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An ethnopharmacological study and the therapeutic reference values of phytomedicines used for relieving minor CNS disorders

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Abstract

The current study aims to evaluate the practice of prescribing and dispensing herbal medicines by patients and herbalists for treating minor CNS disorders. Two groups of participants were recruited: adults who admitted using herbal medications and herbalists. A questionnaire with multiple compartments was distributed using social media. The sample size was 384, which was compatible with the non-probability convenience sampling strategy. The reference therapeutic, used and combined values were computed. The majority of the respondents were females (69 %) in their second and third decades (36.2 and 34.9 respectively), acquired at least a college degree (~72.9 %). They admitted having a good knowledge of alternative therapy and considered them safe (76.8 % and 58.6 % respectively). Around 55 % of the respondents have trust issues with health service providers and prefer to seek the help of expert herbalists. The computed therapeutic values disclosed significant differences between the analyzed herbs. The highest parameter was for the anise (0.4133 ± 0.11719), reflecting that it has the highest concentration. Peppermint occupied the second order (0.19 ± 0.036060). Tea placed third (0.1333 ± 0.07572), followed by chamomile (0.1033 ± 0.10017), Ginger (0.0333 ± 0.03055) and lemon balm (0.05 ± 0.05568). Rosemary and Marjoram showed comparatively lower means. The herbalists were in complete agreement on the use of anise and chamomile for anxiety, lemon balm and anise for insomnia, hibiscus for tachycardia, caraway for COVID-related stress and cinnamon for premenstrual syndrome. Despite the approved efficiency and safety of some herbal remedies, it is mandatory to strengthen trust in healthcare.

Keywords

anti-anxiety; phytotherapy; insomnia; ethnopharmacology

Introduction

Generalized anxiety is a common disorder affecting around 10 % of the adult population. The patient undergoes unfocused, persistent and excessive worries about unpredicted events unrelated to recent stressful circumstances. Nevertheless, the symptoms might be exacerbated by day-to-day stressful situations (1, 2). Restlessness, irritability, feeling endangered, tachycardia, sweating, interrupted sleep and others are characterized symptoms of general anxiety (3, 4). Therefore, anxiety is not only a psychological state that could affect behaviour and cognitive ability, but it is also considered a physiological disorder (5).

It is relatively obscure how the anxiety disorder evolved, even though some scientific pieces of evidence supposed that the dysregulation in the transmission of neurotransmitters such as serotonin and Gamma-aminobutyric acid (GABA) might have a substantial role (4).

Sleep disturbances could arise from various physiological and psychological disorders. Insomnia is either a chronic matter that lasts longer than 3 months or a short-term one where the symptoms are momentary or brief (5). It was reported that almost 50 % of those suffering from insomnia are developing it chronically (6). Females are more susceptible to insomnia, according to a recently published study, where almost 60 % of the female -study sample has experienced sleep disorder (1, 7). Emphasis on that, Yang and colleagues have reported in a cross-sectional study that the symptoms of anxiety and poor sleep quality in women exceed those in men in a population of patients diagnosed with heart failure with preserved ejection fraction (8). Moreover, poor sleep quality might precipitate anxiety or exacerbate the existing disorder (9). Analogously, exposure to stressful situations will unequivocally impair the sleep quality (10). Other forms of anxiety are phobias, panic and social and obsessive-compulsive disorders. The symptoms range from mild to moderate and severe (11).

Health care workers, university students and individuals affected by the COVID pandemic are with increased prevalence of mental disorders (12). China and Italy recorded the highest prevalence rates of anxiety, depression and insomnia among their healthcare workers; Jordanian health staffs have relatively comparable rates (13). During the coronavirus pandemic, a high prevalence of poor sleep regimens was reported, with a percentage exceeding 65 % of the studied population, according to a recently published data (9). Based on published data, sleep disturbances affect 7 % of Europeans adults, 9-20 % of the American adults, 37 % of the United Kingdom adults and 19 % of French adults, whereas 28 % of the Polish population have experienced insomnia (10, 14).

