Review

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The Potential of Polyphenols Derived from *Satureja montana* (Lamiaceae) in Prevention and Treatment of Various Mental Disorders, Including Dementia

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Abstract: *Satureja montana* (SM) is recognized as one of the most pharmacologically significant members of the extensive Lamiaceae family, native to the Bal-kan region. Historically, this plant has been utilized as a flavorful spice, particularly in traditional Bulgarian cuisine. Furthermore, it is well established that mental health is influenced by the type and quality of dietary intake. Results: Ethnopharmacological studies highlight the potential of SM to affect various chronic conditions, such as depression and anxiety. The plant is characterized by a diverse array of secondary metabolites that exhibit a wide range of biological activities, including antioxidant, anti-diabetic, anti-inflammatory, analgesic, antibacterial, antiviral, and an-tifungal properties. Notably, two of its active phenolic compounds, rosmarinic acid and carvacrol, demonstrate significant anxiolytic and anti-depressive effects. This review will examine the potential of SM to enhance mental health through its abundant phenolic constituents. Recent literature suggests their ability in addressing Alzheimer's type dementia. There is a strong correlation between depression, anxiety, and cognitive decline, including dementia. Given that Alzheimer's disease (AD) is a complex disorder, it necessitates multi-targeted therapeutic approaches for both prevention and treatment. Conclusions: SM emerges as a promising candidate for the prevention and management of various mental health disorders, including dementia.

Keywords: *Satureja montana*; dementia; cognitive impairment; polyphenols; Alzheimer's disease

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1. Introduction

Throughout history, medicinal and herbal plants have served as remedies for a variety of ailments and as means to alleviate disease symptoms. Despite advancements in pharmaceutical manufacturing, it is estimated that 80-90% of the global population continues to depend on traditional medicine for disease treatment. The World Health Organization reports that 80% of

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individuals worldwide utilize herbal remedies [1], with the market valued at approximately US$ 83 billion in 2019 and projected to reach US$ 550 billion by 2030 [2]. However, despite the growing interest from the pharmaceutical sector in naturally derived compounds [3], only a small fraction of the therapeutic properties and biological activities of medicinal plants have been thoroughly researched [4–6]. The investigation of a medicinal plant's potential as a therapeutic agent is inherently complex, requiring comprehensive studies that encompass its application, cultivation, extraction, and identification of active compounds, efficacy, safety, and clinical assessment [7–9]. While various parts of medicinal plants, such as roots, seeds, leaves, and fruits, have historically been recognized as sources of bioactive compounds and natural products (e.g., salicylates, digitalis, quinine), the journey from natural sources to drug development remains a challenging and labor-intensive process.

Polyphenol-rich plants are of considerable importance in the field of ethnopharmacology, attributed to their wide-ranging biological activities and associated health benefits. Numerous cultures incorporate polyphenol-rich plants into their traditional healing practices [10–12]. Polyphenols are particularly recognized for their potent antioxidant activities, which involve the neutralization of free radicals and the safeguarding of cells against oxidative damage. Such properties are vital in the prevention of chronic diseases, including cardiovascular pathologies cancer, and neurodegenerative conditions [13,14]. Furthermore, polyphenols demonstrate notable anti-inflammatory effects, which can be advantageous in the management of ailments such as arthritis and other inflammatory disorders. For example, extracts from *Rhamnus prinoides* have been reported to exhibit significant anti-inflammatory activity [15]. Additionally, polyphenols are endowed with antimicrobial properties, rendering them effective against various pathogens, including bacteria, fungi, and viruses. This characteristic is particularly valuable in traditional medicinal practices for the treatment of infections [16–18].

Lamiaceae consists of over 230 genera with more than 7000 species [19], including thyme, mint, lemon balm, oregano, basil, rosemary, sage, and Balkan savory [20–25]. *Satureja montana* (Figure 1), also known as Balkan savory, is one of the most pharmacologically active representatives of the large Lamiaceae family [26].

Figure 1. *Satureja montana* (Balkan savory) (photo by Kurt Stüber - caliban.mpiz-koeln.mpg.de/mavica/index.html part of www.biolib.de, CC BY-SA 3.0, https://commons.wikimedia.org/w/index.php?curid=3405).

SM has widespread distribution on the Balkan Peninsula and is an endemic plant of Bulgaria [23–25]. Extracts of *Satureja montana* have been shown to contain high levels of total polyphenols and flavonoids, which contribute to its various biological activities [27]. Specific phenolic compounds identified in *Satureja montana* include rosmarinic acid, caffeic acid, and luteolin, which were found in significant quantities in various extracts [28–30]. The phenolic compounds in SM contribute to its broad spectrum of biological activities, including antimicrobial and antioxidant properties.

