**ORIGINAL ARTICLE**

# Comparing the Effect of Herbal Drugs and Non-steroidal Anti-Inflammatory Drugs on Primary Dysmenorrhea in Iran: a Systematic Review and Meta-Analysis

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**ABSTRACT:** Several studies have been conducted to investigate the effects of herbal drugs and Non-steroidal anti-inflammatory drugs on the primary dysmenorrhea, but their results have been different.The aim of this study was to compare the effects of herbal drugs and NSAIDon the primary dysmenorrheausing meta-analysis method.A literature search was conducted in Scopus, Pub med, and Google scholar databases from1996 to December 2016 in English and Persian languages using the search keywordsof *primary dysmenorrhea* combined with *herbal* and *NSAID*. The random effect model was adoptedto combine the results of the studies, and $I^2$ index was used to check heterogeneity. One hundred and ninety-nine studies were obtained, and after reading the abstracts, 21 articles were included in the study. The total number of samples was 2041 people. The standard mean difference(SMD)betweenherbal drugs and Non-steroidal anti-inflammatory drugs in the pain reduction in the first intervention was estimated atSMD= 0.2(95%CI:(-0.340.74 ),   z=0.73, p=0.463), and in second intervention it was SMD=-0.59(95%CI: (-1.650.47),Z=1.09 and p=0.278). also, the SMD for the duration of menstrual variable SMD=0.18(95%CI:( 0.02 0.34) , z=2.20, p=0.027) in favor of NSAID drugs and interval cycle of menstrual variable was SMD=0.07(95%CI:(-0.140.28), z=0.68, p=0.496).Mean difference of pain intensity reduced relatively better by administering herbal medicines, which is supported by the majority of studies, and the herbal drugs were found to be more effective than the NSAIDs drugs. Finally, given the many side effects of non-steroidal anti-inflammatory drugs, herbal drugs can be used at the standard dosageand considering the side effects.

## INTRODUCTION

Dysmenorrhea is a common gynecological complaint [1]that affects 60% of women during menstruation [2]. The prevalence of dysmenorrhea in women inreproductive age varies from 11% to 16% [3]. It is estimated that 10 to 30%of women lose their 3 working days due to dysmenorrhea each month [4]. Because women comprise at least 42% of adult workforce, millions of hours are wasted every year, for example in the United States, in the case of no treatment for dysmenorrhea, about 600 million hours are lost per year [5]. More than 70% of Iranian womenexperience painful menstruation (1). In Iran, generally 74.5% of teenage girls suffer from dysmenorrhea [6]. Dysmenorrhea is categorized into primary and secondary types. Primary dysmenorrhea involves menstrual pain without a pelvic pathology and is mostly seen in young girls. In the secondary type, painful menstruation is accompanied with pelvic pathology [7]. The pain associated with primary dysmenorrhea usually begins a few hours prioror just after the onsetof menstrual cycle and continues foraround 72-48 hours [8-9].

It is believed that the cause of pain is the excessiveendometrial production of prostaglandins during ovulation, which results in uterine contraction and ischemia [10]. These eventsdecrease the uterine blood flow and increase the sensitivity of peripheral nerves whichcause pain [11-13]. To reduce the effects of dysmenorrhea on social and economic activities, effective treatment of dysmenorrhea is necessary [14].

Common treatments for dysmenorrhea include non-steroidal anti-inflammatory drugs (NSAIDs), hormonal medications, and non-pharmaceuticalinterventionssuch as acupuncture and trans-electrical nerve stimulation (TENS) [9-10]. Nowadays,NSAIDs and oral contraceptives, which both work by reducing uterine contractions, are particularly popular [7-8]. These drugs; however, are ineffective in 20% to 25% of women. Moreover,there have been complaints about digestive side effectswhile taking thesedrugs[15], which have led people towards using alternative therapeuticssuch as herbal drugs [16].In Iran, some plants such as fennel, chamomile, marigold, and thyme are used to treat dysmenorrhea [17]. Nevertheless, the rate of response to herbal medicinehas been controversial [4].

As meta-analysis studies are important sourcesforhealth care evidence, and due to the high popularity of medicinal plants among Iranian women and the lack of valuable information and clinical evidence on the effects of medicinalplants indysmenorrhea, we performed a meta-analysis ofclinical trials to compare the efficacy of herbal and NSAIDs in thetreatment of primary dysmenorrhea, which can providea high-quality data source tothe physicians and healthproviders of the field.

## MATERIALS AND METHODS

### Data Source

The present systematic review and meta-analysis wasconducted using preferred reporting items for systematic reviews and meta-analysis (PRISMA) guidelines. To avoid bias, data extraction and study selection were performedby two researchers independently.

### Search strategy

A comprehensive search on the following national and international databases was performed until December 2016:Pubmed, Scopus, Google scholar, SID, Iranmedex, Irandoc, Magiran, Google scholar, and IRCT. The goal was to identify studies addressing primary dysmenorrhea combined with herbaland NSAID by MeSH keywords of*Primary dysmenorrheal*, *Herbal drugs*, *Non-steroidal Anti-Inflammatory Drugs* in English and Persian equivalents. We also examined the reference lists of the retrieved articles.

### Inclusion and exclusion criteria

### Inclusion criteria

-Studies addressing the comparison effect of herbal and NSAIDS drugs with English or Persian language:

I. Being double or triple-blindrandomized controlled trial

II. Focusing on theexpression of pain intensitywith appropriate statistical indicators in primary dysmenorrhea

III. The exposure of interest beingintake of herbal drugs from foods or foods and supplements combined (total).

Exclusion criteria:

-Studies conducted outside Iran

-Studies non-relevant to the topic,

-Conference presentations, letters to editors and review article.

-Non-random sample size

-Non-Iranian patients

Using appropriate statistical indicators.

