour after administration from M. officinalis extract [10]. Further, after consumption of 200mg RA from Perilla extract in a fasted state, a peak concentration of 1.15 ± 0.28 umol/L was seen in plasma after 30 minutes [11].

Since topical treatments often contain RA-rich extracts, skin absorption is also being researched. The epidermis is where RA builds up, according to an ex vivo investigation on intact human skin; penetration into the hydrophilic dermis may essentially be ignored. Olive oil may have natural penetration enhancers because higher levels of RA were found when it was added in the formulation [12].

Distribution: As rosmarinic acid is largely insoluble in water [13], plasma proteins carry it throughout the circulatory system. In vitro research on the interaction between RA and human serum albumin revealed that RA is most likely carried via these proteins. A reasonably strong connection is created between these proteins and RA as a result of hydrophobic interactions [14, 15]. RA was discovered in soft tissues of internal organs like the spleen, liver, lungs, and heart after being injected into rats. Rats treated topically for RA developed dispersion into their blood, skin, bones, and muscles. Following intraperitoneal injection to mice, the kidneys were found to have the highest concentration of RA, followed by the lungs, spleen, and liver [16]. Another noteworthy aspect of RA's distribution is the level of focus obtained in the brain. The evidence shows that the hematoencephalic barrier effectively prevents entrance into the central nervous system [16]. To overcome the blood-brain barrier and reach larger concentrations in the brain, a targeted method using a specific pharmaceutical formulation via intranasal administration also results in a reduction in the amount of RA that is disseminated to be digested.

Metabolism: The breakdown of RA into 2 phenolic acids would enable further absorption, and it was shown in vitro in Caco-2 cell culture that microbial esterases, rather than the esterase found in the mucosa of the intestinal tract, were responsible for cleaving the bond of the RA molecule [17].

Some of the investigations looked into how the content of RA was impacted by gut bacteria. In one investigation, microorganisms from rat faeces were used to do an in vitro colonic fermentation of a rosemary extract containing RA. It has been shown that this process results in the loss of 14% of the RA content. In contrast, a different study found that under ideal circumstances probiotic Lactobacillus strains may hydrolyze an even higher proportion of RA (> 90%) in vitro [18]. Finally, a study was conducted to in vitro ferment the phenolic chemicals found in thyme (Thymus vulgaris) using samples from human faeces. After 6 hours of fermentation, RA content quickly decreased, and by 12 hours, it had been reduced to trace levels. The amount of RA found in human participants' faeces after drinking olive oil enhanced with thyme for three weeks was also examined as part of the same study. This investigation revealed no RA, confirming a significant level of gastrointestinal tract deterioration [19].

Preliminary information on the metabolites that are likely to show up in plasma and urine was provided by studies done on rats [20-22]. Later studies have revealed that although the primary metabolic pathways are quantitatively somewhat different, the majority of the metabolites found in human participants are the same. Some of the in vitro results acquired in Caco-2 and Hep G2 cell cultures, which serve as models of the small intestine and liver, respectively, showed that both the pure substance and rosemary extracts containing RA can be partially absorbed and metabolised in the aforementioned cells [23]. The most likely metabolites of RA were identified by the metabolites found in this investigation [23], as well as the study assessing the metabolism of RA in human liver microsomes [24]. These metabolites were also confirmed in experiments on human volunteers. When food and RA are consumed simultaneously, the plasma concentration of RA decreases somewhat and it takes longer to reach its maximal level. Additionally, the substance can be found as a sulphate, glucuronide, and/or sulphoglucuronide [11]. The primary metabolic pathway for RA, according to an in vitro investigation using human liver microsomes, is glucuronidation. It became clear from comparing the two dosages (250mg and 500mg of RA) that an increase in dosage was followed by an increase in the concentration of free RA, whilst the concentration of conjugated forms rose barely at all. All of this points to saturation kinetics as the defining characteristic of conjugational processes [10].

A conjugation reaction of RA methoxylation also takes place concurrently with the mechanisms previously outlined, making it possible to identify methyl conjugate (met-RA) in blood. The highest concentration of this molecule (0.65±0.07mol/L, following a dosage of 200mg of RA) is reached 2 hours after consumption due to the slower metabolic reaction [11]. It is interesting to note that met-RA glucuronide was identified as the primary marker metabolite of RA's sub-chronic consumption in a study after a 30-day intake of spearmint (Mentha spicata) extract high in RA [25].