Unfortunately, generalized anxiety is not an easy-treatable disorder. The anxiety characterized by recurrent relapsing courses and the intervention might not lead to a complete resolution of the accompanied symptoms. Psychological, social, behavioural and pharmacological treatments might be effective in treating short and medium-term anxiety (3). Long-term insomnia and poorly treated anxiety have a negative impact on the overall health status of the patients, contribute to an increased risk for cardiovascular illnesses, negatively affect diabetes, obesity, immune system and are related to increased suicidal tendency (1, 4). Individuals who are suffering from insomnia and poor sleep quality were at doubled risk of developing depression compared to those who exhibit normal-sleep cycles, as concluded from a meta-analysis of prospective cohort studies (15). In the bargain, long-term insomnia might have deleterious effects on memory, cognition, intelligence and daytime activities (16). The detrimental consequences on the health economy are crucial to be considered (10).

The use of conventional medicines in alleviating anxiety and stress symptoms may not be readily accessible to all patients. In addition to the need for a prescription, it incurs various adverse effects along with a high risk of tolerance (4, 16). As a consequence, it was noted that adult patients seeking complementary and herbal remedies for the relieving of the symptoms. In the United States, 28.9 % of adults were reported to consume at least one type of medicinal herb (17). In another study, 44 % of the psychiatric inpatients in the study sample admitted the use of herbal medicine for therapeutic purpose (18).

The current research study aims to screen the most herbal used by individuals in Jordan for the relief of anxiety and insomnia, as well as have an insight into the recommendations of the herb providers, the herbalists, for the best medicinal plants following folkloric and traditional recipes besides their own experience after recording customers' feedback.

Materials and Methods

This analysis study was conducted in April-October 2023 to understand and evaluate the Jordanian attitudes and knowledge regarding the non-prescribed use of herbal medications for the relief of anxiety symptoms and to improve sleep quality. Two groups of participants were recruited to accomplish the aim of the study: The first was adults who admitted using herbal medications and the second was herbalists who prescribed and sold medicinal herbs for calming and hypnotic claims.

A questionnaire of multiple compartments was distributed using social media applications. Adults who experienced using herbal remedies for claims of benefits for psychotic disorders were the target population. The questionnaire was categorized into a demographic part including gender, age, geographical distribution and educational type and level. The second part was to measure the knowledge and perception towards complementary medicine. The last 2 parts were to correlate the use of certain herbal medicines and the common anxiety and insomnia symptoms among the participants. The sample size was 384 which were compatible with the non-probability convenience sampling strategy. The questionnaire was developed in accordance with previous studies (19, 20) and validated by three different experts in the pharmaceutical field.

Herbalists (n = 15) from different geographical regions in Jordan were asked face-to-face in a short conversation by the researchers after obtaining their approval to participate. The purpose of the study was explained to the participants at the start. The participation was voluntary and the herbalists were free to quit the conversation at any point. The anonymity of the herbalists was preserved and their personal data were not collected. The research adheres to the declaration of Helsinki's ethical standards and approved by the research and ethical committee (Approval number SREC-2024/264).

Statistics

Statistical Packages for Social Sciences (SPSS software, version 22) were used to analyze the data statistically. The therapeutic value of each included herbal medicine was analyzed using a one-way ANOVA test. A Multi-comparison test was performed to acquire insight regarding the therapeutic value of each plant. The following equations were used to estimate the therapeutic values:

Relative used value = the number of medicinal plants used by the patient/total number of the included medicinal herbs

Relative combination therapy value = the number of medicinal plants used as an added therapy/total number of plants used as an added therapy

Therapeutic value = (Relative used value + relative combination therapy)/ (total relative used value + total relative combination therapy value)

Results

Socio-demographic characteristics

The distributed questionnaire target was adult Jordanians using herbal remedies for treatment. A total of 384 individuals responded to the survey, of which ~69 % were females. Participants in their twenties and thirties were of the highest percentage (36.2 and 34.9 respectively). The respondents were distributed geographically among south, middle and northern cities (58.9 %, 26.6 % and 14.3 % respectively). In terms of educational level: post-graduate studies (12.8 %), bachelor's degree (41.9 %), college (18.2 %) and secondary school certificate (26.8 %). Almost half of the participants received a literary education type (47.4 %) and those who graduated from a scientific branch accounted for 32.3 %.

