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Research Article

Chamomile (*Matricaria chamomilla* L.) Essential Oil and its Potential Against Stress, Anxiety, and Sleep Quality

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ABSTRACT

Introduction: This investigation aimed to evaluate the effect of *Matricaria chamomilla L* essential oil on stress, anxiety, and sleep quality. **Methods:** The essential oils were extracted by hydrodistillation using a modified Clevenger-type apparatus, and the chemical composition was performed by Gas chromatography-mass spectrometry (GC–MS). Furthermore, a study was conducted where 128 participants were divided into two groups: a control group and an experimental group treated with essential oils. Stress, anxiety, and sleep quality were evaluated using the Perceived Stress Scale (PSS–10), the Zung Self-Rating Anxiety Scale (SAS), and the Pittsburgh Sleep Quality Inventory (PSQI). In addition, cortisol was measured. **Results:** Chemical analysis showed that α-Bisabolol oxide A exhibited the highest concentration at 30.42%, followed by α -Bisabolol (10.94%), α-Bisabolone oxide A (9.82%), and spathulenol (8.83%). Stress, anxiety, sleep quality, and cortisol scores decreased in the post-test study phase compared to the pre-test in the experimental group ($p<0.05$). Important effect size was found in the case of anxiety ($d = 1.203$; $\Delta = 1.246$), while medium effects were observed for stress ($d = 0.701$; $\Delta = 0.633$) and sleep quality ($d = 0.888$; $\Delta = 0.732$), while cortisol showed small changes ($d=0.374$; $\Delta =0.357$). **Conclusion:** The study showed the potential of Chamomile essential oils to reduce stress and anxiety levels and improve sleep quality.

Key words: essential oils, stress, anxiety, sleep quality, *Matricaria chamomilla*.

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INTRODUCTION

Based on the existing literature, it is assumed that the destabilizing effects of the coronavirus pandemic may not be immediately apparent but become more pronounced once the pandemic phase has passed [1]. The current findings imply that stress related to COVID-19 has a double impact on mental health; one year after the pandemic's apex, anxiety, depression, and other mental disorders still coexist in the population[2]. Stress significantly impacts mental health, as evidenced by activating the stress axis in anxiety and depressive disorders[3].

In addition, anxiety disorders exhibit the highest prevalence among mental illnesses, affecting up to 34% of the adult population throughout their lifetimes[4]. These disorders encompass a variety of conditions, including panic disorder with or without agoraphobia, generalized anxiety disorder (GAD), social anxiety disorder (SAD), specific phobias, and separation anxiety disorder[5].

Additionally, sleep disturbances are frequently observed among the general population, escalating their incidence during the pandemic [6]. Individuals affected by sleep disorders often exhibit dissatisfaction with the quality, timing, and quantity of their sleep[7].

Aromatherapy is a complementary and alternative medicine that utilizes essential oils (EOs) to attain significant therapeutic goals[8]. The use of natural aromatherapy as a supplementary treatment for mental diseases, specifically anxiety, and depression, has increased significantly in recent years; in addition, there is a growing body of research dedicated to investigating the therapeutic mechanisms underlying this form of treatment[9].

EOs are the secondary metabolites derived from aromatic plants, comprising an intricate blend of volatile organic compounds (VOCs)[10]. EOs are contained within several structures of the plants' thallus, including reservoirs, glandular hairs, specialized cells, and intracellular spaces[11]. These oils are crucial in safeguarding plants against pathogenic contacts and temperature variations[12].

Matricaria chamomilla has been widely employed in several traditional medical traditions. Numerous preclinical and clinical studies have been conducted to evaluate the various activities exhibited by M. chamomilla, including antibacterial, antioxidant, anti-inflammatory, antiulcer, hypoglycemic, hypolipidemic, cardioprotective, hepatoprotective, neuroprotective, nephroprotective, antispasmodic, wound healing, and anticancer properties, as well as medical conditions including anxiety, sleep deprivation, and depression[13].

This study evaluates the effects of Chamomile (*Matricaria chamomilla* L.) essential oil on stress, anxiety, and sleep quality.