1.1. Ethnopharmacological Background

For centuries *Satureja montana* is widely used as a tasty spice, especially in Bulgarian traditional dishes. This is a versatile medicinal plant with significant ethnopharmacological relevance. The ethnobotanicity index (EI) measures the extent of traditional knowledge and use of plants within a community. *Satureja montana* has a high EI in regions where it is traditionally used for medicinal purposes [31,32]. Another index, Fidelity Level (FL), indicates the percentage of informants claiming the use of a particular plant for the same major purpose. Balkan savory shows high FL values for treating digestive and respiratory disorders.

In folk medicine, it is used to treat several diseases. SM possesses diverse composition of secondary metabolites with rich biological activities (antioxidant, antidiabetic, anti-inflammatory, analgetic, antibacterial, antiviral, antifungal, etc.) as shown on Figure 2.

Figure 2. Biological activities of *Satureja montana*.

Respiratory problems can be positively affected by SM [3,33,34]. Ethnobotanical surveys in various regions, including the Apennine and Alpine areas, have documented the use of *Satureja montana* for treating digestive system disorders and respiratory infections [31,32]. But the herb has been traditionally used for treating also gastrointestinal, urinary and excretory diseases [28,35,36].

Satureja montana exhibits a broad-spectrum antimicrobial activity against various bacteria and fungi, which can indirectly support the immune system by reducing the microbial load *[31,37–39*]. *Satureja montana* may exhibit potential antiviral properties, and it has been proposed that this herb could serve as a dietary supplement to enhance immune system function, especially in relation to viral infections such as COVID-19 [40]. Research indicate that there is evidence regard-ing the impact of SM on diabetes and metabolic disorders [22,41]. Folk medicine indicates that *Satureja montana* may be effective in treating allergies and possesses immune-modulating properties [42]. Nevertheless, there is a lack of direct evidence supporting its specific use as an allergy remedy. Some information does, however, point to its potential immune-modulating effects. *Satureja montana* has shown notable antioxidant capabilities, which may aid in alleviating oxida-tive stress and inflammation. These beneficial properties are largely due to its rich concentration of phenolic compounds, including rosmarinic acid, caffeic acid, and flavonoids [28,30,43]. The plant's extracts have shown hepatoprotective and anti-inflammatory effects in animal models, in-dicating its potential to modulate immune responses [43]. In a study involving burn wounds, *Satureja montana* extracts were found to enhance the immune response by increasing the number of Ki-67-positive cells (indicating cell proliferation) and reducing CD-45-positive cells (indicating reduced inflammation) [44].

The majority of the advantageous effects of Balkan savory on human health can be attributed to its notable antioxidant and anti-inflammatory properties. Research has confirmed the presence of free radical-scavenging activity through three distinct in vitro methods, leading the authors to classify the examined dry extract of SM as an effective antioxidant. Notably, SM exhibited superior antioxidant activity when compared to findings associated with other species within the Satureja sp. [45]. Both in vitro and in vivo studies demonstrated SM ability to neutralize free radicals and to influence the endogenous antioxidant system of the human body. Simultaneously, it was determined that SM possesses a local anti-inflammatory effect that is comparable to that of diclofenac. SM demonstrates a propensity to lower serum levels of IL-6, IL-1b, and TNF in both acute and chronic stress models. The authors proposed that the inhibition of cyclooxygenase is the most probable mechanism underlying the action of SM. In addition, akin to its antioxidant properties, the anti-inflammatory effect of the extract is notably more significant when compared to the effects of rosmarinic acid and carvacrol used independently [45].

In a comparative analysis of different species within the Lamiaceae family, *Satureja montana* emerged as one of the plants demonstrating significant acetylcholinesterase (AChE) inhibitory activity at a concentration of 1 mg/ml [46]. The anti-cholinesterase properties of SM has garnered attention for its possible therapeutic uses, especially concerning Alzheimer's disease. The supercritical nonvolatile fractions of Balkan savory, which are rich in bioactive compounds including (+)-catechin, chlorogenic acid, vanillic acid, and protocatechuic acid, exhibited particularly strong activity against BChE [47]. Essential oils extracted from *Satureja montana* also demonstrated inhibitory effects on AChE, suggesting their potential use in therapeutic applications [48,49].

The aim of present review is to examine the potential of SM, as medicinal herb and tradi-tional spice, to enhance mental health through its abundant phenolic compounds.