The participant's behaviour concerning using herbal medicines for treating minor CNS disorders

A high percentage of the participants believe that they have a good knowledge of alternative therapy (76.8 %) and more than half (58.6 %) consider the herbal remedies safe. On the other hand, around 55 % of the respondents have doubts about the physicians' prescriptions and 64.8 % have more confidence in herbalists with expertise than those with knowledge or a specified degree.

As per the specified inclusion criteria, the participants should experience anxiety or insomnia before responding. It was found that 88.3 % of them have at least been afflicted by insomnia and a relatively similar percentage (87.5 %) has experienced insomnia. Most of the participants claimed that they had experienced sleep disorders and stress after encountering social or emotional discomforts (73.4 % and 82.8 % respectively). It was disclosed that 75 % of those who experienced insomnia had herbal remedies as their first choice and almost the same ratio exhibits the same behaviour to seek relief from anxiety. A single herbal treatment was preferred over a combined formula by 71.4 % of the patients. Fig. 1 displays the distribution ratios of the preferred medicinal plants in treating anxiety and sleep disorders.

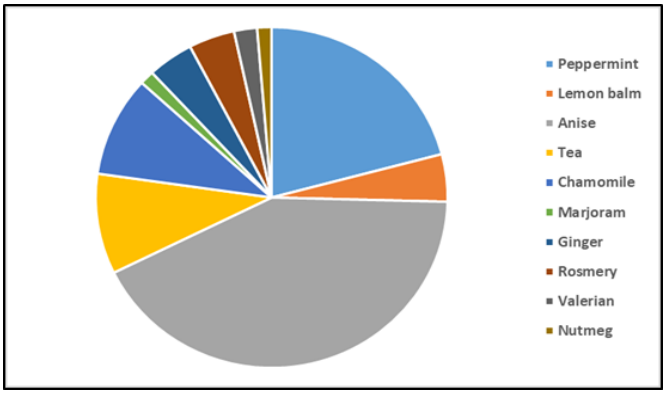

Fig. 1. The distribution ratios of the preferred medicinal plants in treating anxiety and sleep disorders.

The therapeutic value of each plant was computed using a one-way ANOVA analysis test which also disclosed significant differences with a *P*-value ≤ 0.001. Further examination was performed using multi-comparison tests. The highest parameter mean value was found for the anise (0.4133 ± 0.11719) reflecting that it has the highest concentration with significant differences (*P*-value ≤ 0.001) compared to the other analyzed samples. Peppermint occupied the second order with a mean value of 0.19 ± 0.03606 with a comparatively high concentration. Tea placed third (0.1333 ± 0.07572), followed by chamomile (0.1033 ± 0.10017), Ginger (0.0333 ± 0.03055) and lemon balm (0.05 ± 0.05568). Rosemary and Marjoram showed comparatively lower means.

The comparative therapeutic values and multi-comparative analysis results are shown in Fig. 2 and Table 1 respectively. The relative therapeutic value, the relative used value and the relative combined therapeutic value of anxiety and insomnia are illustrated in Fig. 3.

The herbalists' in-person survey

On the other hand, herbalists from different geographical locations were verbally interviewed by a research member team. Six of them were from middle Jordan, 5 from northern cities and 4 from the south. Ten of them acquired a secondary school certificate, 4 had a bachelor's degree and 1 had a diploma.