MATERIALS AND METHODS

Plant material and oil isolation

The flowers of *Matricaria chamomilla* L were purchased from a Peruvian supplier (Ayacucho,

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Perú). The samples were ground, and the powdered plant material (100g) was placed in a round bottom flask with 1000 ml of distilled water and connected to a modified Clevenger-type apparatus. Hydrodistillation was completed for three hours after boiling. Finally, the oil was dried with anhydrous sodium sulfate (Na_2SO_4) and stored in a refrigerator in amber glass vials at +4°C for further use in experiments[14].

Essential oil analysis

The gas chromatography-mass spectrometry (GC/MS) analyses were conducted on a Hewlett-Packard 6890 gas chromatograph equipped with a column HP-5MS (30 m x 0.25 mm inner diameter, 0.25 µm film thickness) and a Hewlett-Packard 5972 mass spectrometer. The initial temperature of the column was set at 50 ° C, which was maintained for 6 minutes, followed by an increase of temperature by 3 ° C per minute to 240°C, followed by an increase of temperature by 15 ° C per minute to 300°C, which was maintained for 3 minutes. The injector port temperature was 290°C, and 1.5 mL/min of helium was used as the carrier gas. The mass spectrometer's ionization voltage in the EI mode was 70 eV. The ionization source temperature was 250 ° C. Essential oil constituents were identified by comparing their mass spectra and retention indices (RI) to those of authentic samples or the NIST 2011 mass spectra library and the Wiley and Adams libraries spectra[15].

Study design and sample

An experimental study with measures at pretest-posttest was conducted. A power analysis was completed using 'G Power 3' with a moderate effect size, an α level of 0.05, and a power of 0.80. The number of participants required to determine the difference in effect was 128, 64 per group, comprising a control group (CG) treated with a placebo and an experimental group (EG) treated with aromatherapy based on *Matricaria chamomilla* essential oil (MCEO).

Instruments

Perceived Stress Scale (PSS–10):

This ten-item scale measures stressful life circumstances and situations. On a 5-point Likert scale (never = 0; almost never = 1; sometimes = 2; fairly often = 3; very often = 4), respondents are asked to indicate their frequency of occurrence). Items 4, 5, 7, and 8 were reversed [16]. For this study, the validity and reliability test for the local population and context was determined using the item test method, with values greater than 0.51 for each item; additionally, the reliability coefficient of 0.98 was found using the split-half method.

Zung Self-Rating Anxiety Scale (SAS): This scale consists of 20 items, scored each from 1 to 4 (1= non or a little of the time, 2 = some of the time, 3 = good part of the time, 4 = most of the time)[17]. This instrument shows the validity and reliability for the applied population [18].

Pittsburgh Sleep Quality Inventory (PSQI): This questionnaire contains 18 items grouped into seven components. The score of each item ranges from 0 to 3. The sum score of these seven components is considered as the total PSQI score, which is 0–21. Scores greater than 5 show low sleep quality[19]. This instrument demonstrates validity and reliability for the applied population [20].

Secondary outcomes measures

Cortisol: A blood sample was collected from the subjects at 8 a.m. to ascertain cortisol levels. The concentration of serum cortisol (ug/dL) was quantified using the Electro-Chemiluminescence method using the Cobas e411 machine (USA) and the Roche kit (Germany). The referential range was 6.20-19.40 ug/dL[21].

