

Aromatherapy with Iranian Herbal Medicines for Premenstrual Syndrome and Primary Dysmenorrhea: A Systematic Review and Meta-Analysis

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Abstract

Background: Primary dysmenorrhea is painful bleeding in the absence of any confirmed pelvic disorder, which is often accompanied by nausea, vomiting, and headache. The tendency of patients to use herbal and alternative medicine is more than the past. Regarding the fact that no meta-analytical study has been done to evaluate aromatherapy with Iranian herbal medicines, this study was conducted to evaluate the effect of aromatherapy with different herbs on premenstrual syndrome and primary dysmenorrhea.

Materials and Methods: English and Persian electronic databases were systematically searched without any time limit until May 5, 2019. The references of review articles and clinical trials were also reviewed. Two authors independently reviewed the titles and abstracts, if the subject of the article was relevant, the full article was extracted and criticized. Comprehensive Meta-Analysis software was used to conduct meta-analysis.

Results: Finally, 14 studies were entered into a meta-analysis. The mean standard difference between two groups of aromatherapy with different plants and control group was -1.06 (95%CI: -1.33 to -0.848; $p < 0.001$). Aromatherapy with roses (SMD=-1.35; 95%CI= -0.01 to -2.69; $p=0.048$), and aromatherapy with lavender (SMD= -1.08; 95% CI: -0.73 to -1.43; $p < 0.001$) compared to the control group had better effect in reduction of pain severity. According to three studies, aromatherapy with Geranium 2% essential oil, Citrus aurantium blossom essential oil, and Rosa damascena were more effective than control group regarding mental and physical signs.

Conclusion

This meta-analysis showed that aromatherapy with different Iranian herbs such as lavender and rose could significantly reduce primary dysmenorrhea and premenstrual syndrome. This treatment can be used specifically in patients who cannot tolerate conventional treatments.

Key Words: Aromatherapy, Dysmenorrhea, Herbal Medicines, Iran, Premenstrual Syndrome.

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1- INTRODUCTION

Premenstrual syndrome and dysmenorrhea are of the chief causes of distress in women, resulting in a considerable deficiency of time and proficiency in the workplace (1). One of the most prevalent gynecologic disorders in women is dysmenorrhea (2). Primary dysmenorrhea means cramping pain under the abdomen without a specific pelvic pathology, which usually occurs before or during menstruation (3). The incidence rate of dysmenorrhea is different in the world, and according to various studies, it has been reported between 28 and 71.7% (4). The incongruent prevalence could be due to the different definitions and lack of a standard assessment method (3). In a systematic review, the lowest incidence was reported in Bulgaria (8.8%), and the highest prevalence in Finland (94%) (5).

The results of various studies have indicated that the dysmenorrhea is a serious disease that affects physical, social and psychological parameters such as social, emotional and mental health (6). The dysmenorrhea can interfere with sports activities, reduce communication with family and friends (7), and also decrease life quality (8). Besides, women who suffer from dysmenorrhea endure physical problems such as pain, nausea, vomiting, appetite loss, headache, faintness, and lethargy. Irritability is the most common emotional problem that has been reported in this disease (6).

The primary dysmenorrhea occurs due to the uterine contraction, vasoconstriction, inflammation, and the release of inflammatory mediators. Lessening the mass of progesterone at the end of the luteal phase leads to the activation of the silicone secretion enzyme and prostaglandin biosynthesis. Boosted production of prostaglandin precedes a raise in the uterus and its contractions, followed by dysmenorrhea (9). The drug

therapy of primary dysmenorrhea is based on the theory of the cause. Non-steroidal anti-inflammatory drugs (NSAIDs) reduce pain by lowering prostaglandins (9). The results of a review study exhibited that although these drugs are efficient in alleviating pain, according to some studies, and gastrointestinal complications following their administration (10). Moreover, chronic use of these drugs heightens the risk of acute myocardial infarction and venous thromboembolism (11, 12). Using hormonal agents, such as oral combined pills is another dysmenorrhea medication.

