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Effects of orally administered *Thymus vulgaris* leaves on memory, anxiety, depression, and sleep quality in university students: a randomized controlled trial

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Abstract. – OBJECTIVE: The aim of this study was to evaluate the effects of orally administering *Thymus vulgaris* leaves on memory performance, anxiety, depression, and sleep quality in a sample of university students.

PATIENTS AND METHODS: This randomized controlled trial included 106 students who were randomly assigned to one of two groups. The first group received 500 mg of *Thymus vulgaris* leaves twice daily, while the second group received a placebo. The intervention period lasted for one month. The participants' memory performance (both prospective and retrospective), levels of anxiety and depression, and sleep quality were assessed using the Prospective and Retrospective Memory Questionnaire (PRMQ), Hospital Anxiety and Depression Scale (HADS), and Pittsburgh Sleep Quality Inventory (PSQI) at the beginning of the study and after one month.

RESULTS: The findings revealed significant reductions in the scores of all scales and subscales, with the exception of the sleep latency and sleep duration components of the Pittsburgh Sleep Quality Inventory, among the group that received *Thymus vulgaris* leaves in comparison to the control group.

CONCLUSIONS: *Thymus vulgaris* leaves, a traditional food source, demonstrate potential for enhancing both prospective and retrospective memory, alleviating anxiety and depression, and improving sleep quality in university students.

Key Words:
Thymus vulgaris leaves, Memory performance, Anxiety, Depression, Sleep.

Introduction

Thymus vulgaris belongs to the *Lamiaceae* family and is a flowering plant. It can be found worldwide, although its origin is in southern Europe[1]. This plant is characterized by its compact, bushy nature and evergreen shrub structure. Its leaves are small, gray-green colored, highly aromatic, and it produces clusters of purple or pink flowers[2]. *Thymus vulgaris* is commonly used as a spice to enhance the flavor of food. It is also utilized in the form of dietary supplements, such as capsules or essential oils[3]. Throughout history, *Thymus vulgaris* has been employed in folk medicine due to its remarkable antimicrobial and anti-inflammatory properties[4]. In Jordanian traditional medicine, it is frequently utilized as an antiseptic, bronchial, sedative, and spasmolytic agent, as well as to improve cognitive function and memory[5-8]. Numerous studies[9-18] have reported various health benefits associated with *Thymus vulgaris* leaves, including antioxidant[9], diuretic[10], anti-inflammatory[11], antiviral[12], anti-cancerous[13], cholesterol-lowering[14], glucose-lowering[15], anticonvulsant[16], anti-anxiety[17] and sedative-hypnotic activities[18].

The primary constituents of *Thymus vulgaris*, notably thymol, p-cymene, γ-terpinene, linalool, and carvacrol, possess various neuropharmacological properties, including anti-anxiety, sedative, anticonvulsant, memory-enhancing, and anti-Alzheimer's disease effects[19]. Asadbegi et

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al[20] conducted a study demonstrating that thymol exhibited neuroprotective properties by reducing memory impairment caused by intrahippocampal injection of the amyloid beta (Aβ) peptide in rats fed a high-fat diet. Furthermore, Capibaribe et al[21] confirmed the significant antidepressant-like effect of thymol by observing its ability to reverse behaviors associated with chronic corticosterone exposure and decrease BDNF levels in female mice. Azizi et al[22] demonstrated that carvacrol and thymol exerted neuroprotective effects against Aβ25-35-induced damage, potentially through the attenuation of oxidative stress and the modulation of protein kinase C (PKC) activity, a protein associated with memory function. Additionally, within the monoterpenes and sesquiterpenes, β-myrcene and caryophyllene have been identified as major compounds. β-myrcene is known for its analgesic, anxiolytic, and anti-inflammatory effects[23].

Multiple studies[24,25] have highlighted the positive impact of *Thymus vulgaris* on memory, anxiety, and depression. Akan et al[24] conducted research on rats using the Morris water maze and found that *Thymus vulgaris* L. exhibited beneficial effects against diabetes mellitus-induced neuropathy and cognitive impairment. They attributed these effects to specific components like thymol, carvacrol, 8-terpinene, p-cymene, and α-pinene present in high amounts in the essential oil composition. Similarly, Rabiei et al[25] suggested that *Thymus vulgaris* extract demonstrated anti-amnesic properties in rats with Sco-induced memory deficits, as assessed by the Morris water maze and passive avoidance tests. The authors proposed that this effect could be linked to the extract's antioxidant activity or its influence on the cholinergic system, with carvacrol and thymol playing significant roles based on their chemical composition. Additionally, an ethanol extract derived from *Thymus vulgaris* leaves displayed an anxiolytic profile in rats during the elevated pulse maze (EPM) test, unaffected by locomotor activity[17]. Finally, in the context of Alzheimer's disease, a neurodegenerative disorder involving cholinergic neuron loss, the administration of thyme oil to *Caenorhabditis elegans* enhanced neurotransmission by regulating synaptic acetylcholine levels[26].

