REVIEW

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The effects of lemon balm (*Melissa officinalis* L.) on depression and anxiety in clinical trials: A systematic review and meta-analysis

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A systematic review and a meta-analytic approach were considered to investigate the effects of lemon balm as a medicinal herb on anxiety and depression in clinical trials and its side effects. All randomized clinical trials published up to October 30, 2020 that examined lemon balm in patients with symptoms of depression or anxiety, with acute or chronic manifestations, were searched in 12 online databases. Statistical analysis was performed using RevMan software. Continuous data were analyzed using standardized mean differences. Statistical heterogeneity was assessed using Chi^2, I^2, and p value tests. Based on meta-analysis results, lemon balm significantly improved mean anxiety and depression scores compared with the placebo (SMD: -0.98; 95% CI: −1.63 to −0.33; $p = 0.003$), (SMD: -0.47; 95% CI: −0.73 to −0.21; $p = 0.0005$) respectively, without serious side effects. Current evidence suggests that lemon balm may be effective in improving anxiety and depressive symptoms, particularly in the acute setting. Due to the high level of heterogeneity between studies, results should be interpreted with caution. The small number of clinical trials and differences between their methods were the limitations of the present study. Further high-quality studies are needed to firmly establish the clinical efficacy of the lemon balm.

KEYWORDS
anxiety, depression, lemon balm, *Melissa officinalis*, systematic review

1 | INTRODUCTION

Anxiety disorders are the most widespread psychiatric disorders (Bandelow & Michaelis, 2015). According to population-based studies,

up to 33.7% of people suffer from an anxiety disorder during their lifetime (Bandelow & Michaelis, 2015). Anxiety can be defined as a behavioral, cognitive, and psychological response to threatening situations; it is an unpleasant sensory state and disabling condition

(Young & Liberzon, 2002). Depression is the fourth most expensive disease and a common psychiatric disorder impacting approximately 300 million people in the world (WHO, 2020). It is a leading cause of disability, plays a major role in the global disease burden (Lépine & Briley, 2011), and by 2030, it will be the main cause of disease burden worldwide. (WHO, 2017) Prevention and treatment of depression should be considered a medical priority for the 21st century. (Lépine & Briley, 2011).

Different studies have shown that most medical drugs used to treat mental disorders have many side effects, such as cognitive dysfunction, excessive sedation, respiratory depression, withdrawal syndrome, and other problems caused by long-term drug use or high drug resistance (Julien Cases et al., 2010; de Niet et al., 2009; A. Seldenrijk et al., 2017; Adrie Seldenrijk et al., 2015). Herbal medicines are a proposed adjunctive treatment that may provide benefit while demonstrating a low level of toxicity and may be more easily accessible (Heshmati et al., 2020; Liu et al., 2015). For this reason, over the recent decades, physicians and patients have developed an interest in the use of alternative and complementary therapies and herbal medicine (Faridi et al., 2014; Rezaeizadeh et al., 2009; Sahoo, & S, B., 2019; Taheri-Targhi et al., 2019).

Melissa officinalis L. is a plant belonging to the Lamiaceae family and a cultivated perennial lemon-scented herb known as the common lemon balm. Lemon balm is one of the most popular and widely used medicinal plants in central and southern Europe, the Mediterranean region, and west Asia (Ulbricht et al., 2005). Lemon balm has been widely used in Asian traditional medicine to treat many psychiatric disorders, such as depression, anxiety, insomnia, anxiety-induced palpitation, and stress (Shakeri et al., 2016). In clinical studies on the CNS system, lemon balm has shown anxiolytic, anti-depressant, anti-insomnia, and neuroprotective effects (Lopez et al., 2009), and its effects on improving mood, cognitive performance, and memory function have been investigated (Shakeri et al., 2016; Ulbricht et al., 2005).

While the primary bioactive compounds remain to be elucidated, the main constituents of lemon balm are hydroxycinnamic acid derivatives, especially caffeic acids, chlorogenic acid, metrilic acid, and rosmarinic acid (RA) (Uritu et al., 2018). RA is the most important biomarker used for the standardization of this plant (Arceusz et al., 2015; Noguchi-Shinohara et al., 2015; Shakeri et al., 2016), and it is able to cross the blood–brain barrier (Fale et al., 2011). Therefore, the neurological effects of this plant are attributed to RA (Ghazizadeh et al., 2020; Jin et al., 2013).

Previous animal studies suggest that fluoxetine was more effective than lemon balm in improving depressive behaviors in nonstressed rats, (Taiwo et al., 2012); however, in a recent clinical trial, the antidepressant effects of lemon balm and fluoxetine were not significantly different (Araj-Khodaei et al., 2020). Due to the anxiolytic effect of lemon balm reported in several studies, the European Scientific Cooperative on Phytotherapy (ESCOP) recommends the use of lemon balm to relieve of mild symptoms of anxiety, including mental stress, restlessness, and irritability (Phytotherapy, 2003). In contrast, a single dose of *Melissa officinalis* and *Valeriana officinalis* showed an increase in anxiety symptoms in stress-induced volunteers (David

O. Kennedy et al., 2006). The FDA has reported lemon balm to be generally recognized as safe (GRAS) (Ulbricht et al., 2005); nevertheless, headache, reduced alertness, and sleep disturbances are some of the neuropsychiatric side effects of lemon balm that have been reported (Buechner et al., 1974; Cerny & Schmid, 1999; D. O. Kennedy et al., 2002).

With the annual publication of hundreds of thousands of articles, there is a need for a structured and scientific review of existing studies so that researchers can easily summarize various studies around the world (Gopalakrishnan & Ganeshkumar, 2013). In addition, systematic reviews and meta-analyses are at the top of the clinical evidence hierarchy (Izzo et al., 2016). While there are several randomized clinical trials (RCTs) that investigated the effects of lemon balm on depression and anxiety, a systematic review and meta-analysis have not been performed to synthesize the results of these studies. Therefore, we conducted a systematic review and meta-analysis to evaluate the effects of lemon balm in clinical trials on depression and anxiety (chronic or acute) as primary outcomes, as well as the side effects of lemon balm as a secondary outcome.

2 | METHODS

This systematic review and meta-analysis were conducted according to the Cochrane Collaboration framework guidelines (Higgins et al., 2019), and Preferred Reporting Items of Systematic Reviews and Meta-Analysis (PRISMA) guideline was followed to conduct and report the present study (Moher et al., 2009). The review protocol was registered with PROSPERO (registration number: CRD4202 0162013).

2.1 | Data source and identification of studies

2.1.1 | Types of studies

We evaluated all RCTs that assessed lemon balm's effects on depression or anxiety as the main outcome. Animal studies were not considered.

2.1.2 | Participants

Participants were individuals who had chronic or acute symptoms of depression or anxiety, with no age or sex limitations.

2.1.3 | Types of interventions

Lemon balm intervention involved the use of the plant or its products, regardless of the form or dosage of the consumed drug. The control group consisted of those prescribed placebo, standard medications, or any other approved products.

2.1.4 | Outcomes

Outcomes were classified as primary, including depression or anxiety, and secondary as side effects of lemon balm. Primary outcomes were considered in acute or chronic manifestations.

2.2 | Information sources

English databases, including Cochrane Library, Web of Sciences, Scopus, PubMed, ProQuest, Trip Database, Clinical Key, and Google Scholar, and Persian databases, including Magiran, Iranmedex, Iran Doc, and SID, were searched until October 30, 2020, without time limitation. The cited references of the selected studies were reviewed to find other related studies.

2.3 | Search strategy

The search strategy of the articles in the present study was in accordance with the MeSH glossary. The keywords that were used alone or in combination with other terms included the following: anxiety, anxiety disorder(s), generalized anxiety disorder, neuroses anxiety, anxiety state(s), neurotic anxiety state(s), social phobia, post-traumatic stress disorder, panic disorder, agoraphobia, obsessive compulsive disorder, depression(s), depressive symptom(s), emotional depression, depressive disorder(s), neurosis depressive, depressive neuroses, endogenous depression, depressive syndrome, neurotic depression, melancholia(s), unipolar depression, and Melissa, *Melissa officinalis*, Officinalis Melissa, lemon balm(s), balm(s) lemon, Bādranjbūye. Furthermore, the keywords side effect(s), adverse effect(s), and adverse reaction(s) were used to search for the lemon balm side effects as the secondary outcome in the selected papers.