It is widely recognized that mental health is influenced by the type and quality of food consumed. Recent research is increasingly elucidating the relationship between dietary habits and mental well-being, with numerous studies indicating a significant association between the two [50]. The functionality, structure, and composition of the brain depend on the availability of essential amino acids, lipids, vitamins, and minerals, thereby rendering cognitive performance and mental health vulnerable to nutritional changes [*50–54*]. Evidence suggest that adherence to a nutritious diet, characterized by high intakes of spices, vegetables, fruits, fish, nuts, and whole grains—such as that found in the Mediterranean diet—can yield beneficial effects, safeguard mental health, and lower the risk of depression [*55–58*]. Moreover, investigations into the impact of poor dietary choices on mental health and cognitive abilities further underscore the necessity of maintaining a healthy diet [*59–63*]. Additionally, elements such as neurotransmitters, neuropep-tides, endogenous gut hormones, and gut microbiota are also subject to alterations resulting from changes in dietary composition [*64–68*].

2. Results

2.1. Composition and Phenolic Bioactive Compounds of Satureja montana

The primary constituents of the essential oil include carvacrol, p-cymene, γ-terpinene, and thy-mol. Carvacrol is the most abundant phenolic monoterpene, with concentrations ranging from 44.5% to 45.7% [69,70]. P-cymene accounts for approximately 12.6% to 16.9%, while γ-terpinene is present in amounts between 8.1% and 8.7% [69,70]. Thymol is also present in considerable quanti-ties, reaching up to 81.79% in certain studies [26].

In terms of phenolic compounds, rosmarinic acid is recognized as a significant phenolic component in the dry extract of *Satureja montana* [29]. Additional phenolic acids identified in SM include caffeic acid, chlorogenic acid, and ellagic acid [26,28,71].

The flavonoid constituents present in the extracts of *Satureja montana* comprise quercetin and its derivatives, such as quercetin-3-O-α-L-rhamnopyranoside and quercetin-7-O-glucopyranoside [72], as well as luteolin derivatives, including luteolin-7-rhamnoside-4′-O-β-glucopyranoside and luteolin-7-O-glucopyranoside [72], along with rutin [26,28]. A summary of the available data is presented in Table 1.

Table 1. Major components of *Satureja montana* extracts.

Component	Percentage/Presence	Activity
Carvacrol	44.5% - 45.7%	Antimicrobial, Antioxidant
p-Cymene	12.6% - 16.9%	Antimicrobial
γ-Terpinene	8.1% - 8.7%	Antioxidant
Thymol	Up to 81.79%	Antimicrobial, Antioxidant
Rosmarinic Acid	Major phenolic compound	Antioxidant, Anti-inflammatory
Caffeic Acid	Present	Antioxidant
Chlorogenic Acid	Present	Antioxidant
Ellagic Acid	Present	Antioxidant, Anti-inflammatory
Quercetin	Present in various derivatives	Antioxidant, Antimicrobial
Luteolin	Present in various derivatives	Antioxidant, Anti-inflammatory
Rutin	Present	Antioxidant

Satureja montana possesses a high concentration of phenolic compounds and essential oils, which exhibit notable antioxidant and antimicrobial characteristics. This makes the plant an important resource for both medicinal applications and preservation purposes.

Two of SM active phenolic compounds rosmarinic acid and carvacrol possess strong anxiolytic and anti-depressive effects [73,74]. Each of these two phenolic compounds exhibits also antiviral, antibacterial, antioxidant, antimutagenic, anti-inflammatory, and anxiolytic effects [75–80].

A comprehensive study on *Satureja montana* was recently conducted in Bulgaria by Vilmosh et al. (2022). The dry methanol-water extract of SM was standardized based on its rosmarinic acid and carvacrol content. The findings indicated that the total phenolic content of the dry extract of SM was greater than that reported in previous literature [81]. The results obtained from liquid chromatographic and spectrophotometric analyses of the dry extract provided insights into its pharmacological effects and toxicity profile. The effective dose of the standardized dry extract was assessed in Wistar rats following oral administration, revealing that the extract is non-toxic at doses significantly higher than the therapeutic range. No instances of acute or chronic oral toxicity were observed in the Wistar rats. Over a 90-day period of daily oral intake, there were no significant changes noted in complete blood counts, basic biochemical parameters, aspartate aminotransferase, alanine aminotransferase, or uric acid levels. Histological evaluations of parenchymal organs showed no microscopic alterations in their normal architecture [45,81]. Furthermore, new findings indicate that SM exhibits a notable analgesic effect, comparable to that of Metamizole. Notably, the analgesic effect of the dry stand-ardized SM extract is more pronounced than that of rosmarinic acid and carvacrol when administered individually.