The high prevalence of anxiety, depression, and sleep disorders among university students can significantly affect their memory function[27,28]. Consequently, an increasing number of university students have turned to using stimulant drugs to improve their memory performance and attention, despite the fact that such usage is unauthorized and not intended for therapeutic purposes[29]. However, the use of these drugs is associated with various side effects[30,31]. This has led neuroscience researchers to show a growing interest in identifying cognitive-enhancing drugs that healthy individuals can safely use without any detrimental effects.

Based on the provided information, it is hypothesized that *Thymus vulgaris* could potentially serve as a safer alternative to stimulant drugs for enhancing memory among university students. Furthermore, *Thymus vulgaris* may offer additional benefits in terms of reducing both anxiety and depression and improving sleep quality. However, it should be noted that the current research on the effects of orally administered *Thymus vulgaris* on the brain and nervous system is limited, and further studies are required to fully explore its potential advantages. Therefore, the purpose of this study is to investigate the effects of oral *Thymus vulgaris* on memory performance, anxiety, depression, and sleep quality in university students.

Patients and Methods

Ethical Considerations

The Ethical Committee of Hashemite University granted approval for the current study (IRB #:22/6/2022/2023). Also, this trial is registered in the U.S. National Library of Medicine (ID#: NCT05987228). All participants who were enrolled in this study provided a signed consent form.

Study Design and Participants

A randomized controlled trial with a double-blinded design was conducted between August and December 2022 at the Hashemite University in Zarqa, Jordan. The trial specifically involved participants aged between 19 and 23 years. Both the participants and the researcher responsible for evaluating the outcomes were unaware of the treatment assignments to ensure unbiased results. To maintain the study's integrity, individuals with medical diseases, psychiatric disorders, those using any medications (including complementary and alternative medicines), as well as pregnant and lactating individuals, were excluded from participating. Initially, 110 students agreed to participate, but ultimately, the trial was completed by 106 students. For a visual representation of the trial's progress, please refer to Figure 1, which displays the consort flow diagram.

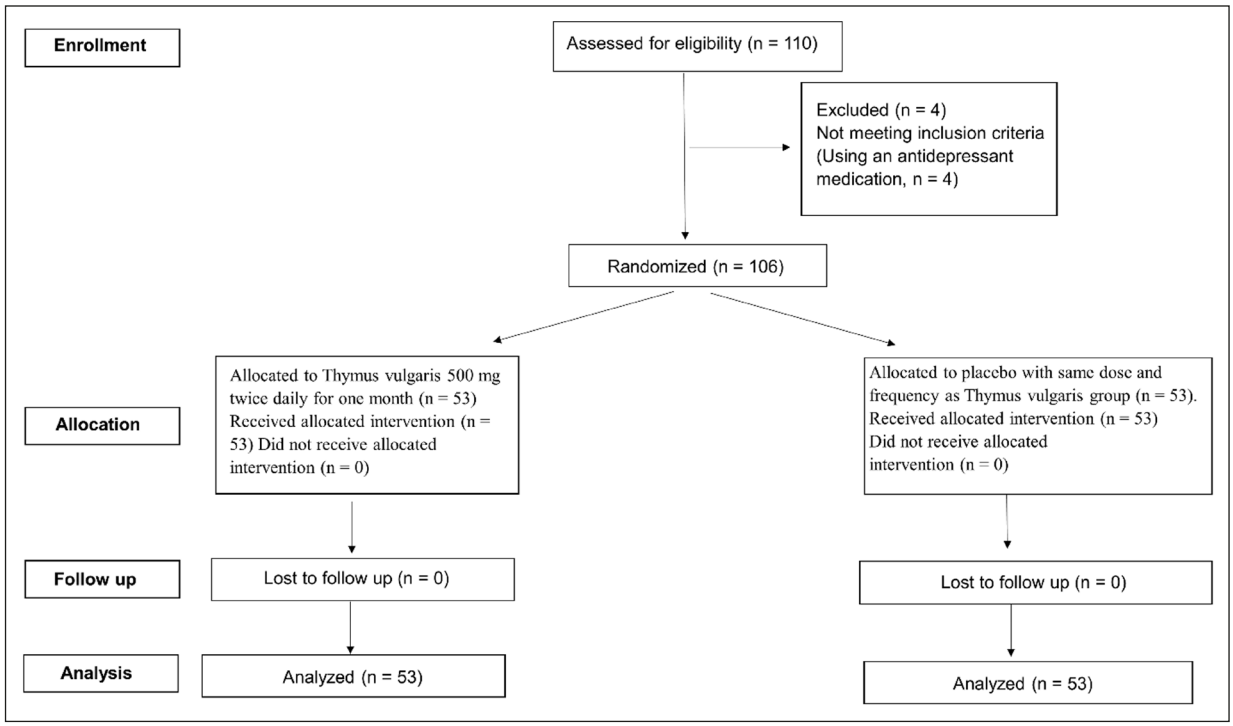

Figure 1. The diagram illustrates the disposition of participants in the study. Out of the initial pool of 110 potential volunteers, a total of 106 participants were randomly assigned to two different treatment groups. Specifically, 53 participants were allocated to the placebo group (treatment A), while 53 participants were assigned to the *Thymus vulgaris* group (treatment B).