I. Failure to report the results for the study (Mean and Standard deviation)

II. Using herbaceous drugs as superficial gels and perfume drugs.

III. Reporting general rather than individual findings .

IV. Failure to present comparison between herbal and NSAID drugs.

V. Involving those on menstrual cycle.

VI. Case reports, editorials, abstracts, reviews, and non-RCT studies

### *Study selection*

First, the articles were collected with title of primary dysmenorrhea and after the completion of the search, a list of abstracts wasprepared. The full text of articles was abstracted independently by two investigators. If an article was rejected, the causes of its rejection were mentioned. If there was disagreement between the two investigators,

differences of opinion were resolved through adjudication by athird investigator.

### *Statistical analysis*

Studies were combined based on the sample size, Mean and SD. The average variance was calculated using the formula of two integrated variance. The mean difference was computed using the following formula:

$$\delta = \frac{\mu_t - \mu_c}{\sigma}, \ \sigma^2 \text{ is the pooled variance where } \mu_t \text{ is}$$

the case mean; $\mu_c$ is the control mean, calculated through $\sigma^2 = (n_1\sigma_1^2 + n_2\sigma_2^2)/(n_1 + n_2 - 2)$were the variances of the case group and control group, respectively. Also, $n_1$ and $n_2$ stand forthe number of participants in each group. In order to evaluate heterogeneity of the studies, Cochran test and the $I^2$ index were used. Due to significant heterogeneity in the studies, a model with random effects was used.In order to examine publication bias, Begg Plot and regressions method were used. A P-value of less than 5% [$P < 0.05$] was considered as a significant heterogeneity test. Furthermore, sensitivity analyses were pre-specified and statistical analyses were performed using STATA version 11.2.

Random effects model was adoptedto combine the results of studies.To investigate the relationship between cardiac complications andserum ferritin, the mean of serum ferritin was estimated in the case andcontrol groups. Data were analyzed using Stata Ver.11.1 software ($P < 0.05$ was considered significant).To explore potential sources of heterogeneity, weconducted subgroup analysis for differentmethodsandassays.Publication bias was assessed by Egger's and Begg's

### RESULTS

We identified 199 clinical trial studies.One hundred and eighty were excluded after reading abstracts, because they were not reviewed NSAIDs drugs such as separate groups.Twenty-nine articles remained and entered meta-analysis stage.Two articles were recorded on the website of Iranianregistry of clinical trials (IRCT); as the full text was

not found, we called the authors and they informed us that their papers werein press.Six articles were excludeddue to the expression of frequency of variables rather than stating Mean and SD, and due to a general expression of variables and not to separate groups.Finally, 21 articles were selected (Figure 1).

The characteristics of studies eligible for the meta-analysis are mentioned in table 1.Among the twenty-one selected articles assessing the pain intensity,nineevaluated the duration of menstruationandsix studies assessed interval cycle of menstruation.

A total of 2041 eligible patients were recruited in the twenty-one trials, 1016 in the herbal group and 1025 in the NSAID group. The characteristics of patients in the twenty-one studies are summarized in Table 2.

In the present study,there was no significant difference between the effects of herbs on the primary dysmenorrhea pain intensity in the first and second involving.As evident in Figure 2, the effect of herbal medicines and NSAID drugs on the primary dysmenorrhea pain intensity in general and individually is represented based on a random effects model for all studies at95% confidence level .The standard mean difference between the primary dysmenorrhea pain reduction with two drugs in the first
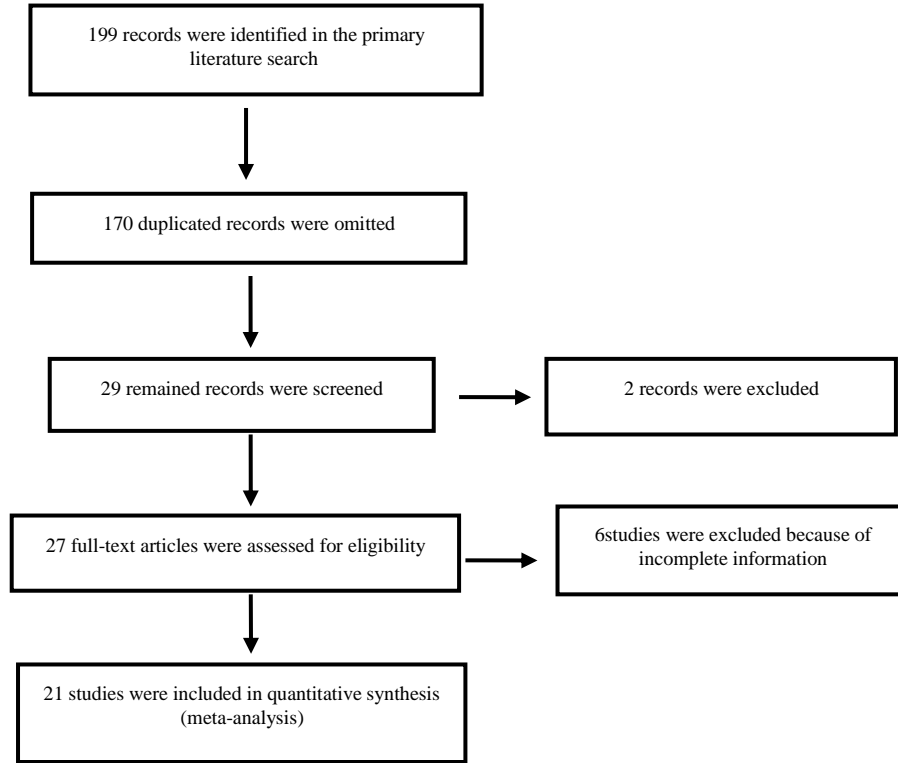
intervention was 0.2 (95% CI:(-0.340.74) z=0.73, p=0.463). But in the second intervention, primary dysmenorrhea pain reduction was -0.59(95% CI:(-1.650.47), z=1.09, p=0.278). In Figure 3, the effect of herbal medicines and NSAID drugs on the primary dysmenorrhea pain intensity is shown in general and separately for all studies.