2.2. Relation of Stress to the Pathogenesis of Certain Mental Disorders

Stress, as a variable significantly shaped by lifestyle choices, in addition to being a physio-logical defense response of the body, is considered a major risk factor associated with mental disorders, as shown on Figure 3.

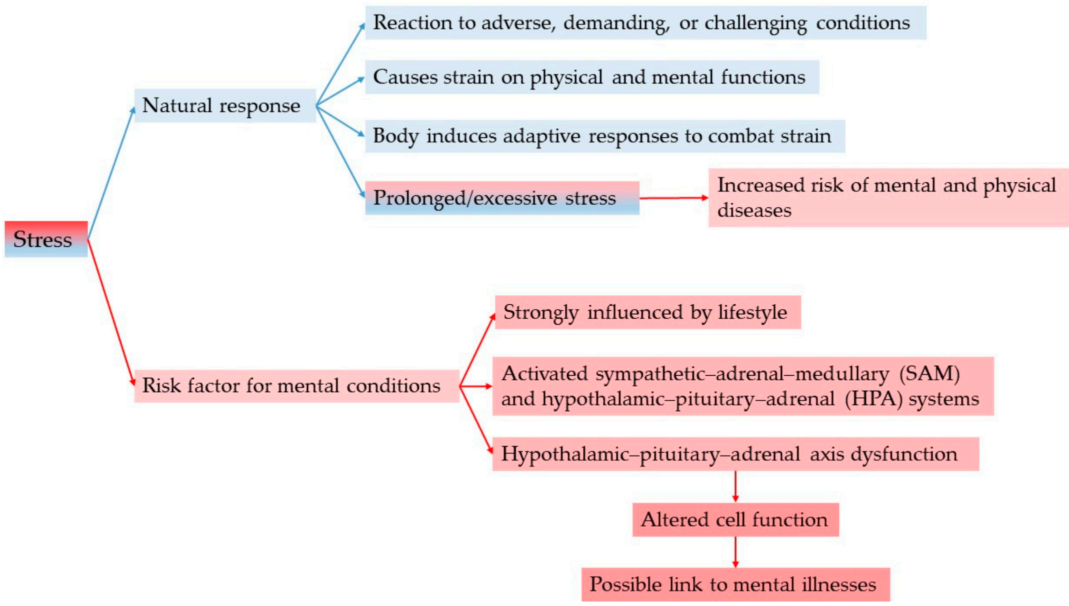

Figure 3. The dual role of stress.

Stress causes the activation of the sympathetic–adrenal–medullary (SAM) and hypothalamic–pituitary–adrenal (HPA) systems, with the hypothalamus triggering the "fight or flight" response leading to increased heart rate, blood pressure, and glucose levels and presenting a possible connection between stress and mental illnesses due to the dysfunction of the HPA axis leading to the production of cell alterations [82–86].

There are several mechanisms through which stress is thought to influence mental status (Figure 4).