Study procedure

A free aromatherapy course was offered through social media to recruit participants. One hundred thirty-nine people were enrolled, and 128 participated in this investigation between February 2023 and March 2023. The inclusion criteria encompassed adult male and female participants. In addition, they were required to have PSS-10 scores above 9, SAS scores above 49, and PSQI scores above 5. Meanwhile, exclusion criteria were participants who had engaged in prior meditation, tai chi, or yoga practices, had psychiatric or pharmaceutical treatment, were pregnant, had flu symptoms, or experienced loss of smell due to COVID-19. A total of 64 individuals were randomly assigned to each group using a random number table, with the randomization process being conducted by an individual who was not directly involved in the study. After group selection, a basic questionnaire of sociodemographic characteristics was applied to characterize the participants. In addition, instruments were administered, and cortisol levels were recorded (pretest). The course explained the benefits of aromatherapy and how to apply essential oils, providing the oils to everyone for a live demonstration. Afterward, each participant received a weekly aromatherapy kit with everything they needed for oil applications, including an instruction manual. However, those in the EG received the kits with chamomile essential oil. In contrast, the participants in the control group received the placebo kit, a commercial shampoo (Johnson's® baby shampoo, free from sulfates and parabens). Each kit was delivered to everyone each week until the investigation was completed. Additionally, online meetings were held weekly to monitor applications and provide feedback. The EOs application was according to the methodology of Reza et al.[22] with a few modifications, where the participants were asked to pour two drops of EOs or placebo on a cotton ball using a dropper. Next, the cotton ball was held under the participant's nose while they closed their eyes and took ten deep breaths. Next, the cotton was pinned to the collar of the participant for 30 minutes. After that, the participant unpinned and disposed of the cotton ball. The applications were every day for eight weeks. It was suggested that applications be made at night, 5 minutes before bedtime, and upon awakening. At the end of the intervention, the posttest was taken using the same procedures as in the pretest (Fig. 1). All participants were informed about the investigation program goals and signed a consent form in which confidentiality and anonymity were guaranteed. The study protocol was approved by the Institutional Review Board (IRB). Furthermore, this investigation was carried out by the Declaration of Helsinki.

Data Analysis

Data were presented as mean ± standard deviation (SD). Differences in sociodemographic and clinical data of participants were analyzed using the Pearson Chi-Square and Likelihood-ratio tests. The Mann-Whitney U test was used to determine significant differences between the groups. In contrast, the Wilcoxon test was used to determine significant differences between the study phases, in which $p < 0.05$ was considered statistically significant. These tests were used because the data did not conform to the normal distribution. Cohen's D and Glass's Δ Posttest were calculated between the groups for post-test scores and statistical power. Statistical analysis was performed using SPSS v.27.0 (IBM Corp., Armonk, NY, USA) and Prism 8 (GraphPad, CA, USA).

RESULTS

Table 1 revealed the chemical composition of the Chamomile Essential Oil, where 31 compounds were detected, representing 95.23% (area percent) of the total oil content. Notably, α-Bisabolol oxide A exhibited the highest concentration at 30.42%, followed by α -Bisabolol (10.94%), α-Bisabolone oxide A (9.82%), spathulenol (8.83%), cis-en-yn-Dicycloether (6.94%), and Trans-β-farnesene (5.36%) as the most predominant.

The comparison between the CG and the EG is presented in Table 2. Both groups were predominantly female, with 68.5 percent (n=37) of the CG and 73.2 percent (n=41) of the EG being female. The majority of participants in both groups were between the ages of 36 and 45, with

Table 1: Main chemical constituents (%) of the essential oils of *Matricaria chamomilla* L.

N°	Compounds	RI	%
1	α-pinene	930	0.36
2	Camphene	956	t
3	Butyl butyrate	998	0.14
4	para-Cymene	1023	0.25
5	n-Octanol	1049	0.12
6	Linalool	1086	0.18
7	Borneol	1120	0.29
8	para-Cymene-8-ol	1135	0.12
9	3-Decanol	1142	0.20
10	Ethyl octanoate	1154	0.17
11	Hexyl 3-methyl butanoate	1173	0.40
12	Trans-anethol	1205	0.36
13	Azulene	1226	0.14
14	β-Elemene	1260	0.12
15	β-Caryophyllene	1277	1.10
16	γ-Elemene	1283	0.70
17	Trans-β-farnesene	1342	5.36
18	Germacrene D	1349	0.31
19	α-muurolene	1358	0.65
20	γ-Cadinene	1365	0.22
21	Spathulenol	1422	8.83
22	Caryophyllene oxide	1565	0.37
23	Viridiflorol	1588	1.59
24	γ-Eudesmol	1623	2.10
25	α-Bisabolol oxide B	1650	9.35
26	α -Bisabolol	1696	10.94
27	α-Bisabolone oxide A	1743	9.82
28	α -Bisabolol oxide A	1752	30.42
29	Chamazulene	1773	2.40
30	cis-en-yn-Dicycloether	1890	6.94
31	trans-en-yn-dicycloether	1912	1.28
	Total identified (%)		95.23

RI, Retention index; t= traces (<0.1%)

Table 2. Sociodemographic and Clinical Characteristics of Participants.