2.4 | Study selection

Two members (J.G.H. and S.S.-E.) of our team independently studied the titles and then the abstracts of the studies in order to match the eligibility criteria. In the absence of sufficient information on the titles and abstracts of the articles, the full text of the articles was studied to decide on the inclusion or exclusion of the paper. Ultimately, the judgments of the two authors were compared, and in cases of disagreement, a third person (M.M.) was consulted, and the final decision was ultimately made.

2.5 | Data extraction and management

Study-related data, including the authors, methodology, research environment, study design, timing, type and route of lemon balm administration, placebo or alternative medication in the control group, treatment duration, duration of follow-up, inclusion and exclusion criteria, sample size, randomization, participant characteristics and attrition, primary and secondary outcomes, outcome measures, results of the study, and side effects were independently extracted by the two authors (J.G.H. and S.S.-E.).

2.6 | Assessment of risk of bias in the included studies

The risk of bias was assessed separately by two authors (J.G.H. and S.S.-E.) based on the Cochrane handbook for bias criteria, which included six domains (Higgins et al., 2019). Risk of bias for each item was classified as "low," "high," or "unclear."

2.7 | Statistical analysis

Review Manager software 5.3 (RevMan; The Cochrane Collaboration, Oxford, UK) was used to perform the statistical analysis of the data. The effect size of lemon balm was assessed on continuous data with mean and standardized mean difference (SMD). For the RCTs that reported both the means and standard deviations (SDs) for the baseline and follow-up data for intervention and control groups, the means and SDs for change in the outcome were calculated for the trial groups. The mean changes for each continuous data were calculated as score at the follow-up period minus score at the baseline. SD for the change score was calculated using the following formula:
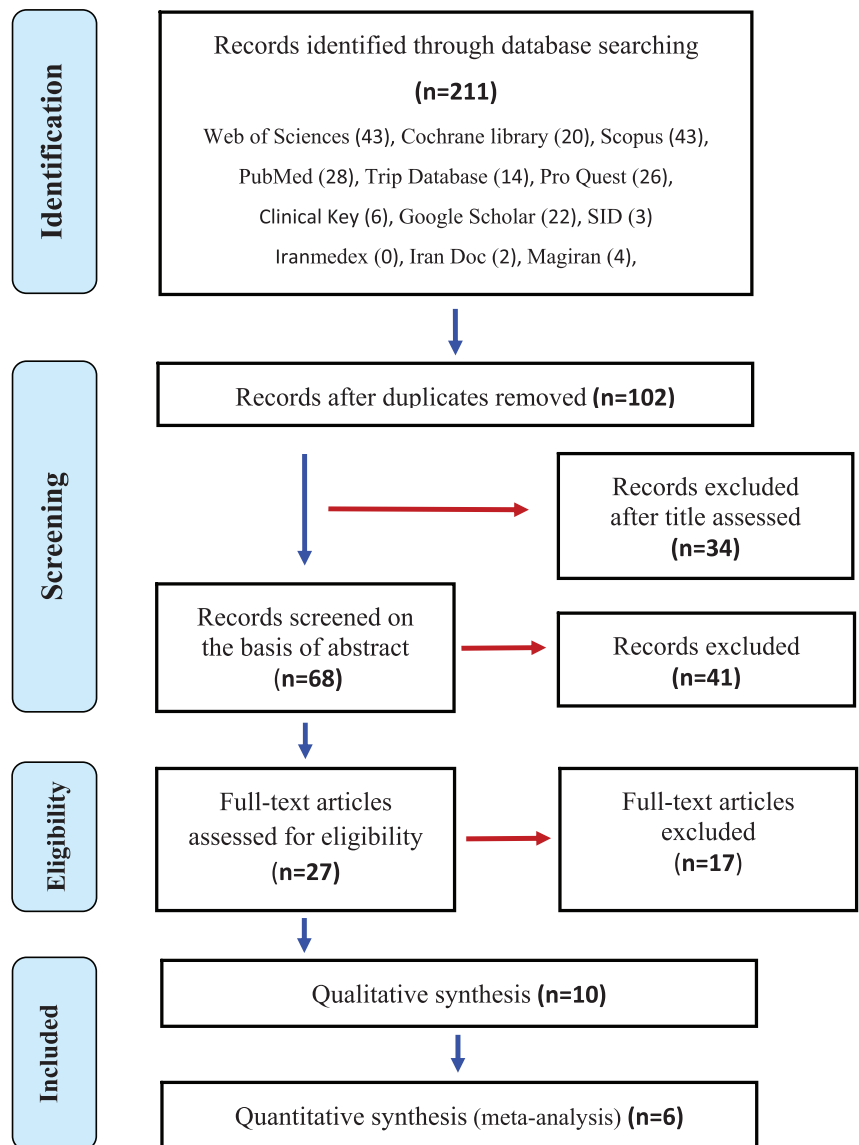
$$SD_{Ch.S} = \sqrt{SD_b^2 + SD_f^2 - 2 \times r \times SD_b \times SD_f}$$

$SD_{Ch.S}$: Change score, SD_b: SD at the baseline, SD_f: SD at the follow-up, r: Correlation between the baseline and the follow-up score (Fu et al., 2013 Jul 25.). Statistical heterogeneity was assessed using Chi^2, I^2, and p value tests. Significant efficacy of the intervention was considered if $p < 0.05$, and significant heterogeneity was considered if $p < 0.05$ and $I^2 > 75\%$ (Higgins et al., 2019). Random effects model was used instead of fixed effects model if heterogeneity was high. The forest plot was used to present the results of the current meta-analysis.

3 | RESULTS

3.1 | Study selection

Based on our search, 211 records were identified. One hundred and nine articles were excluded because of duplication, and 34 articles were excluded due to unrelated titles. The abstract of 68 studies and the full text of 27 articles were evaluated. Following this evaluation, 17 studies were excluded as they were not RCT or did not have a control group. Finally, 10 articles with 632 participants were included in the qualitative synthesis, and six articles with 435 participants were included in the quantitative synthesis (meta-analysis) (Figure 1).

FIGURE 1 PRISMA flow diagram of the study

Identification

Records identified through database searching

(n=211)

Web of Sciences (43), Cochrane library (20), Scopus (43), PubMed (28), Trip Database (14), Pro Quest (26), Clinical Key (6), Google Scholar (22), SID (3) Iranmedex (0), Iran Doc (2), Magiran (4),

Screening

Records after duplicates removed **(n=102)**

Records excluded after title assessed **(n=34)**

Records screened on the basis of abstract **(n=68)**

Records excluded **(n=41)**

Eligibility

Full-text articles assessed for eligibility **(n=27)**

Full-text articles excluded **(n=17)**

Included

Qualitative synthesis **(n=10)**

Quantitative synthesis (meta-analysis) **(n=6)**

3.2 | Characteristics and interpretation of the studies

The main information of the RCTs is presented in Table 1. The total number of participants was 632, depression was studied on 369 patients and anxiety on 527 patients. One hundred and five participants were depressed, 263 were anxious, and 264 participants had both depression and anxiety disorders. The sample sizes studied in the RCTs varied from 36 (J. Cases et al., 2011; Chehroudi et al., 2016) to 100 (Heydari et al., 2018) volunteers with a mean of 63 and SD of ±21. Sixty-five percent of participants had an acute form of depression or anxiety, and only 35 % of participants suffered from chronic illness (Alijaniha et al., 2015; Araj-Khodaei et al., 2020; Haybar et al., 2018; Saeidi et al., 2020). Characteristics of the participants were stress-induced (Scholey et al., 2014), healthy individuals (Heydari et al., 2018), outpatients (Alijaniha et al., 2015; Araj-Khodaei et al., 2020; Saeidi et al., 2020), or hospitalized patients (Beihaghi et al., 2019; Chehroudi et al., 2016; Haybar et al., 2018; Lotfi

et al., 2019; Soltanpour et al., 2019), which include 7.3%, 15.8%, 22.9%, and 54% of the total participants, respectively. The age range of participants in the articles also varied, 78.5% of the participants in these studies were adults (eight studies) and 15.8% were adolescents. (Heydari et al., 2018) The gender of participants was 58.1% female and 36.2% male. It should be noted that in one study, the age range and gender of participants were not reported (Chehroudi et al., 2016). In all RCTs, the participants were divided into intervention or control groups that used lemon balm products as intervention. Eight studies used placebo controls and two studies used active controls. With the exception of one case (Lotfi et al., 2019) in other studies, the oral route was the option of choice for drug administration. In half of the studies, the extract (four studies) or essence (one study) of lemon balm was prepared, and in five studies, researchers prescribed lemon balm as a dried powder. Lemon balm products were processed in different dosage forms. Capsules that were filled from dried leaves powder, extract or essence, were a common form of lemon balm prescription in studies (60% of the studies). Lemon balm was