***Secondary outcome***

A total of 304 and 314 subjectswere evaluatedin the group of herbal medicines and no steroidal anti-inflammatory drug, to study the duration of menstruation. The standard mean difference was estimate at 0.18(confidence interval 0.02,0.34) in favor of NSAID medicines (z=2.20,p=0.027) (Figure 4).

***The third outcome (interval cycle of menstruation)***

The standard mean difference result of the interval cycle of menstruation, between 175 and 185 subjects of herbal drugs and NSAID drugs was -0.07(95% CI:(-0.14.28),z=0.68,p=0.496). Figure 5 on Begg'sfunnel plot shows no evidence of publication bias (p>0.192) (Figure 6).

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│ 199 records were identified in the   │
│ primary literature search            │
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                  │
                  ▼
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│ 170 duplicated records were omitted  │
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│ 29 remained records were screened    │──────▶│ 2 records were excluded   │
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│ 27 full-text articles were assessed  │──────▶│ 6studies were excluded    │
│ for eligibility                      │       │ because of incomplete     │
└─────────────────────────────────────┘       │ information               │
                  │                            └──────────────────────────┘
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┌─────────────────────────────────────┐
│ 21 studies were included in          │
│ quantitative synthesis               │
│ (meta-analysis)                      │
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**Figure 1.** Flowchart of the studies in the systematic review and meta-analysis

**Table 1.** Characteristics of twenty-one included studies.

| First author | Publication year | location | Sample size | Number of sample H/N | Type of Herbal | Dose of Herbal |
|---|---|---|---|---|---|---|
| Namavarjahromi | 2002 | Shiraz | 48 | 24/24 | Fennel | 25drop/4h |
| Bokaie | 2013 | Tehran | 59 | 29/30 | Fennel | 25drop/6h |
| Salamlian | 2014 | Mazandaran | 56 | 28/28 | Thymus vulgaris | 25drop/6h |
| Ahmad shirvani | 2015 | Mazandaran | 122 | 61/61 | Ginger | 250mg/6h |
| Bani | 2014 | Tabriz | 184 | 92/92 | Rosadamascena | 200mg/6h |
| Direkvandmoghadam | 2012 | Ilam | 120 | 60/60 | Thymus Vulgaris | 5ml/stat |
| Mohammadinia | 2013 | Zahedan | 100 | 50/50 | Dill | 10drop/8h |
| Jenabi | 2012 | Hamadan | 99 | 49/50 | Valerianaofficinalis | 250mg/8h |
| Modaress | 2011 | Tehran | 160 | 80/80 | Matricariachamomilla | 400mg/6h |
| Mohajeri | 2006 | Mashhad | 58 | 29/29 | Fennel | 25drop/8h |
| Delaram | 2015 | Shahrekord | 44 | 23/21 | Vitexagnuscastus | 3.2mg/8h |
| Heidarifar | 2014 | Qom | 47 | 23/24 | Dill | 1000mg/12h |
| Jaafarpour | 2015 | Ilam | 78 | 38/38 | Cinnamon | 420mg/TDS |
| Tavasoli | 2005 | Mashhad | 200 | 100/100 | Carumcarvi | 65mg/8h |
| Roozbahani | 2006 | Arak | 214 | 107/107 | Thymus vulgaris | 15gr/stat |
| Khodakarami | 2009 | Isfahan | 112 | 57/55 | SCA | 500mg/8h |
| Nazarpour | 2007 | Mazandaran | 72 | 36/36 | Fennel | 20-30drop/4-8h |
| Shobeiri | 2012 | Hamadan | 55 | 25/30 | Fennel | 30drop/4h |
| Rezaeyan | 2014 | Lorestan | 60 | 30/30 | Olive | 25cc/daily |
| Ozgoli | 2007 | Tehran & | 100 | 50/50 | Ginger | 250mg/6h |

**Table 1.** Continued

| | | Isfahan | | | | |
|---|---|---|---|---|---|---|
| **Zeraati** | 2014 | Hamadan | 55 | 25/30 | Fennel | 30drop/4h |

Abbreviations: M, mean; H, Herbal drugs; N,NSAID drugs; RCT, randomized controlled trial; SCA:Celeryseed,Saffran and Anise