These medicines by reducing prostaglandins lessen menstrual pain efficiently. If dysmenorrhea is untreated, it is suggested to use either non-steroidal anti-inflammatory drugs or to persuade the patient to use a contraceptive method (13). Despite the impact of these drugs on diminishing pain, the occurrence of irregular bleeding causes women to be dissatisfied with hormonal treatments (14). There are some other side effects following the use of these drugs: headache, nausea, mood changing, and weight gaining, to name but a few (15).

Premenstrual syndrome refers to the relapse of a period of psychological or physical symptoms, or a set of both, which occurs in the luteal phase of the menstrual cycle and vanishes when menstrual periods initiate or over the menstruation. Low-grade premenstrual syndrome is diagnosed in 95% of women in reproductive stage, but in 5% of women, the symptoms are so serious that they inhibit daily activity. These symptoms are divided into two physical and psychological categories. Physical symptoms comprise pain, abdominal discomfort, weight gain, painful breasts, and lack of energy, headache, and exacerbation of chronic diseases (Asthma, allergies, epilepsy, and migraine). Psychosomatic symptoms consist of irritability, anxiety, tension, a feeling of

disability, loss of control, and so on (16). Theories about the syndrome include interactions between sex steroids and neurotransmitters including (endorphin-acid gamma-aminobutyric), hyperaldosteronism, increased adrenal function, hyperprolactinemia, hypoglycemia, zinc, magnesium, vitamin B6, and decrease in fatty acids are essential. Nowadays the strongest and most acceptable theory is the reduction in serotonergic function in the luteal phase (17). Premenstrual syndrome can be treated by pharmacological and non-pharmacological strategies.

As primary therapies in this regard hormone therapy (estrogen, oral contraceptives, GnRH analogs, danazole and progesterone), diuretics, antidepressants, bromocriptine, surgery, psychotherapy and serotonin reuptake inhibitors (SRIS) could be mentioned. In addition, fluoxetine, paroxetine, and sertraline are suggested to control symptoms impressively. The side effects of pharmacological treatments, however, have been pointed out in different studies (18). On the other hand, the usage of herbal medicines has become more popular today. The side effects of chemical drugs, discontent with these drugs, the intricacies of diseases and their variation are the reasons of the tendency towards plant treatments (19).

Aromatherapy is a special approach in complementary and alternative medicine (CAM) used to evaporate essential oils containing special compounds (20). The results of this study indicated that the aromatherapy with a mixture of essential oils of lavender, rose and seaweed reduced the pain intensity in the primary dysmenorrhea, and no side effects have been reported due to the massage with essential oils (20). Although numerous herbal remedies have been used to treat dysmenorrhea, no meta-analysis by Iranian herbal medicines has been conducted to

evaluate aromatherapy up to now. Hence, considering the prominence of meta-analytic studies and the efficient treatment with the slightest side effects, the present study was carried out to evaluate the effect of aromatherapy with different herbs on premenstrual syndrome and primary dysmenorrhea. Two authors independently reviewed the titles and abstracts of the articles. If the subject of the article appeared related, they extracted and reviewed the full-text article. Finally, the articles that met the inclusion criteria were assessed.

2- MATERIALS AND METHODS

2-1. Strategy search

The present study was conducted based on the Cochran's guidelines. An extensive search, according to Mesh Terms, was performed on the Medline, EMBASE, Scopus, Cochrane library, and Web of Science until May 05, 2019. In addition, a manual search was conducted in Google motor engine, Google Scholar, and bibliography of related articles and reviews. Also, equivalent Persian keywords were searched in Persian databases such as Irandoc, Magiran, Medlib, SID, and Barakatksn.

To conduct this systematic review and meta-analysis, English database such as Medline (via PubMed), Scopus, EMBASE, and Web of Science were systematically searched without any time restriction until May 5, 2019. The following keywords were used to find the articles related to the effects of aromatherapy on dysmenorrhea: [((Dysmenorrhea) OR (Premenstrual Syndrome) OR (Pain *, Menstrual) OR (Menstrual Pain *) OR (Menstruation *, Painful) OR (Painful Menstruation *) OR (Menstrual cramp)) AND ((Aromatherapy) OR (Aroma *) OR (Essential oil))]. Two authors independently reviewed the titles and abstracts of the articles. If the subject of the article appeared related, they

extracted and reviewed the full-text article. Finally, the articles that met the inclusion criteria were assessed.