TABLE 1 Summary of included RCTs in the systematic review

Study year	Study design	Participants, sample size, aged	Outcomes (acute/chronic)	Intervention, comparison	Dosage form, Intake dose, Duration	Utilized questionnaire for *anxiety/depression	Results	Side effects
Scholey et al., 2014	Randomized, double-blind, placebo-controlled, balanced-crossover, clinical trial	Healthy individuals who were induced to mild stress in the laboratory, n = 46, 18–39 years old,	Stress (anxiety), cognitive, acute	Standardized aqueous extract of lemon balm leaves. Placebo beverage or yoghurt	Foodstuffs containing lemon balm, 300, 600 and 600 mg of single extract dose	*VAS[a] *POMS[b] *STAI[c]	Improvements in cognitive and/or mood performance	There were no side effects during the treatment.
Alijaniha et al., 2015	Randomized, double-blind, placebo-controlled, clinical trial	Outpatients with palpitation for 3 months n = 55 (out of 71) 18–60 years old	Palpitation, somatization, anxiety, insomnia, social dysfunction, severe depression, chronic	Lyophilized aqueous extract of lemon balm leaves. Placebo (bread crumb)	Capsule 500 mg (twice a day) 14 days	*GHQ-28[d] GHQ-28	Decrease in the number of patients with: Severe depression; not effective (p = 1) anxiety; significant (p = 0.004)	From 19 complications that were investigated; lemon balm extract was not considerable side effects, except for increased appetite.
Chehroudi et al., 2016	Randomized clinical trial	Hospitalized patients with second- or third-degree burns, 35%–55% of the body surface area n = 36 age not reported,	Depression, anxiety, insomnia, serum-antioxidant levels, acute	Aerial part of the lemon balm plant. Placebo (black tea)	Tea-bag 2.5 g. (twice a day) 20 days	*Kettle[e] BDI[f]	Lemon balm significantly decreased anxiety (p = 0.023) and depression (p = 0.002) in participants	Side effects were not considered in this study.
Heydari et al., 2018	Randomized, double-blind, controlled, clinical trial	Female high school students with PMS n = 100 14–18 years old	Depression, anxiety and sleeping disorders, social-disorders, somatoform-symptoms, acute	Essence of the lemon balm. Placebo (starch)	Capsule 600 mg (twice a day) 21 days (7 days a month for 3 cycles)	*GHQ-28 GHQ-28	Lemon balm significantly reduced the mean scores of sleeping and anxiety disorders(p < 0.001) and depression (p = 0.001)	Lemon balm had no obvious side effects.
Haybar et al., 2018	Randomized double-blind controlled clinical trial	Hospitalized patients with chronic stable angina n = 73 40–75 years old	Anxiety depression stress sleep disorders chronic	Powder of aerial part of the lemon balm. Placebo (corn-starch)	Capsule 1,000 mg (3 times a day) 56 days	*DASS-21[g] DASS-21	Lemon balm receiving group had a significant reduction in scores of depression and anxiety with the compared control group. (P < 0.001).	Side effects were not considered in this study.
Beihaghi et al., 2019	Randomized, triple-blind, placebo-controlled, clinical trial	Hospitalized women who underwent c. section n = 60 18–35 years old	Depression (blues) acute	Dried powder of lemon balm, placebo	Capsule 500 mg (3 times a day) 10 days	BDI EPDS[h]	Postpartum depression incidence was significantly lower in the treatment group compared to the placebo group. (p < 0.001)	There were no possible side effects.
Lotfi et al., 2019	Randomized, single-blind, placebo-controlled, clinical trial	Hospitalized patients at CCU suffering from acute coronary artery syndrome, n = 92 (out of 96) 20–75 years old	Anxiety acute	Lemon balm extract, placebo (odorless sesame oil)	Aroma inhalation, inhale three drops twice a day for 30 minutes, 3 days	*STAI	Lemon balm aromatherapy significantly reduced the anxiety state in the intervention group compared to the placebo group. (p ≤ 0.05)	Not reported
Soltanpour et al., 2019	Randomized, double-blind, placebo-controlled clinical trial	Hospitalized patients with coronary artery bypass graft. n = 80 30–70 years old	Sleep quality, anxiety, acute	Dried leaf powder of lemon balm, placebo (wheat starch)	Capsule 500 mg (3 times a day) 7 days	*HADS[i] SMHSQ[j]	Lemon balm reduced the levels of anxiety in participants by 49% and improved the sleep quality by 54%.	Lemon balm was well tolerable by the patients and had no specific side effects.

TABLE 1 (Continued)

Study	Design	Condition	Population	Intervention	Dose/Duration	Scale	Results	Side effects
Saeidi et al., 2020	Randomized, single-blind, clinical trial	Anxiety, chronic	Employees of an office who were suffering from severe anxiety, n = 45 30–45 years old	Concentrated extract of lemon balm or lavender, control no medication	Oral drop solution, 5 drops twice a day for 5 days	*BAI[k]	Lemon balm and lavender significantly reduced anxiety symptoms in the intervention groups compared to the control group. (p < 0.05)	Side effects were not considered in this study.
Araj-Khodaei et al., 2020	Randomized, double-blind, clinical trial	Depression chronic	Outpatients with mild to moderate depression n = 45 out of 50, 18–65 years old	Powder of dried leaves of lemon balm and lavender, fluoxetine	Plant's powder kept in capsules, 1,000 mg twice a day, fluoxetine 10 mg twice a day, 56 days	HAM-D[l]	There was no significant difference in the improvement of mild to moderate depression between the intervention groups and the fluoxetine group. (p = 0.192)	From 10 complications that were investigated, the lemon balm had no serious side effects.

[a] Bond–Lader visual analogue scales (VAS) questionnaire.
[b] Profile of Mood States (POMS).
[c] Spielberger State–Trait Anxiety Inventory (STAI).
[d] General Health Questionnaire-28.
[e] Kettle's Anxiety Questionnaire.
[f] Beck Depression Inventory.
[g] Depression, Anxiety and Stress Scale (The shortened 21-item version).
[h] Edinburgh Postnatal Depression Scale (EPDS).
[i] Hospital Anxiety and Depression Scale-Persian version.
[j] St Mary's Hospital Sleep Questionnaire (SMHSQ).
[k] Beck Anxiety Inventory (BAI).
[l] Hamilton Rating Scale for Depression.

prescribed orally in different doses, varying from 300 mg (Scholey et al., 2014) to 5,000 mg (Chehroudi et al., 2016) per day. The duration of lemon balm administration was not the same, with the shortest duration being a single dose (Scholey et al., 2014 and the longest duration being 56 days (Araj-Khodaei et al., 2020; Haybar et al., 2018).

The questionnaires used to assess the outcomes are as follows: General Health Questionnaire-28(GHQ-28), Kettle's anxiety questionnaire (Kettle), Beck depression inventory (BDI), Beck Anxiety Inventory (BAI), Hospital Anxiety and Depression Scale (HADS), Depression, Anxiety, and Stress Scale-the shortened 21-item version (DASS-21), Hamilton Rating Scale for Depression (HAM-D), Spielberger State–Trait Anxiety Inventory (STAI), Edinburgh Postnatal Depression Scale (EPDS), and St Mary's Hospital Sleep Questionnaire (SMHSQ).

3.3 | Description of the studies

Ten studies were included in the current review. Six RCTs provided sufficient numerical information about the outcomes and were included in the quantitative synthesis. A qualitative synthesis of all the included studies has been performed, so first we describe the results of individual studies narratively.

