Therapeutic applications of lemon balm (Melissa officinalis) for obstetrics and gynecological health issues: A systematic review

Zainab Alimoradi, Elahe Jafari, Fatemeh Abdi, Mark D. Griffiths

PII: S2210-8033(23)00129-X

DOI: https://doi.org/10.1016/j.hermed.2023.100751

Reference: HERMED100751

To appear in: *Journal of Herbal Medicine*

Received date: 6 November 2022
Revised date: 26 May 2023
Accepted date: 28 August 2023

Please cite this article as: Zainab Alimoradi, Elahe Jafari, Fatemeh Abdi and Mark D. Griffiths, Therapeutic applications of lemon balm (Melissa officinalis) for obstetrics and gynecological health issues: A systematic review, *Journal of Herbal Medicine,* (2023) doi:https://doi.org/10.1016/j.hermed.2023.100751

Therapeutic applications of lemon balm (Melissa officinalis) for obstetrics and gynecological health issues: A systematic review

Zainab Alimoradi[1*], Elahe Jafari[1], Fatemeh Abdi[2], Mark D. Griffiths[3]

[1] Social Determinants of Health Research Center, Research Institute for Prevention of Non-Communicable Diseases, Qazvin University of Medical Sciences, Qazvin, Iran.
Email: EJ (eljafari@yahoo.com); ZA (zainabalimoradi@yahoo.com)
[2] Non-Communicable Diseases Research Center, Alborz University of Medical Sciences, Karaj, Iran. Email: abdi@sbmu.ac.ir
[3] International Gaming Research Unit, Psychology Department, Nottingham Trent University, Nottingham, UK. Email: mark.griffiths@ntu.ac.uk

Corresponding authors:
Dr. Zainab Alimoradi
Social Determinants of Health Research Center, Research Institute for Prevention of Non-Communicable Diseases, Qazvin University of Medical Sciences, Qazvin, Iran.
zainabalimoradi@yahoo.com

Abstract

Introduction: *Melissa officinalis* (lemon balm) is a medicinal herb with several proposed therapeutic uses. The present paper systematically reviewed relevant evidence regarding the applications of *M. officinalis* for obstetrics and gynecological health issues.

Methods: Utilizing a systematic approach, academic electronic databases including *PubMed, Scopus, ProQuest, Web of Science*, the *Cochrane Library* were searched up to September 21, 2022. The Cochrane Risk of Bias Assessment Toolkit was used to assess methodological quality of included studies. Due to methodological heterogeneity among a small number of retrieved studies, evidence was pooled utilizing a narrative synthesis.

Results: In total, 15 studies were included. *M. officinalis* appears to be useful in pain reduction (childbirth after pain and primary dysmenorrhea), improving premenstrual symptoms, and postpartum blues. However, no effect was seen on intensity of menstrual bleeding and effectiveness was mixed in relation to sexual functioning and menopausal-related symptoms. Due to selection bias in almost all studies, the evidence level of the included studies was considered as high risk of bias. In most studies no side effects were reported among the intervention groups. When reported they were minor (e.g., diarrhea, constipation, flatulence, stomach pain, and sleep disturbance).

Discussion/Conclusions: This intervention might have benefit for gynecological conditions but it is not strongly supported by the available evidence. Consequently, further studies are needed with (i) larger sample sizes, (ii) more rigorous methodologies using *Melissa officinalis* alone to

avoid synergistic or antagonistic effects, (iii) adjustment for potential covariates, (iv) toxicity assessment to establish optimal doses, and (v) the most effective forms of preparation.

Keywords: *Melissa officinalis*; lemon balm; obstetrics; premenstrual syndrome; postpartum pain; sexual dysfunction; dysmenorrhea

1. Introduction

The use of herbal medicinal drugs as natural products has been used all over the world (Baghbahadorani & Miraj, 2017; Bahmani, Farkhondeh, & Sadighara, 2012; Masoudi, Miraj, & Rafieian-Kopaei, 2016). In recent years, more attention has been paid to herbal medicine which some have claimed has better curative effects and fewer adverse reactions (Yuan, Ma, Ye, & Piao, 2016). Around the world, the number of people who want to use herbal products as an alternative to prescription drugs is increasing (Abdi, Alimoradi, Roozbeh, Amjadi, & Robatjazi, 2023). Herbal medicines also account for more than $60 billion annually in the global market (Gunjan et al., 2015). Natural chemical compounds found in herbal medicines appears to fulfill many individuals' primary needs in helping them to overcome their illnesses (Baharvand-Ahmadi et al., 2015; Eddouks, Chattopadhyay, De Feo, & Cho, 2012; Shaygannia, Bahmani, Zamanzad, & Rafieian-Kopaei, 2016). The use of local medical herbs is also recommended by the World Health Organization (2019). Traditional Iranian remedies have been passed down from generation to generation and include the use of Melissa officinalis Lamiaceae or lemon balm which has been used as an alternative clinical option for a wide variety of medical and physical problems (e.g., poor sleep, liver functioning, skin problems, stomach aches, menstrual pain relief, migraine relief, slimming aid, etc.) (Rezaeizadeh, Alizadeh, Naseri, & Shams, 2009; Shoara et al., 2015). The fact that this plant is used in Iran for women's health problems requires more research. Studies have investigated the use of herbal medicinal drugs in East Asia, such as China (Khalid, Hu, Cai, & Hussien, 2009; Watson, Hatcher, & Good, 2019).

Melissa (M.) officinalis, a medicinal plant with five types of perennial herb from the *Lamiaceae* (mint) family, is commonly called lemon balm (Sofowora, Ogunbodede, & Onayade, 2013). *M. officinalis* is an indigenous medical planet in central Asia, Europe and Iran (Gurčík, Dúbravská, & Miklovičová, 2005; Jastrzębska-Stojko, Stojko, Rzepecka-Stojko, Kabała-Dzik, & Stojko, 2013; Miraj, Rafieian-Kopaei, & Kiani, 2017; Rasmussen, 2011). Several therapeutic uses have been proposed for *M. officinalis* based on modern pharmacological studies including antidepressant, antianxiety, antioxidant, antimicrobial, anticancer, antispasmodic, glycemic and lipidemic control, sedative, and anti-inflammatory (Dastjerdi et al., 2019; Mirabi, Namdari, Alamolhoda, & Mojab, 2017; Mirghafourvand, Malakouti, Charandabi, Khalili, & Homayi, 2016). Several studies have reported the therapeutic benefits of *M. officinalis* including pain

reduction, improved sexual functioning, antispasmodic activity, and antioxidant activity (Dastjerdi et al., 2019; Heydari, Dehghani, Emamghoreishi, & Akbarzadeh, 2019). *M. officinalis* is a safe ingredient, and no side effects of its administration have been reported among humans (Shirazi, Jalalian, Abed, & Ghaemi, 2021). The biological properties of the lemon balm herb can be accompanied with the existence and combined action of bioactive compounds such as terpenoids, rosmarinic acid, caffeic acid, and phenolic antioxidants. The variety of these bioactive molecules makes them an encouraging candidate for the development of nutraceuticals and cosmeceuticals (Sharifi-Rad, Quispe, Herrera-Bravo, Akram, Abbaass, Semwal, Painuli, Konovalov, Alfred, & Kumar, 2021).

M. officinalis has been used to alleviate psychological symptoms because its extract is claimed to mildly inhibits monoamine oxidase and benefit individuals' mental health (López et al., 2009). It has been proposed that *M. officinalis* can act as cholinesterase inhibitor because it enhances the action of the brain's acetylcholine synapses. Consequently, it might be useful for Alzheimer's disease (Cummings, 2000; Ellis, 2005). *M. officinalis* extract can increase cell proliferation and neuroblast discrimination, as well as decrease serum's corticosterone levels and gamma-aminobutyric acid (GABA)-T levels (Hassanzadeh et al., 2011; Yoo et al., 2011). The positive effect of this herbal medicine on depression, anxiety, restlessness, insomnia, and poor cognition have been reported (Abuhamdah & Chazot, 2008; Gyllenhaal, Merritt, Peterson, Block, & Gochenour, 2000; Kennedy, Little, & Scholey, 2004; Kennedy, Scholey, Tildesley, Perry, & Wesnes, 2002). Aromatherapy with extract of *M. officinalis* is also used in treatment of migraines, headaches, mood disorder, rheumatic pains, sexual disorders, immune disorders and menopausal symptoms due to its sedative and antispasmoic effects (Brown & Gerbarg, 2001; Mirabi et al., 2017; Wheatley, 2005). There is limited (and controversial) evidence concerning the effectiveness of *M. officinalis* for improving obstetrics and gynecological health issues.

1.1. Aim of the present study

The present study aimed to evaluate the effectiveness and safety of *M. officinalis* for obstetric and gynecological health issues comprising a systematic review to synthesize the empirical evidence.