2-2. Selection criteria

The inclusion criteria were all clinical trials investigating the effect of aromatherapy on premenstrual syndrome and primary dysmenorrhea. Exclusion criteria were non-specific articles (meta-analysis, systematic review, and letter to the editor), and studies lacking the control group.

2-3. Quality Assessment

The 5-item Jadad scale (21) was used to assess the quality of the articles found in the search, expressing the following areas: randomization, method of randomization, blindness, method of blindness, and dropout/withdrawals and their reasons. We reported total score of Jadad scale ranged from 0-5.

2-4. Data extraction

A table which was designed to extract the data contains the variables of the first author of the article, the year and type of study, the inclusion criteria, the intervention used, the instructions of usage, the control group, the instructions used in the control group, the pain measurement tool, and the ultimate outcome of the study (comparing the pain intensity between the two groups after the intervention) (**Table.1**) (*Plase see the table at the end of paper*).

2-5. Statistical analysis

The software which was used for data analysis is called Comprehensive Meta-Analysis. Eventually, the heterogeneity index was determined between studies using Cochran's Q test and I^2 . Based on the suggestion of Higgins et al., the I^2 value of less than 25% shows low homogeneity, 25-75% exhibits a moderate homogeneity and more than 75% indicates a high level of homogeneity. According to heterogeneity results, a random or fixed-effect model was used to estimate the effect of aromatherapy on the severity of dysmenorrhea with a 95% confidence interval within the forest plots (22). To illustrate meta-analysis results, a plot was used, in which the square of the sample represents the number of samples in each study, and the lines drawn on both sides display a 95% confidence interval for the effect size of each study.

3- RESULTS

In the initial search for English databases, 399 articles were found. After searching the Persian databases and excluding the duplicates, the title or abstract of 253 articles was reviewed, with 239 irrelevant articles. Moreover, 17 articles were individually scrutinized, of which 3 were not explicitly referred to as essential oil and aromas (23-25), and, as a result they were excluded (**Figure.1**). Finally 14 articles were evaluated and a critique of the results of the above articles in terms of quality are shown in **Table.1** (*Plase see the table at the end of paper*).