Socio-demographic data	CG	EG	Total	p-Value
Gender				
Male	17 (31.5%)	15 (26.8%)	32 (29.1 %)	0.588[a]
Female	37 (68.5%)	41 (73.2%)	78 (70.9%)	
Age(yr)				
18-25	9 (16.7%)	11 (19.6%)	20 (18.2%)	0.901[a]
26-35	19 (35.2%)	20 (35.7%)	39 (35.5%)	
36-45	26 (48.1%)	25 (44.7%)	51 (46.3%)	
Level of education				
Undergraduate	10 (18.5%)	11 (19.6%)	21 (19.1%)	0.862[a]
Graduate	28 (51.9%)	31 (55.4%)	59 (53.6%)	
Postgraduate	16 (29.6%)	14 (25.0%)	30 (27.3%)	
Marital status				
Married	29 (53.7%)	31 (55.4%)	60 (54.5%)	0.920[b]
Unmarried	20 (37%)	21 (37.5%)	41 (37.3%)	
Divorced	5 (9.3%)	4 (7.1%)	9 (8.2%)	
Clinical treatment provided				
Psychological	8 (14.8%)	11 (19.6%)	19 (17.3%)	0.503[a]
Pharmacological	0 (0%)	0 (0%)	0 (0%)	
None	46 (85.2%)	45 (80.4%)	91 (82.7%)	

[a]p-value is calculated by the Pearson Chi-Square test.
[b]p-value is calculated by the Likelihood-ratio test.

Table 3. Pretest and posttest scores of psychological variables and physiological parameters.

Groups	Pretest		Posttest		p-Value[b]
	Mean	SD	Mean	SD	
CG					
Stress	22.13	±5.79	22.19	±6.79	0.670
Anxiety	58.98	±4.88	59.41	±5.83	0.823
Sleep Quality	8.11	±6.05	8.06	±5.60	0.539
EG					
Stress	22.16	±5.98	17.89	±5.38	0.001*
p-value[a]	0.945		0.000*		
Anxiety	59.03	±5.09	52.14	±6.24	0.001*
p-value[a]	0.897		0.020*		
Sleep Quality	8.55	±6.51	3.96	±3.35	0.001*
p-value[a]	0.914		0.040*		

*p<0.05
[a]p-value is calculated by the Whitney U test between groups.
[b]p-value is calculated by the Wilcoxon test between study phases.

Table 4. Cohen's D and Glass's Δ Posttest between the Control group and Experimental group in posttest outcomes and observed power (1-β).

Variables	Cohen's d Posttest	Glass's Δ Posttest	1-β
Stress	0.701	0.633	0.944
Anxiety	1.203	1.246	0.999
Sleep Quality	0.888	0.732	0.994
Cortisol	0.374	0.357	0.475

48.1 percent (n=26) of CG and 44.7 percent (n=25) of EG in this age range. More than half of the participants in both groups had a graduate or post-graduate degree. Notably, the majority of participants in both groups, 85.2% (n=46) in the CG and 80.4% (n=45) in the EG, did not receive clinical treatment. Using the Pearson Chi-square test, there were no statistically significant differences between these outcomes (p>0.05). Finally, regarding marital status, a little more than half of the participants in both groups were married, with 53.7 percent (n=29) for CG and 55.4 percent (n=31) for EG. In addition, 37.5% (n=20) of CG and 37.5% (n=21) of EG were single, and only a tiny minority were divorced. The likelihood ratio test did not reveal a statistically significant difference (p>0.05) between the group conformations.