**Table 2.** Characteristics of patients in twenty-one included studies.

| | Treatment group | Sample Size | Different in pain intensity (M±SD) | Duration of menstrual (M±SD) | The interval cycle of menstrual (M±SD) |
|---|---|---|---|---|---|
| **Bokaie** | H | 29 | 8.70±2.4* | 6.30±1.2 | 29.69±4.14 |
| | N | 30 | 9.40±1.9 | 1.50±1.2 | 28.8±2.16 |
| **Ahmad shirvani** | H | 61 | 4.34±NM | 6.62±1.2 | - |
| | N | 61 | 3.90±NM | 6.24±1.22 | - |
| **Delaram** | H | 23 | 4.98±1.65 | 5.78±1.31 | 21.52±7.46 |
| | N | 21 | 4.77±1.83 | 6.10±1.17 | 19.27±3.42 |
| **Heidarifar** | H | 23 | 4.39±2.2 | 6.86±1.42 | 25.95±4.6 |
| | N | 24 | 4.17±1.74 | 6.45±2.12 | 27.45±4.88 |
| **Shobeiri** | H | 36 | 4.21±1.3 | 7.84±4.6 | 26.52±5.43 |
| | N | 25 | 4.19±0.8 | 6.17±1.41 | 27.03±3.81 |
| **Zeraati** | H | 25 | 2.50±1.3 | 6.24±1.66 | 27.36±3.63 |
| | N | 30 | 4.10±1.8 | 6.17±1.41 | 27.03±3.81 |
| **Jaafarpour** | H | 38 | 4.10±0.5 | 6.30±1.3 | - |
| | N | 38 | 2.00±0.1 | 5.90±1 | - |
| **Rezaeyan** | H | 30 | 2.40±1.7 | 4.70±1.5 | - |
| | N | 30 | 4.70±2.3 | 4.50±1.5 | - |
| **Ozgoli** | H | 50 | - | 6.60±1.1 | 22.6±2.3 |
| | N | 50 | - | 6.40±1 | 22.4±2 |
| **Mohajeri** | H | 29 | 3.07±NM | - | - |
| | N | 29 | 2.97±NM | - | - |
| **Salamlian** | H | 28 | 1.21±1.06 | - | - |
| | N | 28 | 1.48±1.62 | - | - |
| **Bani** | H | 92 | 1.20±0.83 | - | - |
| | N | 92 | 0.85±0.06 | - | - |
| **Jenabi** | H | 49 | 4.84±1.4 | - | - |
| | N | 50 | 4.17±0.91 | - | - |
| **Tavasoli** | H | 100 | 8.10±1.9 | - | - |
| | N | 100 | 7.46±1.79 | - | - |
| **Roozbahani** | H | 107 | 2.75±0.22 | - | - |
| | N | 107 | 3.07±0.26 | - | - |
| **Khodakarami** | H | 57 | 3.00±NM | - | - |
| | N | 55 | 3.6±NM | - | - |
| **Nazarpour** | H | 36 | 8.68±NM | - | - |
| | N | 36 | 8.33±NM | - | - |
| **Direkvandmoghadam** | H | 60 | 5.37±1.59 | - | - |
| | N | 60 | 5.31±0.95 | - | - |

**Table 2.** Continued

| | | | | | |
|---|---|---|---|---|---|
| **Modaress** | H | 80 | 1.56±0.72 | - | - |
| | N | 80 | 2.98±0.99 | - | - |
| **Namavarjahromi** | H | 24 | 6.04±NM | - | - |
| | N | 24 | 5.33±NM | - | - |
| **Mohammadinia** | H | 50 | 3.89±0.8 | - | - |
| | N | 50 | 3.10±0.6 | - | - |

Abbreviations: M, mean; SD, standard deviation; NM, Non Mention; H, Herbal; N, NSAID

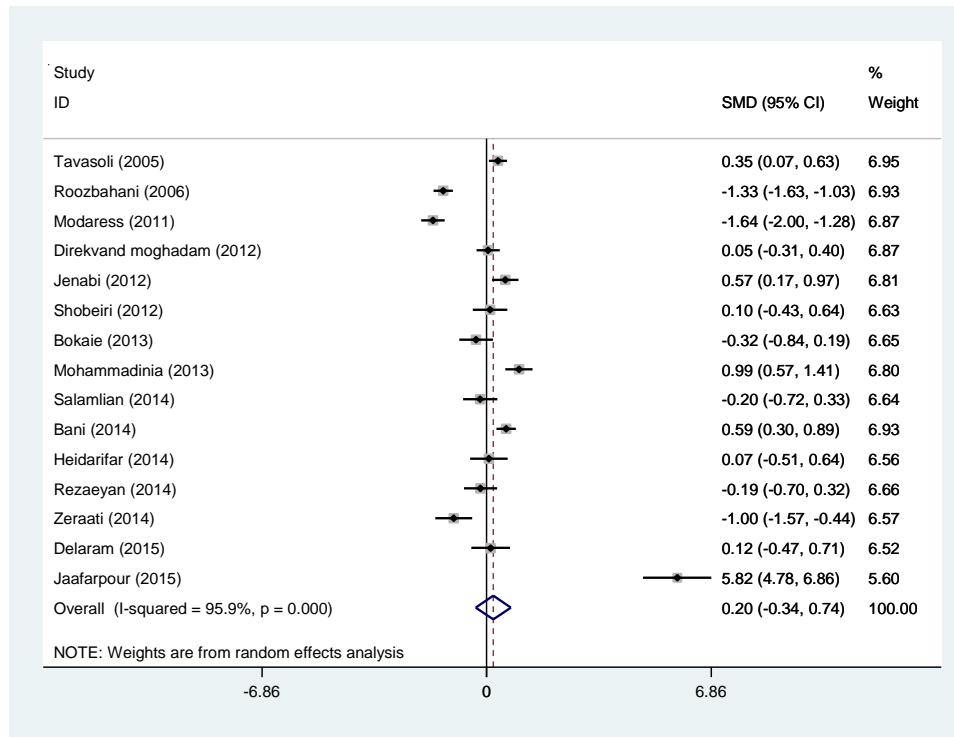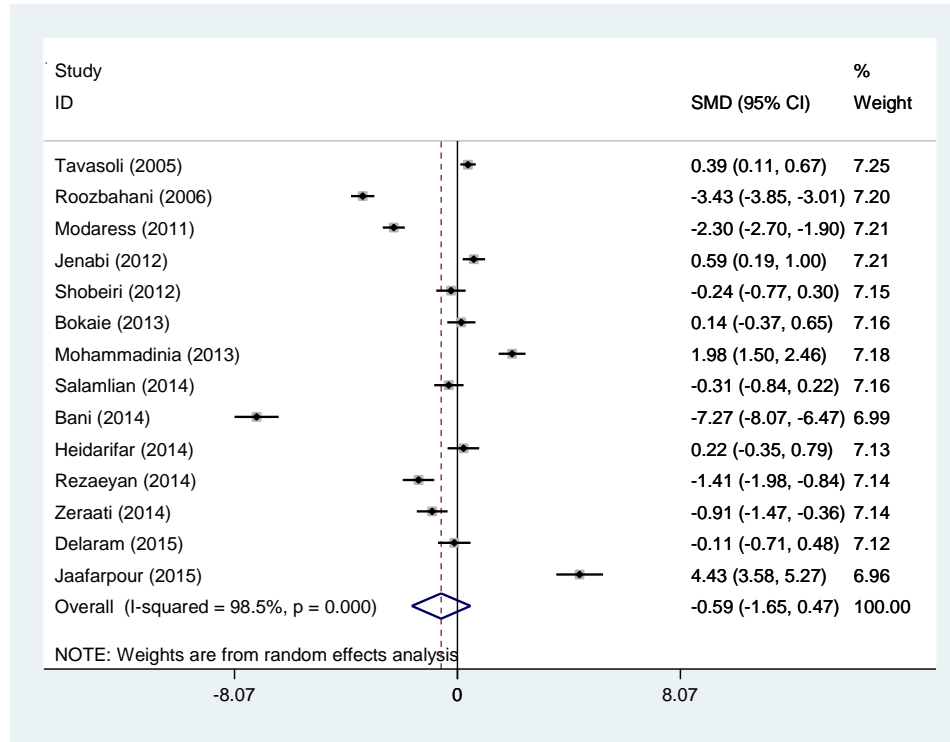*if confidence interval include zero, there are not significance different in the pain intensity before and after treatment



