

Review Article



The Effect of Oral Chamomile on Anxiety: A Systematic Review of Clinical Trials

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Conflict of Interest

The authors declare that they have no competing interests.

ABSTRACT

Anxiety disorder is a prevalent psychiatric issue that affects 4.05% of the global population. As complementary and alternative medicine gains popularity, many individuals with anxiety symptoms seek herbal remedies. This systematic review aims to explore the sedative efficacy of chamomile as an herbal medicine for anxiety treatment. Our search was conducted in PubMed, Google Scholar, and Scopus databases until August 2023. Among 389 papers found, after removing duplicates and irrelevant papers, 10 clinical trials investigating the effect of oral consumption of chamomile on anxiety were included. Two researchers independently completed all steps, including the screening process and data extraction. Out of the 10 articles selected, 9 studies have concluded that chamomile is effective in reducing anxiety. Even though, the exact mechanism of chamomile's anxiolytic action is not well understood, evidence suggests that its active compounds, including apigenin, may modulate the function of the hypothalamic-pituitary-adrenocortical axis by affecting neurotransmitter pathways. This systematic review showed that chamomile potentially has an anxiolytic effect. In addition, due to the side effects of drugs used to treat anxiety disorders, the use of chamomile seems to be effective and less dangerous.

Keywords: Anxiety disorder; Anxiety; Chamomile; Systematic review

INTRODUCTION

Anxiety is a natural fear response that humans experience when they are in stressful or threatening situations, but when it becomes too overwhelming or lasts for a prolonged period, it can be classified as an anxiety disorder [1]. Around 301 million individuals worldwide, which is about 4.05% of the world population, suffer from anxiety disorders. This number has risen by over 55% from 1990 to 2019 [2]. Anxiety can have unpredictable and significant impacts on various aspects of life [3]. It is a predictor for depression [4] and can affect attention, cognitive and information processing [5], academic performance [6], and work capacity [7]. Additionally, research has shown that anxiety can also impact arterial pressure [8], increase stress levels and inflammatory agents [9,10], it is associated with migraines [11], and reduces the activity of the immune system [9].

Author Contributions

Conceptualization: Saadatmand S, Zohroudi F, Tangestani H; Data curation: Saadatmand S, Zohroudi F, Tangestani H; Formal analysis: Saadatmand S, Zohroudi F, Tangestani H; Investigation: Saadatmand S, Zohroudi F, Tangestani H; Supervision: Tangestani H; Writing – original draft: Saadatmand S, Zohroudi F; Writing – review & editing: Tangestani H.

There are several types of anxiety disorders, including generalized anxiety disorder (GAD), panic disorder, social anxiety disorder, and separation anxiety disorder. Treatments for these conditions consist of psychological therapy and drug therapy. Current drug treatments for anxiety include Benzodiazepines and selective serotonin reuptake inhibitors or serotonin-norepinephrine reuptake inhibitors (SSRIs/SNRIs) [12,13]. However, some patients may not respond well to this treatment, while others may experience side effects such as addiction, seizures, sexual dysfunction, headaches, weight gain, digestive problems, and even suicide [14,15]. As a result, individuals who suffer from anxiety often turn to complementary medicines, such as herbal remedies like chamomile, to manage their condition. These products are viewed as safer alternatives to pharmacotherapy, with a lower risk of adverse effects or creating dependence [16,17].

Chamomile (*Matricaria chamomilla* L. or *Matricaria recutita*) is among the herbal remedies that have been studied for their potential to relieve anxiety [18,19]. While multiple clinical trials have been conducted, the results have been inconsistent [20,21] and inconclusive [22]. In addition, previous reviews have been written based on a small number of human studies. Therefore, this systematic review aims to study the efficacy of chamomile in treating anxiety, providing a comprehensive understanding of its potential benefits to individuals suffering from this condition.

MATERIALS AND METHODS

This systematic review was written and reported according to the guidelines provided in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [23].

Search strategy

A comprehensive search was performed using PubMed, Scopus, and Google Scholar search engines from the beginning until August 2023, utilizing both Medical Subject Headings (MeSH) and text keywords. The following keywords were applied to find relevant articles on the effect of chamomile in treatment of anxiety; chamomile, *Matricaria*, *Matricaria Recutita*, German chamomile, Hungarian chamomile, wild chamomile, blue chamomile, scented mayweed, anxiety, anxiety disorders, panic disorder, general anxiety disorder, social anxiety disorder and GAD. Following our systematic review process, 2 investigators, SS and FZ, separately conducted a literature search that was not bound by any restrictions concerning the date of publication or the language of the papers, thus allowing for a broad and inclusive survey of available literature. To ensure an effective and efficient screening process, the results of this expansive literature search were imported into the EndNote library (version 20 for Windows by Thomson Reuters, Philadelphia, PA, USA) and this software was utilized as a strategic tool to aid in the management and organization of the amassed literature, thereby facilitating the subsequent screening process.