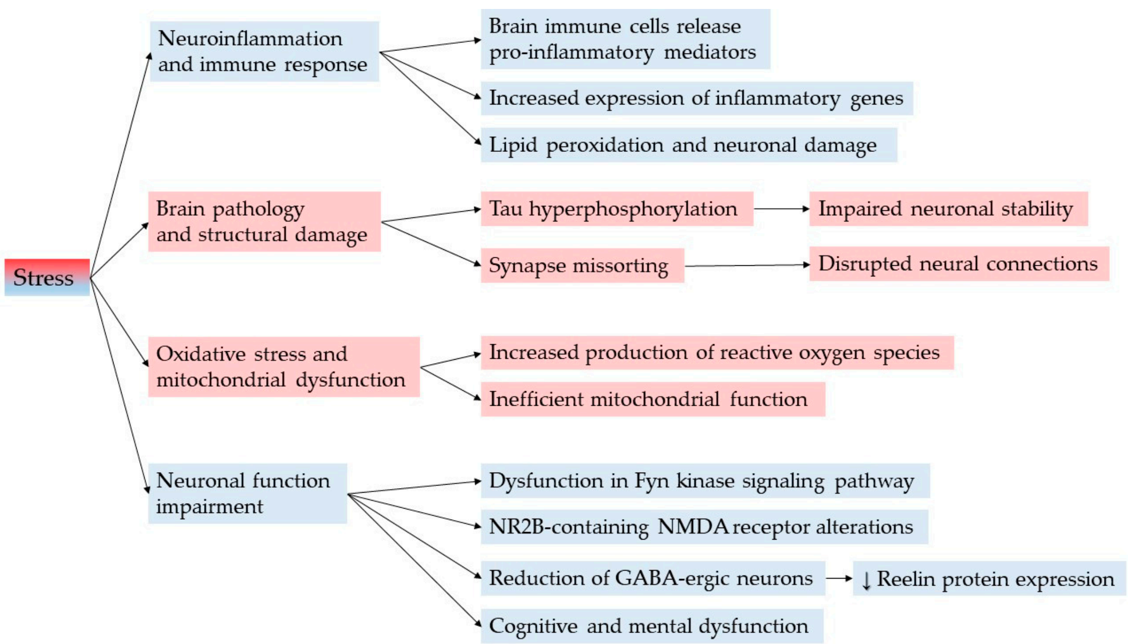

Figure 4. Molecular mechanisms linking stress to mental diseases.

Stress can lead to the activation of brain immune cells, resulting in the release of pro-inflammatory mediators. This process may enhance the expression of inflammatory genes and promote lipid peroxidation, ultimately jeopardizing both the structure and function of neurons [87]. Chronic stress may affect brain pathology through with crucial mechanism such as tau hyperphosphorylation and synapses missorting [88]. Another possible link is oxidative stress, in

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large due to the production of reactive oxygen species (ROS) causing inefficient mitochondrial function [89]. Furthermore, stress may cause impairment of neuronal functions and structures such as the signaling pathway Fyn kinase and the NR2B-containing N-methyl-D-aspartate (NMDA) receptors, causing reduction of GABA-ergic neurons and decrease in expression of Reelin protein expression [90,91].

A natural response of the body when presented with adverse, demanding or challenging conditions, stress causes strain on both physical and mental functions. While the body induces adaptive responses designed to combat this strain, prolonged or excessive stress can lead to depression, anxiety, cognitive dysfunction, and may even increase the risk of development of mental and physical disease [85,92,93].

Chronic stress is known to lead to cognitive impairment. This is most likely due to elevated levels of glucocorticoids and corticotropin-releasing hormone causing neurotransmitter alterations, atrophy in the hippocampus and cortex, and shortening of the dendritic branches [94–102].

Stress is frequently involved in development of anxiety and depression. Affecting approximately 300 million people worldwide, anxiety and depression are one of the most prevalent and debilitating mental disorders [103–105]. Signs of chronic systemic inflammation such as elevation in pro-inflammatory cytokines, dysregulation in myelopoiesis and lymphopoiesis and disruptions in the gut-epithelium barriers and blood-brain barrier may be observed in individuals with stress-induced illnesses [106–110].

Ethnopharmacology reports the potential of SM to affect some stress related chronic mental diseases, including anxiety, depression, mild cognitive impairments and dementia.

2.3. Anti-Stress and Anxiolytic Activity of Satureja montana

As reported by the World Health Organization, approximately 4% of the global population was affected by anxiety disorders as of 2019 [111]. Furthermore, it is noteworthy that many anxiety disorders often go undiagnosed [112]. Several challenges are associated with the treatment of depression and anxiety, including factors such as age, polypharmacy or polypragmasy, an increase in adverse drug reactions, comorbid conditions, diminished quality of life, and rising treatment costs. The COVID-19 pandemic and its accompanying restrictions have led to a more than 25% increase in the prevalence of these psychiatric disorders [113]. All pharmacological agents utilized in the treatment of depressive disorders and anxiety can lead to adverse side effects, including addiction, headaches, seizures, sexual dysfunction, and suicidal ideation, as well as dependence [114]. Due to the potential for adverse effects and delayed therapeutic efficacy, many patients demonstrate reluctance when it comes to the prescription of psychotropic medications, which may result in non-adherence to the recommended treatment [115,116]. The limitations surrounding the use of these medications underscore the necessity for research into new therapeutic alter-natives for these conditions [114,117].

In an animal model of acute stress, the dry extract of *Satureja montana* significantly increased locomotor activity and social interaction time, and reduced anxiety-related behaviors [81]. Acute cold stress markedly diminished the novel object recognition time in laboratory rats, and this suggests a notable anxiolytic effect of SM. The roles of neurotransmitters such as 5-hydroxytryptamine and gamma-aminobutyric acid (GABA) were considered [118]. The active compounds in *Satureja montana*, such as rosmarinic acid and carvacrol, also demonstrated moderate anxiolytic effects [81]. In a rat model of chronic stress, the dry extract of SM demonstrated anxiolytic effects. Chronic stress led to a notable decrease in the duration spent in the open arms of the elevated plus maze. The administration of SM dry extract in effective dose (250 mg/kg b.wt. orally) resulted in a statistically significant reduction in the time spent in the closed arms. Rosmarinic acid did not significantly influence the time spent in either the open or closed arms, whereas carvacrol notably increased the time spent in the open arms and decreased the time in the closed arms. Spontaneous locomotor activity of the experimental rats also was changed [119,120] in support of some of the behavioral tests for the determination of anxiolytic and antidepressant effect [118,121]. The precise mechanisms remain