Interventions

The students who were enrolled in the study were randomly allocated to two groups using block randomization. These groups were named the *Thymus vulgaris* group and the control group, each consisting of 53 students. In the *Thymus vulgaris* group, participants received twice a day (morning and evening) dried powdered leaves of *Thymus vulgaris* (500 mg capsule), while the control group received starch as a placebo. To maintain blinding, both the *Thymus vulgaris* and placebo capsules were identical in terms of shape, color, and outer packaging. However, it is important to note that participants who received *Thymus vulgaris* capsules may have been able to identify them due to the distinct flavor and aroma associated with *Thymus vulgaris*. The *Thymus vulgaris* leaves used in the study were purchased from a local market and authenticated by a botanist (J.S.). A voucher specimen, labeled with the Herbarium number HU. No. 4266 was submitted to the Hashemite University herbarium in Zarqa, Jordan, for future reference. Before use, the *Thymus vulgaris* leaves were ground separately into a fine powder.

Measurements

The cognitive and mental well-being of the participating students was measured using self-reported questionnaires at the beginning and after one month. Validated instruments were utilized to assess various factors such as prospective and retrospective memory performance, depression, anxiety, sleep quality, sleep latency, and sleep duration. To evaluate everyday memory problems, the Prospective and Retrospective Memory Questionnaire (PRMQ), consisting of 16 items, was employed[32]. Participants rated the frequency of memory problems on a scale of 1 (never) to 5 (very often), with lower scores indicating fewer issues. The PRMQ comprised two subscales: prospective memory (8 items) and retrospective memory (8 items). Anxiety and depression levels were measured using the Hospital Anxiety and Depression Scale (HADS), a 14-item questionnaire[33]. Each item was scored from 0 to 3, with the questionnaire including two subscales: anxiety (7 items) and depression (7 items). Severity levels were categorized based on the scores, ranging from normal to severe. Sleep quality was assessed using the validated version of the Pittsburgh Sleep Quality Inventory (PSQI),

which consisted of 7 components[34]. The focus of the study was on sleep latency and sleep duration. Higher scores on the PSQI indicated poorer sleep quality, and participants with scores above 5 were classified as poor sleepers. By employing these questionnaires, the study aimed to evaluate prospective and retrospective memory performance, levels of anxiety and depression, as well as sleep quality, including sleep latency and duration, among the participants.

Statistical Analysis

All statistical analyses in this study were conducted using the Statistical Package for the Social Sciences (SPSS) version 20 (IBM Corp., Armonk, NY, USA). Prior to analysis, the data's normal distribution was confirmed using the Kolmogorov-Smirnov test. To evaluate differences in demographic characteristics, anxiety grades, depression grades, and sleep quality grades between the *Thymus vulgaris* and control groups, two-tailed *t*-tests and Chi-square tests (or Fisher's exact test when appropriate) were employed. Mixed model analysis of variance was used to examine changes over time in scores for each scale between the two groups. Additionally, paired sample *t*-tests were conducted within each group to compare changes over time in scores for the respective scales. In all analyses, a significance level of $p<0.05$ was considered statistically significant.

Results

Table I presents the demographic information for the 106 participants, showing a mean ± SD age of 21.45±1.5 years. Of the students who took part, 46 (43.4%) were male, and 60 (56.6%) were female. Statistical analysis indicated no significant differences in demographic data between the *Thymus vulgaris* and control groups.

Table II displays the anxiety, depression, and sleep quality statuses of the students in both groups at baseline and after one month. Initially, there were no significant differences between the two groups regarding these statuses. However, after one month, a noticeable difference was observed in the students' anxiety status between the *Thymus vulgaris* and control groups. However, no significant differences were found for depression and sleep quality.

Table I. The demographic characteristics of the participants in both the placebo (control) and *Thymus vulgaris* conditions.

Variable	*Thymus vulgaris* Number (%)	Control Number (%)	[a]*p*-value
Age (Mean±SD)	21.1±1.4	21.8±1.7	[b]0.75
Sex			0.78
Male	22 (41.5%)	24 (45.3%)	
Female	31 (58.5%)	29 (54.7%)	
Discipline			0.16
Doctor of Pharmacy	20 (37.7%)	18 (34.0%)	
Doctor of Medicine	18 (34.0%)	16 (30.2%)	
Bachelor of Nursing	12 (22.6%)	11 (20.7%)	
Bachelor of Allied Health	3 (5.7%)	8 (15.1%)	
Year in school			0.07
Second	15 (28.3%)	18 (34.0%)	
Third	18 (34.0%)	14 (26.4%)	
Fourth	15 (28.3%)	16 (30.2%)	
Fifth	5 (9.4%)	5 (9.4%)	
Marital status			0.06
Single	52 (98.1 %)	51 (96.2%)	
Married	1 (1.9 %)	2 (3.8%)	
Residence			0.13
Dormitory	3 (5.7%)	5 (9.4%)	
Home	50 (94.3%)	48 (90.6%)	

[a]Based on Chi-square or Fisher-exact test. [b]Based on Independent *t*-test.