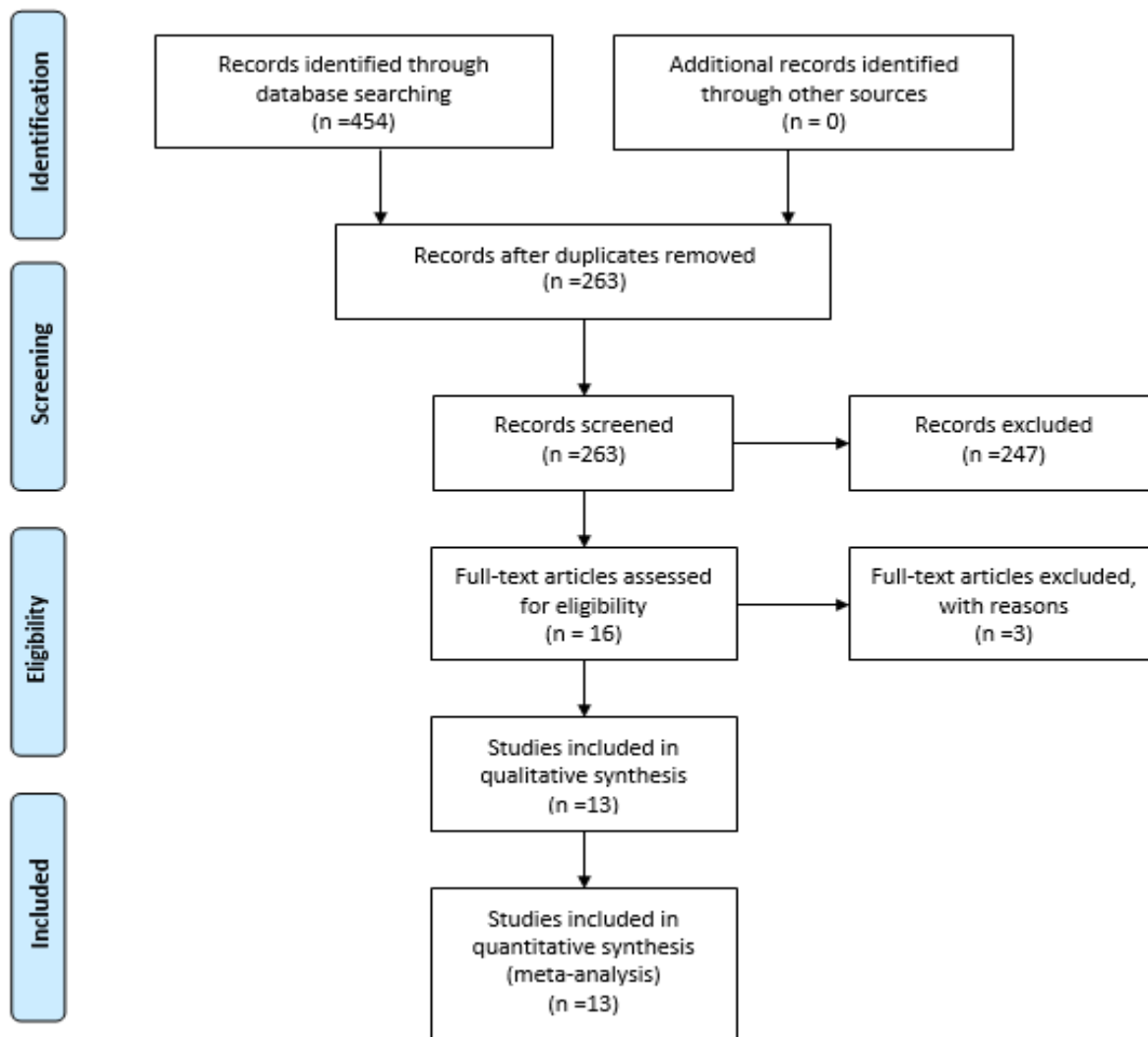
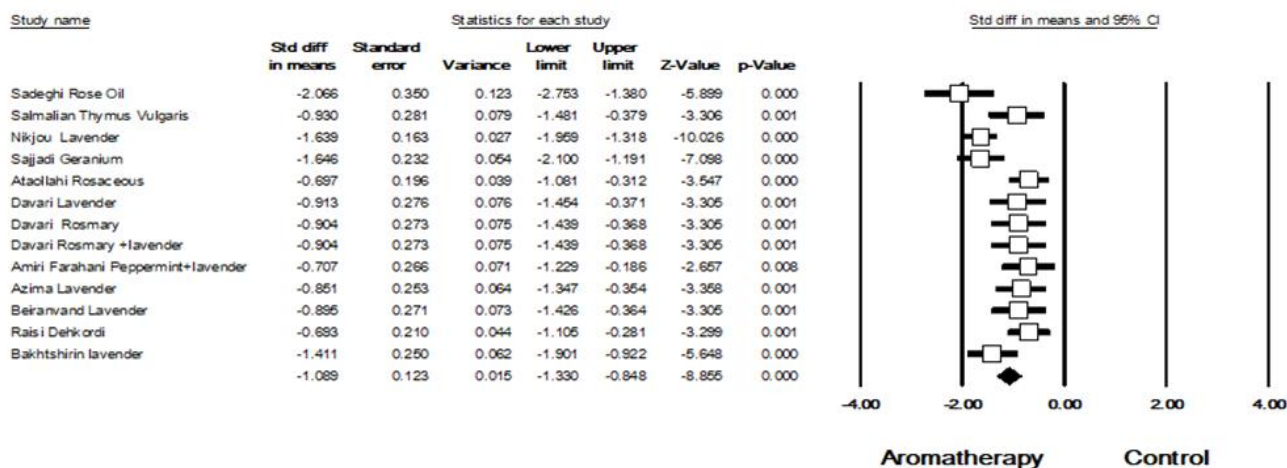


Fig.1: PRISMA flochart.