2. Methods

2.1. Design and registration

The Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines were used to conduct and report the present study (Puljak et al., 2020). The protocol of the present study was registered in the international Prospective Register of Systematic Reviews database PROSPERO (decree code: CRD42022326663) (Alimoradi Z, 2022).

2.2. Study objectives

The study's key objective was to answer the following questions: (i) What are the therapeutic applications of *M. officinalis* for obstetric and gynecological health issues? (ii) Does *M. officinalis* have side effects when used for obstetric and gynecological health issues? (iii) What

doses of *M. officinalis* are used for obstetric and gynecological health issues? and (iv) What is the application form of *M. officinalis* for obstetric and gynecological health issues?

2.3. Eligibility criteria

The eligibility criteria were constructed based on PICOS components: women with any kind of obstetric and gynecological health issues were the selected **Population** group; *M. officinalis* in any form was selected as the **Intervention**; any kind of control group (e.g., placebo, other treatments or routine care) was selected the **Comparison**; the assessment of obstetric and gynecological physical and mental health issues with valid and reliable psychometric scales was selected as the **Outcome**; and trials with any design were selected as the eligible **Study** design. No limitation was considered regarding publication time or language.

2.4. Information sources

An extensive systematic search was performed utilizing five academic databases (i.e., *Scopus, PubMed/MEDLINE, ProQuest, Cochrane,* and *Web of Science*). Because all the studies were Iranian, a further search was conducted in an Iranian national database called SID (Scientific Information database). The search used keywords extracted from Medical Subject Headings from inception to October 21, 2022.

2.5. Search strategy

In the present study, *M. officinalis* was selected as the intervention. The search syntax was adopted based on the advanced search guidelines of each abovementioned database. The two-component searched syntax included population and intervention. The search terms used were: (Melissas OR "Melissa officinalis" OR "Melissa officinali" OR (officinalis AND Melissa) OR "lemon balm" OR (balm AND lemon) OR (lemon AND balms) OR "lemon balms") AND (women OR woman OR girl* OR female*). The search process was conducted without filters or language limitations by two researchers independently. The search strategy for each database is reported in Supplementary Materials 1.

2.6. Study selection

The title and abstract of retrieved potential studies were read. Duplicates and irrelevant studies were omitted. The full texts of potentially relevant papers were reviewed based on eligibility criteria.

2.7. Quality assessment

Methodological quality was assessed using the six main domains suggested in Cochrane Risk of Bias Assessment Toolkit (Puljak et al., 2020). Using this checklist, each included study was assessed to find risk of performance, selection, detection, reporting, attrition, and other biases. Four items were assessed as other biases including: (i) how sample size was determined; (ii) clearly stated eligibility criteria; (iii) the interventions for each group with sufficient essential

details; and (iv) completely defined outcome measures. Details of assessed items in each domain is provided in Table 1.

2.8. Data extraction and management

For this step, an *Excel* spreadsheet was designed to extract required information from included studies. The extracted data included the first author's name, study region, publication date, number of participants based on study groups and their mean age, measurement time points, intervention description, side effects, and main findings. Three steps (study selection, quality assessment, and data extraction) were carried out independently by two reviewers. Any disagreements were resolved by discussion.

2.9. Data synthesis

Due to the small number of included papers and their methodological heterogeneity, data were synthesized utilizing a narrative approach. In a narrative approach, evidence regarding the study aims were summarized and reported including: (i) the specific type of obstetric and gynecological health issues; (ii) side effects of *M. officinalis* for obstetric and gynecological health issues; (iii) different doses of *M. officinalis;* and (iv) different form of *M. officinalis* used for obstetric and gynecological health issues.

3. Results

3.1. Study selection

The initial literature search retrieved 1,415 papers: *PubMed Central* (n=93), *ProQuest* (n=164), *Scopus* (n=545), *ISI Web of Knowledge* (n=62), and *Cochrane Library* (n=11), and *SID* (n=540) from inception up to the end of September 2022. After excluding duplicate and irrelevant papers not meeting the eligibility criteria, 15 studies remained in the review. Figure 1 shows the PRISMA flowchart.

3.2. Study characteristics

All 15 studies were conducted in Iran. All studies were single or double blinded except for two studies (Afshar et al., 2020; Mirghafourvand, Malakouti, Mohammad, Farshbaf, & Ghanbari, 2016) which were triple blinded. Studies were published between 2013 and 2021. In total, there were 1362 participants (sample size ranged from 43 to 200 participants) with an age range of 14 to 54 years. A summary of these studies is provided in Table 1.

3.3. Methodological quality

All studies had detailed explanation on the interventions and placebo. Methodological quality total scores are provided in Table 1 and details of quality assessment in each domain are presented in Supplementary Materials 2. All studies had completely defined outcome measures, randomization process, clearly stated eligibility criteria, and blinding of participants. Due to selection bias in almost all of the included studies (i.e., not carrying out proper random sequence

generation and allocation concealment), the evidence level of the studies reviewed was considered to contain a high risk of bias.

3.4. M. officinalis characteristics

Treatment protocol of *M. officinalis* varied based on the selected outcome and characteristics of participants. Collectively, the most commonly used therapeutic formulation were capsules containing *M. officinalis* essence comprising different doses: 80 mg (Taavoni, Nazem Ekbatani, & Haghani, 2013), 300 mg (Amin et al., 2018), 330 mg (Mirabi, Alamolhoda, Yazdkhasti, & Mojab, 2018; Mirabi et al., 2017), 395 mg (Dastjerdi et al., 2019), 600 mg (Akbarzadeh et al., 2015; Heydari et al., 2019), 500 mg (Beihaghi, Yousefzade, Mazloom, Modares Gharavi, & Hamedi, 2019; Darvish-Mofrad-Kashani et al., 2018; Mirghafourvand, Malakouti, Charandabi, et al., 2016; Mirghafourvand, Malakouti, Mohammad, et al., 2016), 1000 mg (Afshar et al., 2020), and 1200 mg (Akbarzadeh et al., 2018). Almost all included studies used capsules and only one study used a tea bag (Safdari Dehcheshmeh & Parvin, 2016). More specifically, ten studies used placebo starch capsules (Akbarzadeh et al., 2015, 2018; Afshar et al., 2020; Darvish-Mofrad-Kashani et al., 2018; Heydari et al., 2019; Mirabi et al., 2017, 2018; Mirghafourvand, Malakouti, Charandabi, et al., 2016; Mirghafourvand, Malakouti, Mohammad, et al., 2016; Shirazi et al., 2021), two studies used capsules with 250mg mefenamic acid (Dastjerdi et al., 2019; Safdari Dehcheshmeh & Parvin, 2016), and two used citalopram capsules (Amin et al., 2018; Shirazi et al., 2021). One study used a normal tea bag as placebo (Safdari Dehcheshmeh & Parvin, 2016). Additional treatment components are included in Table 1.

3.5. Treatment outcome assessment

The obstetric and gynecological health problems that were treated therapeutically with *M. officinalis* were childbirth after-pain (Dastjerdi et al., 2019), symptoms of premenstrual syndrome (Akbarzadeh et al., 2015; Heydari et al., 2019; Mirghafourvand, Malakouti, Charandabi, et al., 2016; Safdari Dehcheshmeh & Parvin, 2016), severity of primary dysmenorrhea (Mirabi et al., 2017, 2018; Safdari Dehcheshmeh & Parvin, 2016), menstrual bleeding (Mirabi et al., 2018; Mirghafourvand, Malakouti, Mohammad, et al., 2016), sexual functioning (Afshar et al., 2020; Akbarzadeh et al., 2018), menopausal related symptoms (Amin et al., 2018; Shirazi et al., 2021; Taavoni et al., 2013), and postpartum blues (Beihaghi et al., 2019).

For postpartum after-pain (Shirazi et al., 2021), the analgesic effect of *M. officinalis* was investigated in comparison to mefenamic acid. The results showed that *M. officinalis* had significantly more pain relief effect compared mefenamic acid. Both groups received capsules every six hours for 24 hours. Greater pain reduction was found among the *M. officinalis* group in the third hour after the first dose.

For symptoms of premenstrual syndrome (Akbarzadeh et al., 2018; Darvish-Mofrad-Kashani et al., 2018; Heydari et al., 2019; Mirghafourvand, Malakouti, Charandabi, et al., 2016), the effectiveness of *M. officinalis* was compared to placebo (capsules containing starch). All

participants were female adolescents at high school or college. The treatment pattern comprised two capsules containing 600mg *M. officinalis* administered daily through the menstrual period for three cycles (Akbarzadeh et al., 2015; Heydari et al., 2019; Safdari Dehcheshmeh & Parvin, 2016), and capsules with 500mg *M. officinalis* used twice daily for two consecutive menstrual cycles during the luteal phase (Mirghafourvand, Malakouti, Charandabi, et al., 2016). Total scores on scales assessing premenstrual psychosocial and physical symptoms all decreased significantly in the intervention group compared to the placebo (Akbarzadeh et al., 2015, 2018; Heydari et al., 2019; Mirghafourvand, Malakouti, Charandabi, et al., 2016). Also, improved quality of life was reported among the experimental group vs. placebo in both physical and psychological aspects by the end of the second month of intervention (Mirghafourvand, Malakouti, Charandabi, et al., 2016).