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elucidated. Research has demonstrated that rosmarinic acid influences T-type calcium ion channels within the central nervous system, alongside modulating GABAergic and cholinergic pathways [76]. Drawing from existing literature, Vilmosh et al. (2022) hypothesize that the anxiolytic action may primarily involve the modulation of ion channels in the central nervous system and cholinergic mediation [81]. The lack of a significant increase in shock licks during the Vogel test also suggests that GABA is unlikely to play a role in the observed anxiolytic effect. Obviously multiple mechanisms contribute to the anxiolytic properties of the dry extract of SM. The research conducted by Melo et al. (2010) indicates that carvacrol interacts with various neurotransmitters, including GABA, noradrenaline, and serotonin [122]. These findings may elucidate the results related to changes in locomotor activity and social interaction after SM treatment, reported by Vilmosh et al. (2022).

Chronic low-grade inflammation and oxidative stress are implicated in the etiology of anxiety, which correlates with elevated plasma levels of corticosterone, a byproduct of stress responses [123–125]. Consequently, when evaluating the anxiolytic properties of rosmarinic acid and carvacrol, it is essential to consider their antioxidant and anti-inflammatory effects [77,126,127].

Apart from the investigations by Vilmosh et al. (2022), our literature review did not reveal any studies addressing the impact of the dry extract of SM on anxiety, which indicate that the dry extract exhibits a more pronounced anxiolytic effect than the individual active compounds when administered separately. This observation provides a basis for hypothesizing a synergistic interaction between rosmarinic acid and carvacrol [81].

2.4. Effects of Satureja montana on Depression

Epidemiological studies indicate that the prevalence of depression aligns closely with that of anxiety disorders. The presence of depressive disorder significantly diminishes an individual's quality of life [128]. This condition typically manifests in an episodic manner; however, it remains unpredictable regarding the frequency and duration of episodes, as well as the efficacy of various treatment options. The recovery process is often extended, accompanied by a considerable risk of relapse [128]. Similar to anxiety, depression serves as an independent risk factor for several health issues, including diabetes, cardiovascular diseases, chronic respiratory conditions, and arthritis, as well as cognitive impairments and neurodegenerative disorders such as Alzheimer’s disease.

The antidepressant properties of *Satureja montana* can be assessed through the acute cold stress model. The forced swim test is widely recognized as a primary method for evaluating depressive behaviors in experimental animals and for screening potential antidepressant effects of novel pharmacological agents; therefore, it was incorporated into the current study's design [121,129]. In the experiments of Vilmosh et al. (2022) the administration of the dry extract of SM at a dosage of 250 mg/kg body weight significantly prolonged the duration of active struggle com-pared to the positive control group. However, this effect was not observed at higher doses of the extract (500 mg/kg bw), nor in groups treated with rosmarinic acid or carvacrol. It is noteworthy that only the dry extract of *Satureja montana* at 250 mg/kg body weight demonstrated a significant increase in active struggle duration. According to two separate investigations from 2021, rosmarinic acid has been shown to produce a significant antidepressant effect by reducing the duration of immobility in the forced swim test [130,131]. Conversely, Vilmosh et al. (2022) reported that rosmarinic acid influenced depressive-like behavior solely within the context of a chronic stress model [81]. This discrepancy may be attributed to the extended treatment duration and the distinct physiological mechanisms activated in the two stress models employed. Chronic stress is linked to a reduction in the activity of dopaminergic neurons in the ventral tegmental area, while rosmarinic acid is known to elevate dopamine levels, thereby elucidating its observed antidepressant effects [132,133].

In opposition to the results concerning rosmarinic acid, the study by Vilmosh et al. (2022) demonstrated that carvacrol failed to show any antidepressant effects, thereby challenging the conclusions drawn in the current body of literature [134,135]. This discrepancy may be attributed to variations in the experimental doses and the models employed to induce depression. While carvacrol is known to influence dopamine and serotonin neurotransmission [134], it is plausible that these

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mechanisms are insufficient to counteract the stress-induced alterations within the central nervous system.