Finally, 14 studies were enrolled in this meta-analysis. According to the results of the Cochran's Q test, which showed heterogeneity amongst the outcomes of several different studies, the model with random effect was used in meta-analysis. In this model, the parameter variations among the studies are also taken into account in the computations. Therefore, the results of this model in the heterogeneous conditions might be more generalizable than the model with fixed effect. The mean standardized difference between two intervention and control groups (95% confidence interval [CI]: -.33 to -0.848) is -1.06. This difference is

statistically significant ($p < 0.001$), and indicates that aromatherapy is effective (Figure.2). However, due to the heterogeneity index ($I^2 = 69\%$, $p < 0.001$), the incidence of heterogeneity is high among studies. Due to the heterogeneity of studies, sensitivity analysis was performed; the effect of each study on the conclusive result and degree of heterogeneity was appraised. The results of the sensitivity analysis indicated that none of the studies were under the critical influence of neither the outcome nor the degree of heterogeneity of the study.



Meta Analysis

Fig.2: Effect of aromatherapy with different plants on the severity of dysmenorrhea based on random effects model. The midpoint of each section of the line approximates the mean and line breaks represent a 95% confidence interval in each study. The diamond sign indicates a mean improvement in pain intensity in the studies.

Subgroup analysis was performed based on the type of treatment with essential oil of rose (26, 33). The results of red roses analysis showed that the standardized mean difference between two intervention and control groups was -1.35 (95% CI: -01 to -2.69), which is statistically significant (p=0.048), and indicates that red roses can

significantly reduce the severity of primary dysmenorrhea compared with the control group (**Figure.3**). However, due to the heterogeneity index ($I^2 = 91\%$; $p < 0.001$), the incidence of heterogeneity is high among the studies.

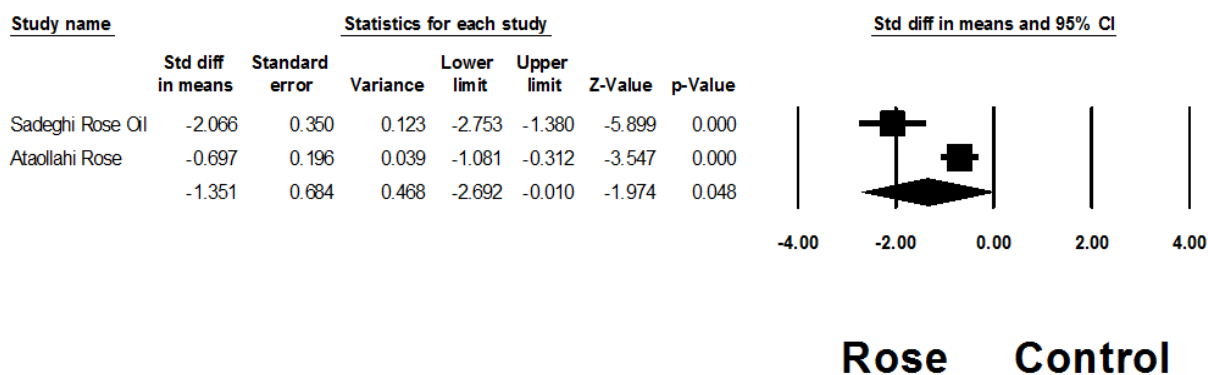


Fig.3: Aromatherapy effect of Rose plant on the severity of dysmenorrhea based on random effects model. The midpoints of each section of the line estimates the mean and line breaks represent a 95% confidence interval in each study. The diamond sign indicates a mean improvement in pain intensity in the studies.

The results of lavender subgroup analysis showed that the standardized mean difference between two intervention and control groups was -1.08 (95% CI: -0.73 to -1.43), which is statistically significant ($p < 0.001$), and shows that aromatherapy with lavender in comparison with control group can significantly reduce the severity of dysmenorrhea (**Figure.4**). Regarding the heterogeneity index ($I^2 = 78\%$; $p < 0.001$), there is a heterogeneity among many studies, so that the study of Nikjou

et al. (32) had a significant impact on the overall estimate of the meta-analysis, so the overall estimate of the difference of the standardized mean after the exclusion of this study performed using a randomized model was -0.93 (95% CI: -0.717 to -0.15). This difference was statistically significant ($p < 0.001$). As seen, the heterogeneity index had a significant change compared to the exclusion of this study. The heterogeneity index value ($I^2 = 21\%$ $p = 0.27$) was unnecessary.