**Figure 2.** Analysis of pain intensity reduction in primary dysmenorrhea in the first intervention by random effects model.

(Abbreviation: SMD, Standard Mean Difference; CI: Confidence Interval)

**Figure 3.** Analysis of pain intensity reduction in primary dysmenorrhea in the second intervention by random effects model.
(Abbreviation: SMD, Standard Mean Difference; CI: Confidence Interval ).
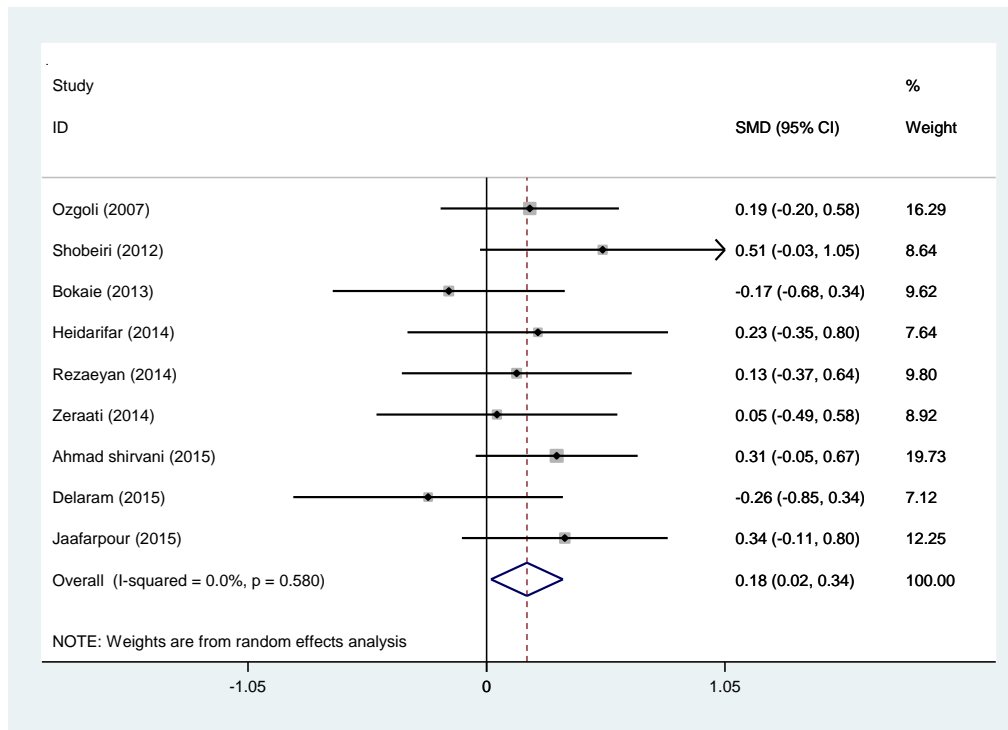


**Figure 4**. Analysis of duration of menstrual in primary dysmenorrhea by random effects model.
(Abbreviation: SMD, Standard Mean Difference; CI: Confidence Interval )
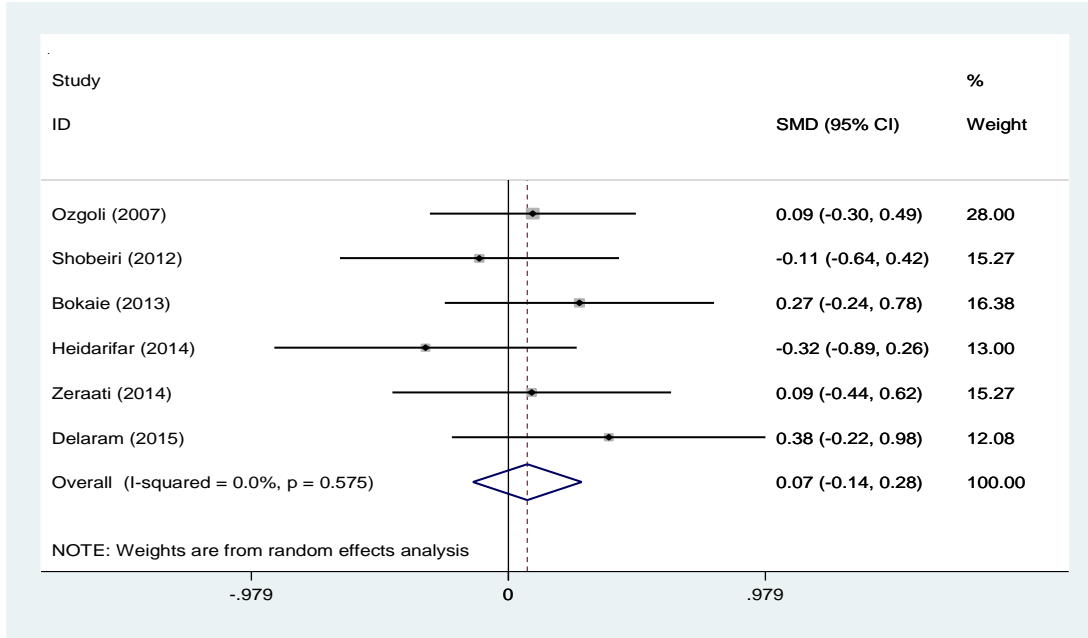
**Figure 5.** Analysis of interval cycle of menstrual in primary dysmenorrhea by random effects model.