Additionally, there is a scarcity of literature that addresses the antidepressant properties of the dry extract of SM. Nevertheless, the research conducted by Vilmosh et al. (2022) revealed that the dry extract of SM notably reduced immobilization time in two stress models employed [81]. Research employing both acute and chronic stress models has revealed that the dry extract of SM produces markedly more potent anxiolytic and antidepressant effects than those observed with rosmarinic acid and carvacrol administered independently in both experimental stress scenarios. This increased effectiveness is presumably due to the synergistic interactions between the two active constituents found in the extract. According to authors, the primary mechanism underlying this action seems to involve the modulation of serotonin, dopamine, and noradrenaline neuro-transmitters in the central nervous system. Notably, a dosage of 250 mg/kg body weight SM proved to be the most effective in the experimental assessment of analgesic, anti-inflammatory, anxiolytic, and antidepressant properties [45].

2.5. Relation of Anxiety and Depression to Cognitive Disorders and Dementia

There exists a significant interrelationship among depression, anxiety, and cognitive impairments, as well as cognitive decline. Anxiety has been linked to an elevated risk of both the onset and progression of somatic diseases [136,137]. Furthermore, a correlation has been identified between this psychiatric condition and complications arising from cardiovascular diseases [137]. Individuals suffering from insulin resistance (IR) who also experience anxiety are at a heightened risk of developing type 2 diabetes, with the coexistence of these two conditions further increasing the probability of adverse outcomes [138,139]. Each of the aforementioned disorders is linked to a greater likelihood of developing additional mental health issues [136,140]. Specifically, anxiety is associated with a higher risk of developing coexisting anxiety disorders or depression [136]. Depression itself is further connected to neurotic, somatoform, and personality disorders, as well as substance abuse and behavioral syndromes. The prevalence of comorbidity tends to escalate with the severity of depressive symptoms [140–144]. Moreover, depression and anxiety are closely associated with cognitive impairments and dementia. While Alzheimer's disease primarily affects cognitive functions and memory, it is not uncommon for neuropsychiatric symptoms to manifest throughout the disease's progression. Anxiety prevalence ranges from 9.4% during the preclinical phase to as high as 39% in cases of mild to severe cognitive decline, whereas depression prevalence varies between 14.8% and 40% in mild to moderate stages of Alzheimer's disease [145–151].

Mild Cognitive Impairment (MCI) is a significant transitional stage between typical aging and the onset of dementia. The prevalence of MCI among the elderly population is estimated to range from 5.0% to 36.7%, with approximately 11% to 13% of individuals with MCI progressing to dementia within a two-year period [152–155]. Psychological symptoms frequently associated with MCI include depression and anxiety, both of which can adversely affect cognitive functioning and contribute to the progression toward dementia [156,157]. Notably, cognitive deficits are more pronounced in individuals experiencing both depression and anxiety [158,159]. Depression has been identified as a significant risk factor for the advancement of cognitive decline and the development of either dementia, while anxiety may influence this progression directly or indirectly [160–163].

Among individuals with MCI, the prevalence of depression is approximately 32%. The use of antidepressants does not appear to provide a protective effect against the onset of dementia, and those with MCI are at an increased risk for developing severe cognitive impairment [164–166]. The conversion rate from MCI to dementia is notably higher in those with depression, ranging from 25% to 28%, with a significant conversion rate of 31% to AD in depressed patients compared to 13.5% in those without depression [167]. Although anxiety has been less extensively studied than depression, its relationship with cognitive function is complex, with prevalence rates between 9.9% and 52% in individuals with MCI, particularly affecting executive functions [161,168–171]. Dementia and anxiety can serve as significant clinical indicators; specifically, anxiety may act as a predictor of cognitive

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deterioration, whereas depression can help identify individuals with MCI who are at an increased risk of progressing to Alzheimer's disease [167,171].

2.6. Effects of Satureja montana on Dementia and Alzheimer's Disease

Natural products containing polyphenols are multi-target compounds. They possess rich variety of activities, including antioxidant, anti-inflammatory, anticholinergic, etc., and can attack several targets of AD as multi-factorial disease.

Oral administration of the dry extract of SM in effective dose notably enhanced the duration of social interaction in a rat model subjected to induced chronic stress, in comparison to the positive control group. This enhancement was similarly observed in rats treated with carvacrol; however, it was not evident in those receiving treatment with rosmarinic acid [81]. The oral administration of a dry extract of SM (250 mg/kg body weight) and rosmarinic acid significantly prolonged the duration of active struggle in comparison to the positive control group, as evidenced by the Forced Swim Test. However, the existing literature presents conflicting findings regarding the impact of rosmarinic acid on recognition memory [172,173]. The cognitive enhancements observed in animals treated with phenolic acids are likely attributable to their neuroprotective effects [172,173]. In a manner similar to rosmarinic acid, carvacrol has also been shown to enhance cognitive function in rodent models [174,175], which contrasts with the findings reported by Vilmosh et al. (2022) [81]. These discrepancies may be explained by the variations in memory impairment models employed and the differing durations of treatment with the phenolic compounds.