Eligibility criteria and study selection

The process of data screening was carried out in 2 steps: initial screening, where the title and abstract were examined, followed by a detailed screening, involving a thorough review of the full text. Two independent reviewers (SS and FZ) carried out the screening. Any reviewer disagreements were resolved through discussion, with a third reviewer (HT) providing input. The inclusion criteria for this review were: 1) clinical trials, 2) investigating the effect of chamomile on anxiety. We excluded studies based on the following criteria: 1) reviews,

cellular and molecular studies, animal studies, study protocols, or duplicate datasets; 2) conference papers, letters, notes, books, or editorials; 3) irrelevant topics, like aromatherapy interventions; 4) inaccessible full text; and 5) interventions in which, one or more other substances were examined along with chamomile. Our thorough search found 389 references from PubMed, Scopus, and Google Scholar. After the screening process, we excluded 379 references, and finally 10 clinical trials were included.

Data extraction and synthesis

Two independent researchers (SS and FZ) conducted data extraction. The information extracted from each study includes: the study's first author, country, publication year, study population, sample size, age, intervention type, intervention dose and duration, and the mean outcomes of the intervention.

RESULTS

Search results

In our initial search, 389 articles were found overall in PubMed, Scopus and Google Scholar databases. By eliminating the duplicated (55 papers), 334 articles were chosen for primary screening. Primary screening was done based on the title and abstract by the 2 researchers (SS, FZ); 303 articles were excluded, thus 31 were chosen for the final screening process. From the remaining 31, 21 were eliminated after the full-text screening process for the following reasons: Four were animal studies [24-27]; 1 was a study protocol [28]; 3 used duplicated datasets [29-31]; 5 were irrelevant to the subject [21,32-35]. Eight studies were reviews [36-43]. The inclusion process of this systematic review is presented in **Figure 1**.

Systematic review

Table 1 shows the extract of the included studies [18,20,22,44-50]. This systematic review is based on 10 clinical trials. The first randomized clinical trial regarding this subject took place in the United States [18], and four subsequent studies in the U.S. examined the long-term effectiveness of chamomile use or its efficacy in diagnosed subjects [20,44-46]. One study was conducted in Indonesia [47], and four were performed in Iran [22,48-50]. The studies spanned from 2009 to 2022. Age of the participants in different studies varied from 19 to 69. Overall, these trials included 844 subjects which ranged from 18 to 179 participants in different studies. Seven of these studies were carried out on both genders [18,20,22,44-47], and three focused on female participants [48-50].

Four of the study populations were carried out on outpatients of GAD, with different intensities from moderate to severe [18,44-46]. One study was performed on men and women who met the criteria for primary insomnia [20]. One article included participants from a home for elderly in Indonesia [47], one of the Iranian papers was based on their study on cancer patients [22], two articles included female university students [48,50], one of them was specified to young women experiencing dysmenorrhea. One study surveyed postmenopausal women [49].

In most of the included studies, intervention was done using capsules with dosage ranging from 250 mg to 2 g daily. Three of the studies that used chamomile tea as intervention, using 1 to 2 cups of tea, daily [22,47,50]. Duration of these clinical trials ranged from 2 to 26 weeks.