The effectiveness of *M. officinalis* on severity of primary dysmenorrhea (Mirabi et al., 2017, 2018; Safdari Dehcheshmeh & Parvin, 2016) was investigated using 330mg of the herb in form of capsules compared to capsules containing starch (Mirabi et al., 2018; Mirabi et al., 2017), and a teabag compared to mefenamic acid (Safdari Dehcheshmeh & Parvin, 2016). Capsules were given three times daily in first three days of menstruation (Mirabi et al., 2017), and teabags were used every eight hours when menstruation pain started until its alleviation for three months (Safdari Dehcheshmeh & Parvin, 2016). Severity of pain (Mirabi et al., 2017; Safdari Dehcheshmeh & Parvin, 2016), and intensity of dysmenorrhea-related systemic symptoms (Mirabi et al., 2018) was more greatly reduced in the experimental group ($p<0.05$). Pain duration (Safdari Dehcheshmeh & Parvin, 2016) was not affected by intervention.

The effectiveness of *M. officinalis* on menstrual bleeding (Mirabi et al., 2018; Mirghafourvand, Malakouti, Mohammad, et al., 2016), was investigated using 330 mg (Mirabi et al., 2018) and 500 mg (Mirghafourvand, Malakouti, Mohammad, et al., 2016) of the herb in form of capsule compared to capsules containing starch. Capsules were either given twice daily in the luteal phase for two consecutive menstrual cycles (Mirghafourvand, Malakouti, Mohammad, et al., 2016) or three times daily in first three days of menstruation (Mirabi et al., 2018). This herbal treatment had no significant effect in decreasing menstrual bleeding (Mirabi et al., 2018; Mirghafourvand, Malakouti, Mohammad, et al., 2016).

The effectiveness of *M. officinalis* on sexual functioning was investigated using 500mg capsules (Darvish-Mofrad-Kashani et al., 2018) and 1000mg capsules (Afshar et al., 2020) compared to placebo capsules of starch. Two treatment patterns of twice a day for four weeks (Darvish-Mofrad-Kashani et al., 2018) and one capsule per day for eight weeks (Afshar et al., 2020) were used (both provided the same dose of 1000mg *M. officinalis* daily). In the first study, sexual functioning was significantly improved in the intervention vs. placebo group (Darvish-Mofrad-Kashani et al., 2018). However, in the second study, sexual functioning of menopausal women did not improve. Given that the researchers used *M. officinalis* in combination with some other herbs including *Foeniculum vulgare (Fennel)*, and *Nigella sativa* seed powder, the antagonist effect of this combination might have been responsible for this finding (Afshar et al., 2020).

The effectiveness of *M. Officinalis* on menopause-related symptoms was investigated among menopausal women with sleep disorder (Amin et al., 2018; Shirazi et al., 2021; Taavoni et al., 2013). Oral capsules with different doses of *M. officinalis* including 80 mg in combination with valerian (Taavoni et al., 2013) 300 mg in combination with fennel fruits extract and *Nigella sativa* powder (Amin et al., 2018), and 500 mg of aqueous extract of *M. officinalis* (Shirazi et al., 2021) were used. One study used both placebo and citalopram comparison (Shirazi et al., 2021), two others had a placebo (Taavoni et al., 2013) and citalopram comparison (Amin et al., 2018). Two treatment protocols of one capsule (Mirghafourvand, Malakouti, Mohammad, et al., 2016) and two capsules (Taavoni et al., 2013) every day for eight weeks (Amin et al., 2018; Shirazi et al., 2021) were administered. Findings were inconsistent. More specifically, one study reported improved menopausal-related symptoms in *M. officinalis* group compared with citalopram and placebo (Shirazi et al., 2021), while no significant difference in the improvement of menopausal symptoms was reported in the other study for *M. officinalis* compared to citalopram (Amin et al., 2018). Sleep disorder was the main menopausal-related symptom assessed after using a combination of valerian and *M. officinalis*, and significant improvement compared to placebo was reported (Taavoni et al., 2013). For postpartum blues (PB) (Beihaghi et al., 2019), the effect of *M. officinalis* was investigated in comparison to placebo. Greater PB reduction was found among the *M. officinalis* group on the fourteenth day after childbirth.

3.6. Adverse side effects

Eight studies did not report any negative side effects during the intervention and follow-up period (Afshar et al., 2020; Akbarzadeh et al., 2018; Heydari et al., 2019; Mirabi et al., 2018; Mirabi et al., 2017; Shirazi et al., 2021; Taavoni et al., 2013; Beihaghi et al., 2019). Five studies did not report evidence regarding any potential side effects (Akbarzadeh et al., 2015; Amin et al., 2018; Dastjerdi et al., 2019; Mirghafourvand, Malakouti, Charandabi, et al., 2016; Safdari Dehcheshmeh & Parvin, 2016). Some side effects were reported in two studies including stomach pain and flatulence in the placebo group and sleep disturbances among the intervention group (Mirghafourvand, Malakouti, Mohammad, et al., 2016), and diarrhea and constipation among both study groups (Darvish-Mofrad-Kashani et al., 2018).

4. Discussion

The present systematic review collated and narratively synthesized available empirical evidence regarding the therapeutic application of *M. officinalis* for obstetric and gynecological health issues. Overall, 15 studies assessed the therapeutic effect of *M. officinalis* on childbirth after-pain (Dastjerdi et al., 2019), symptoms of premenstrual syndrome (Akbarzadeh et al., 2015, 2018; Heydari et al., 2019; Mirghafourvand, Malakouti, Charandabi, et al., 2016), severity of primary dysmenorrhea (Mirabi et al., 2017, 2018; Safdari Dehcheshmeh & Parvin, 2016), menstrual bleeding (Mirabi et al., 2018; Mirghafourvand, Malakouti, Mohammad, et al., 2016), sexual functioning (Afshar et al., 2020; Darvish-Mofrad-Kashani et al., 2018), menopausal-related symptoms (Amin et al., 2018; Shirazi et al., 2021; Taavoni et al., 2013), and postpartum

blues (Beihaghi et al., 2019). The results from included studies showed different effects for different conditions.

M. officinalis appears to be useful in pain reduction including childbirth after pain (one study, greater pain reduction with *M. officinalis* [Dastjerdi et al., 2019]) and primary dysmenorrhea (three studies, reduced severity of pain and intensity of dysmenorrhea-related systemic symptoms but not pain duration with *M. officinalis* [Mirabi et al., 2017, 2018; Safdari Dehcheshmeh & Parvin, 2016]). Also, improvement of physical and psychological symptoms and quality of life among participants suffering PMS were reported in four studies (Akbarzadeh et al., 2015, 2018; Heydari et al., 2019; Mirghafourvand, Malakouti, Charandabi, et al., 2016), and one additional study reported *M. officinalis* reduced the occurrence of postpartum blues (Beihaghi et al., 2019). However, no effect was reported in relation to intensity of menstrual bleeding (two studies, no significant effect in decreasing amount of menstrual bleeding with *M. officinalis* [Mirabi et al., 2017; Mirghafourvand, Malakouti, Mohammad, et al., 2016]). Moreover, its efficacy was mixed in relation to sexual functioning with two studies reporting inconsistent results regarding effect of *M. officinalis* (Afshar et al., 2020; Darvish-Mofrad-Kashani et al., 2018). Findings were also mixed for menopausal-related symptoms with three studies reporting inconsistent results regarding the effect of *M. officinalis* (Amin et al., 2018; Shirazi et al., 2021; Taavoni et al., 2013). However, considerable selection bias was found in the studies reviewed.

In some studies, *M. officinalis* was used in combination with other herbs. These combinations produced different results. Administration of *M. officinalis* alone or in combination with Nepeta Menthoides (*N. Menthoides)* did not decrease menstrual bleeding among students with premenstrual syndrome (Mirghafourvand, Malakouti, Mohammad, et al., 2016). Similarly, the other study which used *M. officinalis* alone, did not report a significant effect of this herb on menstrual bleeding (Mirabi et al., 2018). Regarding the effect of *M. officinalis* on sexual functioning, two studies with inconsistent results were reported. Improved sexual functioning was reported when *M. officinalis* was used alone (Darvish-Mofrad-Kashani et al., 2018), whereas no improvement was reported in combination with fennel extract, and *Nigella sativa* powder (Afshar et al., 2020). This inconsistency was also found in relation to the effect of *M. officinalis* on menopause-related symptoms. These symptoms were improved when *M. officinalis* alone was administered (Shirazi et al., 2021), but when combined with fennel fruits extract and *Nigella sativa* powder, no effect was observed (Amin et al., 2018). In another study, the combination of *M. officinalis* with valerian was useful in reducing symptoms of sleep disorder among menopausal women (Mirghafourvand, Malakouti, Mohammad, et al., 2016). This different therapeutic effect might be due to the probable synergistic or antagonistic effect of the herbal combinations (Afshar et al., 2020).