The study of Alijaniha et al. (2015), a randomized double-blind placebo-controlled clinical trial, was conducted on 55 adult outpatients suffering from benign palpitations who experienced for at least 3 months (it should be said chronically). Researchers have investigated the efficacy and safety of lemon balm on palpitation and psychiatric symptoms. Two outcomes were evaluated: primary outcome was palpitation and secondary outcomes were psychiatric symptoms (somatization, anxiety and insomnia, social dysfunction, and severe depression). Measurement tools used before and after the interventions were as follows: visual analogue scale (VAS) questionnaire for palpitations and GHQ-28 for psychiatric symptoms. The intervention was a dried lyophilized aqueous extract of lemon balm leaves that was kept inside a capsule and by which patients were treated. The placebo was bread crumbs that were filled in similar capsules. Intake dose was one capsule containing 500 mg of dried extract twice a day for 14 days. As a result of the study, lemon balm significantly reduced (p = 0.004) the number of anxious (anxiety and insomnia) patients by 42.8% in the intervention group, but it was not effective in severe depression. The mean frequency of palpitations was 36.8% lower than at the beginning of the intervention. This decrease was significant compared with the placebo group (p < 0.0001). With the exception of increased appetite, no serious side effects were observed compared with the control group. It is important to mention the extract of lemon balm was not standardized based on any bioactive component.

Chehroudi et al. (2016) conducted a randomized clinical trial on 36 participants. The aims of the research were evaluation effects of lemon balm on mood and sleep quality as well as serum antioxidant levels in hospitalized patients with a stay of approximately 20 days, due to second or third-degree burns. Therefore, the outcomes

anxiety, depression, and insomnia were acute, each of which was measured by using the BDI, Kettle, and Petersburg questionnaires, respectively, and serum levels of antioxidants. The intervention group was given aerial parts of lemon balm, and the control group received black tea, both in the form of tea bags. Intake dose was 2.5 g of lemon balm twice a day for 20 days. The results of the RCT were as follows: the percentages of anxiety and depression in lemon balm receiving group were significantly less than the control group (p value: 0.023 and 0.002, respectively), as well as, sleep quality increased significantly in lemon balm group (p value: 0.031). Lemon balm intakes did not affect severe anxiety, but it reduced mild and, especially, moderate anxiety. The authors have not investigated the side effects of the lemon balm in this study.

Heydari et al. (2018), in their randomized double-blind clinical trial, have evaluated the effects of lemon balm on mental health in girls with premenstrual syndrome (PMS). Participants were female high school students (14–18 years old) with PMS who were selected via the premenstrual symptom screening test (PSST), and the sample size was 100 people who were randomly divided into two groups: the intervention group received 600 mg of lemon balm essence twice a day, and the control group was given starch as a placebo, both in the form of capsules. The duration of the trial was overall 21 days, which was divided into three 7-day periods: from the first day to the end of the menstrual cycle for three consecutive periods. It can be said that the participants had acute problems. The outcomes were depression, anxiety and sleeping disorders, psychosomatic symptoms, social function disorder, which were measured after finishing the intervention by GHQ-28 and compared with the control group. As a result, the mean scores of psychosomatic symptoms ($p < 0.001$), anxiety and sleeping disorder ($p < 0.001$), depression ($p = 0.001$), and social functions disorder ($p = 0.021$) were significantly lower in the experimental group than in the control group. Administration of lemon balm essence had no reported side effects.

Haybar et al. (2018) conducted a randomized, double-blind placebo-controlled clinical trial to determine the effects of lemon balm on chronic psychiatric disorders in patients with chronic stable angina. The researchers considered four outcomes, including anxiety, depression, stress, and sleep disorders, which were measured before and after the intervention by DASS-21, and Pittsburgh sleep quality index questionnaires, respectively. The sample size was 73 (out of 80) adult patients suffering from chronic stable angina who were randomly divided into two intervention and control groups. Dried powder of the lemon balm was administered to the intervention group in 1000 mg capsules three times a day for 56 days, and the control group has received corn-starch as a placebo in similar capsules at the same intake dose and duration. At the end of the RCT, analysis of the results of lemon balm's effects in the experimental group compared with the control group showed a significant reduction in the mean scores of depressions, anxiety, and stress ($p < 0.001$) in the lemon balm receiving group, and it was also significantly effective in reducing ($p = 0.033$) sleep disorders. Side effects were not investigated in this study, and the lemon balm intervention was not standardized.

Soltanpour et al. (2019) conducted a double-blind, randomized placebo-controlled clinical trial to evaluate the efficacy of lemon balm on anxiety and sleep disorders as an acute problem, after cardiac surgery. Absence of notable sleep disturbance in the 30 days prior to the trial was the first inclusion criteria. The main outcomes in this research were sleep quality and anxiety. To assess these outcomes, SMHSQ and HADS questionnaires were used, respectively. The sample size was 80 adult in-patients with coronary artery bypass grafting. Participants were randomly divided into intervention and control groups. Dried leaves powder of lemon balm was a medicine for intervention in the form of capsules: 500 mg was administered to patients three times a day for 7 days. Wheat starch was used as a placebo for the control group. After the intervention, the effects of lemon balm were successful in reducing anxiety levels and improve the sleep quality in the participants by 49% and 54%, respectively. According to the form completed by the researchers, lemon balm was well tolerated by the participants, and there were no side effects. Unlike the previous studies, the phenolic and flavonoid compounds of lemon balm were assayed in this study.

Araj-Khodaei et al. (2020) conducted a double-blind, randomized clinical trial to evaluate the efficacy of lemon balm and lavender on mild to moderate depression compared with fluoxetine. The sole outcome of the RCT was depression, which was assessed by the HRSD-17 items questionnaire. The sample size was 45 adult outpatients suffering from mild to moderate chronic depression based on Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-5). Participants were randomly assigned to three groups: lemon balm, lavender, and fluoxetine. Interventions were 1,000 mg twice a day of the dried leaves powder of the lemon balm or lavender, which were given in capsules. This study did not have a placebo group, but the two groups of interventions were compared with the control group that received fluoxetine (10 mg/BD) as a standard medication. For blinding, fluoxetine powder was stored in the matching capsules to the herbal intervention. At the end of the intervention, it was found that in the treatment of mild to moderate depression the effects of lemon balm and lavender were similar to those of fluoxetine, which is commonly used in medicine. However, the side effects of lemon balm and lavender were less than those of fluoxetine, although this difference was not significant. The authors' assessment was that lemon balm and lavender were well tolerated compared with fluoxetine, caused fewer complications, induced less drug dependence and no return to depression after discontinuation, and had no serious side effects. The fluoxetine group suffered more insomnia, sexual dysfunction, anxiety, and decreased appetite than the lemon balm or lavender recipients. Total phenolic and flavonoid compounds were determined in both plants, and the results about lemon balm were similar to those reported by Soltanpour et al. (Soltanpour et al., 2019).

Another RCT, which was conducted by Beihaghi et al. (Beihaghi et al., 2019), was a triple-blind placebo-controlled clinical trial performed on 60 women aged 18–35 years who underwent cesarean section, and the effect of lemon balm on the incidence of postpartum low mood was evaluated. The main outcome was postpartum acute depression using the BDI and EPDS questionnaires. The participants

were randomly divided into two equal groups of intervention and placebo. The intervention group was treated with 500 mg capsules of lemon balm powder, three times a day for 10 consecutive days and compared with the control group. The results of this RCT showed that postpartum depression incidence was significantly ($p < 0.001$) lower in the intervention group than those in the placebo group. The earliest effective role of the lemon balm in preventing postpartum depression was identified on the third to fifth days of the intervention. There were no side effects.

The effect of lemon balm on acute anxious cardiac patients was the subject of a study by Lotfi et al. (Lotfi et al., 2019). The study was designed as a randomized, single-blind placebo-controlled clinical trial and was performed on 92 adult patients admitted to the CCU with acute coronary artery syndrome. The standard STAI questionnaire was the tool used to assess anxiety states. Participants were equally assigned into case and control groups. The intervention was the aroma of the lemon balm extract, whereby three drops of extract were poured on a cotton patch, and patients were allowed to inhale twice a day for 30 min for three consecutive days. In the control group, odorless sesame oil was used as a placebo. After the intervention, lemon balm aromatherapy significantly ($p \leq 0.05$) reduced the anxiety state in the case group compared with the control group.