Table II. Classification of the students' anxiety, depression, and sleep quality status in the two groups at the beginning of the study and then again after one month.

Measurement	Baseline Number (%)		After one month Number (%)		[a]*p* baseline	[a]*p* after one month
	Thymus vulgaris	Control	*Thymus vulgaris*	Control		
Hospital anxiety scale					0.65	**0.04**
Normal (0-7)	27 (51.0%)	30 (56.6%)	40 (75.5 %)	31 (58.5 %)		
Mild (8-18)	11 (20.7 %)	12 (22.6 %)	10 (18.9%)	13 (24.5%)		
Moderate (11-14)	9 (17.0 %)	7 (13.2%)	3 (5.6 %)	7 (13.2%)		
Severe (15-21)	6 (11.3 %)	4 (7.6%)	0 (0.00%)	2 (3.8%)		
Hospital depression scale					0.84	0.87
Normal (0-7)	37 (69.8%)	41 (77.4%)	44 (83.0%)	42 (79.2%)		
Mild (8-18)	10 (18.9%)	8 (15.1%)	6 (11.3%)	7 (13.3%)		
Moderate (11-14)	6 (11.3%)	4 (7.5%)	3 (5.7%)	4 (7.5%)		
Severe (15-21)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)		
Pittsburg sleep quality inventory					0.20	0.18
Good sleeper (≤5)	25 (47.2%)	23 (43.4%)	35 (66.0%)	22 (41.5%)		
Poor sleeper (>5)	28 (52.8%)	30 (56.6%)	18 (34.0%)	31 (58.5%)		

[a]Based on Chi-square or Fisher-exact test.

The statistical analyses conducted in this study showed significant main effects of time (within-subjects factor) for all scales and subscales, except for the sleep duration component of the PSQI. Additionally, the interaction between time and group was found to be statistically significant for all scales and subscales, except for the sleep latency and sleep duration components of the PSQI. However, the main effect of the group (as a between-subjects factor) did not reach statistical significance for any of the scales and subscales. Table III provides an overview of the score changes for each scale in both the *Thymus vulgaris* and control groups at the beginning of the study and after one month.

Table III summarizes the results of the study, indicating that in the *Thymus vulgaris* group, there was a significant reduction in the mean scores for all scales and subscales, except for sleep duration, after one month. However, in the control group, there was no significant difference in the mean scores for any of the scales and subscales after one month. This suggests that the *Thymus vulgaris* group experienced notable improvements in cognitive and mental well-being, while the control group did not show significant changes.

Throughout the course of the study, participants reported not experiencing side effects attributed to *Thymus vulgaris*.

Discussion

The findings of the present study indicate that *Thymus vulgaris* leaves have significant effects on enhancing memory performance, reducing anxiety and depression, and improving sleep quality among university students. While there have been limited human studies examining the effects of *Thymus vulgaris* leaves on memory, some animal studies[25] have shed light on this aspect. For instance, the Administration of *Thymus vulgaris* extract significantly restored memory and learning impairments induced by scopolamine in the passive avoidance test and Morris water maze test[25]. Also, there are some reports[20] that showed that thymol, the main monoterpene phenol found in *Thymus vulgaris* essential oil, affects the learning and memory in animal models of high-fat diet-induced cognitive deficits through decreasing high-fat diet (HFD)-induced Aβ deposition and tau hyperphosphorylation in the hippocampus, which may be correlated with the inhibition of hippocampal oxidative stress and inflammation, and further investigation showed that this effect of thymol is mediated by activating nuclear factor erythroid 2-related factor 2 (Nrf2)/ Heme oxygenase-1 (HO-1) signaling pathway which regulates many antioxidant enzyme level in the cells[35]. Therefore, the positive effects of *Thymus*

Table III. Changes in scores for each scale in *Thymus vulgaris* and control groups at the initial assessment and subsequently after one month.