Lemon balm (*Melissa officinalis*) is a perennial herbaceous plant in the mint family *Lamiaceae* and native to south-central Europe, the Mediterranean Basin, Iran, and Central Asia, but is now naturalized in the Americas and elsewhere (Moradkhani et al., 2010). Lemon balm

plants grow bushy and upright to a maximum height of 100 cm with heart-shaped leaves of 2–8 centimeters. Leaves are long, with a rough, veined surface. They are soft and hairy with scalloped edges, and have a mild lemon scent. During summer, small white or pale pink flowers appear (Moradkhani et al., 2010). Different parts of this herb including leaves, aerial parts, stems, and flowers are used fresh or dried. Leaves are the most useful part of the herb, frequently used in different countries (Shakeri, Sahebkar, & Javadi, 2016). All included studies in the present systematic review used herbal leaves to produce the product. The preparation procedure comprised drying the herbal leaves, ground by electrical grinder, and then the resultant powder was extracted using alcohol. In the next phase, the resulting extract was removed, its concentration and alcoholic content were determined, and it was condensed in a rotary vacuum-drum filter to remove its alcohol. The resulting liquid was poured onto metal trays and dried in an autoclave. This resulted in a powder containing *M. officinalis* extract. The dried powder was poured into empty capsules (Dastjerdi et al., 2019; Mirabi et al., 2017). Oral administration of *M. officinalis* is reported to be well tolerated for up to eight weeks in different clinical trials (Cases, Ibarra, Feuillère, Roller, & Sukkar, 2011; Shakeri et al., 2016).

M. officinalis comprises different chemical components including tannins, alkaloids, saponins, flavonoids, and phenolic compounds (Abdel-Naime, Fahim, Fouad, & Kamel, 2019) including rosmarinic acid, ursolic acid, oleanolic acid, caffeic acid, p-coumaric acid, gallic acid, chlorogenic acid, salicylic acid, ellagic acid, rutin, isoquercitrin, and quercetin (Sharifi-Rad, Quispe, Herrera-Bravo, Akram, Abbaass, Semwal, Painuli, Konovalov, Alfred, Kumar, et al., 2021). These bioactive ingredients of lemon balm herb have different biological effects which might be reason of its effectiveness for different health issues including those related to obstetrics and gynecology. There are some proposed mechanisms for the effectiveness of *M. officinalis* in treating pain (e.g., dysmenorrhea and childbirth after pain). The sedative impact of *M. officinalis* is attributed to rosmarinic acid (Allahverdiyev, Duran, Ozguven, & Koltas, 2004). Rosemarinic acid extracted from the herb's leaves is an ester of caffeic acid, known as 3,4-dihydroxyphenyl lactic acid (Wang, Provan, & Helliwell, 2004).

In addition, another possible mechanism for the analgesic effect of this plant may be related to its antispasmodic and antioxidant effect. Antioxidants inhibit the function of lipoxygenase and cyclooxygenase, therefore inhibiting prostaglandins' production (Kalvandi, Alimohammadi, Pashmakian, & Rajabi, 2014). Moreover, it appears that *M. officinalis* exerts its analgesic effect through the cholinergic system and nitric oxide pathway. Cholinergic, nitric oxide and glutaminergic systems are involved in the analgesic effect of *M. officinalis*, and the opioid system is not implicated. Oxidative stress may also be involved in the pathogenesis of pain. Different antioxidants can reduce both pain and neuropathic pain. It may be that the antioxidant properties of *M. officinalis* are effective in their analgesic effect (Rastegarian et al., 2020). Increased production of prostaglandins is one of the causes of dysmenorrhea and postpartum pain (Barcikowska, Rajkowska-Labon, Grzybowska, Hansdorfer-Korzon, & Zorena,

2020; Ferries-Rowe, Corey, & Archer, 2020) that *M. officinalis* can help to eliminate with these two mechanisms.

The other obstetric health issue examined in the included studies was premenstrual syndrome, a prevalent menstrual-related problem of childbearing age women (Kroll & Rapkin, 2006). This syndrome comprises recurrent physical, mentally bothersome and/or behavioral changes which are experienced during the week before commencement of menstrual hemorrhage (Ussher & Perz, 2013). Fatigue, irritability, depression, anxiety, anger, feeling out of control, greater or lesser appetite, confusion, sleep problems, breast bloating and tenderness, are most prevalent symptoms of this syndrome (Eissa, 2010; Karout, Hawai, & Altuwaijri, 2012; Surana et al., 2020). While the main cause of this syndrome is not well known, it is proposed that serotonin level plays a role. It has been proposed that the reduction of serotonin might cause related psychological complaints (Charles, 2001). Serotonin contributes in controlling psychological symptoms including sleep, sexual behavior, mood, aggression, pain, and appetite (Young, 2007). Also, dopamine level might be another probable mechanism related to premenstrual symptoms, because increased levels improve the symptoms (Halbreich et al., 2006).

It has also been proposed that *M. officinalis* can increase the level of both dopamine and serotonin in the brain, and leads to an alleviation of premenstrual-related symptoms (Cases et al., 2011). The other related mechanism is role of *M. Officinalis* in increasing the transmission of GABA via affecting its receptor. This increased transmission is due to some of the main constituents of *M. officinalis* including rosmarinic acid, β-caryophyllene oxide, linalool, tannins, phenolic acid, geraniol, and caffeic acid (Cases et al., 2011). Increased transmission of GABA alleviates insomnia, anxiety, and its associated symptoms (Cases et al., 2011). Therefore, *M. officinalis* might have positive effect on psychological symptoms related to premenstrual symptoms (López et al., 2009; Taiwo et al., 2012).

Sexual dysfunction, the other obstetric health issue examined in the included studies, is prevalent and a multifactorial problem. Sexual dysfunction occurs due to physical, psychological, and social factors (Basson et al., 2000). Sexual dysfunction is the experience of disorder during each phase of the sexual activity cycle including desire, arousal, and orgasm (Niles, Lebeau, Liao, Glenn, & Craske, 2012). *M. officinalis* can improve an individual's sexual function through its effect in increasing level of norepinephrine (Blumenthal, Goldberg, & Brinckmann, 2000), dopamine (Berek, 2019; Danforth, 2008), and acetylcholine (Alijaniha et al., 2015; Berek, 2019) as well as having a sedative effect (references missing). By increasing norepinephrine, psychological mood disorders such as anxiety related to sexual functioning are alleviated (Blumenthal et al., 2000). When dopamine is increased, an individual's sexual desire and subjective arousal improve and lead to experiencing more pleasant sexual functioning (Berek, 2019; Danforth, 2008). By releasing acetylcholine, physical changes during sexual arousal are facilitated (Alijaniha et al., 2015; Berek, 2019). Its sedative effect via the opioid system can alleviate dyspareunia (Chavan, More, Mulgund, Saxena, & Sontakke, 2007; Darvish-

Mofrad-Kashani et al., 2018; Kalvandi et al., 2014; Wang et al., 2004). Consequently, *M. officinalis* appears to affect sexual functioning via different mechanisms.

Postpartum blues, the other obstetric health issue examined in the present review, is a typical and multifactorial problem. *M. officinalis* can extensively reduce anxiety and depression and enhance sleep quality (Chehroudi et al., 2017). Ernst et al. (2007) claimed that *M. officinalis* influences GABA receptors and might be useful in treating mild to moderate anxiety and mood disorders.

4.1. Limitations

Although the present study had a systematic review approach with a comprehensive search in academic databases to gather and integrate the available evidence on the effectiveness of *M. officinalis* for obstetric health issues, there are several limitations regarding both the studies reviewed and the systematic review itself.

Limitations of the studies reviewed. There were few studies which investigated the mechanisms of this medicinal herb. In addition, despite most studies showing effective results of using *M. officinalis* in selected outcomes, there were significant differences in dosage and study protocols without examining other probable covariates such as psychological status or blood factors. In addition, in almost all studies, the consequences were evaluated using self-report and therefore there were very few objective evaluations of the outcome measures. In most cases, the outcomes were evaluated in the short-term. Therefore, the long-term effect of *M. officinalis* is not clear. Due to the significant differences in the selected outcomes and its measurement and different treatment protocols in included studies, it was not possible to combine the data and carry out a meta-analysis.

Limitations of the systematic review. The present study attempted to conduct a systematic search in the main academic databases with no language limitation. Because all the included studies were Iranian, other Iranian national databases were searched. However, there was a limitation that other non-English databases especially Asian ones (where this herb is abundant) were not searched and which may have provided additional studies. Moreover, given the high risk of bias found in the studies reviewed, meta-analysis was not possible.