Table 3 presents the average score and standard deviations for stress, anxiety, and sleep quality. It is observed that there were no significant variations in the pretest scores across the groups, as indicated by a p-value greater than 0.05. Nevertheless, it is worth noting that there were notable disparities observed in the post-test results between the control group (CG) and the experimental group (EG) at a statistically significant level (p<0.05). The above outcomes were computed using the Mann-Whitney U test to compare between groups. Furthermore, regarding the study phase, there were no significant variations in CG scores between the pretest and posttest (p>0.05). However, it is worth noting that significant variations were seen among all variables during the various study periods (p<0.05). The Wilcoxon test was utilized to calculate all of the results mentioned above.

Figure 2 shows the cortisol scores before and after intervention in CG and EG, where pretest scores did not differ between groups, as demonstrated by a p> 0.05. However, substantial differences in post-test outcomes were identified between the CG and EG (p<0.05). Comparisons between groups were made using the Mann-Whitney U test. CG scores did not differ between pretest and posttest (p>0.05) over the study term. However, substantial differences were observed in cortisol scores across study phases (p<0.05). All findings were calculated using the Wilcoxon test.

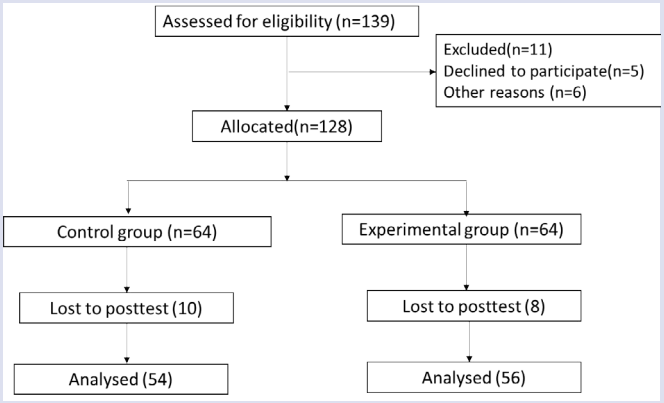

Figure 1. Flowchart of the study.

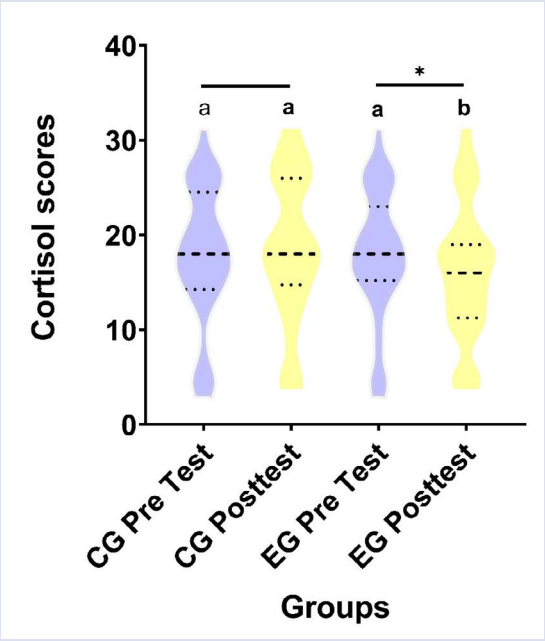

Figure 2. Cortisol scores before and after intervention in CG and EG.

Without*: p>0.05. With*: p<0.05, calculated by Wilcoxon test between study phases.

a: p>0.05. b: p<0.05, calculated by Mann Whitney U test between groups.

Besides, Table 4 shows the scores obtained by the Cohen's D and Glass's Δ tests, as well as the statistical power (1-β), where values between 0.2 and 0.5 show small changes as in the case of cortisol (d=0.374; Δ=0.357). Scores superior to 0.5 until one shows moderate changes, such as stress (d = 701; Δ = 0.631) and sleep quality (d=0.888; Δ=0.732). Scores over one are considered a large effect, as in the case of anxiety (d = 1.203; Δ = 1.246). Finally, this table shows the observed power (1-β), where stress (1-β=0.944), anxiety (1-β=0.999), and sleep quality (1-β =0.994) showed an adequate statistical. It is noteworthy to specify that the standard for the desired power is 0.80.