Variable	Group	Baseline Mean±SD	After one month Mean±SD	[a]*p*-value	[b]*p*-value Effect of time	[b]*p*-value Time by group interaction
Prospective and Retrospective Memory Questionnaire	*Thymus vulgaris*	34.21±2.3	30.42±3.2	**0.002**	**0.006**	**0.005**
	Control	35.12±4.2	34.44±5.1	0.81		
Prospective Memory subscale	*Thymus vulgaris*	19.61±2.3	18.32±1.1	**0.003**	**0.02**	**0.003**
	Control	20.81±1.5	20.41±2.3	0.77		
Retrospective Memory subscale	*Thymus vulgaris*	17.21±2.6	14.81±1.1	**0.002**	**0.03**	**0.01**
	Control	15.95±1.4	15.52±1.2	0.71		
Hospital Anxiety Scale	*Thymus vulgaris*	7.33±0.8	5.82±0.6	**0.003**	**0.01**	**0.03**
	Control	7.62±0.9	7.39±0.4	0.71		
Hospital Depression Scale	*Thymus vulgaris*	5.85±0.8	4.31±0.5	**0.002**	**0.01**	**0.003**
	Control	6.61±0.7	4.52±0.7	0.81		
Pittsburg Sleep Quality Inventory	*Thymus vulgaris*	5.14±1.2	4.01±0.5	**0.002**	**0.01**	**0.02**
	Control	5.15±0.7	5.24±0.5	0.81		
Sleep latency component	*Thymus vulgaris*	1.11±0.2	0.62±0.1	**0.001**	**0.03**	**0.31**
	Control	1.25±0.4	1.21±0.1	0.83		
Sleep duration component	*Thymus vulgaris*	0.79±0.1	0.82±0.1	**0.53**	**0.69**	**0.62**
	Control	0.81±0.2	0.86±0.3	0.72		

SD: Standard Deviation. [a]Paired *t*-test. [b]Mixed model analyses of variance.

vulgaris extract on the improvement of memory impairment observed in the present study can be partially attributed to the thymol in the *Thymus vulgaris* extract.

Thymus vulgaris extract has been found to possess antioxidant properties and has the ability to impact the formation of reactive oxygen species (ROS). In a reported study[36], *Thymus vulgaris* essential oil decreased lipid peroxidation and increased superoxide dismutase (SOD), glutathione (GSH) and glutathione peroxidase (GPx) in the zebrafish model of cognitive dysfunction. Therefore, the positive effects of *Thymus vulgaris* extract on the improvement of memory observed in the present study can be partially ascribed to the antioxidant properties of *Thymus vulgaris* extract.

Thymus vulgaris extract also reduced seizure-induced memory impairment, which resulted in a significant improvement in memory retention in passive avoidance test compared with the Pentylenetetrazole (PTZ) treated group[37]. In addition, *T. vulgaris* extract treatment protects the seizure-induced memory deficit by lowering NO and restoring the antioxidant enzyme CAT and SOD levels[16]. The findings revealed that *Thymus vulgaris* extract exhibits significant inhibitory activity and impedes seizure-induced memory impairment by inhibiting oxidative stress damage.

Apart from essential oils, *T. vulgaris* is a rich source of bioactive compounds such as rosmarinic acid and its derivatives, with rosmarinic acid being reported as the main component[38,39] along with luteolin, apigenin, caffeic acid and their derivatives, and eriodictyol[40]. Rosmarinic acid demonstrated positive effects on the behavioral and cognitive functions of rats treated with scopolamine and displayed potent inhibitory effects on acetylcholine esterase (AChE) and butyrylcholinesterase mRNA levels in the brain, along with a reduction in amyloid precursor protein beta-secretase (BACE) mRNA expression in the frontal cortex and hippocampus. Furthermore, rosmarinic acid exhibited a robust stimulatory effect on butyrylcholinesterase in the hippocampus[41]. Moreover, luteolin had a significant positive impact on alleviating the spatial learning and memory impairment caused by streptozotocin (STZ) treatment. The administration of STZ led to a noticeable reduction in the thickness of the

CA1 pyramidal layer of the hippocampus, but the use of luteolin completely countered this inhibitory effect induced by STZ. These results strongly imply that luteolin could potentially offer protective benefits against learning deficits and preserve hippocampal structures in Alzheimer's disease (AD)[42]. Moreover, a study[43] investigated the impact of apigenin on cognitive function in APP/PS1 double-transgenic mice with AD and explored the underlying mechanisms involved. Over a three-month period of oral treatment with apigenin, significant improvements in learning deficits and memory retention in the APP/PS1 mice were observed. Apigenin was found to influence β-amyloid precursor protein (APP) processing, leading to a reduction in Aβ burden by down-regulating BACE1 and β-CTF levels, thus alleviating Aβ deposition and decreasing insoluble Aβ levels. Furthermore, apigenin demonstrated its efficacy as a superoxide anion scavenger, enhancing the activity of antioxidative enzymes like superoxide dismutase and glutathione peroxidase, which contributed to its ability to combat oxidative stress. Additionally, in the cerebral cortex, apigenin restored the neurotrophic ERK/CREB/BDNF pathway, further contributing to its beneficial effects. Suggesting that apigenin appears to be a promising intervention for ameliorating AD-related learning and memory impairments. Its mechanisms of action involve alleviating Aβ burden, inhibiting the amyloidogenic process, reducing oxidative stress, and restoring the extracellular signal-regulated protein kinase/cyclic adenosine monophosphate-responsive element binding protein/brain-derived neurotrophic factor (ERK/CREB/BDNF) pathway. As such, apigenin holds potential as an alternative therapeutic option for the prevention and treatment of AD. Another study[44] aimed to explore the therapeutic effects of caffeic acid in a rat model of Alzheimer's type dementia induced by STZ. The researchers administered STZ directly into the brains of Wistar rats on two separate days. Caffeic acid was then administered orally at different doses, starting one hour after STZ infusion and continuing for 21 days. To assess learning and memory, the rats underwent Morris water maze and object recognition tasks. At the end of the study, the researchers measured AChE activity and the levels of oxide-nitrosative stress markers in the cortical and hippocampal brain regions. The results showed that STZ administration caused significant impairments in learning, memory, and cholinergic functions in the rats, along with increased levels of oxido-nitrosative stress. However, treatment with caffeic acid significantly and dose-dependently improved these behavioral and biochemical abnormalities induced by STZ. The researchers suggested that the cognitive improvement observed with caffeic acid may be attributed to its antioxidant activity and its ability to restore cholinergic functions in the brain.