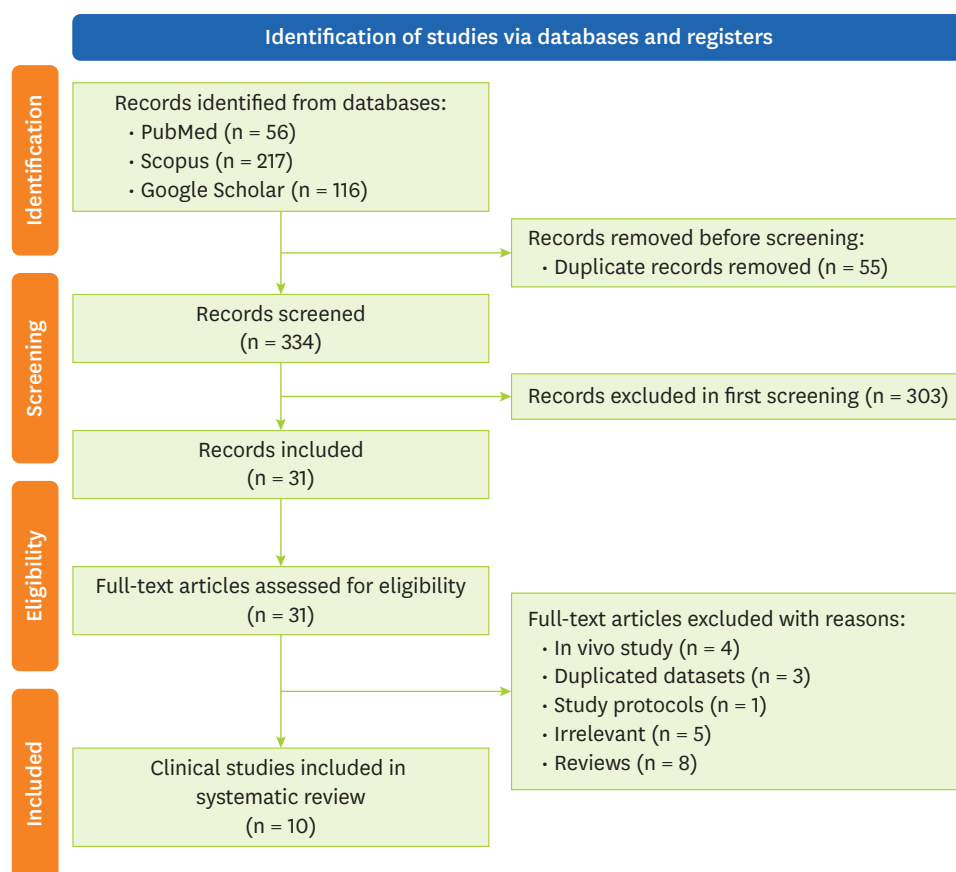


Figure 1. The process of study selection.

Three hundred eighty-nine articles were found in databases. After removing duplicate articles ($n = 55$), 324 articles were excluded by 2 steps of screening. Finally, 10 articles were included in the systematic review.

DISCUSSION

This systematic review showed that oral intake of chamomile can help improve anxiety symptoms and this effect is not limited to diagnosed patients with anxiety disorders, and can help relieve anxiety symptoms in different groups for example, the anxiety that women experience during their menstrual cycle, postmenopausal women who show the anxiety symptoms, people suffering from insomnia and anxiety, and patients in the recovery phase of their psychological disorder. Most studies showed that daily consumption of chamomile is effective in improving anxiety and no threatening or adverse side effects were reported.

In patients diagnosed with anxiety disorder, most studies reported that they observed significant improvements regarding to anxiety symptoms [18,44-46]. Moreover, Mao et al. [45] study reported that long-term chamomile use had better effects on the GAD patients' psychological well-being; they also witnessed improved blood pressure and weight profiles. Results also showed that GAD patients with comorbid depression experienced a substantial reduction in depressive symptoms, suggesting that chamomile might possess primary antidepressant activity [46]. However, the trials carried out on undiagnosed GAD participants, showed more contradictory and less assertive outcomes. The study performed on adults suffering from insomnia who also experienced anxiety showed a moderate effect size [20], which may be attributed to a short study period. Ghamchini et al. [22] observed no

Table 1. Characteristics of included studies (n = 10)