Findings of a study conducted by Saeidi et al. (2020) showed that both lemon balm and lavender significantly ($p < 0.05$) reduced chronic severe anxiety symptoms in the intervention groups compared with the control group. This RCT was single-blind and was performed on 45 adult employees of an office who were selected by purposive sampling and suffering from severe anxiety. The participants were divided randomly into three equal groups. Patients in the intervention groups received five drops of concentrated extract of lemon balm or lavender twice a day for 5 days. Patients in the control group did not take any medication. The levels of anxiety were assessed by BAI. The therapeutic effect of lavender in reduction of anxiety was more effective than lemon balm ($p < 0.001$).

Scholey et al. (2014) evaluated the anti-stress and cognitive effects of a single dose of lemon balm by conducting a randomized, placebo-controlled, balanced crossover clinical trial on healthy individuals who were induced to mild stress in the laboratory. The novelty of this study was that instead of lemon extract, which is administered in capsules or coated tablets, they used foodstuffs mixed with lemon balm in the form of a tea-like beverage and a yogurt drink, to show that people can improve their negative mood responses to stress if they changed their daily diet. They prescribed two products containing a standardized aqueous extract of lemon balm, which had an RA content of >6%. Forty-six adult participants who were divided into three intervention groups and one control group received single dose of 300, 600, and 600 mg lemon balm and placebo, respectively. These results demonstrate that receiving 300 mg lemon balm was associated with a lower state of anxiety and better memory performance at both 1 and 3 h post-intervention. At this dose, it is determined that the lemon balm has a constant anti-anxiety effect for a period of about 3 h, an effect similar to that seen in the case of benzodiazepines. It was also found that at the same time, after receiving lemon balm, the serum level of RA was at its highest, and the level of cortisol in saliva was reduced. There were no side effects during the treatment.

3.4 | Meta-analysis results

Four of 10 studies were not included in the meta-analysis, because in three studies continuous data in the form of mean and standardized mean differences were not reported (Alijaniha et al., 2015; Chehroudi et al., 2016; Scholey et al., 2014), the fourth study (Araj-Khodaei et al., 2020) was not compatible with other studies, because in all RCTs except this one, the intervention was compared with a placebo.

3.4.1 | Anxiety

The meta-analysis results of the five studies in 375 participants showed a significant decrease in mean anxiety scores in the lemon balm receiving group compared with the control group (SMD: −0.98; 95% CI: −1.63 to −0.33; $p = 0.003$). There was also considerable heterogeneity between the studies, $I^2 = 88\%$, ($p < 0.00001$). Three studies with 272 participants were included in the acute anxiety subgroup analysis, with this result suggesting a significant difference (SMD: -0.69; 95% CI: −1.38 to −0.01; $p = 0.05$). In chronic anxiety subgroup analysis of 103 participants from two studies, the results were not significant (SMD: -1.69; 95% CI: −4.20 to 0.82; $p = 0.19$). There were also considerable heterogeneity between the studies, $I^2 = 87\%$, ($p < 0.0006$) and, $I^2 = 94\%$, ($p < 0.0001$) respectively. (Higgins et al., 2019) (Figure 2)

3.4.2 | Depression

The meta-analysis results of the three studies on the 233 participants identified a significant reduction in mean depression score in the lemon balm receiving group compared with placebo group (SMD: -0.47; 95% CI: −0.73 to −0.21; $p = 0.0005$). There was no important heterogeneity between the studies, $I^2 = 0\%$, ($p = 0.41$). The subgroup analysis results of two studies on 160 participants in acute depression and one study on 73 participants in chronic depression reported similarly significant results (SMD: −0.55; 95% CI: −0.87 to −0.23; $p = 0.0007$ and SMD: −0.29; 95% CI: −0.75 to −0.17; $p = 0.22$, respectively). There was no heterogeneity between the studies, $I^2 = 0\%$, ($p = 0.33$) in the subgroup analysis of acute depression (Higgins et al., 2019) (Figure 3)

3.5 | Methodological quality and risk of bias

Sequence generation bias was identified as high risk in four studies (Araj-Khodaei et al., 2020; J. Cases et al., 2011; Lotfi et al., 2019; Saeidi et al., 2020) and low risk in the remaining eight studies.
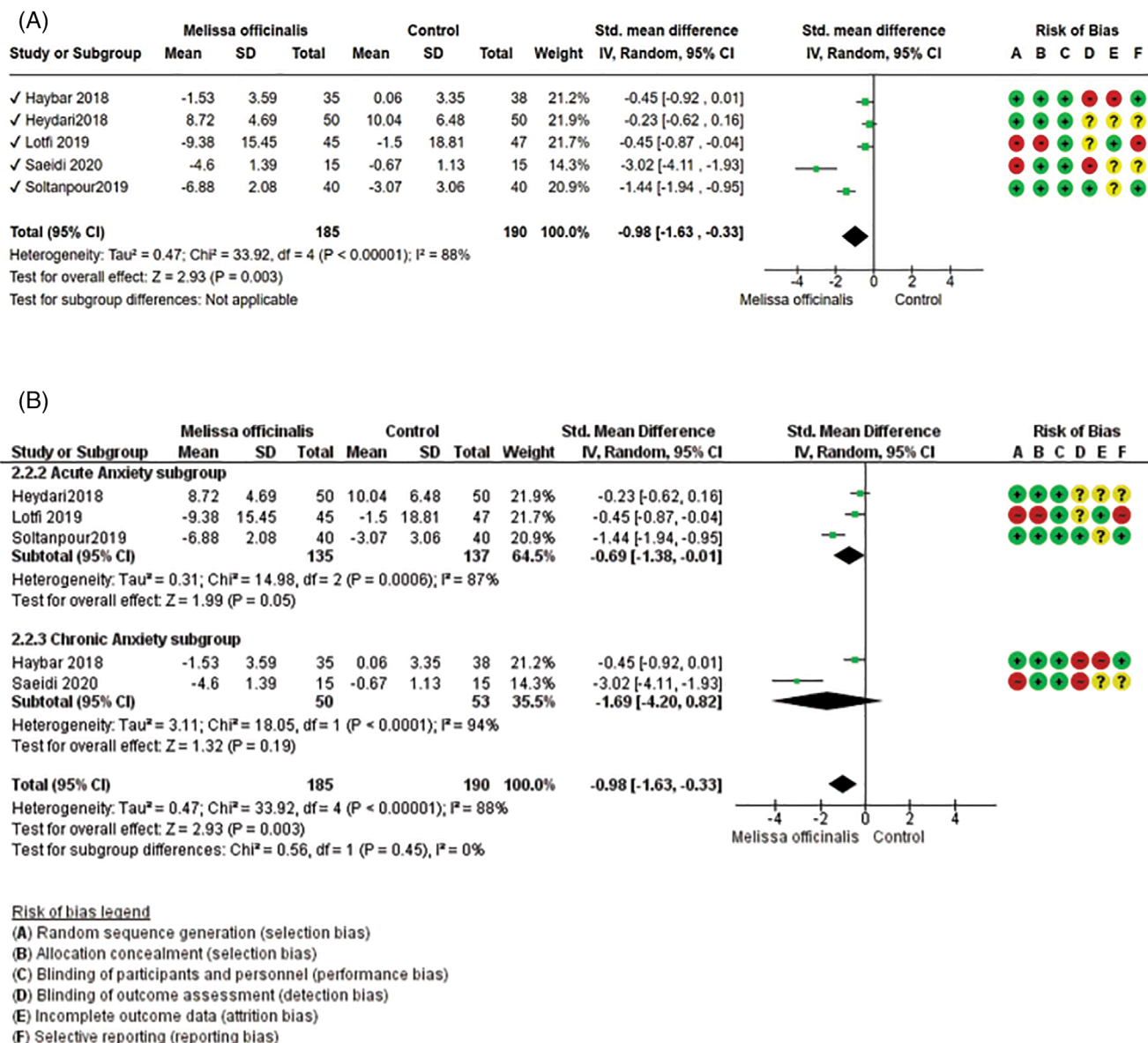
FIGURE 2 Forest plot, the effect of lemon balm on anxiety. (a) All studies included based on anxiety outcome. (b) Subgroup analysis, acute and chronic anxiety

Allocation concealment bias was specified as unclear in one study (Chehroudi et al., 2016) high risk in one study, (Lotfi et al., 2019) and low risk in the remaining 10 studies. Blinding of participants and personnel bias was determined as high risk in two studies (J. Cases et al., 2011; Chehroudi et al., 2016) and low risk in the remaining 10 studies. Blinding of outcome assessors bias was identified as high risk in three studies (Chehroudi et al., 2016; Haybar et al., 2018; Saeidi et al., 2020), unclear in three studies (J. Cases et al., 2011; Heydari et al., 2018; Lotfi et al., 2019), and low risk in the remaining six studies. Incomplete outcome data bias was identified as high risk in two studies (Haybar et al., 2018; Tavares-Silva et al., 2019), unclear in three studies (Heydari et al., 2018; Saeidi et al., 2020; Soltanpour et al., 2019), and low risk in the remaining seven studies. Selective outcome reporting bias was identified as high risk in one study (Lotfi et al., 2019), unclear in four studies (J. Cases et al., 2011;

Heydari et al., 2018; Saeidi et al., 2020; Scholey et al., 2014), and low risk in the remaining seven studies. The details are shown in Figure 4.