None of the herbalists practiced the profession according to a specified academic degree. Out of them, 60

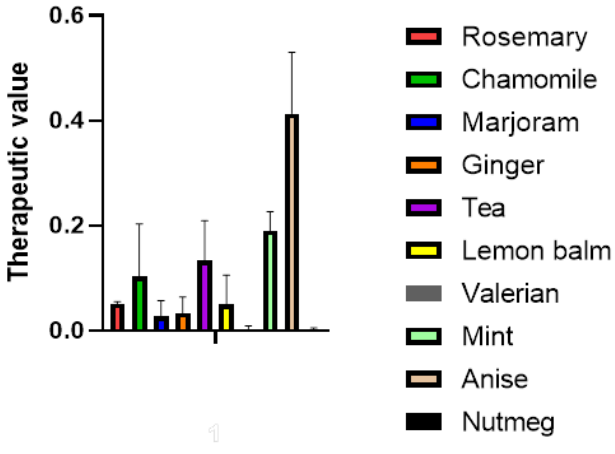

Fig. 2. The comparative therapeutic values of the selected medicinal plants (confidence interval for mean of 95 %).

Table 1. The multiple comparison analysis of the therapeutic values of selected medicinal plants at a significant level of 0.05, confidence interval of 95 %.

Comparison	*P*-value
Rosemary vs Chamomile	0.297 ^{ns}
Rosemary vs Marjoram	0.625 ^{ns}
Rosemary vs Ginger	0.722 ^{ns}
Rosemary vs Tea	0.107 ^{ns}
Rosemary vs Lemon balm	0.984 ^{ns}
Rosemary vs Valerian	0.341 ^{ns}
Rosemary vs Mint	0.010**
Rosemary vs Anise	p ≤ 0.001***
Rosemary vs Nutmeg	0.328 ^{ns}
Chamomile vs Marjoram	0.132 ^{ns}
Chamomile vs Ginger	0.168 ^{ns}
Chamomile vs Tea	0.546 ^{ns}
Chamomile vs Lemon balm	0.288 ^{ns}
Chamomile vs Valerian	0.054 ^{ns}
Chamomile vs Mint	0.091 ^{ns}
Chamomile vs Anise	p ≤ 0.001***
Chamomile vs Nutmeg	0.051 ^{ns}
Marjoram vs Ginger	0.893 ^{ns}
Marjoram vs Tea	0.041*
Marjoram vs Lemon balm	0.638 ^{ns}
Marjoram vs Valerian	0.638 ^{ns}
Marjoram vs Mint	0.003**
Marjoram vs Anise	p ≤ 0.001***
Marjoram vs Nutmeg	0.619 ^{ns}
Ginger vs Tea	0.054 ^{ns}
Ginger vs Lemon balm	0.737 ^{ns}
Ginger vs Valerian	0.546 ^{ns}
Ginger vs Mint	0.004**
Ginger vs Anise	p ≤ 0.001***
Ginger vs Nutmeg	0.528 ^{ns}
Tea vs Lemon balm	0.104 ^{ns}
Tea vs Valerian	0.015*
Tea vs Mint	0.260 ^{ns}
Tea vs Anise	p ≤ 0.001***
Tea vs Nutmeg	0.014*
Lemon balm vs Valerian	0.351 ^{ns}
Lemon balm vs Mint	0.010**
Lemon balm vs Anise	p ≤ 0.001***
Lemon balm vs Nutmeg	0.337 ^{ns}
Valerian vs Mint	0.001**
Valerian vs Anise	p ≤ 0.001***
Valerian vs Nutmeg	0.978 ^{ns}
Mint vs Anise	p ≤ 0.001***
Mint vs Nutmeg	0.001**
Anise vs Nutmeg	p ≤ 0.001***

•One star (*) indicates p-value < 0.05, Two stars (**) indicate p-value < 0.01, Three stars (***) indicate p-value < 0.001, NS indicate no significant differences

% declared that they took it after their parents and the rest acquired the knowledge from their own experiences. All the acquisition herbalists expressed that the customers have a high confidence level in alternative therapy and 60 % preferred the medicinal plants of low cost. The remaining (40 %) were convinced that more expensive plants are better. The herbalists' preferences and prescriptions for each mild CNS disorder are listed in Table 2. All of the participating herbalists proclaimed that their customers place a high level of trust in the provided prescriptions.