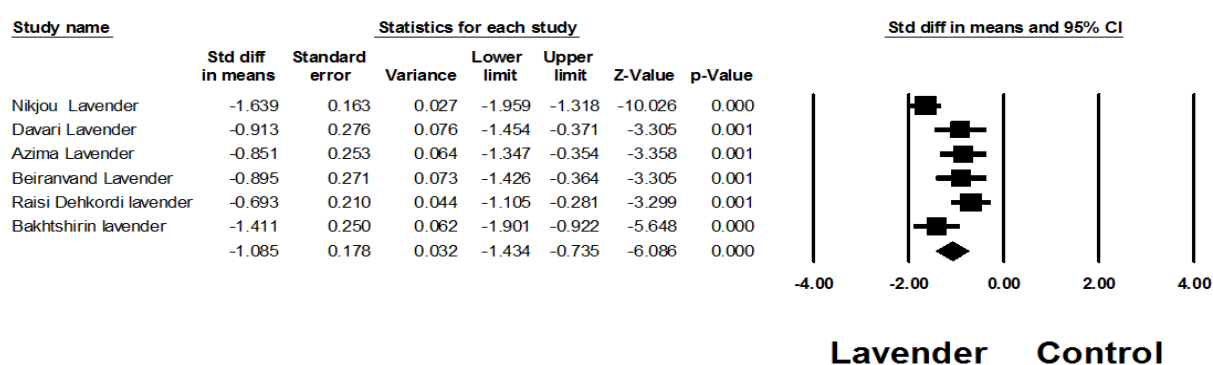


Fig.4: Effect of aromatherapy with lavender on the severity of dysmenorrhea based on random effects model. The midpoints of each section of the line estimates the mean and line breaks represent a 95% confidence interval in each study. The diamond sign indicates a mean improvement in pain intensity in the studies.

Three studies (35-37) assessed the effect of aromatherapy with herbal medicine on premenstrual syndrome. However, data were not enough to be included in the meta-analysis. According to three studies, aromatherapy with eranium 2% essential oil, Lotfi Citrus aurantium blossom essential oil, and Rosa damascena were more effective than control group regarding mental and physical sign.

4- DISCUSSION

According to our study, the present study was the first meta-analysis performed on clinical trials to evaluate the efficacy of aromatherapy on the severity of primary dysmenorrhea and premenstrual syndrome. The results of this study

showed that aromatherapy compared with control group improves primary dysmenorrhea. Essential oils, such as lavender, rose, and honeydew, may also have beneficial effects on the improvement of primary dysmenorrhea. These essential oils are used in combined and single substance forms, and it is fully accepted that the effects of a mixture of more than one essential oil are greater than the effects of one essential oil that is known as synergistic effect. The results of our study showed that the aromatherapy with the mixture of essential oils of lavender (27-32), rose (26, 33), and rosemary (30) or combination (30) reduces the pain intensity of primary dysmenorrhea. Lavender, *Lavandula*

angustifolia, with the Arabic name of the Khazami-makhzania belongs to the family Lamiaceae. Its chemical compositions contain linalil acetate, linalool, coumarin, tannin, saponin, and ether compounds that are consumed as brewed or aromatherapy in traditional Persian medicine for the treatment of muscle and rheumatic pain, joint pain, morning nausea in pregnant women, menstrual periods, depression, and premenstrual emotional stresses (30). In this meta-analysis, the decrease in the severity of dysmenorrhea in the lavender group was more eminent than placebo (27-32). One of the herbal medicines used to treat dysmenorrhea is rosemary (30). The rosemary, *Rosemarinus officinalis*, with the Arabic name of Aklyl al-Jabal or Hesaliaban belongs to the family Lamiaceae. The drug forms are stewed, essential oil, tincture, liquid extract, dried extract of distilled water and syrup. From this plant, about 1.5% of colorless essential oil is obtained with a density of 0.9, which contains pinen, camphon, boronel and camphor. New studies have shown that camphon and boronol have the effect of regulating prostaglandin concentration in the body and also relieve pain, inflammation and swelling, and blood pressure (30). Mint essential oil has a relaxing effect on the muscles and analgesic effect (20). One of the studies in the meta-analysis investigated the effects of rosemary, the results of that study showed that the rosemary alone or in combination with mint can significantly reduce the severity of dysmenorrhea compared to the control group (30).