3.6 | Sensitivity analysis

In a sensitivity analysis of the anxiety outcomes that removed two outlier studies, Saeidi et al (SMD: −0.63; 95% CI: −1.13 to −0.13; $p = 0.01$) and Soltanpour et al (SMD: −0.84; 95% CI: −1.54 to −0.14; $p = 0.02$), the effect estimate remained significant. Furthermore, by removing these two outlier studies together, the sensitivity analysis result remained similar to the overall effect estimate (SMD: −0.37; 95% CI: −0.61 to −0.13; $p = 0.003$). There was no important heterogeneity between the studies, $I^2 = 0\%$, ($p = 0.69$) (Figure 5) (Table 2).

(A)
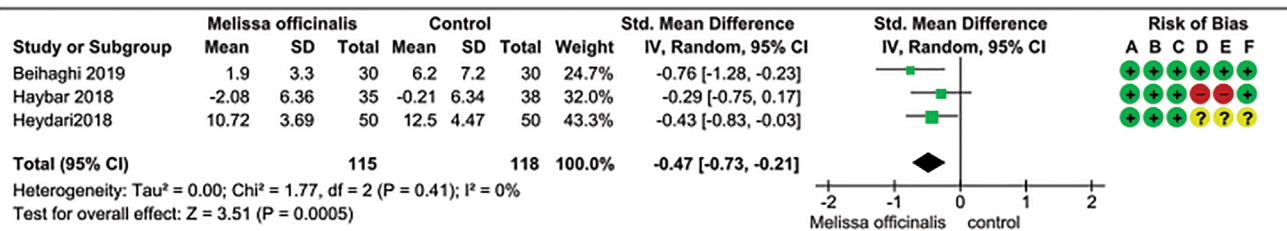
(B)
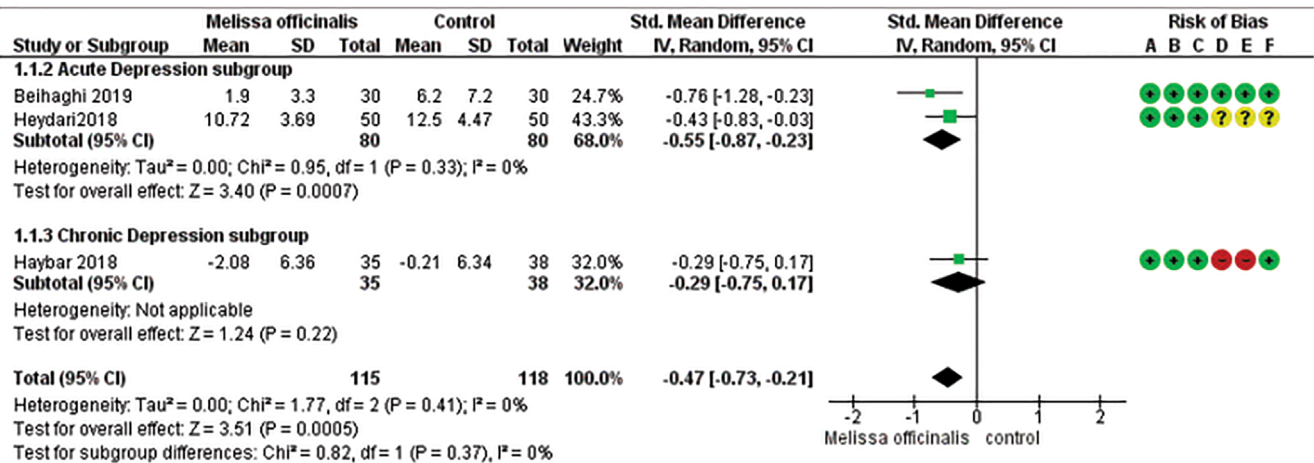
Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)

FIGURE 3   Forest plot, the effect of lemon balm on depression. (a) All studies included based on depression outcome. (b) Subgroup analysis, acute and chronic depression

4 | DISCUSSION

According to the results of all included eligible RCTs in this systematic review and meta-analysis, oral administration of lemon balm may be beneficial for anxiety and depression symptoms, particularly in the acute manifestations, without considerable side effects. It should be noted that the efficiency, safety, and quality of a nutraceutical product in the market is less than in the pharmaceutical sector. It may be due to a lack of fine-tuning, so many available products may be ineffective. (Izzo et al., 2016; Williamson et al., 2020).

4.1 | Depression

Several previous preclinical studies have reported that lemon balm has antidepressant and anxiolytic effects on the animals, such as antidepressant-like activity similar to imipramine in the forced swimming test in non-stressed mice (Emamghoreishi & Talebianpour, 2009), antidepressant-like properties in non-stressed rats (Taiwo et al., 2012),

serotonergic antidepressant activity in rats (Lin et al., 2015), and anxiolytic and antidepressant effects in restraint stress-induced mice (Ghazizadeh et al., 2020). These results are in good agreement with the qualitative and quantitative syntheses of the RCTs. It was found that administration of lemon balm has significant remedial effects on mild to moderate depression, reported by all of the RCTs included in the present review that studied depression. Especially in one of the RCTs, the antidepressant effect of lemon balm has evaluated equal to fluoxetine (Araj-Khodaei et al., 2020). It should be noted that only one study has examined lemon balm on depressed patients with a sample size of 15 participants. Therefore, one should be careful in analyzing the results (Figure 3).

4.2 | Anxiety

On the other hand, in all eligible RCTs, lemon balm has been significantly successful in improving anxiety symptoms in comparison with the control groups. Lemon balm extract has also been shown to

FIGURE 4   Risk of bias summary

reduce the agitation of patients with Alzheimer's disease (Akhondzadeh et al., 2003). Cases et al. in a pilot clinical trial showed a significant improvement in participant's anxiety manifestations (J. Cases et al., 2011). Animal studies conducted by Ibarra et al. (Julien Cases et al., 2010) and Taiwo et al. (Taiwo et al., 2012) have also supported the anxiolytic effect of lemon balm. Further studies by Kennedy et al. also support the anti-anxiety effect of lemon balm in combination with Valerian (David O. Kennedy et al., 2006) as well as mood (calmness, contentedness, and alertness) modulator properties of lemon balm alone (D. O. Kennedy et al., 2004; D. O. Kennedy et al., 2002; D. O. Kennedy et al., 2003). Also, findings of anti-anxiety effects of lemon balm have been reported in previous reviews (Shakeri et al., 2016; Ulbricht et al., 2005; Weeks, 2009). Our findings are consistent with these reports. Data analysis of eligible studies in this systematic review and meta-analysis represent a significant improvement in anxiety disorders compared with placebo after treatment with lemon balm (Figure 2).

To differentiate the efficacy of lemon balm on acute or chronic types of anxiety and depressive outcomes, subgroup analyses were performed. From the results of the subgroup analysis, lemon balm may be more successful in treating the acute symptoms. This finding has been confirmed by previous studies (David O. Kennedy et al., 2006; D. O. Kennedy et al., 2004); however, it should be noted that due to the insufficient number of studies in each subgroup, the obtained estimates are not robust and require further investigation in future studies.