An important aspect of this study is the absence of reported side effects associated with *Thymus vulgaris* consumption. This suggests that the intervention was well-tolerated by the participants, further supporting the safety profile of *Thymus vulgaris* as a potential natural intervention for cognitive and mental health concerns.

Conclusions

The findings of the study indicate that incorporating *Thymus vulgaris* leaves into traditional food in a safe amount could potentially boost both future-oriented and past-oriented memory, reduce anxiety and depression symptoms, and enhance sleep quality in university students. Consequently, *Thymus vulgaris* leaves may be regarded as a viable substitute for nonmedical stimulant drug consumption among university students.

Authors' Contributions

Conceptualization, A.A., and E.Q.; methodology, Y.B.; software, O.G.; validation B.O. and A.A.; formal analysis, O.G.; investigation, B.O.; resources, A.A.; data curation, M.W.; writing-original draft preparation, A.A.; writing-review and editing, A.A.; visualization, A.A.; supervision, E.Q.; project administration, A.A.; funding acquisition, B.O. All authors have read and agreed to the published version of the manuscript.

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Ethics Approval

The Ethical Committee of Hashemite University granted the approval for the current study (IRB #:22/6/2022/2023). This trial is registered in the U.S. National Library of Medicine (ID#: NCT05987228).

Data Availability

Data is available upon reasonable request.

Conflicts of Interest
The authors declare no conflicts of interest.

Informed Consent
All participants who were enrolled in this study provided a signed consent form.