4-1. Study Limitations

In this systematic review, there are several limitations that need to be addressed. The first and main limitation is the moderate-to-high heterogeneity of studies that results from aromatherapy with different herbs (lavender, rose and rosemary), only lavender and only rose. Although the sensitivity analysis showed that, the

heterogeneity would decrease to zero by excluding one of the studies of meta-analysis of lavender. However, the sensitivity analysis on different plants (Figure.2) showed that the exclusion of individual studies did not affect the outcome and the degree of heterogeneity of the study. This can be due to the use of different types of plants, each of which has a different effect. The different ages of samples, the severity of dysmenorrhea in the subjects are other factors, which were not included in most standardization studies. Despite the fact that most studies have shown the effectiveness of aromatherapy, the mechanism of the effect of each plant on dysmenorrhea has not yet been determined. It is suggested that this study should be conducted in forthcoming studies. In some studies, several aromatic herbs were used in combination form. Determining the effectiveness of each plant was challenging. Some of the systematic reviews had low methodological quality. These deficiencies were the lack or inappropriate reporting of randomized sequencing, the lack or inappropriate reporting of blindness, the lack of intention to treat analysis, so that the future studies are suggested to be based on the CONSORT design. Other limitations of this study include a small number of studies and a small sample size, indicating the need for further studies with a larger sample size in this regard. The results of some studies may change if the sample size is increased.

5- CONCLUSIONS

Iranian plants used in aromatherapy such as lavender, rose and rosemary can have beneficial effects on reducing dysmenorrhea. Due to the interest of patients in complementary and low-cost medicine, the effectiveness of this method can be applied as a useful method for the improvement of dysmenorrhea. The findings of these studies should be

cautiously interpreted due to the high heterogeneity of studies, low number of studies and small sample size of articles.

6- CONFLICT OF INTEREST: None.

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Table-1: Baseline characteristics and some clinical features of studies in systematic review.

First author, Year, Reference	Type of study	Inclusion criteria (primary pain intensity)	Intervention group	Instruction of intervention group	Control group	Instruction of control group	Measuring tools	Outcomes	Total Jadad score
Amiri et al., 2012, (20)	RCT	Students (MSC=2, 3)	Lavender EO + Mint + Massage (n=90)	One week before the menses, 15 minutes a day, 2 consecutive cycles	1. Almond Oil + Massage (n=90) 2. Just massage (n=90).	One week before the start of the menses, 15 minutes a day, 2 consecutive cycles	VAS	The pain intensity in the aroma group was only lower than that of the just massage group (P=0.014).	4
Ataollahi et al., 2015, (26)	RCT	Medical students (severe/moderate pain)	Rose EO (n=55)	The first three days of the cycle, twice a day, 2 consecutive cycles	Placebo (n=55)	The first three days of the cycle, twice a day, 2 consecutive cycles	VMQ	The pain intensity was lower in the intervention group (p<0.001).	5
Azima et al., 2014, (27)	RCT	Non-medical students (VAS>5)	Lavender EO + Massage (n=34)	The first two days of the cycle, daily, 2 consecutive cycles	1. Reflexology (n=34) 2. No treatment (n=34)	20 minutes a day, 10 days before the cycle (each leg), 2 consecutive cycles	VAS	The pain intensity was lower in the intervention group (p<0.001).	5
Bakhtshirin et al. 2015, (28)	RCT Crossover	Nursing/Midwifery Students (VAS>6)	Lavender EO + massage (n=40)	First day of the cycle, 15 minutes, 2 consecutive	Placebo + massage (n=40)	The first day of the cycle, 15 minutes, 2 consecutive cycles	VAS	The pain intensity was lower in the intervention group (p<0.001).	4
Beiranvand et al., 2015, (29)	RCT Crossover	Students (VAS>5)	Lavender EO + massage (n=30)	48 hours before and after starting of the cycle, 15 minutes, 2 times a day	Almond Oil + Massage (n=30)	48 hours before and after starting of the cycle, 15 minutes, twice a day	VAS	The pain intensity was lower in the intervention group (p<0.001).	5
Davari et al., 2014, (30)	RCT Crossover	Students Mood disorder questionnaire	1. Rosemary essence (n=30), 2. Lavender essence (30 people), 3. Rosemary EO + Lavender (n=30)	The first 3 days of the cycle, 15 minutes, twice a day, 2 consecutive cycles	1. Mefenamic acid 2. Placebo	The first 3 days of the cycle, 15 minutes, twice a day, 2 consecutive cycles	VAS	The pain intensity was lower in rosemary (p<0.001), lavender and both co-administration and Mefenamic acid (p<0.01) compared to placebo.	4
Raisi-Dehkordi et al., 2014, (31)	RCT Crossover	Students (VMQ=2,3)	Lavender (n=48)	The first 3 days of the cycle, every 6 hours, 2 consecutive cycles	Placebo (essential oil) (n=48)	The first 3 days of the cycle, every 6 hours, 2 consecutive cycles	From 1 to 4 grading*	The pain intensity was lower in the intervention group (p<0.001).	4