The herbalists were in complete agreement on the use of anise and chamomile for anxiety, lemon balm for insomnia and hibiscus for tachycardia. Almost all of them prescribe anise for insomnia, caraway for COVID-related stress and cinnamon for premenstrual syndrome. Around 50 % prescribe anise for COVID-related stress, peppermint for insomnia, ginger for tachycardia, fennel, artemisia and teucrium for premenstrual syndrome.

Discussion

Alternative or complementary medicine has gained a wide reputation among a large population for its efficacy, safety and reduced cost, particularly in developing nations (21). The output of the current study has assured that people in a developing country predominately used herbal medications for treating minor CNS disorders, which led to a high confidence in the herbalists regardless of their background education. It was reported that almost ~70 % of the participants who declared using herbal medications in therapy were in their second and third decades, which conflicted with previous studies findings that relate an increasing rate of using traditional medicines with increase age (22, 23). Nevertheless, educated people with at least a college degree have higher odds of using herbal medicines; these results were in parallel with a previously published study in Sweden (23).

Despite that a big portion of the participants believe that they have a good knowledge of the herbals and consider them as safe, major concerns have been raised lately regarding the safety of the complementary medicines (24). Unfortunately, developing countries lack specified regulatory guidelines to assure the quality of medicinal herbs and herbal-based products therefore, the safety of the sold herbals is not guaranteed (25). Moreover, it was not surprising to find trust issues in the prescriptions of medical doctors, as it is a reflection of poor public trust in the healthcare system in developing countries (26). The inadequate counselling provided by Jordanian community pharmacists has contributed to the current practice among patients seeking remedies for insomnia (27).

The preferences and self-prescribing of selected medicinal plants by the participants matched with the herbs' traditional use and their availability in the local environment. Anise, peppermint, tea, lemon balm and chamomile were the most prescribed for sleep aid and stress relief. The results have coincided with previous findings that reported using herbal medicines in treating minor CNS disorders or investigated their efficacy after *in vitro* and *in vivo* investigations (4, 18, 27, 28).

Health technology agencies have used the concept of therapeutic reference value as the absolute difference in the effectiveness of a new therapy compared with a current treatment. The combined therapeutic value estimates the therapeutic benefits of the new agent in terms of effectiveness and safety setting side by side with existing and approved medications (29). It was not surprising to find that the computed parameters of anise, mint, chamomile, and lemon balm recorded the highest therapeutic and used values parameters from the patient's perspectives. The long-term use of these herbal medicines in treating cases of anxiety and insomnia has been supported by numerous scientific pieces of evidence.

Anise (*Pimpinella anisum* L.) is rich in several active secondary metabolites such as anethol, anisaldehyde, estragole and coumarins, which are of value for human health (30). Anise oil has been used traditionally in Persian medicine in treating neurological disorders and has shown