5. Conclusion

The present systematic review aimed to answer the following questions: (i) What are the therapeutic applications of *M. officinalis* for obstetric and gynecological health issues? (ii) Does *M. officinalis* have side effects when used for obstetric and gynecological health issues? (iii) What doses of *M. officinalis* are used for obstetric and gynecological health issues? and (iv) What is the application form of *M. officinalis* for obstetric and gynecological health issues? In response to the first research question, the pooled evidence suggests that *M. officinalis* has been used for obstetric and gynecological health issues including reducing childbirth after-pain, reducing symptoms of premenstrual syndrome, reducing the severity of primary dysmenorrhea, and reducing postpartum blues. No effect was reported regarding menstrual bleeding, and there

were inconsistent results regarding sexual functioning, and menopausal-related symptoms. Based on the empirical data, *M. officinalis* can be used in therapeutic applications for obstetric health issues due to its potential antidepressant, antianxiety, anti-nociceptive, anti-inflammatory and spasmolytic properties. In relation to the second question, *M. officinalis* has very few side effects. In relation to the third question, different doses of *M. officinalis* have been used in therapeutic interventions (from 160 mg to 1580 mg total daily dose). In relation to the final question, different applications were used including oral capsules and teabags.

Consequently, the use of *M. officinalis* might be useful for some obstetrics and gynecological situations. However, it is not strongly supported by the available evidence due to considerable selection bias within the studies reviewed. Further studies with larger sample sizes, more rigorous methodologies, using *M. officinalis* alone to avoid a synergistic or antagonistic effect, and adjustment for potential covariates are needed to establish more conclusive findings regarding the therapeutic efficacy of *M. officinalis*. Moreover, toxicity studies and clinical trials are needed to establish optimal doses of *M. officinalis* along with studies to establish the most effective forms of preparation.

Author contributions: ZHM and ZA developed the concept; ZA, ZHM and FA contributed to the design; ZHM and EJ searched the databases; EJ and ZA contributed to the study selection, data extraction and quality assessment; ZA and FA drafted the preliminary manuscript; MDG contributed to the literature review and substantially edited the first draft of the paper and the many revised versions following reviewers' comments. All authors critically revised the manuscript, agreed to be fully accountable for ensuring the integrity and accuracy of the work, and read and approved the final manuscript to be published. All authors met the criteria for authorship and that all entitled to authorship were listed as authors in the title page.

Financial support: The project was supported financially by Qazvin University of Medical Sciences, Qazvin, Iran.

Declaration of competing interests: The authors have no conflict of interest to declare.

Acknowledgements: Not applicable.

Data availability: Not applicable. The study was a literature review and no primary data were collected.

References

Abdel-Naime, W., Fahim, J., Fouad, M., & Kamel, M. (2019). Antibacterial, antifungal, and GC–MS studies of Melissa officinalis. *South African Journal of Botany, 124*, 228-234.

Abdi, F., Alimoradi, Z., Roozbeh, N., Amjadi, M. A., & Robatjazi, M. (2021). Does acupuncture improve sexual dysfunction? A systematic review. *Journal of Complementary and Integrative Medicine, 20*(1), 1-16.

Abuhamdah, S., & Chazot, P. L. (2008). Lemon balm and lavender herbal essential oils: old and new ways to treat emotional disorders? *Current Anaesthesia & Critical Care, 19*(4), 221-226.

Afshar, S., Afshar, F., Rezazade, A., Ardakani, Z. S., Azar, Z. J., Amin, G., . . . Haghollahi, F. (2020). Effects of a combination of Foeniculum vulgare, Melissa officinalis Extract, and Nigella saliva powder on healthy menopausal women with sexual dysfunction: A randomized clinical trial. *Jundishapur Journal of Natural Pharmaceutical Products, 15*(3).

Akbarzadeh, M., Dehghani, M., Moshfeghy, Z., Emamghoreishi, M., Tavakoli, P., & Zare, N. (2015). Effect of Melissa officinalis capsule on the intensity of premenstrual syndrome symptoms in high school girl students. *Nursing and Midwifery Studies, 4*(2), e27001.

Akbarzadeh, M., Moshfeghy, Z., Dehghani, M., Emamghoreishi, M., Tavakoli, P., & Zare, N. (2018). Comparison of the effect of Melissa officinalis capsule and care educational programs on the intensity of physical, mental and social symptoms of premenstrual syndrome in high school female students. *Int J Women's Health Reprod Sci, 16*, 18-26.

Alijaniha, F., Naseri, M., Afsharypuor, S., Fallahi, F., Noorbala, A., Mosaddegh, M., . . . Sadrai, S. (2015). Heart palpitation relief with Melissa officinalis leaf extract: double blind, randomized, placebo controlled trial of efficacy and safety. *Journal of Ethnopharmacology, 164*, 378-384.

Alimoradi Z, J. E., Griffiths MD, Abdi F, Marznaki ZH. (2022). The therapeutic applications of lemon balm (Melissa officinalis) for obstetric health issues: A systematic review PROSPERO: International prospective register of systematic reviews; 2022 [June 15, 2022]. Available from: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42022326663.

Allahverdiyev, A., Duran, N., Ozguven, M., & Koltas, S. (2004). Antiviral activity of the volatile oils of Melissa officinalis L. against herpes simplex virus type-2. *Phytomedicine, 11*(7-8), 657-661.

Amin, G., Mousavi Pharm, A., Vosough, S., Jafary Azar, Z., Shariat, M., Haghollahi, F., & Afshar, S. (2018). Therapeutic effect of combination of Nigella sativa, Melissa officinalis extract and fennel fruit with citalopram on menopausal symptoms. *Tehran University Medical Journal TUMS Publications, 76*(6), 417-425.

Baghbahadorani, F. K., & Miraj, S. (2017). The impact of silymarin on improvement of hepatic abnormalities in patients with severe preeclampsia: A randomized clinical trial. *Electronic Physician, 9*(8), 5098.

Baharvand-Ahmadi, B., Bahmani, M., Naghdi, N., Saki, K., Baharvand-Ahmadi, S., & Rafieian-Kopaei, M. (2015). Review on phytochemistry, therapeutic and pharmacological effects of myrtus (Myrtus communis). *Der Pharmacia Lettre, 7*(11), 160-165.

Bahmani, M., Farkhondeh, T., & Sadighara, P. (2012). The anti-parasitic effects of Nicotina tabacum on leeches. *Comparative Clinical Pathology, 21*(3), 357-359.

Barcikowska, Z., Rajkowska-Labon, E., Grzybowska, M. E., Hansdorfer-Korzon, R., & Zorena, K. (2020). Inflammatory markers in dysmenorrhea and therapeutic options. *International Journal of Environmental Research and Public Health, 17*(4), 1191.

Basson, R., Berman, J., Burnett, A., Derogatis, L., Ferguson, D., Fourcroy, J., . . . Laan, E. (2000). Report of the international consensus development conference on female sexual dysfunction: Definitions and classifications. *The Journal of urology, 163*(3), 888-893.

Beihaghi, M., Yousefzade, S., Mazloom, S. R., Modares Gharavi, M., & Hamedi, S. S. (2019). The effect of Melissa officinalis on postpartum blues in women undergoing cesarean section. *Journal of Midwifery and Reproductive Health, 7*(2), 1636-1643.

Berek, J. S. (2019). *Berek & Novak's gynecology*: Lippincott Williams & Wilkins.

Blumenthal, M., Goldberg, A., & Brinckmann, J. (2000). *Herbal medicine. Expanded commission E monographs*: Integrative Medicine Communications.

Brown, R. P., & Gerbarg, P. L. (2001). Herbs and nutrients in the treatment of depression, anxiety, insomnia, migraine, and obesity. *Journal of Psychiatric Practice, 7*(2), 75-91.

Cases, J., Ibarra, A., Feuillère, N., Roller, M., & Sukkar, S. G. (2011). Pilot trial of Melissa officinalis L. leaf extract in the treatment of volunteers suffering from mild-to-moderate anxiety disorders and sleep disturbances. *Mediterranean Journal of Nutrition and Metabolism, 4*(3), 211-218.

Charles, B. (2001). *Obstetric and gynecology for medical students* (5th Edition). Baltimore, MD: Lippincott Williams

Chavan, S. N., More, U., Mulgund, S., Saxena, V., & Sontakke, A. N. (2007). Effect of supplementation of vitamin C and E on oxidative stress in osteoporosis. *Indian Journal of Clinical Biochemistry, 22*(2), 101-105.

Chehroudi, S., Fatemi, M. J., Isfeedvajani, M. S., Salehi, S. H., Akbari, H., & Samimi, R. (2017). Effects of Melissa officinalis L. on reducing stress, alleviating anxiety disorders, depression, and insomnia, and increasing total antioxidants in burn patients. *Trauma Monthly, 22*(4), 7.

Cummings, J. L. (2000). Cholinesterase inhibitors: a new class of psychotropic compounds. *American Journal of Psychiatry, 157*(1), 4-15.

Danforth, D. N. (2008). *Danforth's obstetrics and gynecology*: Lippincott Williams & Wilkins.