Further research on the caffeic acid region of the RA structure's metabolism revealed many metabolites produced by different processes. Blood was shown to contain ferulic acid [10]. The hydroxyl group of this molecule may be further sulphated and methoxylated [11], and it is a by-product of the catabolism of RA by caffeic acid. This reaction occurs quickly, much as the conjugation of RA (detection 0.5 hours after administration of 200mg of RA revealed 0.36±0.17 mol/L) [10]. 2,4,5-trimetoxycinnamic acid was found in human plasma to be another catabolic product. This substance is likewise broken down by RA's caffeic acid, but it proceeds through hydroxylation, dihydroxylation, and methoxylation processes instead [22]. Additionally, m-coumaric acid and its conjugates can be produced by human beings' metabolism of the caffeic acid segment [11]. Additionally, a study conducted in vitro suggested that 2-(3,4-dihydroxyphenyl)propionic acid is a crucial intermediate substance [21]. The first metabolic pathway, specifically, results in the formation of phenylacetic acid as seen in an in vitro study of RA fermentation with human faecal samples [21], whereas the second metabolic pathway results in the formation of protocatechuic acid as seen in human subjects consuming Origanum onites extract containing RA [26]. Vanillic acid and its sulphate conjugate or p-hydroxybenzoic acid are the next two chemicals that

can be produced from the latter substance [25,26]. However, it is most likely that enzymatic processes in the hepato-intestinal tract and bacteria combined to produce the metabolites.

Excretion: Studies in rats have shown an elevated RA content in the kidneys, indicating renal clearance; certain metabolites were also discovered in the bile [27]. Following oral administration to humans, free, conjugated, and methyl-RA were found in the urine of healthy volunteers. Lower quantities of caffeine, ferulic, 2,4,5-trimetoxycinnamic acid, m-coumaric acid, vanillic, and p-hydroxybenzoic acid were also discovered [11, 22, 26]. The elimination is likewise quick, much like the metabolism. In particular, the majority of metabolites are largely removed within 6 hours of consumption, but it becomes more difficult to detect evidence of other metabolites after 24 to 48 hours [11]. Specifically, a steady state is reached with continuous infusion, but after the infusion is stopped, a rapid reduction in the blood concentrations of RA and its metabolites and an increase in their levels in urine are seen.

The elimination half-life of RA taken by the oral route as per the pharmacokinetic study in rats was reported to be 63.68±1.11 minutes [28]. The analgesic effects of rosmarinic acid seen at doses of 50 and 100 mg/kg were reduced during the experiment over time indicating the short half-life of this molecule reported to be about 45 minutes [29].

Rosmarinic acid for sleep

In addition to being a biological requirement, sleep also has a physiological urge. The consequences of not getting enough sleep go beyond minor inconveniences; they also have an impact on our mood and performance at job, school, home, and while driving. Additionally, lost sleep builds up over time; according to experts in the field, the more "sleep debt" a person accumulates, the worse the effects become [30].

Sleep is crucial for several brain processes, including the communication between neurons. Several organs of the body including brain, heart, and lungs, as well as the metabolism, immune system, mood, and resistance to disease, are all impacted by sleep. According to research, illnesses like high blood pressure, cardiovascular disease, diabetes, depression, and obesity are all made more likely by persistent sleep deprivation.

There are five stages of sleep: waking, N1, N2, N3, and REM. Non-rapid eye movement (NREM) sleep is categorised into stages N1 through N3, with each stage corresponding to a deeper state of sleep. The NREM stages account for about 75% of sleep, with the N2 stage accounting for the majority of share [31]. The progression of the various stages of sleep occurs in the following order: N1, N2, N3, N2, REM, during the course of 4 to 5 sleep cycles in a typical night. A typical sleep cycle lasts between 90 and 110 minutes. The first REM phase is brief, and as the night goes on, longer REM phases and less time in deep sleep (NREM) take place [32].

The inhibitory neurotransmitter known as GABA plays an important role in sleep. It is one of the inhibitory neurotransmitters and is crucial for the central nervous systems' ability to regulate sleep. Both REM and NREM sleep cause the rostral hypothalamus GABA-ergic neurons to fire. Inhibitory neurons that release GABA make up the majority of the preoptic/anterior hypothalamic area, which has been discovered to be a powerful sleep-improving location [33]. The GABA receptors are composed of five pentameric subunits each with four membrane-spanning domains chosen from a variety of polypeptide classes. GABA appears to interact between and at two places, causing chloride channels to open and cause membrane hyperpolarization as a result [34]. When benzodiazepines bind at a single location between and subunit, it helps mice open their chloride ion channels. According to some theories, benzodiazepine's sedative, amnesic, and ataxic effects are caused by its 1 subunit at $GABA_A$ receptors, whereas its 2 and 3 subunits are responsible for its anxiolytic and muscle-relaxing properties [35,36]. However, glutamic acid decarboxylase (GAD65/67), an enzyme that produces GABA, also plays a significant role in sleep [37]. The synapse, or extracellular region between the neurons, receives GABA release. Cl ion channels open and the intracellular influx of Cl ions increases when released GABA is linked to postsynaptic $GABA_A$ receptors, causing the cells to become hyperpolarized and induce anti-anxiety or sleep [38].