DISCUSSION

Natural medicines have unique advantages in preventing and treating mental health issues compared to chemically synthesized medications [23]. In this sense, it is imperative to search for natural compounds to find new sources to help to solve mental health problems. In this order of ideas, the results of this investigation found that α-Bisabolol oxide A exhibited the highest concentration, followed by α -Bisabolol, α-Bisabolone oxide A, and spathulenol are the most predominant. These findings partially agreed with two investigations [15,24]. However, other studies found that (E)-β-farnesene [14,25] was the major compound. Indeed, several elements, including the isolation method, ambient conditions, and various pressures, can significantly influence the composition and overall quality of the extracted essential oil [26]. An experiment showed that the contents of Chamazulene and α-Bisabolol increased after the treatment with salicylic acid and heat stress conditions[27]. In the same way, the irrigation regime can also influence the composition of Chamomile EOs[24]. Thus, the type of essential oil profile and flowering are controlled genetically, whereas their quantities depend on changeable external factors, explaining the variability of chemical composition.

On the other hand, concerning the sociodemographic data of participants, our results coincide with previous studies where the users of Complementary and Alternative Medicine (CAM) are predominantly women, middle-aged, and more educated [28,29]. In Latin America, the scenario is almost the same; the prevalence of the use of CAM is high in women and those with a higher education [30]. This phenomenon can be attributed to the fact that individuals with higher educational attainment and occupational status tend to possess more excellent knowledge regarding CAM and have more significant financial resources to afford such treatments; additionally, disparities in values and personality traits between genders may contribute to the higher utilization of CAM among women [31]. Nonetheless, additional research is needed to gain a more comprehensive understanding of these differences.

A study mentions that the main components of Chamomile EOs evidenced different pharmacological activities like antidepressants and antistress [32]. In addition, a study evidenced decreased stress levels after inhalation of Chamomile EOs [33]. This follows the results in this investigation, where a moderate stress level was found before the intervention, and after the application of the EOs, stress decreased to low levels with moderate effect size and adequate statistical power. It is known that the main components of *M. chamomilla* EOs, such as α-bisabolol [34,35] and spathulenol [36], are anti-inflammatory agents. The literature revealed that changes in the production of pro-inflammatory cytokines take part in the homeostatic responses to psychological stress [37,38]. In this sense, the relationship between inflammation and stress is complex and poorly understood. Some biobehavioral interventions can alleviate the inflammatory burden associated with chronic stress [39,40]; in the same way, anti-inflammatory properties of Chamomile EOs reducing inflammation may help alleviate some of the symptoms of stress, but more research is needed to understand this relationship as well to test this hypothesis thoroughly.

In this study, while the post-intervention scores demonstrated a significant reduction in anxiety levels, the average scores did not transition from the 'mild anxiety' to 'normal anxiety' category according to the Zung scale norms. However, it is crucial to highlight that the observed change in scores was associated with large effect size, emphasizing the practical significance of the intervention's impact on anxiety reduction. Further bolstering these findings is the robust statistical power. As evidence that backs up our conclusions, there is also evidence of the anxiolytic effect of Chamomile EOs in clinical conditions [33,41-43]. This property can be attributed to α-Bisabolol, a sesquiterpene whose mechanism for anxiety involves the GABAergic transmission system. The $GABA_A$ receptor is an ion channel that, when activated, allows the influx of chloride ions into the neuron, leading to hyperpolarization and decreased neuronal excitability. Specifically, bisabolol may enhance the activity of GABA by binding to the $GABA_A$ receptors or increasing GABA release in the brain. This leads to increased inhibition of neuronal activity and reduced anxiety[44].