Darvish-Mofrad-Kashani, Z., Emaratkar, E., Hashem-Dabaghian, F., Emadi, F., Raisi, F., Aliasl, J., . . . Zafarghandi, N. (2018). Effect of Melissa officinalis (lemon balm) on sexual dysfunction in women: a double-blind, randomized, placebo-controlled study. *Iranian Journal of Pharmaceutical Research: IJPR, 17*(Suppl), 89-100.

Dastjerdi, M. N., Darooneh, T., Nasiri, M., Moatar, F., Esmaeili, S., & Ozgoli, G. (2019). Investigating the effect of Melissa officinalis on after-pains: A randomized single-blind clinical trial. *Journal of Caring Sciences, 8*(3), 129-138.

Eddouks, M., Chattopadhyay, D., De Feo, V., & Cho, W. C. (2012). Medicinal plants in the prevention and treatment of chronic diseases. *Evidence-Based Complementary and Alternative Medicine, 2012*, 458274.

Eissa, M. (2010). Personality and psychosocial factors affecting premenstrual syndrome. *Current Psychiatry, 17*(1), 55-62.

Ellis, J. M. (2005). Cholinesterase inhibitors in the treatment of dementia. *Journal of the American Osteopathic Association, 105*(3), 145-158.

Ernst, E. (2007). Herbal remedies for depression and anxiety. *Advances in Psychiatric Treatment, 13*(4), 312-316.

Ferries-Rowe, E., Corey, E., & Archer, J. S. (2020). Primary dysmenorrhea: diagnosis and therapy. *Obstetrics & Gynecology, 136*(5), 1047-1058.

Gunjan, M., Naing, T. W., Saini, R. S., Ahmad, A., Naidu, J. R., & Kumar, I. (2015). Marketing trends & future prospects of herbal medicine in the treatment of various disease. *World Journal of Pharmaceutical Research, 4*(9), 132-155.

Gurčík, Ľ., Dúbravská, R., & Miklovičová, J. (2005). Economics of the cultivation of Salvia officinalis and Melissa officinalis. *Agricultural Economics, 51*(8), 348-356.

Gyllenhaal, C., Merritt, S. L., Peterson, S. D., Block, K. I., & Gochenour, T. (2000). Efficacy and safety of herbal stimulants and sedatives in sleep disorders. *Sleep Medicine Reviews, 4*(3), 229-251.

Halbreich, U., O'Brien, P., Eriksson, E., Bäckström, T., Yonkers, K. A., & Freeman, E. W. (2006). Are there differential symptom profiles that improve in response to different pharmacological treatments of premenstrual syndrome/premenstrual dysphoric disorder? *CNS Drugs, 20*(7), 523-547.

Hassanzadeh, G., Pasbakhsh, P., Akbari, M., Shokri, S., Ghahremani, M., Amin, G., … Tameh, A. A. (2011). Neuroprotective properties of Melissa officinalis L. extract against ecstasy-induced neurotoxicity. *Cell Journal, 13*(1), 25.

Heydari, N., Dehghani, M., Emamghoreishi, M., & Akbarzadeh, M. (2019). Effect of Melissa officinalis capsule on the mental health of female adolescents with premenstrual syndrome: a clinical trial study. *International Journal of Adolescent Medicine and Health, 31*(3), 1-6.

Jastrzębska-Stojko, Ż., Stojko, R., Rzepecka-Stojko, A., Kabała-Dzik, A., & Stojko, J. (2013). Biological activity of propolis-honey balm in the treatment of experimentally-evoked burn wounds. *Molecules, 18*(11), 14397-14413.

Kalvandi, R., Alimohammadi, S., Pashmakian, Z., & Rajabi, M. (2014). The effects of medicinal plants of Melissa officinalis and Salvia officinalis on primary dysmenorrhea. *Avicenna Journal of Clinical Medicine, 21*(2), 105-111.

Karout, N., Hawai, S., & Altuwaijri, S. (2012). Prevalence and pattern of menstrual disorders among Lebanese nursing students. *EMHJ-Eastern Mediterranean Health Journal, 18*(4), *346-352, 2012*.

Kennedy, D., Little, W., & Scholey, A. (2004). Anxiolytic effects of a combination of Melissa officinalis and Valerlana officinalis during laboratory induced stress. *Journal of Psychopharmacology, 18*(3), A45-A45.

Kennedy, D. O., Scholey, A. B., Tildesley, N. T., Perry, E. K., & Wesnes, K. A. (2002). Modulation of mood and cognitive performance following acute administration of Melissa officinalis (lemon balm). *Pharmacology Biochemistry and Behavior, 72*(4), 953-964.

Khalid, K. A., Hu, W., Cai, W., & Hussien, M. S. (2009). Influence of cutting and harvest day time on the essential oils of lemon balm (Melissa officinalis L.). *Journal of Essential Oil Bearing Plants, 12*(3), 348-357.

Kroll, R., & Rapkin, A. J. (2006). Treatment of premenstrual disorders. *Journal of Reproductive Medicine, 51*(4 Suppl), 359-370.

López, V., Martín, S., Gómez-Serranillos, M. P., Carretero, M. E., Jäger, A. K., & Calvo, M. I. (2009). Neuroprotective and neurological properties of Melissa officinalis. *Neurochemical Research, 34*(11), 1955-1961.

Masoudi, M., Miraj, S., & Rafieian-Kopaei, M. (2016). Comparison of the effects of Myrtus communis L, Berberis vulgaris and Metronidazole vaginal gel alone for the treatment of bacterial vaginosis. *Journal of Clinical and Diagnostic Research, 10*(3), Qc04-07.

Mirabi, P., Alamolhoda, S. H., Yazdkhasti, M., & Mojab, F. (2018). The effects of lemon balm on menstrual bleeding and the systemic manifestation of dysmenorrhea. *Iranian Journal of Pharmaceutical Research: IJPR, 17*(Suppl2), 214-223

Mirabi, P., Namdari, M., Alamolhoda, S., & Mojab, F. (2017). The effect of Melissa officinalis extract on the severity of primary dysmenorrha. *Iranian Journal of Pharmaceutical Research: IJPR, 16*(Suppl), 171-177.

Miraj, S., Rafieian-Kopaei, & Kiani, S. (2017). Melissa officinalis L: A Review study with an antioxidant prospective. *Journal of Evidence-Based Complementary & Alternative Medicine, 22*(3), 385-394.

Mirghafourvand, M., Malakouti, J., Charandabi, S. M. A., Khalili, A. F., & Homayi, S. G. (2016). The efficacy of lemon balm (Melissa officinalis L.) alone and combined with lemon balm—Nepeta menthoides on premenstrual syndrome and quality of life among students: a randomized controlled trial. *Journal of Herbal Medicine, 6*(3), 142-148.

Mirghafourvand, M., Malakouti, J., Mohammad, A. C. S., Farchbaf, K. A., & Ghanbari, H. S. (2016). The effects of lemon balm (Melissa officinalis l.) alone and in combination with nepeta menthoides on the menstrual bleeding in students with premenstrual syndrome: A randomized controlled trial. *Iranian Red Crescent Medical Journal, 18*(12), e28941.

Moradkhani, H., Sargsyan, E., Bibak, H., Naseri, B., Sadat-Hosseini, M., Fayazi-Barjin, A., & Meftahizade, H. (2010). Melissa officinalis L., a valuable medicine plant: A review. *Journal of Medicinal Plants Research, 4*(25), 2753-2759.

Niles, A. N., Lebeau, R. T., Liao, B., Glenn, D. E., & Craske, M. G. (2012). Dimensional indicators of generalized anxiety disorder severity for DSM-V. *Journal of Anxiety Disorders, 26*(2), 279-286.

Puljak, L., Ramic, I., Naharro, C. A., Brezova, J., Lin, Y.-C., Surdila, A.-A., . . . Pericic, T. P. (2020). Cochrane risk of bias tool was used inadequately in the majority of non-Cochrane systematic reviews. *Journal of Clinical Epidemiology, 123*, 114-119.

Rasmussen, P. (2011). Lemon balm-Melissa officinalis; also known as lemon balm, bee balm, garden balm, Melissa, melissengeist. *Journal of Primary Health Care, 3*(2), 165-166.

Rastegarian, A., Abedi, H., Jahromi, H. K., Zarei, S., Nematollahi, A., Mansouri, E., & Sameni, H. (2020). Analgesic effect of intrathecal Melissa officinalis in the rat model of hot-water and formalin-induced pain. *Journal of Acupuncture and Meridian Studies, 13*(1), 19-24.

Rezaeizadeh, H., Alizadeh, M., Naseri, M., & Shams, A. M. (2009). The traditional Iranian medicine point of view on health and disease. *Iranian Journal of Public Health, 38*(Suppl. 1), 36-39

Safdari Dehcheshmeh, F., & Parvin, N. (2016). The effect of mefenamic acid and melissa officinalis on primary dysmenorrhea: A randomized clinical trial study. *International Journal of Pharmacognosy and Phytochemical Research, 8*(8), 1286-1292.