4.3 | Dosage

In animal studies, the prescribed doses of lemon balm for depression have been reported from 25 to 300 mg/kg (Shakeri et al., 2016). In clinical trials in adults, a single oral dose of 300 mg of lemon balm extract has been shown to have anti-stress and anti-anxiety effects (Scholey et al., 2014). While another clinical trial used a minimum prescribed dose of 600 mg per day (J. Cases et al., 2011). The effectiveness of lemon balm seems to depend on the duration of administration (Taiwo et al., 2012). In the abovementioned RCTs, the shortest duration of oral therapy that led to improvement in anxiety disorders was 5–7 days (Saeidi et al., 2020) (Soltanpour et al., 2019). However, longer periods of between 10 days and 8 weeks (Beihaghi et al., 2019) (Araj-Khodaei et al., 2020) were required to improve depressive symptoms in individual studies.

4.4 | Side effects

The neuropsychiatric side effects reported in several studies for lemon balm include the following: Headache (Buechner et al., 1974), EEG Changes (Schulz et al., 1998), reduced alertness (D. O. Kennedy et al., 2002), sleep disturbances (Cerny & Schmid, 1999; Soulimani et al., 1991), and withdrawal symptoms (Demirci et al., 2015). It has been repeatedly pointed that lemon balm should be used with caution in patients with thyroid dysfunction because it can inhibit thyroid hormone (Auf'mkolk et al., 1985; Santini et al., 2003; Sourgens et al., 1982; Wong et al., 1998). Nonetheless, lemon balm is known to be a safe medicinal plant (Ulbricht et al., 2005). No toxicity was reported by Bounihi et al. following oral administration of lemon balm essence at doses of 300 and 2000 mg/kg in rats (Bounihi et al., 2013). Also lemon balm did not exhibit any toxicity or behavioral changes at 2000 mg/kg dose level in mice (Bhat et al., 2012). Stojiljković et al. reported that the essential oil of lemon balm is only moderately toxic (oral LD_{50}; 2.57 g/kg), and the toxic effects in mice begin from 1,000 mg/kg (Stojanović et al., 2019). In 6 of the 10 RCTs included in the current review, it was reported that lemon balm had no considerable side effects, and lemon balm products were well tolerated by participants. In the remaining four studies, side effects were not investigated (Chehroudi et al., 2016; Haybar et al., 2018; Lotfi et al., 2019; Saeidi et al., 2020).

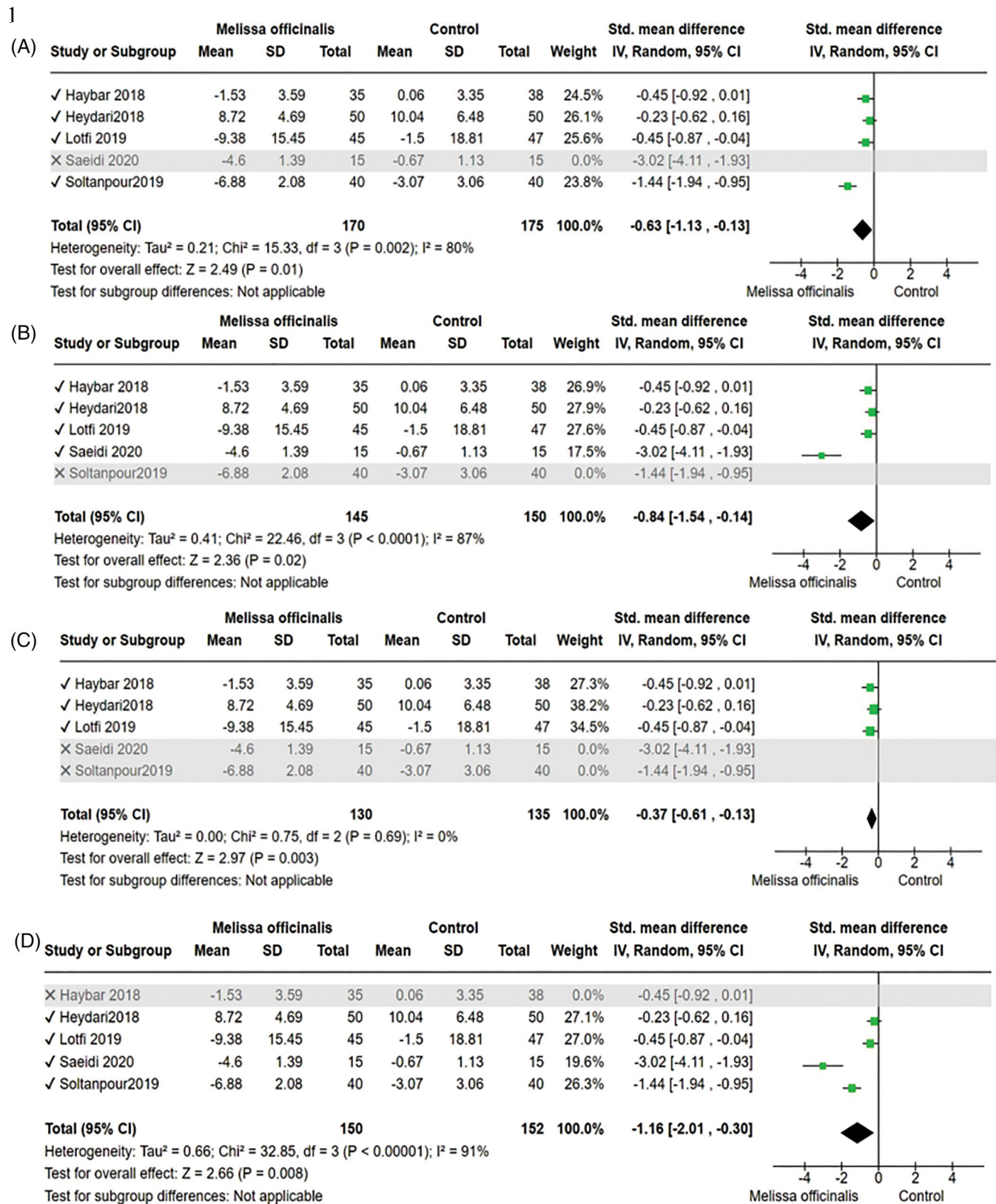**FIGURE 5** Sensitivity analysis by omitting the outlier studies on anxiety outcome. (a) The overall effect by omitting of Saeidi study. (b) The overall effect by omitting of Soltanpour study. (c) The overall effect by omitting Saeidi and Soltanpour studies. (d) The overall effect by omitting Haybar study. (e) The overall effect by omitting Heydari study. (f) The overall effect by omitting Lotfi study
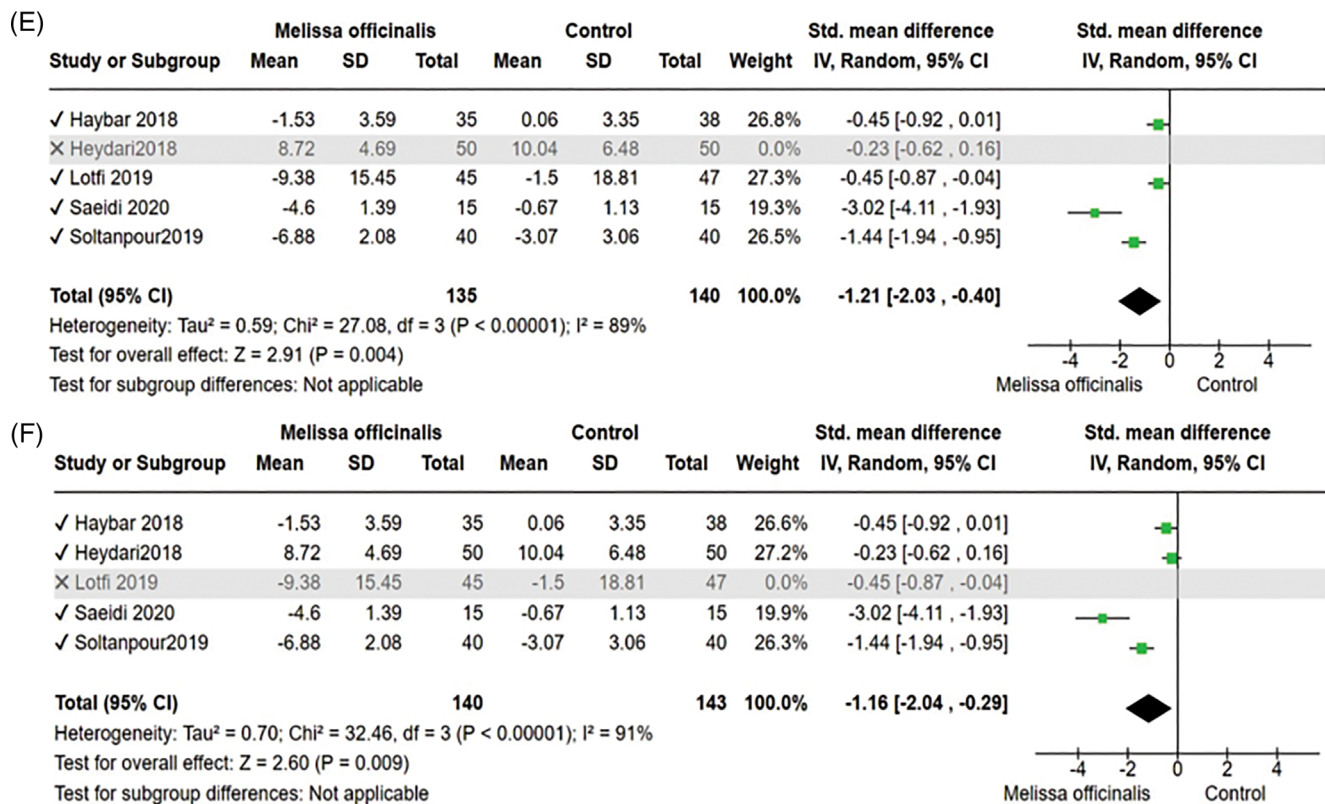
(E)