In the study conducted by Kwon et al. 2017 [39], Perilla frutescens containing rosmarinic acid was used to determine whether it may improve pentobarbital-induced sleep in rodents by activating $GABA_A$ receptors. The study showed that RA increased the total sleep time and decreased sleep latency in mice who received pentobarbital at a dose of dose of 42 mg/kg intraperitoneally (i.p.). After receiving sub-hypnotic pentobarbital dose of 28 mg/kg i.p., RA also enhanced the amount of time spent sleeping and the number of sleeping mice. Further, RA at the dose of 2.0 mg/kg showed an increase in total and NREM sleep in rats with an increase in δ-waves and the decrease in α-waves during electroencephalogram (EEG) recording while simultaneously reducing the counts of sleep/wake cycles and REM sleep. Rosmarinic acid at the dose of 0.5, 1.0 and 2.0 mg/kg decreased the locomotor activity in mice. The protein expression of GAD65/67 and all other $GABA_A$ receptor subunits, with the exception of subunit 1, was elevated by oral administration of RA in mice. Additionally, the primary cultured hypothalamus cells of rats showed enhanced intracellular chloride ion influx in response to RA at doses of 0.1, 1.0, and 10 ug/ml. The study concluded that has RA has positive effects on treating insomnia through GABA-ergic systems.

In the study conducted by Kim et al. 2022 [40], a pentobarbital-induced sleep test, electroencephalography/electromyography (EEG/EMG), and immunohistochemistry were used in mice to assess the hypnotic effect of rosmarinic acid. The mechanistic studies were carried out by using 8-cyclopentyl-1,3-dipropylxanthine (DPCPX) and SCH5826, antagonists for adenosine A1R and A_2AR, respectively and receptor binding assays. With a Ki of 14.21 ± 0.3 uM and agonistic activity for A1R, rosmarinic acid shows direct binding action. Additionally, rosmarinic acid considerably reduced the amount of fragmented sleep and the onset latency of NREM sleep, and that DPCPX completely reversed these effects. Rosmarinic acid increased neuronal activity in the ventrolateral preoptic nucleus, a region that promotes sleep, while decreasing neuronal activity in wake-promoting brain regions, such as the basal forebrain and the lateral hypothalamus, according to the results of c-Fos immunostaining. All of these effects were significantly inhibited by DPCPX.

The postmenopausal cholinergic deficit may be the cause of sleep disturbance and cognitive impairment in menopausal women. The protective effects of rosmarinic acid on brain activity, memory, and cholinergic indicators in ovariectomized rats were assessed in the study by Kantar et al. 2022 [41]. Four weeks treatment with RA improved the oscillatory power and amplitude variations were considerably improved in ovariectomized rats. Further, rats in the RA group showed higher object localization memory index than the untreated rats. The RA treated group showed decreased acetylcholinesterase activity and elevated acetylcholine levels compared to the untreated group.

The experiment conducted by Zhang et al. 2021 [42] evaluated the effects of a mixture of L-theanine (L-THE) 20% and Neumentix proprietary spearmint extract (PSE) rich in rosmarinic acid 14.5–17.5% and total phenolphenols 24–37% on sleep using a series of four experiments: direct sleeping test, pentobarbital-induced sleeping test, sub-hypnotic pentobarbital-induced sleeping test, and sodium barbital-induced sleeping test. Liquid chromatography mass spectrometry (HP LC-MS) was used in these experiments to identify the presence of neurotransmitters in brain tissue. When given in combination with pentobarbital or sodium barbital, L-THE and L-THE/PSE mixture reduced sleep latency and increased sleep duration. When administered in conjunction with sub-hypnotic doses of pentobarbital, the mixture also accelerated the process of falling

asleep. Additionally, the brain's acetylcholine (Ach), -aminobutyric acid (GABA), and serotonin (5-HT) concentrations were all significantly altered by L-THE, PSE, and L-THE/PSE. These findings concluded that the GABA receptor and neurotransmitter systems are involved in the regulation of sleep disorders by the L-THE/PSE mixture.