Shakeri, A., Sahebkar, A., & Javadi, B. (2016). Melissa officinalis L. – A review of its traditional uses, phytochemistry and pharmacology. *Journal of Ethnopharmacology, 188*, 204-228.

Sharifi-Rad, J., Quispe, C., Herrera-Bravo, J., Akram, M., Abbaass, W., Semwal, P., . . . Calina, D. (2021). Phytochemical constituents, biological activities, and health-promoting effects of the Melissa officinalis. *Oxidative Medicine and Cellular Longevity, 2021*, 6584693.

Shaygannia, E., Bahmani, M., Zamanzad, B., & Rafieian-Kopaei, M. (2016). A review study on Punica granatum L. *Journal of Evidence-Based Complementary & Alternative Medicine, 21*(3), 221-227.

Shirazi, M., Jalalian, M. N., Abed, M., & Ghaemi, M. (2021). The effectiveness of Melissa officinalis L. versus citalopram on quality of life of menopausal women with sleep disorder: A randomized double-blind clinical trial. *Revista Brasileira de Ginecologia e Obstetrícia, 43*, 126-130.

Shoara, R., Hashempur, M. H., Ashraf, A., Salehi, A., Dehshahri, S., & Habibagahi, Z. (2015). Efficacy and safety of topical Matricaria chamomilla L. (chamomile) oil for knee osteoarthritis: A randomized controlled clinical trial. *Complementary Therapies in Clinical Practice, 21*(3), 181-187.

Sofowora, A., Ogunbodede, E., & Onayade, A. (2013). The role and place of medicinal plants in the strategies for disease prevention. *African Journal of Traditional, Complementary and Alternative Medicines, 10*(5), 210-229.

Surana, A., Rajesh, D., Tank, R., Singh, A., Gupta, V., Agrawal, D., & Chhoker, V. K. (2020). Social determinants of menstrual hygiene among school-going girls in a rural area of Southern Haryana, India. *Social Health and Behavior, 3*(3), 117-121.

Taavoni, S., Nazem Ekbatani, N., & Haghani, H. (2013). Valerian/lemon balm use for sleep disorders during menopause. *Complementary Therapies in Clinical Practice, 19*(4), 193-196. doi: 10.1016/j.ctcp.2013.07.002

Taiwo, A. E., Leite, F. B., Lucena, G. M., Barros, M., Silveira, D., Silva, M. V., & Ferreira, V. M. (2012). Anxiolytic and antidepressant-like effects of Melissa officinalis (lemon balm) extract in rats: Influence of administration and gender. *Indian Journal of Pharmacology, 44*(2), 189-192.

Ussher, J. M., & Perz, J. (2013). PMS as a process of negotiation: Women's experience and management of premenstrual distress. *Psychology & Health, 28*(8), 909-927.

Wang, H., Provan, G. J., & Helliwell, K. (2004). Determination of rosmarinic acid and caffeic acid in aromatic herbs by HPLC. *Food Chemistry, 87*(2), 307-311.

Watson, K., Hatcher, D., & Good, A. (2019). A randomised controlled trial of lavender (lavandula angustifolia) and lemon balm (melissa officinalis) essential oils for the treatment of agitated behaviour in older people with and without dementia. *Complementary Therapies in Medicine, 42*, 366-373.

Wheatley, D. (2005). Medicinal plants for insomnia: a review of their pharmacology, efficacy and tolerability. *Journal of Psychopharmacology, 19*(4), 414-421.

World Health Organization (2019). *WHO global report on traditional and complementary medicine* World Health Organization.

Yoo, D. Y., Choi, J. H., Kim, W., Yoo, K.-Y., Lee, C. H., Yoon, Y. S., . . . Hwang, I. K. (2011). Effects of Melissa officinalis L. (lemon balm) extract on neurogenesis associated with serum corticosterone and GABA in the mouse dentate gyrus. *Neurochemical Research, 36*(2), 250-257.

Young, S. N. (2007). How to increase serotonin in the human brain without drugs. *Journal of Psychiatry & Neuroscience, 32*(6), 394.

Yuan, H., Ma, Q., Ye, L., & Piao, G. (2016). The traditional medicine and modern medicine from natural products. *Molecules, 21*(5), 559-577.

Figure 1- PRISMA Diagram representing the process of Identification of studies via databases and registers to inclusion

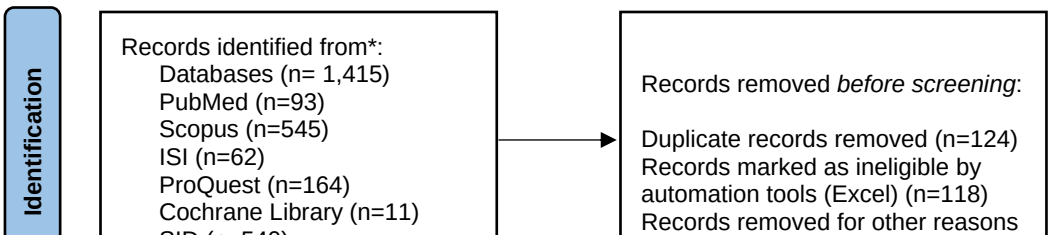

Table 1- Summarized characteristics of included studies

Health-related issue	First author (year)	Country	Design	Participants	Main outcome	Statistical results	Sample size	Mean age (years)	Intervention	Control	Treatment protocol	Total daily dose (mg)	Form of *Melissa officinalis*	Side effects	Results
Childbirth after-pains	Dastjerdi, 2019 (Dastjerdi et al.,	Iran	Single-Blind RCT	Childbirth moderate to severe	Severity of pain (first interven	1) p=0.09 at one	110	29.31 years	395mg of *M. officinalis*	250 mg of mefenami	Every 6 hours 24	1580 mg	Oral capsul	NR	More pain reduction was found

Table 1- Summarized characteristics of included studies

Health-related issue	First author (year)	Country	Design	Participants	Main outcome	Statistical results	Sample size	Mean age (years)	Intervention	Control	Treatment protocol	Total daily dose (mg)	Form of *Melissa officinalis*	Side effects	Results
	2019)			after-pains	tion)	hour 2) p=0.73 at two hours 3) p=0.01 at three hours				c acid	hours		es		in *M. officinalis* group.
PMS	Heydari, 2018 (Heydari et al., 2019)	Iran	Double blind RCT	Female adolescents with premenstrual syndrome	1) Psychosomatic symptom 2) Anxiety and sleep Disturbance 3) Social function disturbance 4) Depression	1) p<0.001 2) p<0.001 3) p=0.0214)p=0.001	100	14-18	600 mg capsules	Starch capsules	Two capsules daily from the first day through to the end of the menstrual period for three cycles	1200 mg	Oral capsules	No side effect was observed	*M. officinalis* significantly improved mental health and social function.
	Akbarzadeh, 2018 (Akbarzadeh et al., 2018)	Iran	Randomized, placebo-controlled trial	High school female students	1) Social Symptoms 2) Emotional symptoms	NR	200	16	600 mg capsules	Starch capsules	Two capsules daily from the first day through end of the	1200 mg	Oral capsules	No side effect was observed	Overall, *M. officinalis* capsules significantly decrease total Score of

Table 1- Summarized characteristics of included studies

Health-related issue	First author (year)	Country	Design	Participants	Main outcome	Statistical results	Sample size	Mean age (years)	Intervention	Control	Treatment protocol	Total daily dose (mg)	Form of *Melissa officinalis*	Side effects	Results
											menstrual period for three cycles				premenstrual symptoms compared to placebo and control group with no intervention.
	Akbarzadeh, 2015 (Akbarzadeh et al., 2015)	Iran	Randomized, placebo-controlled trial	High school female students	1)Physical 2)Psychological 3)Social	1), 2), 3) $p<0.001$	100	16.2	1200mg *M. officinalis* essence (two 600mg capsules)	Starch capsules	Daily from the first to the last day of their menstrual cycle for three cycles	1200 mg	Oral capsules	NR	*M. officinalis* significantly reduced the severity of premenstrual symptoms.
	Mirghafourvand, 2016 (Mirghafourvand, Malakouti, Charandabi, et al., 2016)	Iran	Triple-blind RCT	Female students	1) Physical component 2) Psychological component	1) $p=0.009$ 2) $p=0.001$	93	23	500mg capsule of *M. officinalis*	Starch capsules	Twice daily during the luteal phase of two consecutive menstrual cycles	1000 mg	Oral capsules	NR	A significant decrease in PMS symptoms besides significant improvement in quality of life aspects were reporte

Table 1- Summarized characteristics of included studies

Health-related issue	First author (year)	Country	Design	Participants	Main outcome	Statistical results	Sample size	Mean age (years)	Intervention	Control	Treatment protocol	Total daily dose (mg)	Form of *Melissa officinalis*	Side effects	Results
															d in intervention group.
Dysmenorrhea	Mirabi, 2017 (Mirabi et al., 2017)	Iran	Double-blind matched randomized clinical trial	University students	Pain severity	p<0.001	100	21.11	330 mg of the herb	Starch capsules	Three times a day over three days at the onset of hemorrhage	990 mg	Oral capsules	No side effect	*M. officinalis* significantly reduced the severity of premenstrual symptoms.
	Mirabi, 2018 (Mirabi et al., 2018)	Iran	Double-blind placebo controlled trial	University students	1) Fatigue 2) Nausea and vomiting 3) Lack of energy 4) Headache 5) Diarrhea 6) Mood swings 7) Faint	1) p=0.02 2) p=0.82 3) p<0.001 4) p=0.69 5) p=0.31 6) p<0.001 7) p<0.36	100	21.11	Capsules containing 330 mg extract of the herb	Starch capsules	Three times a day over three days at the onset of hemorrhage	990 mg	Oral capsules	No side effect	*M. officinalis* significantly decreases the severity of menstruation related symptoms, but no effect was found on the severity of bleeding and the duration of menstruation.