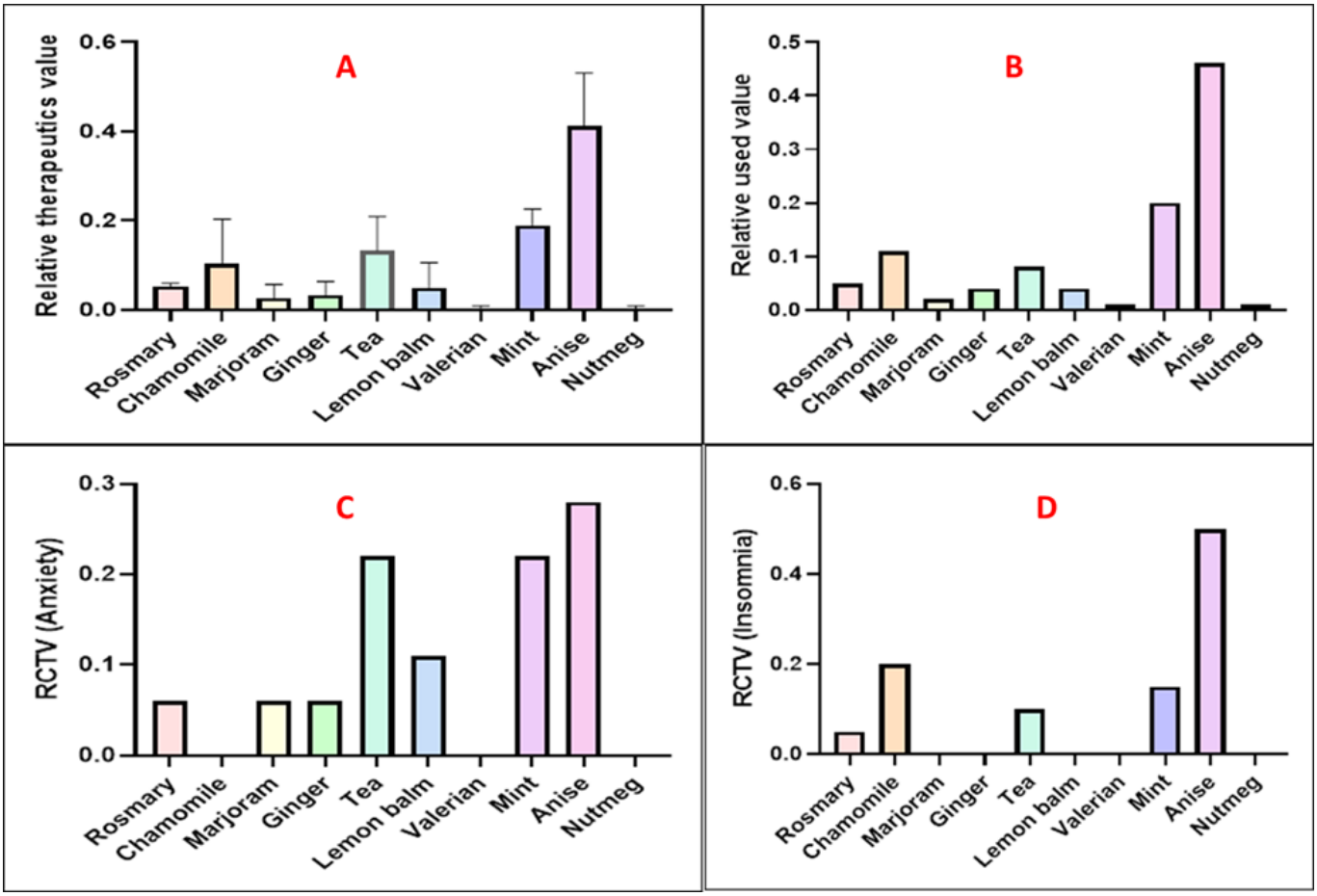

Fig. 3. A represents the relative therapeutic value, B represents relative used value, C represents the relative combined therapeutic value (RCTV) for treating anxiety and D represents the relative combined therapeutic value (RCTV) for treating insomnia.

Table 2. The frequency of medicinal plants prescriptions by the participating herbalist (n = 15).

CNS disorder Plant	Anxiety	Insomnia	Fear	Tachycardia	PMS	Covid-related stress
***Pimpinella anisum* L.**	15	13	10		3	7
***Matricaria chamomilla* L.**	15	5	2			
***Mentha piperita* L.**	4	6	3			
Zingiber officinale		4	4	8	2	4
***Melissa officinalis* L.**		15	3	1		
Cuminum cyminum		1			5	
Melilotus officinalis			5			
Hibiscus sabdariffa				15		
Cinnamomum zeylanicum		1			14	
***Crocus sativus* L.**					5	
Anethum graveolens					5	
Foeniculum vulgare					7	
Illicium verum						5
Rosmarinus officinalis	2	4				
Camellia sinensis			6			4
Hypericum perforatum	1		2			
Artemisia vulgaris					8	2
Teucrium fruticans					8	
Salvia officinalis					5	
***Moringa oleifera* Lam.**			1			1
Nigella sativa						4
Ocimum basilicum						1
Valeriana officinalis	1	3		3		
***Carum carvi* L.**					1	10
Piper nigrum					2	
Theobroma cacao						1
Lavandula angustifolia			3			
Eugenia caryophyllata						4
Curcuma longa						5
Citrus limon		1				
Allium sativum		1				
Honey		1				
Saussurea costus						4

beneficial effects in alleviating seizure episodes (31). Moreover, it exhibited a central tranquillizing activity in animal models (32).