In the clinical study conducted by Tubbs et al. 2021 [2], polyphenol botanical blend (PBB) containing 65mg rosmarinic acid and epigallocatechin gallate, and no more than 4.85mg of caffeine was assessed for its effect in improving sleep and daytime functioning in individuals with subclinical sleep disturbances. A double-blind, randomised experiment with PBB (n = 43) or a placebo (n = 46) was conducted on 89 individuals over the period of 30days. Changes in mood, neurocognitive functioning, and sleep (as measured by a sleep diary and an activity tracker) were observed in the participants. When compared to placebo after 30days, PBB increased the quality of diary sleep ($p = 0.008$) and decreased the severity of insomnia ($p = 0.044$). Other variations in sleep quality weren't noticed. Additionally, PBB had no negative effects on neurocognitive performance, and there was even modest improvement in risk assessment, working memory, and vigilant attention. When compared to a placebo, PBB enhanced neurocognitive functioning, sleep quality, and the severity of insomnia in those with subclinical sleep disorders. These results suggest that polyphenols might be helpful for enhancing some elements of sleep without impairing neurocognitive performance.

Another clinical study conducted by Cases et al. 2010 [43] evaluated the effectiveness of Cyracos® in a prospective, open-label, 15-day supplementation on twenty anxious volunteers who were under stress and had mild to moderate sleep problems. Primary results indicated symptom improvement when using clinician rating criteria. Cyracos® was standardized to contain at least 7% rosmarinic acid and 15% hydroxycinnamic acid derivatives. Cyracos® at the dose of 600mg improved anxiety-related symptoms by 15% ($p<0.01$), decreased sleeplessness by 42% ($p<0.01$), and decreased anxiety manifestations by 18% ($p<0.01$). Up to 95% of the individuals (19/20) showed improvement after receiving treatment, with full remission for anxiety occurring in 70% (14/20), sleeplessness in 85% (17/20), and both in 70% (14/20) of the cases. This was the first study to show that prolonged administration of Melissa officinalis L. reduced the negative consequences of stress. The study was limited due to absence of the placebo group and an open label study design.

The randomized, double-blind, placebo controlled clinical study conducted by Nematolahi et al. 2018 [44] evaluated the effects oral consumption of Rosmarinus officinalis L. on memory performance, anxiety, depression, and sleep quality in university students. In this study, 34 students received 500mg rosemary whereas other 34 students received placebo supplementation for one month. The Pittsburgh Sleep Quality Inventory, the Hospital Anxiety and Depression Scale, and the Prospective and Retrospective Memory Questionnaire were used to assess the students' prospective and retrospective memory performance, depression, anxiety, and sleep quality at baseline and one month later. The study findings showed that rosemary significantly improved memory function, decreased anxiety and despair, and improved sleep quality in college students.

Discussion

Rosmarinic acid is found naturally in several plants like rosemary, sage, Spanish sage, lemon balm, oregano, basil, marjoram, spearmint, peppermint and thyme. Most of these plants have been used as a folk remedy for sedation in oriental countries. Several biological properties, including antidepressant, antioxidant, anti-inflammatory, anti-aging, antiviral, and antibacterial effects, have been attributed to rosmarinic acid [28]. Sleep is a mentally and physically sedentary state. It is characterised by altered consciousness, relatively inhibited sensory activity, decreased muscle activity, and decreased environmental interactions. Insomnia is a common sleep disorder that is characterised by persistent difficulties with sleep onset, maintenance, consolidation, or overall quality. It has also been shown that elevated stress levels affect the structural organisation of sleep, including the duration of each sleep phase. People with chronic stress may spend less time in deep sleep and experience disruptions during REM sleep [45]. Rosmarinic acid has been shown to improve sleep quality and reduce the severity of insomnia [33].

Several in-vitro and animal studies have shown the positive effect of rosmarinic acid on sleep through an increase in total sleep time, decrease in sleep latency, increase in total and NREM sleep in rats with an increase in δ-waves and the decrease in α-waves, increase in GAD65/67 and $GABA_A$ receptor subunits. Further, rosmarinic acid also showed adenosine A1 receptor agonistic activity promoting the hypnotic effects[40]. Additionally, RA showed decreased acetylcholinesterase activity and elevated acetylcholine, GABA, and serotonin (5-HT) concentrations in the rat brain.

Positive impact of rosmarinic acid has been demonstrated in several human clinical studies where RA has shown to improve sleep quality and reduce the severity of insomnia in individuals with subclinical sleep disorders. Further, RA showed an improvement in anxiety-related symptoms, decreased sleeplessness and anxiety in subjects under stress and mild to moderate sleep problems. It also improved the memory function, decreased anxiety and despair, and improved quality of sleep in college students.

Conclusion

Based on the evidence from animal and human clinical studies, rosmarinic acid has the potential to become one of the most promising ingredients for treating sleep disorders. Further research is needed to fully understand the effects of rosmarinic acid on sleep, including its optimal dose, duration of use, and potential side effects in humans.

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