Table 1- Summarized characteristics of included studies

Health-related issue	First author (year)	Country	Design	Participants	Main outcome	Statistical results	Sample size	Mean age (years)	Intervention	Control	Treatment protocol	Total daily dose (mg)	Form of *Melissa officinalis*	Side effects	Results
	Safdari, 2016 (Safdari Dehcheshmeh & Parvin, 2016)	Iran	Single-blind RCT	Women with primary dysmenorrhea	1) Pain Intensity 2) Pain Duration	1) NR 2) NR	43	25	Tea bag	Mefenamic acid 250 mg capsules	Every eight hours from the onset of menstruation pain until pain relief for three consecutive cycles	-	Tea bag	NR	*M. officinalis* significantly decreases pain intensity but not pain duration.
	Mirghafourv, 2016 (Mirghafour, Malakouti, Mohammad, et al., 2016)	Iran	Triple-blind randomized controlled trial	Female students aged 18 years and older	Premenstrual Syndrome	*p*=0.602	93	23.23	500 mg capsules of Lemon balm alone or in combination with N. Menthoides	Starch capsules	Twice daily in the luteal phase for two consecutive menstrual cycles	1000 mg	Oral capsules	Three participants in the placebo group reported stomach pain and flatulence. In the lemon balm only group, one student reported sleep	Treatment with lemon balm and lemon balm N. Menthoides herbs did not decrease menstrual bleeding in students with premenstrual syndrome

Table 1- Summarized characteristics of included studies

Health-related issue	First author (year)	Country	Design	Participants	Main outcome	Statistical results	Sample size	Mean age (years)	Intervention	Control	Treatment protocol	Total daily dose (mg)	Form of *Melissa officinalis*	Side effects	Results
														disturbances	
Sexual dysfunction	Darvish-Mofrad-Kashani, 2018 (Darvish-Mofrad-Kashani et al., 2018)	Iran	Double-blind, randomized, placebo-controlled study	Women suffering from decreased sexual desire	1) Desire 2) Arousal 3) Lubrication 4) Orgasm 5) Satisfaction 6) Pain 7) Total	1) p=0.001 2) p=0.001 3) p=0.005 4) p=0.001 5) p=0.001 6) p=0.002 7) p=0.001	89	35	500 mg of aqueous extract of *M. officinalis*	Starch capsules	Two times a day for four weeks	1000 mg	Oral capsules	Side effects of diarrhea and constipation in both study groups	*M. officinalis* significantly improved sexual function.
	Afshar, 2020 (Afshar et al., 2020)	Iran	Double blind RCT	Healthy menopausal women with sexual dysfunction/ FSFI	1) Desire 2) Arousal 3) Lubrication 4) Orgasm 5) Pain 6) Satisfaction 7) Sexual	1) p=0.051 2) p=0.40 3) p=0.37 4) p=0.70 5) p=0.14 6)	48	41-54	1000 mg capsules (*M. officinalis*, fennel extract, and *Nigella sativa* powder),	Starch capsules	One capsule per day for eight weeks	1000 mg	Oral capsules	No side effect	Intervention did not improve sexual function which might be due to synergism effect of

Table 1- Summarized characteristics of included studies

Health-related issue	First author (year)	Country	Design	Participants	Main outcome	Statistical results	Sample size	Mean age (years)	Intervention	Control	Treatment protocol	Total daily dose (mg)	Form of *Melissa officinalis*	Side effects	Results
					function	*p*=0.487) *p*=0.37									combination *M. officinalis* with *Foeniculum vulgare*, and *Nigella sativa* seed powder.
Menopause related symptoms	Shirazi, 2021 (Shirazi et al., 2021)	Iran	Double blind RCT	Menopausal women with sleep disorder	1) Vasomotor 2) Psycho motor-Social 3) Physical 4) Sexual	1) *p*<0.001 2) *p*<0.001 3) *p*<0.001 4) *p*<0.001	60	51.9	500 mg of aqueous extract of *M. officinalis*	Two comparison groups of citalopram capsules and placebo of starch capsules	One capsule every day for 8 weeks	1500 mg	Oral capsules	No adverse effect was reported in the M. Officinalis L. and placebo groups	The mean for all MENQOL domain scores were significantly improved in the M. Officinalis L. group compared with citalopram and placebo (*p*<0.001).
	Amin, 2018 (Amin et al., 2018)	Iran	Randomized clinical trial	Menopausal women with sleep disord	1)Vosomotor 2)Emotional 3)Physical	1) *p*=0.232 2) *p*=0.041	56	47.09	Combination of 300 mg Melissa	Citalopram 20 mg	One capsule every day for 8	900 mg	Oral capsules	NR	There was no significant difference in

Table 1- Summarized characteristics of included studies

Health-related issue	First author (year)	Country	Design	Participants	Main outcome	Statistical results	Sample size	Mean age (years)	Intervention	Control	Treatment protocol	Total daily dose (mg)	Form of *Melissa officinalis*	Side effects	Results
				er	4)Sexual	3) p=0.4474) p=0.94			officinalis,300 mg fennel fruits extract with 400 mg Nigella sativa powder		weeks				the improvement of menopausal symptoms compared to the citalopram group in the combined product group.
	Taavoni, 2013 (Taavoniet al., 2013)	Iran	RCT	Menopausal women with sleep disorder	sleep disorder	p=0.04	100	50-60	160 mg of essence of Valerian officinalis and 80 mg of lemon balm	Starch capsules	Two capsules every day (duration of treatment period is not mentioned)	160 mg	Oral capsules	No negative effects were observed during the intervention and follow- up period.	Valerian/lemon balm was useful in reducing symptoms of sleep disorder during the menopause
Postpartum Blues	Beihaghi 2018 (Beihaghi et al., 2019)	Iran	RCT	Women undergoing cesarean section	1) Incidence of blues on days 3-5 2) Incidence of blues on	1) p<0.0012) p<0.0013) p=0.001	60	38-42	lemon balm as a 500-mg capsule	capsules containing placebo	capsule three times a day for 10 days	1500 mg	Oral capsules	NR	The usage of lemon balm may want to reduce the

Table 1- Summarized characteristics of included studies

Health-related issue	First author (year)	Country	Design	Participants	Main outcome	Statistical results	Sample size	Mean age (years)	Intervention	Control	Treatment protocol	Total daily dose (mg)	Form of *Melissa officinalis*	Side effects	Results
					day 10 3) Incidence of blues on day 14										occurrence of postpartum blues, that's one of the most common postpartum psychiatric issues, without the event of feasible aspect results

Ethical statement.

The Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines were used to conduct and report the present study (Puljak et al., 2020). The protocol of the present study was registered in the international Prospective Register of Systematic Reviews database PROSPERO (decree code: CRD42022326663) (Alimoradi Z, 2022). Also the protocol was reviewed and approved by IRB and ethics in biomedical research committee affiliated to Qazvin University of Medical Sciences (IR.QUMS.REC.1401.116).

Declaration of Interest

Authors do not have any conflict of interest to declare.

Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Funding statement

The project was partially supported by Qazvin University of Medical Sciences.

Highlights

- Melissa officinalis is a medicinal herb with several proposed therapeutic uses.
- The present paper systematically reviewed relevant evidence regarding the applications of M. officinalis (lemon balm) for obstetrics and gynecological health issues.
- M. officinalis had been used on different obstetrics and gynecological health issues including childbirth after-pain, symptoms of premenstrual syndrome, severity of primary dysmenorrhea, menstrual bleeding , sexual function, and menopausal-related symptoms
- The results from included studies showed different effects for different health issues.
- M. officinalis appears to be useful in pain reduction (childbirth after pain and primary dysmenorrhea), and improving premenstrual symptoms. However, no effect was seen on intensity of menstrual bleeding and its' effectiveness was mixed in relation to sexual function and menopausal-related symptoms.