Nikjou et al., 2016, (32)	RCT	Students	Lavender (n=100)	Once a day, 30 minutes, the first 3 days of the cycle, 2 consecutive cycles	Placebo (diluted milk)	Once a day, 30 minutes, the first 3 days of the cycle, 2 consecutive cycles	VAS	Significant decrease in pain in the intervention group compared to placebo (p<0.001).	4
Sadeghi-aval-shahr et al., 2014, (33)	RCT	Students (VAS>5)	Rose (n=25)	The first day of the cycle, 15 minutes, 2 consecutive cycles	1. Almond Oil + Massage (n=25) 2. Massage (n=25)	The first day of the cycle, 15 minutes, 2 consecutive cycles	VAS	Significant decrease in pain in the intervention group compared with almond oil and massage group (p <0.001) and massage group (p <0.05).	4
Sajjadi et al., 2018, (34)	RCT	Students (VAS>5)	Scented geranium EO (n=30)	The first day of the cycle, 15 minutes, 2 consecutive cycles	1. Almond oil (n=30) 2. No treatment (n=30)	The first day of the cycle, 15 minutes, 2 consecutive cycles	VAS	Significant decrease in pain in the intervention group compared to the control group (p <0.001).	4
Lotfipour-Rafsanjani et al., 2018, (35)	RCT	Medical students (with at least 5 PMS symptoms)	1. Geranium 2% EO+ massage (n=40) 2. Massage+ placebo (n=40)	30 min per week 8 weeks	1. Control (n=40)	30 min per week 8 weeks	PMS	Aromatherapy massage was more effective than control regarding mental and physical sign.	4
Heydari et al., 2018, (36)	RCT	Students (PSST≥20)	Orange EO (Citrus aurantium) (n=33)	One week before the start of the cycle, 5 days, twice a day, 2 consecutive cycles	Placebo (almond oil) (n=33)	One week before the start of the cycle, 5 days, twice a day, 2 consecutive cycles	PSST	Significant decrease in all symptoms of dysmenorrhea (p<0.001).	5
Heydari et al., 2018, (37)	RCT	Medical students (PSST≥20)	Rosa damascena 4%	5 days of luteal phase, 5 minutes, twice daily 2 consecutive cycles	Aromatherapy with placebo (n=31)	5 days of luteal phase, 5 minutes, twice daily, 2 consecutive cycles	PSST	Intervention was more effective than control regarding psychological and physical symptom.	4

RCT: Randomized Clinical Trial; MSC: Multidimensional Spoken Criteria; PSST: Premenstrual Symptoms Screening Tool; VAS: Visual Analogue Scale; EO: Essential Oil; VMQ: Verbal Multidimensional Questionnaire, 1: No pain, 2: Mild, 3: Moderate, 4: Intense. **Mefenamic acid oral capsule was opened and the powder was dissolved in 2 ml of water and placed in the control group in glasses similar to essential oils.