(Abbreviation: SMD, Standard Mean Difference; CI: Confidence Interval )
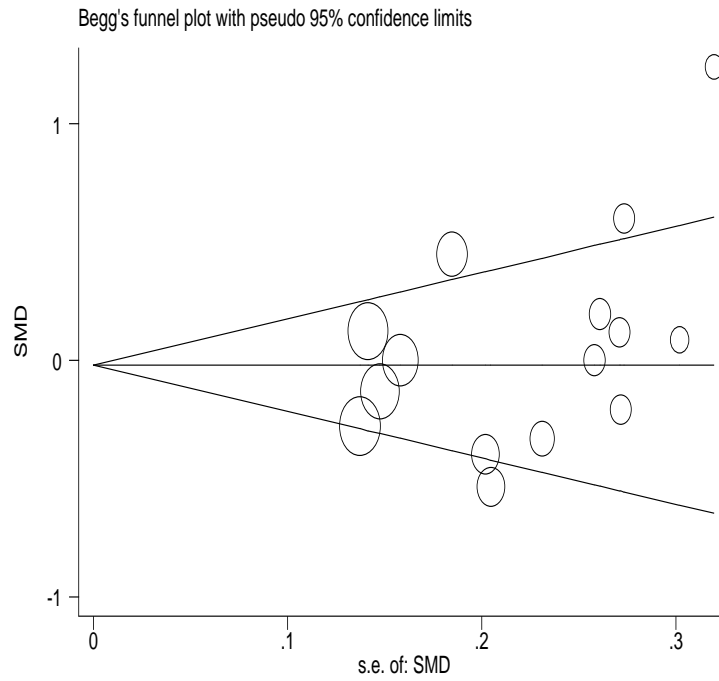


**Figure 6.** Begg's funnel plot for publication bias. The diameter of each circle represents the weight in the meta-analysis.

Each circle represents the RDs according to the standard error of each RDs. The diameter of each circle represents the weight in the meta-analysis.

## DISCUSSION

The total number of subjects in 21 studies was 2041 who entered thestudy from 1996 to 2014. The aim of the present research was to study the effect of herbaceous drugs in comparison to non-steroidal drugs on primary dysmenorrhea in Iran. The findings of this meta-analysis of randomized clinical trials indicated that herbal medicines do not have significant differences with NSAIDs drugs in primary dysmenorrhea pain reduction.However, in longer duration, herbal medicines are better able to reduce the severity of pain in primary dysmenorrhea.Despite this advantage,herbal medicines arenot more efficient than non-steroidal anti-inflammatory drugs on the duration and interval cycle of menstruation.

In some studies,pain intensity is reported to be less through medicinal herbs [19, 27, 28 and 30].Modaress, Zeraati and Shobeirihave expressed the better performance of medicinal herbs such as chamomile, fennel and vitagnus compared to mefenamic acid in reducing the severity of pain in primary dysmenorrhea[19,27,28]. In their study, they demonstrated that pain scores in the intervention group werestatistically significant compared to control. Also, Rezaeianet al.havestated thatolive oil is more effective than Ibuprofen [30].Heidarifar et al. also indicated that the mean score of pain in the intervention group with Dill (Anethumgraveolens) was significantly lower than the control [8]. Despite that, many reports indicated that there is no significant difference between using herbaceous and chemical drugs for reducing the pain of primary dysmenorrhea [1, 6, 10-14, 21-26].On the otherhand,inthe study of Mohammadinia, mefenamic acid was more effective than dill extract [16].

The interpretation of reviewed studies shows that most of the plants have flavonoids compounds or its subgroups , so it can be concluded that flavonoids are effective in treating dysmenorrhea.Flavonoids are analgesic and anti-inflammatory compounds in plants that have a direct effect on the synthesis of prostaglandins [35]. Flavonoids are one of the nitric oxide synthesizing enzymes and can reduce the painby preventing the production of nitric oxide. Also, by inhibiting the production of phospholipase A, these compounds suppress prostaglandin production and reduce pain [36, 37].

The main purpose of meta-analysis studies is to collect the results of various studies and come to a comprehensive view [38- 41].

Notably, our study included quality data of prospective studies with no bias. Also, because of the large volume of data, the effectiveness of herbaceous and chemical drugs could be more reliably represented. However, there are some limitations in this meta-analysis that should be considered:

First, drugs were consumed in various forms such as tablets andsyrup withdifferent doses.Secondly, because our study included articles that have been published there is the possibility of bias; despite this, there was no bias in the study.In this study, there was not statistically significant difference between the two groups in terms of pain and interval cycle of menstruation. The menstrual duration is the only statistically significant difference that was reported.

To more deeply study the efficiency of herbal drugs on the severity of pain, side effects and dosage need to be investigated. For instance, Moddarres[19] referred to the significant impact of chamomile on pain but he indicated that chamomile has some side effects such as skin diseases and blood pressure and it must not be used in high dosages.

### *Study limitation*

The limitation of the current study can be categorized into the following items: non-uniform and incomplete results of published articles, existence and absence of a control group in some articles, absence of standard deviation in some articles, diversity in drugs dosage, and using different herbs in some studies. The article was excluded from the study when reported different standard deviations or had no control group. The study firstly included 30 articles but it was reduced to 12 papers because of the limitations .