In addition, a significant improvement in sleep quality was found after the intervention, with moderate effect size and adequate statistical power. This is in accordance with some reports from various contexts indicating that the administration of Chamomile EOs improves sleep quality [45-47]. According to an investigation, some compounds, including apigenin, chamazulene, bisabolol, and farnesene, bind benzodiazepine sites and induce central nervous system tranquilization[48]. In addition, bisabolol exerts a soothing effect and could improve sleep quality, as sedatives are commonly used to treat insomnia and other sleep disorders[44]. It also could be possible that chamomile EOs on anxiety and sleep have a shared mechanism, with GABAergic and benzodiazepine systems working in tandem, mutually reinforcing, but further investigation is needed to understand these mechanisms better.

Cortisol plays a complex role in stress, anxiety, and sleep [49]. Chronic stress significantly contributes to increased cortisol levels, an overactive hypothalamic-pituitary-adrenal (HPA) axis, and a persistent state of arousal that is anxiety-inducing and sleep-inducing that contribute to the initiation as well as the perpetuation of chronic insomnia [50,51]. This study found a decrease in cortisol levels after the intervention with EOs in the EG. Thus, post-intervention, the observed reduction in cortisol levels could correlate with diminished stress and anxiety alongside enhanced sleep quality. However, the small effect size and inadequate statistical power found for cortisol, despite the contrast with robust statistical power for stress, anxiety, and sleep quality, could be interpreted as the intervention's efficacy in alleviating these adverse states might be mediated through other physiological or psychological pathways, which are not solely dependent on cortisol modulation. These findings underscore that the dynamics of stress, anxiety, and sleep quality are multifactorial, with cortisol being just one of many contributing factors[50,52,53].

Finally, these results are not definitive because of limitations; thus, there is a need for further rigorous investigations to understand better the therapeutic potential and mechanisms of action of Chamomile EOs in managing mental health issues.

CONCLUSION

The study showed the potential of Chamomile Essential Oils to reduce stress and anxiety levels and improve sleep quality. Further research is needed to understand these findings' precise mechanisms and applicability.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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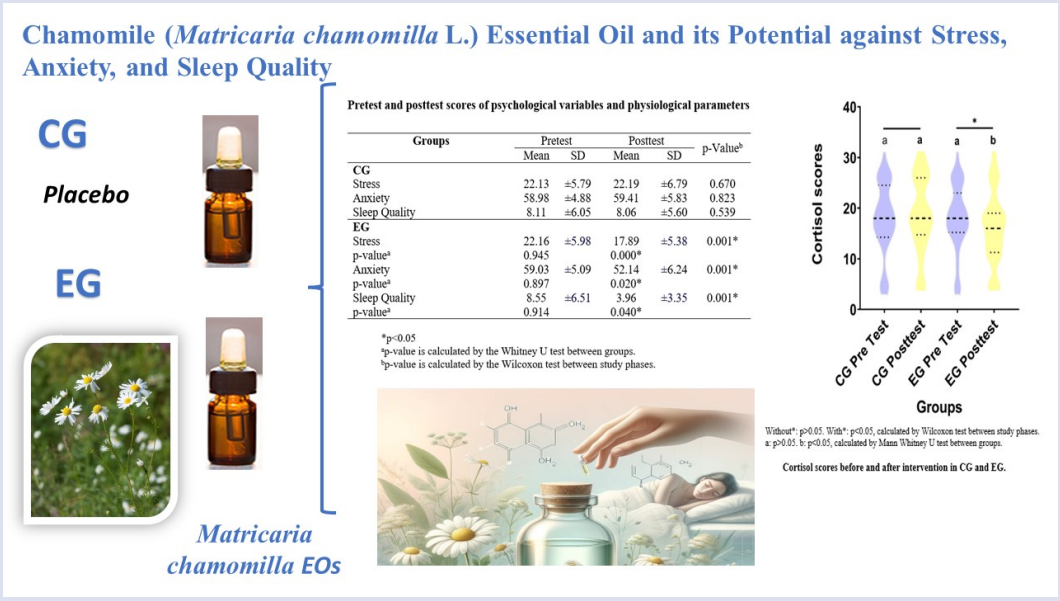
GRAPHICAL ABSTRACT



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