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References

1) Micucci M, Protti M, Aldini R, Frosini M, Corazza I, Marzetti C, Mattioli LB, Tocci G, Chiarini A, Mercolini L, Budriesi R. Thymus vulgaris L. Essential Oil Solid Formulation: Chemical Profile and Spasmolytic and Antimicrobial Effects. Biomolecules 2020; 10: 1-22.
2) Tardugno R, Serio A, Purgatorio C, Savini V, Paparella A, Benvenuti S. Thymus vulgaris L. essential oils from Emilia Romagna Apennines (Italy): phytochemical composition and antimicrobial activity on food-borne pathogens. Nat Prod Res 2022; 36: 837-842.
3) Dauqan EMA, Abdullah A. Medicinal and Functional Values of Thyme (Thymus vulgaris L.) Herb. J Appl Biol Biotechnol 2017; 5: 17-22.
4) Oliveira JR de, de Jesus Viegas D, Martins APR, Carvalho CAT, Soares CP, Camargo SEA, Jorge AOC, de Oliveira LD. Thymus vulgaris L. extract has antimicrobial and anti-inflammatory effects in the absence of cytotoxicity and genotoxicity. Arch Oral Biol 2017; 82: 271-279.
5) Al-Shuneigat J, Al-Sarayreh S, Al-Saraireh Y, Al-Qudah M, Al-Tarawneh I, Albataineh E. Effects of wild Thymus vulgaris essential oil on clinical isolates biofilm-forming bacteria. IOSR J Dent Med Sci 2014; 13: 62-66.
6) Al-Shuneigat J, Al-Sarayreh S, Al-Saraira Y, AlQudah M, Al-Tarawneh I, Al-Dalaen S. Chemical composition and antimicrobial activity of the essential oil of wild Thymus vulgaris grown in South Jordan. IOSR J Pharm Biol Sci 2014; 9: 78-83.
7) Oran SA. The Status of Medicinal Plants in Jordan. J Agric Sci Technol 2014; 4: 461-467.
8) Kamal Al-Halaseh L. Some herbal medicine traditionally used in south Jordan. Al-Azhar J Pharm Sci 2013; 47: 63-82.
9) Nadia Z, Rachid M. Antioxidant and Antibacterial Activities of thymus vulgaris. Med Aromat Plant Res J 2013; 1: 5-11.
10) Al-Bayati FA. Synergistic antibacterial activity between Thymus vulgaris and Pimpinella anisum essential oils and methanol extracts. J Ethnopharmacol 2008; 116: 403-406.
11) Vigo E, Cepeda A, Perez-Fernandez R, Gualillo O. In-vitro anti-inflammatory effect of Eucalyptus globulus and Thymus vulgaris: nitric oxide inhibition in J774A.1 murine macrophages. J Pharm Pharmacol 2004; 56: 257-263.
12) Catella C, Camero M, Lucente MS, Fracchiolla G, Sblano S, Tempesta M, Martella V, Buonavoglia C, Lanave G. Virucidal and antiviral effects of Thymus vulgaris essential oil on feline coronavirus. Res Vet Sci 2021; 137: 44-47.
13) Nasra S, Meghani N, Kumar A. Nanoemulsion-Based System as a Novel and Promising Approach for Enhancing the Antimicrobial and Antitumoral Activity of Thymus vulgaris (L.) Oil in Human Hepatocellular Carcinoma Cells. Appl Biochem Biotechnol 2023; 1-22.
14) Sandi S, Laconi EB, Sudarman A, Wiryawan KG, Mangunwijaja D. The Nutrient Quality of Cassava by Addition of Cow Rumen Fluid Enzyme. Agric Sci Technol 2011; 1: 1122-1125.
15) Thymus L, Dessalegn E. Evaluation of In vitro Antidiabetic Potential of Thymus schimperi R. and Thymus vulgaris L. J Heal Med Nurs 2019; 69: 9-16.
16) Skalicka-Woźniak K, Walasek M, Aljarba TM, Stapleton P, Gibbons S, Xiao J, Łuszczki JJ. The anticonvulsant and anti-plasmid conjugation potential of Thymus vulgaris chemistry: An in vivo murine and in vitro study. Food Chem Toxicol 2018; 120: 472-478.
17) Komaki A, Hoseini F, Shahidi S, Baharlouei N. Study of the effect of extract of Thymus vulgaris on anxiety in male rats. J Tradit Complement Med 2016; 6: 257-261.
18) Simeon JO, Simeon JO, Zubairu SA, Adegbenga AD. Concomitant administration of ethanol leaf extract of Thymus vulgaris on Diazepam - induced Sedation and Hypnosis in Wister Rat. J Pharm Biol Sci 2021; 16: 04-09.
19) Nikolić M, Glamočlija J, Ferreira ICFR, Calhelha RC, Fernandes Â, Marković T, Marković D, Giweli A, Soković M. Chemical composition, antimicrobial, antioxidant and antitumor activity of Thymus serpyllum L., Thymus algeriensis Boiss. and Reut and Thymus vulgaris L. essential oils. Ind Crops Prod 2014; 52: 183-190.
20) Asadbegi M, Yaghmaei P, Salehi I, Komaki A, Ebrahim-Habibi A. Investigation of thymol effect on learning and memory impairment induced by intrahippocampal injection of amyloid beta peptide in high fat diet- fed rats. Metab Brain Dis 2017; 32: 827-839.
21) Capibaribe VCC, Vasconcelos Mallmann AS, Lopes IS, Oliveira ICM, de Oliveira NF, Chaves R de C, Fernandes ML, de Araujo MA, da Silva DMA, Valentim JT, Maia Chaves Filho AJ, Macêdo DS, de Vasconcelos SMM, de Carvalho AMR, de Sousa FCF. Thymol reverses depression-like behaviour and upregulates hippocampal BDNF

levels in chronic corticosterone-induced depression model in female mice. J Pharm Pharmacol 2019; 71: 1774-1783.

22) Azizi Z, Ebrahimi S, Saadatfar E, Kamalinejad M, Majlessi N. Cognitive-enhancing activity of thymol and carvacrol in two rat models of dementia. Behav Pharmacol 2012; 23: 241-249.

23) Surendran S, Qassadi F, Surendran G, Lilley D, Heinrich M. Myrcene—What Are the Potential Health Benefits of This Flavouring and Aroma Agent? Front Nutr 2021; 8: 1-14.

24) Akan Z, Dikildal M, Ozdemir H, Oto G, Yilmaz A. Effects of Thymus Vulgaris L. and Thymbra Spicata L. on diabetes mellitus associated cognitive impairment and neuropathy: Thymus Vulgaris and Cognitive Function Improvements. Med Sci Discov 2014; 1: 16-21.

25) Rabiei Z, Mokhtari S, Asgharzade S, Gholami M, Rahnama S, Rafieian-kopaei M. Inhibitory effect of Thymus vulgaris extract on memory impairment induced by scopolamine in rat. Asian Pac J Trop Biomed 2015; 5: 845-851.