Chamomile (*Matricaria chamomilla* L.) contains flavonoids, coumarins, terpenoids and essential oils (33). It possesses umpteen biological and pharmacological properties, including cardio- and neuroprotective (34). It has a potential therapeutic activity in managing anxiety, sleep disorder and stress by binding to the GABA receptors and modulating monoamine neurotransmitters and neuroendocrine activities. Additionally, chamomile extract showed deactivation activity of glutamic acid and decarboxylases (18). Chamomile tea has long been used in folkloric medicine for relaxation and calmness effects. In a clinical study, chamomile extract was effective in improving sleep quality, latency and total sleep time and in reducing awakenings (17). Although chamomile is considered a safe plant, it is a potent inhibitor of CYP1A2 and CYP3A3, which would induce possible drug interactions (35). A recently published clinical study emphasized the obtained results and clarified the role of chamomile oil in managing stress and enhancing sleep quality (36).

The participants' self-prescribed lemon balm (*Melissa officinalis* L.) for managing minor CNS disorders following the herbalists' recommendation or after heredity recipes. The anxiolytic and calming effect of the plant was referred to as its active constituent, citronellal. The therapeutic anxiolytic dose of the crude essential oil was reported to be 12.5 mg/kg as demonstrated by an *in vivo* study (18, 37). It was proposed that it may exert its sedating activity by inhibiting the MAPK pathway and neuroprotection function by reducing the aggregation of the amyloid beta-protein toxicity (38). In rat brains, lemon balm showed inhibitory activity of GABA transaminase (IC_{50} = 0.35mg/mL), though retard the degradation of endogenous GABA molecules (39, 40).

Some of the participants or the herbalists have suggested some medicinal plants which have sorts of evidence for their anxiolytic and hypnotic activities. Valerian essential oil contains nerolidol and caryophyllene along with other phytoconstituents that are proposed to upregulate the 5-HT1AR receptor leading to eventually activating the serotogenic synapse signalling pathway, which would result in enhancing the clinical symptoms of insomnia and anxiety (16, 41). Besides, lavender essential oil contains eucalyptol, linalool, and limonene and has a potential antidepressant and anxiolytic activity by modulating GABA molecules as published previously (18, 42). In the bargain, Saffron (*Crocus sativus* L.) has been recommended by herbalists for stress associated with pre-menstruation. This prescription has matched its proposed anxiolytic properties, which were demonstrated by modulating serotonin levels among other neurotransmitters (43).

Despite the collected pieces of evidence on the efficiency and safety of herbal remedies, it is mandatory to strengthen the trust in the healthcare system and the community pharmacists as they are a trustworthy source of information. It might be beneficial for health agencies to consider utilizing the booming artificial intelligence equipment for better-delivering counselling or the health service in general (44).

Conclusion

Throughout history, medicinal plants have been used by humans for their calming effects. Some of them were approved safety and efficacy by scientific and clinical studies. It is worth deeply investing in medicinal plants with potential activity in facilitating GABA transmission that outturns anxiolytic and hypnotic effects, as alternative therapies to benzodiazepines with fewer undesirable effects and lower tolerance and dependence reactions. However, it is a warranty to bolster trust in the healthcare system, particularly community pharmacists, for counselling patients on possible drug-herb interactions and health-herb interactions.

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Authors' contributions

Conceptualization: LKA and AA; methodology and data collection: BA; data curation: AA and SA; data analysis: AA; writing primary draft: BA and SA; finalizing the manuscript: LKA. All authors approved the submitted article.

Compliance with ethical standards

Conflict of interest: Authors do not have any conflict of interests to declare.

Ethical issues: The research adheres to the declaration of Helsinki's ethical standards and approved by the research and ethical committee (Approval number SREC-2024/264).

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