## CONCLUSIONS

This meta-analysis suggests that frequent consumption of herbal medicines can haverelatively better effecton the pain intensity in primary dysmenorrhea compared to the NSAIDs drugs.Mean difference of pain intensity reduced relatively better by administering herbal medicines, which is supported by the majority of studies, and the herbal drugs are more effective than the NSAIDs drugs.Finally, given the many side effects of non-steroidal anti-inflammatory drugs, herbal drugs can be effective in alleviating relevant pain through consuming it atthe standard dosage and considering the side effects.

## ACKNOWLEDGEMENTS

## REFERENCES

1. NamavarJahromi B., Tartifizadeh A., Khabnadideh S., 2003. Comparison of fennel and mefenamic acid for the treatment of primary dysmenorrhea. International Journal of Gynaecology Obstetrics. 80(2),153-7.

2. Modaress Nejad V., Motamedi B., 2006. Comparison between the pain-relief effect of fennel and mefenamic acid on primary dysmenorrhea. Journal of Rafsanjan University of Medical Sciences.5(1),1-6.

3. Ju H., Jones M., Mishra G., 2013.The prevalence and risk factors of dysmenorrhea. Epidemiologic reviews.36(1), 104-13.

4.Rehman H., Begum W., Tabasum H., Anjum F., 2014. Primary dysmenorrhea: a review with special reference to Unani concepts. Research &Reviews: A Journal of Unani, Siddha and Homeopathy.1(1), 29-37.

5. 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), 105-11.

6. Bokaie M., Farajkhoda T., Enjezab B., Khoshbin A., Karimi-Zarchi M., 2013. Oral fennel (Foeniculumvulgare) drop effect on primary dysmenorrhea: Effectiveness of herbal drug. Iranian Journal of Nursing and Midwifery Research. 18(2), 128-32.

7. Moslemi L., Bekhradi R., GaliniMoghaddam T., Gholamitabar Tabari M., 2012.Comparative effect of fennel extract on the intensity of primary dysmenorrhea. African Journal of Pharmacy and Pharmacology.6, 1770-3.

8. Salmalian H., Saghebi R., Moghadamnia A.A., Bijani A., Faramarzi M., NasiriAmiri F., Bakouei F., Behmanesh F., Bekhradi R., 2014.Comparative effect of thymus vulgaris and ibuprofen on primary dysmenorrhea: A triple-blind clinical study. Caspian Journal of International Medicine. 5(2), 82–88.

9. Karimian Z., Sadat Z., Abedzadeh M., Sarafraz N., Kafaei Atrian M., Bahrami N., 2013.Comparison the Effect of Mefenamic Acid and MatricariaChamomilla on Primary Dysmenorrhea in Kashan Medical University Students. Journal of Ardabil University of Medical Sciences.13(4), 413-20.

10. Shirvani M.A., Motahari-Tabari N., Alipour A., 2015. The effect of mefenamic acid and ginger on pain relief in primary dysmenorrhea: a randomized clinical trial. Archives of Gynecology and Obstetrics. 291(6), 1277-81.

11. Heidarifar R., Mehran N., Heidari A., Koohbor M., Mansourabad M.K., 2014. Effect of Dill (Anethumgraveolens) on the severity of primary dysmenorrhea in compared with mefenamic acid: A randomized, double-blind trial. Journal of research in medical sciences.Journal of Isfahan University of Medical Sciences.19(4), 326-30.

12. Bani S., Hasanpour S., Mousavi Z., Garehbaghi P.M., Gojazadeh M., 2014. The Effect of Rosa Damascena Extract on Primary Dysmenorrhea: A Double-blind Cross-over Clinical Trial. Iranian Red Crescent Medical

Journal.16(1), 1-3.

13. Direkvand-MoghadamA., Khosravi A., 2012.The impact of a novel herbal Shirazi Thymus Vulgaris on primary dysmenorrhea in comparison to the classical chemical Ibuprofen. Journal of Research in Medical Sciences. 17(7), 668-70.

14. Shobeiri F., Zeraati F., Mansouri Z., Araghchian M., Nazari M.,2012.The comparative effect of herbal extract of vitagnus and mefenamic acid on primary dysmenorrhea. Zahedan Journal of Research in Medical Sciences. 14(5), 30-3.

15. Park J.S., Park S., Cheon C.H., Go H.Y., Sun S.H., Shin Y.C., Jang B.H., Ko S.G.,2012. Effects of Gyejibongnyeong-hwan on dysmenorrhea caused by blood stagnation: study protocol for a randomized controlled trial. Trials.13(3), 1-6.

16. Mohammadinia N., Rezaei M., Salehian T., Dashipoor A., 2013. Comparing the effect of Anethumgravolens with mefenamic acid consumption on treatment of primary dysmenorrhea.Journal of ShahrekordUuniversity of Medical Sciences.15(5), 57-64.

17. Salehian T., Safdari F., Pirak A., Ataradi Z., 2011. Evaluation of the use of herbal medicine to relieve dysmenorrhea in students Iranshahr. Journal of Herbal Drugs.1(4), 57-63.

18. Jenabi E., Asle T.M., Hejrati P., 2012.The comparison of the effects of antiplain of Valerianaofficinalisrisom and mefenamic acid in relief of primary dismenorrhea. Iranian Journal of Obstetrics, Gyneocology and Infertility. 15(2), 44- 8.

19. Modarres M., Mirmohhamad A.M., Oshrieh Z., Mehran A., 2011.Comparison of the effect of Mefenamic Acid and MatricariaCamomilla Capsules on primary dysmenorrhea. Journal of Babol University of Medical Sciences (JBUMS). 13(3), 50-8.