26) Sammi SR, Trivedi S, Rath SK, Nagar A, Tandon S, Kalra A, Pandey R. 1-Methyl-4-propan-2-ylbenzene from Thymus vulgaris Attenuates Cholinergic Dysfunction. Mol Neurobiol 2017; 54: 5468-5481.

27) Ozen NS, Ercan I, Irgil E, Sigirli D. Anxiety Prevalence and Affecting Factors Among University Students. Asia Pac J Public Health 2010; 22: 127-133.

28) Xiao M, Liu X, Huang Q, He S. The effect of loneliness on depression in young people : a multiple mediated effects model. Eur Rev Med Pharmacol Sci 2023; 27: 8614-8627.

29) Sarokhani D, Delpisheh A, Veisani Y, Sarokhani MT, Manesh RE, Sayehmiri K. Prevalence of depression among university students: A systematic review and meta-analysis study. Depress Res Treat 2013; 2013: 1-7.

30) Vrecko S. Just How Cognitive Is "Cognitive Enhancement"? On the Significance of Emotions in University Students' Experiences with Study Drugs. AJOB Neuroscience 2013; 4: 4-12.

31) Partridge BJ, Bell SK, Lucke JC, Yeates S, Hall WD. Smart Drugs "As Common As Coffee": Media Hype about Neuroenhancement. PLoS One 2011; 6: 1-8.

32) Crawford JR, Smith G, Maylor EA, Della Sala S, Logie RH. The Prospective and Retrospective Memory Questionnaire (PRMQ): Normative data and latent structure in a large non-clinical sample. Memory 2003; 11: 261-275.

33) Al-Gamal E. Testing of the Hospital Anxiety and Depression Scale in Patients With Chronic Obstructive Pulmonary Disease. Int J Nurs Knowl 2017; 28: 94-99.

34) Albqoor MA, Shaheen AM. Sleep quality, sleep latency, and sleep duration: a national comparative study of university students in Jordan. Sleep Breath 2021; 25: 1147-1154.

35) Li H, Qin T, Li M, Ma S. Thymol improves high-fat diet-induced cognitive deficits in mice via ameliorating brain insulin resistance and upregulating NRF2/HO-1 pathway. Metab Brain Dis 2017; 32: 385-393.

36) Capatina L, Todirascu-Ciornea E, Napoli EM, Ruberto G, Hritcu L, Dumitru G. Thymus vulgaris Essential Oil Protects Zebrafish against Cognitive Dysfunction by Regulating Cholinergic and Antioxidants Systems. Antioxidants 2020; 9: 1-18.

37) Hosseini A, Azizi V, Allahyari F. Effects of Thymus vulgaris on passive avoidance learning and oxidative stress in pentylenetetrazole-induced model of memory impairment in the male Wistar rats. J Cell Neurosci Oxidative Stress 2021; 13: 985-993.

38) Chizzola R, Michitsch H, Franz C. Antioxidative Properties of Thymus vulgaris Leaves: Comparison of Different Extracts and Essential Oil Chemotypes. J Agric Food Chem 2008; 56: 6897-6904.

39) Pereira E, Pimenta AI, Calhelha RC, Antonio AL, Verde SC, Barros L, Santos-Buelga C, Ferreira ICFR. Effects of gamma irradiation on cytotoxicity and phenolic compounds of Thymus vulgaris L. and Mentha x piperita L. LWT - Food Sci Technol 2016; 71: 370-377.

40) Pacifico S, Piccolella S, Papale F, Nocera P, Lettieri A, Catauro M. A polyphenol complex from Thymus vulgaris L. plants cultivated in the Campania Region (Italy): New perspectives against neuroblastoma. J Funct Foods 2016; 20: 253-266.

41) Ozarowski M, Mikolajczak PL, Piasecka A, Kachlicki P, Kujawski R, Bogacz A, Bartkowiak-Wieczorek J, Szulc M, Kaminska E, Kujawska M, Jodynis-Liebert J, Gryszczynska A, Opala B, Lowicki Z, Seremak-Mrozikiewicz A, Czerny B. Influence of the Melissa officinalis Leaf Extract on Long-Term Memory in Scopolamine Animal Model with Assessment of Mechanism of Action. Evidence-based Complement Altern Med 2016; 2016: 1-18.

42) Wang H, Wang H, Cheng H, Che Z. Ameliorating effect of luteolin on memory impairment in an Alzheimer's disease model. Mol Med Rep 2016; 13: 4215-4220.

43) Zhao L, Wang JL, Liu R, Li XX, Li JF, Zhang L. Neuroprotective, Anti-Amyloidogenic and Neurotrophic Effects of Apigenin in an Alzheimer's Disease Mouse Model. Mol 2013; 18: 9949-9965.

44) Deshmukh R, Kaundal M, Bansal V, Samardeep. Caffeic acid attenuates oxidative stress, learning and memory deficit in intra-cerebroventricular streptozotocin induced experimental dementia in rats. Biomed Pharmacother 2016; 81: 56-62.