Study or Subgroup	Melissa officinalis			Control			Weight	Std. mean difference IV, Random, 95% CI
	Mean	SD	Total	Mean	SD	Total		
✓ Haybar 2018	-1.53	3.59	35	0.06	3.35	38	26.8%	-0.45 [-0.92 , 0.01]
✗ Heydari2018	8.72	4.69	50	10.04	6.48	50	0.0%	-0.23 [-0.62 , 0.16]
✓ Lotfi 2019	-9.38	15.45	45	-1.5	18.81	47	27.3%	-0.45 [-0.87 , -0.04]
✓ Saeidi 2020	-4.6	1.39	15	-0.67	1.13	15	19.3%	-3.02 [-4.11 , -1.93]
✓ Soltanpour2019	-6.88	2.08	40	-3.07	3.06	40	26.5%	-1.44 [-1.94 , -0.95]
Total (95% CI)			**135**			**140**	**100.0%**	**-1.21 [-2.03 , -0.40]**

Heterogeneity: Tau² = 0.59; Chi² = 27.08, df = 3 (P < 0.00001); I² = 89%
Test for overall effect: Z = 2.91 (P = 0.004)
Test for subgroup differences: Not applicable

(F)

Study or Subgroup	Melissa officinalis			Control			Weight	Std. mean difference IV, Random, 95% CI
	Mean	SD	Total	Mean	SD	Total		
✓ Haybar 2018	-1.53	3.59	35	0.06	3.35	38	26.6%	-0.45 [-0.92 , 0.01]
✓ Heydari2018	8.72	4.69	50	10.04	6.48	50	27.2%	-0.23 [-0.62 , 0.16]
✗ Lotfi 2019	-9.38	15.45	45	-1.5	18.81	47	0.0%	-0.45 [-0.87 , -0.04]
✓ Saeidi 2020	-4.6	1.39	15	-0.67	1.13	15	19.9%	-3.02 [-4.11 , -1.93]
✓ Soltanpour2019	-6.88	2.08	40	-3.07	3.06	40	26.3%	-1.44 [-1.94 , -0.95]
Total (95% CI)			**140**			**143**	**100.0%**	**-1.16 [-2.04 , -0.29]**

Heterogeneity: Tau² = 0.70; Chi² = 32.46, df = 3 (P < 0.00001); I² = 91%
Test for overall effect: Z = 2.60 (P = 0.009)
Test for subgroup differences: Not applicable

FIGURE 5 (Continued)

TABLE 2 Summary of sensitivity analysis on anxiety outcome

Omitted study	SMD	Confidence interval	p value	Heterogeneity	
				p	I²
Haybar et al., 2018	−1.16	−2.01, −0.30	=0.008	<0.00001	91%
Heydari et al., 2018	−1.21	−2.03, −0.40	=0.004	<0.00001	89%
Lotfi et al., 2019	−1.16	−2.04, −0.29	=0.009	<0.00001	91%
Saeidi et al., 2020	−0.63	−1.13, −0.13	=0.01	=0.002	80%
Soltanpour et al., 2019	−0.84	−1.54, −0.14	=0.02	<0.0001	87%
Saeidi and Soltanpour	−0.37	−0.61, −0.13	=0.003	=0.69	0%
All studies (without removing any study)	−0.98	−1.63, −0.33	=0.003	<0.00001	88%

4.5 | Mechanisms

Antidepressant activity is exerted in most medicinal herbs by increasing levels of serotonin, norepinephrine, or dopamine in the brain (Martins, & S, B., 2018) Some of the phytochemicals derived from medicinal plants that have anti-anxiety and anti-depressant effects include the following: saponins, alkaloids, polyphenols, triterpenoids, essential oils, fatty acids, and flavonoids (Fajemiroye et al., 2016). Lemon balm is obtained from one of the medicinal plants that have large amounts of phenolic and flavonoid constituents, especially RA (Dastmalchi et al., 2008; de Sousa et al., 2004), which may modulate the serotonergic pathway (Lin et al., 2015), upregulate GABA through

GABA-T inhibition (Awad et al., 2009; Taiwo et al., 2012; Yoo et al., 2011), and inhibit acetylcholine esterase and monoamine oxidase enzyme (Shakeri et al., 2016; Taiwo et al., 2012; Ulbricht et al., 2005). However, the mechanism of lemon balm activity has not been assessed within clinical trials.

5 | HETEROGENEITY

Considerable heterogeneity was observed between studies, so we provided a sensitivity analysis by omitting the studies on anxiety outcome and evaluated the results (Figure 5) (Table 2). It was observed

that by omitting the outlier studies (Saeidi et al. and Soltanpour et al.), both separately and together, the overall effect was still significant. However, when the studies were omitted separately, the heterogeneity between studies remained significant.

6 | LIMITATIONS

It was not possible for us to search for articles in other languages and other countries where herbal medicines are very influential, such as China, Russia, Arabic, France, and Germany; accordingly, there may be a study selection bias. There were high levels of heterogeneity between the included RCTs, because the design of the studies and the type of lemon balm used in the studies were very different methodologically. The small number of clinical trials and undiagnosed anxiety disorders were other limitations of the current systematic review and meta-analysis.

7 | CONCLUSIONS AND FUTURE DIRECTIONS

Current evidence suggests that lemon balm is well tolerated and may improve the anxiety and depressive symptoms; however, due to the high level of statistical heterogeneity, the results should be treated as preliminary until further studies have been completed. Future research using standardized products based on their bioactive components and appropriate treatment duration is required. It is recommended that people with clinical depression and/or anxiety, with larger sample size, be recruited for future trials.

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CONFLICT OF INTEREST
The authors declare no conflict of interest and no competing financial interests exist.

AUTHOR CONTRIBUTIONS
Javid Ghazizadeh, Mohammadali Torbati, Ali Fakhari, Mojgan Mirghafourvand, Somaiyeh Taheri-Tarighi, and Mostafa Araj-khodaei contributed in the conception, design, data collection of the study. Javid Ghazizadeh, Saeed Sadigh-Eteghad, Sanaz Hamedeyazdan, Wolfgang Marx, Mojgan Mirghafourvand, and Mostafa Araj-khodaei contributed in statistical analysis and manuscript drafting. The final version has been read, and was confirmed by all authors for submission.

DATA AVAILABILITY STATEMENT
The data that support the findings of this study are available from the corresponding author upon reasonable request.

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