20. Mohajeri M., Bakhshi S.,Behzadian N.,Tanha A., Nikzad M., 2006.Comparison of therapeutic effect between the herb fennel and mefenamic acid in the treatment of primary dysmenorrhea. Journal of Medical Science of Islamicazad University of Mashhad. 2(7), 355-9. [InPersian].

21. Delaram M., SadeghianDehkordi Z., Parvin N., Kazemiyan A., Shams S., 2015.Comparison of Analgesic Effect of Agnogol with Mefenamic Acid in the Treatment of Primary Dysmenorrhea. Journal of Research Development in Nursing and Midwifery.12(1),1-7.

22. Jaafarpour M., Hatefi M., Khani A., Khajavikhan J., 2015. Comparative effect of cinnamon and Ibuprofen for treatment of primary dysmenorrhea: a randomized double-blind clinical trial. Journal of Clinical Diagnosis Research. 9(4), QC04-7. doi: 10.7860 /JCDR /2015/12084.5783.

23. Tavasoli F., Sharifian J., Mazloom S.,2000.Comparison of mefenamic acid and Zereh for the treatment of primary dysmenorrhea. Persian Journal ofGonabadUniversity of MedicalSciences. 6(2),1-7.

24. Roozbahani N., Jabbari Z., Yazdi S., 2006. The comparison of Shirazi Thymus Vulgaris and Mefenamic acid effects on primary dysmenorrhea.Arak Medical University Journal. 8(3), 23-7.

25. Khodakarami N., Fariborz M., Ataolah G., Solokian S., 2009. The effect of an Iranian herbal drug on primary dysmenorrhea: a clinical controlled trial.Journal of Midwifery Women Health. 54(5), 401-4.

26. Nazarpour S., Azimi H., 2007.Comparison of therapeutic effects of Fennelin and Mefenamic Acid on Primary Dysmenorrhea. Journal of Mazandaran University of Medical Sciences. 17(61), 54-61.

27. Shobeiri F., Zeraati F., Mansouri Z., Araghchian M., Nazari M., 2012. The Comparative Effect of Herbal Extract of Vitagnus and Mefenamic Acid on Primary Dysmenorrhea.Zahedan Journal of Research in Medical Sciences.14(5), 30-3.

28. Rezaeyan M., Abdali N., Araban M.,2014. Comparing analgesic effects of extra virgin olive oil and Ibuprofen on the intensity of primary dysmenorrhea: A crossover clinical trial. Iranian Journal of Nutrition Sciences and Food Technology. 9(2), 67-74.

29. Ozgoli G., Goli M., Moattar F., Valaie N.,2007.Comparing ginger with mefenamic acid and ibubrofen for the treatment of primary dysmenorrhea. Research in Medicine. 31(1), 61-5.

30. Zeraati F., Shobeiri F., Nazari M., Araghchian M., Bekhradi R., 2014.Comparative evaluation of the efficacy

of herbal drugs (fennelin and vitagnus) and mefenamic acid in the treatment of primary dysmenorrhea. Iranian Journal of Nursing And Midwifery Research.19(6), 581-584.

31. Omomiroknabadi M., Sarafraz N.,2011.The effect of super mint (Mentha extract) compared with ibuprofen on primary dysmenorrhea: a randomized clinical trial. Journal of Medical Science of Qom. 5(3), 37-41.

32. Manouchehritareshizi E., Montazeri S., Abedi P., 2005. Comparing the effects of ibuprofen tablets and fennel on primary dysmenorrhea in high school students. Journal of Medical Science of Islamic Azad University of Mashhad.1(3), 17-26. [In Persian].

33. Hejazi S., Amin G., Mahmoudi M., Movaghar M., 2002.Comparison of herbal and chemical drugs on primary dysmenorrhea. Journal of Nursing and Midwifery Shahid Beheshti University of Medical Sciences. 12(42), 54-9.

34. Khabnadide S., Tartifizade A., Namavarjahromi B., 2003. ComparisonofFennel with mefenamic acid in the treatment of primary dysmenorrhea. International Journal of Gynecology & Obstetrics. 80(2), 153-7.

35. Alcaraz M., Hoult J., 1985. Actions of flavonoids and the novel anti-inflammatory flavone, hypolaetin-8-glucoside, on prostaglandin biosynthesis and inactivation. Biochemical Pharmacology. 34(14), 2477-82.

36. Toker G., Küpeli E., Memisoğlu M., Yesilada E., 2004. Flavonoids with antinociceptive and anti-inflammatory activities from the leaves of Tilia argentea (silver linden). Journal of Ethnopharmacology. 95(2-3), 393-7.

37. Özek M., Üresin Y., Güngör M., 2003. Comparison of the effects of specific and nonspecific inhibition of nitric oxide synthase on morphine analgesia, tolerance and dependence in mice. Life sciences.72(17), 1943-51.

38. Vasigh A., Abdi A., Borji M., Tarjoman A., 2019 .The prevalence of neuropathy among type 1 diabetic adolescents in Iran: a systematic review and meta-analysis. Int J Adolesc Med Health . DOI: https://doi.org/10.1515/ijamh-2018-0223

39. Azami M., Parizad N., Sayehmiri K., 2016. Prevalence of Hypothyroidism, Hypoparathyroidism and the Frequency of Regular Chelation Therapy in Patients with Thalassemia Major in Iran: A Systematic Review and Meta-analysis study. Iran J Ped Hematol Oncol. 6(4), 261-276.

40. Hatefi M., Abdi A., Tarjoman A., Borji M., 2019. Prevalence of depression and pain among patients with spinal cord injury in iran: a systematic review and meta-analysis. Trauma Mon.24(4), 1-8.

41. Azami M., Nikpey S., Pakzad I., Sayehmiri K., 2016. Effects of immunization on hepatitis B vaccine in Iranian health staff: A systematic review and meta-analysis study. Koomesh. 17(4), 789-795.