The dry extract of SM and rosmarinic acid demonstrated a statistically significant enhance-ment in novel object learning time and the discrimination index (DI), whereas carvacrol did not exhibit a significant impact on recognition memory. Notably, the dry extract of SM led to a marked increase in the exploration time of the novel object when compared to both rosmarinic acid and carvacrol [81]. However, there is a lack of literature addressing the influence of rosmarinic acid on social interaction. Both administered doses of the dry extract of SM (250 mg/kg b.w. and 500 mg/kg b.w.) resulted in a significant increase in the time allocated to exploring the new object. However, only the higher dose of 500 mg/kg b.w. demonstrated a statistically significant impact on the DI. While rosmarinic acid exhibited a statistically significant effect, carvacrol did not show any significant influence. The findings regarding rosmarinic acid align with existing literature that highlights the anxiolytic properties of this phenolic compound [172,173,176].

Table 2 presents the results from the conducted behavioral tests [81].

Table 2. Comparative effects of *Satureja montana* extract and its active compounds.

Experimental test	*SM* (250mg/kg)	*SM* (500mg/kg)	Rosmarinic acid	Carvacrol	Control
Elevated plus maze	↑ time in closed arms	↓ closed arm entries	Minimal effect	↑ time in open arms	↑ time in closed arms
Social interaction	↑ interaction time	↑ interaction time	Minimal effect	↑ interaction time	↓ interaction time
Novel object recognition	↑ exploration time ↑ discrimination index	↑ exploration time ↑ discrimination index	↑ novel object learning time ↑ discrimination index	No significant effect	↓ exploration time
Forced swim	↑ active struggle time	Minimal effect	Effect on chronic stress only	No effect	↑ mobility time
Locomotor activity with stress model	↑ vertical movement	Minimal effect	No significant effect	↑ activity	↓ movement
Cortisol levels with chronic stress model	↓ cortisol levels	↓ cortisol levels	Moderate reduction	Moderate reduction	↑ cortisol levels

There is a notable absence of data concerning the cognitive effects of the dry extract of SM in the existing literature. While the dry extract of SM did increase the time spent exploring the novel object, it did not significantly alter the discrimination index. Nevertheless, it can be inferred that the impact of Balkan savory on recognition memory may surpass that of rosmarinic acid and carvacrol when administered individually, likely due to the synergistic enhancement of the cognitive effects attributed to the phenolic acid present in the extract [81]. The dry extract of savory, similar to other total extracts derived from medicinal plants, demonstrates superior protective effects in comparison to the two active compounds, carvacrol and rosmarinic acid.

Satureja montana has demonstrated various mechanisms of action, including antioxidant and anti-inflammatory activities. Additionally, it has shown the ability to inhibit acetylcholinesterase, an enzyme associated with Alzheimer's disease [47]. *Satureja montana* extracts have demonstrated considerable inhibitory effects on both AChE and BChE [47].

All above-mentioned mechanisms offer promising prospects for the use of *Satureja montana* in the management of neurodegenerative processes. The benefits of developing appropriate pharmacological products derived from Balkan savory primarily lie in their safety, tolerability, applicability, and cost-effectiveness, which could enhance the management of socially significant conditions such as anxiety, depression, and cognitive impairments.

3. Conclusions

Satureja montana may represent a valuable and promising alternative in the prevention and treatment of various mental health disorders, including dementia. The main mechanisms by which it affects pathological processes in the CNS are significant anxiolytic activity, anticholinergic activity, strong antioxidant and anti-inflammatory properties producing moderate cognitive benefits. However, despite existing literature regarding the composition and biological activity of *Satureja montana*, further research is essential to elucidate its established pharmacological effects and their potential complex mechanisms.

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Abbreviations

The following abbreviations are used in this manuscript:

SM	*Satureja montana*
AD	Alzheimer’s disease
AChE	Acetylcholinesterase
BChE	Butyrylcholinesterase
ROS	Reactive oxygen species
NMDA	N-methyl-D-aspartate
MCI	Mild Cognitive Impairment
DI	Discrimination index
EI	Ethnobotanicity index
FL	Fidelity level

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