First author of study	Country	Year	Study population	Sex	Age	N-Intervention	Dose	Duration	Results
Amsterdam et al. [18]	USA	2009	Outpatients with mild to moderate GAD	Both	25–67	57	1 capsule daily for the first week and increased by 1 during each week	8 weeks	A significantly greater reduction over time in the mean total HAM-A score for chamomile versus placebo
Jenabi and Ebrahimzadeh [50]	Iran	2010	Students experiencing dysmenorrhea	Female	19–23	42	2 chamomile tea cups daily	12 weeks	Drinking chamomile tea is effective for relieving menstrual pain and psychosocial problems caused by it such as anxiety
Zick et al. [20]	USA	2011	Adults who met DSM-IV criteria for primary insomnia \geq 6 months	Both	18–65	34	270 mg of chamomile twice daily	4 weeks	Chamomile had a moderate effect size on the STAI Trait Subscale
Keefe et al. [44]	USA	2016	Adults with moderate to severe GAD	Both	19–78	179	Chamomile extract 1,500 mg/day	8 weeks	A significant reduction was seen in GAD symptom
Mao et al. [45]	USA	2016	Outpatients with a primary diagnosis of moderate-to-severe GAD	Both	19–73	179	Chamomile extract 1,500 mg/day	Phase 1, 12 weeks Phase 2, 26 weeks	A significant improvement in GAD symptoms and psychological well-being but non-significant reduction in GAD relapse
Effendy et al. [47]	Indonesia	2019	Healthy elderly living in the nursing home	Both	60–74	18	N/A	8 weeks	Significant reduction in anxiety were seen
Ghamchini et al. [22]	Iran	2019	Cancer patients	Both	20–69	55	Chamomile tea once a day	2 weeks	No effect on anxiety observed in patient cancer
Amsterdam et al. [46]	USA	2020	Adults diagnosed with GAD	Both	Mean age: 45.7 \pm 15.3	179	1,500 mg daily	8 weeks and 4 additional weeks for responder to chamomile therapy	GAD subjects with comorbid depression demonstrated significant reductions over time for the core HRSD score versus GAD subjects without comorbid depression
Najafi et al. [48]	Iran	2021	Students with regular menstrual cycles	Female	20–28	59	250 mg chamomile capsules every 8 hours	4 weeks	Decrease in anxiety in most of the participants
Bazrafshan et al. [49]	Iran	2022	Postmenopausal women referring to community health centers	Female	Mean age: 60.06 \pm 6.14	32	2,000 mg daily	2 weeks	Consuming chamomile herbal tea might help postmenopausal women feel less anxious

GAD, generalized anxiety disorder; HAM-A, Hamilton Anxiety Rating Scale; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, 4th ed; STAI, State-Trait Anxiety Inventory; N/A, not available; HRSD, Hamilton Rating Scale for Depression.

effects on anxiety in cancer patients. The differences between their results and the findings of another study that investigated cancer patients [51], showed that any cancer patient has a different response to chamomile tea treatment. On the other hand, studies including female participants had more promising results; Bazrafshan et al. [49], reported that chamomile tea might help postmenopausal women feel less anxious. Supporting the same results related to anxiety, Jenabi and Ebrahimzadeh [50] also observed improvements in menstrual pain in women experiencing dysmenorrhea. In line with many studies summarized in the present study, which showed anti-anxiety effects of oral consumption of chamomile, many studies even showed that chamomile in massage therapy and aromatherapy can also show anxiety-reducing effects [52,53].

The exact mechanism of action of chamomile on anxiety has not yet been determined, however most studies suggest that the flavonoid constituent apigenin produces sedative effects through modulation of γ -amino butyric acid (GABA) receptors [20,54,55]. Several lines of evidence suggest that many of its flavonoid constituents may produce anxiolytic activity by affecting GABA, noradrenalin (NA), dopamine (DA), and serotonin

neurotransmission or by modulating hypothalamic-pituitary-adrenocortical axis function. [26,46,56-59]

In several articles, no side-effects were reported, and most symptoms did not require medical intervention [22,44,45,48]. However, several trials conducted on pregnant women showed that chamomile consumption during pregnancy can lead to dangerous outcomes, both for the mother and the newborn. Some papers showed that regular chamomile use during pregnancy resulted in a small for gestational age (SGA) and a shorter height of the newborn [35,60]. Other studies showed that chamomile, as an oxytocic and uterine stimulating herb, may potentially induce spontaneous abortion [61] and has also been reported as a potential trigger of severe anaphylaxis, which may give rise to immediate-type I reactions [62]. Allergenic proteins in chamomile extract can cause immediate-type hypersensitivity reactions, also in other members of the *Compositae* family (family of the flowering-plant order Asterales) [63,64]. Potential drug interactions have also been suggested as side effects of chamomile use for example, a coumarin derivative in chamomile, may interfere with the blood coagulation process, aspirin or anti-inflammatory drugs and central nervous system depressive agents [35,37,61,65,66].

To the best of our knowledge, this systematic review is the most comprehensive and updated study available that examines the effects of chamomile on anxiety both in people with anxiety disorders and in relieving anxiety in other groups, for example, young women with dysmenorrhea or postmenopausal women. Summarizing the results in this way can give us a comprehensive view of the effects of chamomile on the state of anxiety. On the other hand, due to the diversity of the studied population, the possibility of heterogeneity in the studies has increased and meta-analysis was not possible. It seems that there is still a need for research on the effects of chamomile on anxiety. It is suggested that future studies should be conducted with a larger sample size and a better design, and the aim of the studies should be to find the effective dose of chamomile in reducing anxiety.

Based on the current systematic review, oral consumption of chamomile was effective in reducing anxiety in most of the available trials. Future researches should be performed on different populations in terms of effectiveness and side effects of chamomile, to provide a standard and safe dosage for users.

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