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## The effect of saffron on labor and childbirth: A systematic review and meta-analysis

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### Abstract

A growing number of pregnant women are using herbal medicine during labor. The aim of this study is to provide investigate the effect of saffron on labor and childbirth.

Web of Science, PubMed, Scopus, Cochrane Library, Cochrane Central Register of Controlled Trials, EMBASE, Google Scholar, and, Iranian databases such as SID, magiran, and Iranmedex were manually searched. The search strategy followed PRISMA guideline.

There was a significant reduction in the anxiety levels (CI:-0.96- -0.004, p:0.048) and the duration of the first and second stages of the labor (CI:-0.80- -3.84,  $p < 0.001$ ), (CI:-0.94- -0.13, p:0.01), a higher bishop score (CI:0.28-1.07, p:0.001) in women who consumed saffron. Other than nausea no significant adverse effect was reported.

Although saffron consumption can have a positive effect on bishop score, labor anxiety, and duration of first and second stages of labor, further studies with the purified components of saffron are needed.

**Keywords:** Saffron, labor pain, labor duration, childbirth, anxiety, bishop score

### Introduction

Childbirth is a life-changing experience for women <sup>[1]</sup>. Up to one-third of women experience traumatic and or negative labor and delivery <sup>[2]</sup>. A negative childbirth experience can adversely affect the delivery and postpartum outcomes of both mother and her child <sup>[2, 3]</sup>. Postpartum depression, post-traumatic stress disorder, difficulties in resuming sexual activities, and difficulties in breastfeeding and bonding with infant, are among the adverse effect <sup>[2-4]</sup>. World Health Organization (WHO) also emphasizes the importance of positive intrapartum experience <sup>[5]</sup>. Many factors can affect a mother's perception of birth, however, the main factors are lack of social support, labor pain, and emergency C-section <sup>[2]</sup>.

As uterine contraction begins, women feel labor pain. The level of pain perceived by women varies <sup>[6, 7]</sup>. High perceived pain levels cause anxiety which starts the fear and defense cascade <sup>[4, 8, 9]</sup>. As a result of high levels of epinephrine and cortisol circulating in mothers' system, the labor process is disturbed, which can lead to prolonged labor, cesarean, and other adverse effects <sup>[4, 8, 9]</sup>.

Many medications are currently used in order to reduce labor pain and anxiety and or increase labor progress speed. But most of these drugs have unwanted fetal or maternal side effects <sup>[6]</sup>. Many drugs that are used for pain and anxiety reduction intrapartum can prolong labor <sup>[6]</sup>.

During past decades herbal medicine has been acclaimed not only by the general public but also among health care professionals <sup>[10]</sup>. WHO defines herbal medicine as using herbs, herbal materials, herbal preparations, and finished herbal products <sup>[10]</sup>. A growing number of pregnant women are using herbal medicine during pregnancy and labor, and in recent years, plant-based medicines become the subject of medical studies <sup>[11, 12]</sup>. Saffron is one of these plants.

*Crocus Sativus L.* (saffron) is mainly produced in Iran, Spain, India, and Greek <sup>[13-15]</sup>. Saffron historically has been used to treat depressive symptoms, sexual dysfunctions, reduce inflammation, induce menstruation or abortion, and ease hard delivery and placenta delivery <sup>[13-16]</sup>.

Several studies were done on the effect of saffron on labor pain and anxiety, cervical ripening, and labor duration. The aim of this study is to provide comprehensive knowledge of the effect of saffron on labor and childbirth.

### Materials and Methods

#### Search strategy

The present review study was conducted based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist <sup>[17]</sup>. Web of Science, PubMed, Scopus, Cochrane Library, Cochrane Central Register of Controlled Trials (Central), EMBASE

databases, and Google Scholar search engine were manually searched by two researchers independently, without time limitation to October 12, 2021. Also, Iranian databases such as SID, magiran, and Iranmedex were searched.

The search strategy used was: (saffron\* or crocus\* or crocus sativus\*) and (labor or labour or Obstetric or birth or childbirth or delivery). The research question was as follows: Does saffron affect labor and delivery.

### PICOTS Criteria

1. Population: All pregnant women with term pregnancy and no serious complications without age, nationality, and race restriction
2. Intervention: Use of saffron without limitation in amount, route, or duration of consumption
3. Control: Placebo or routine control
4. Outcomes: The primary outcomes were the duration of the first, second, and third stages of labor, and the secondary outcomes were anxiety and pain during labor and bishop score.
5. Time: During labor and delivery
6. Study design: All randomized clinical trials

### Inclusion and exclusion criteria

All clinical trials that evaluate the effect of saffron on labor and delivery of women in English or Persian were included. Non-randomized clinical trials, observational studies, reviews, editorials, animal studies were excluded. There was no time limitation.

### Data Extraction

After removing duplications, the title and abstracts of articles were reviewed by two researchers independently. Irrelevant studies were excluded. In case of disagreement between the two researchers, a third researcher would review the study. Next, the full texts of chosen articles were retrieved, and studies without accessible full text were excluded. Preliminary data including authors' name, year of publication, and sample size in the intervention and control group, type of intervention, outcomes, and results were extracted by two researchers.

### Quality Assessment

Jaded scale was used for methodological quality assessment of the studies. The scale has three main items randomization, blinding, and withdrawal. There are five questions that are answered with yes or no, each yes is one point. The total score is five with a maximum point of two for randomization and blinding each and one point for withdrawal<sup>[18]</sup>. If the studies received 3 or more points out of five it was considered good in quality and studies with a score of lower than 3 were considered of poor quality and were excluded. Disagreements between the two reviewers were resolved by discussion with the corresponding author.

### Quality assessment criteria

- Is randomization mentioned?
- Is the method of randomization appropriate?
- Is blinding mentioned?
- Is the method of blinding appropriate?
- Are the number and the reasons for withdrawal in each group stated?

### Statistical analysis

Comprehensive meta-analysis software (version 2) was used for meta-analyses of the results. Heterogeneity between studies was assessed by I squared test ( $I^2$ )(19). If  $I^2 \geq 50$  results were considered heterogeneous, then Egger's and Begg's tests were performed<sup>[20]</sup>. The confidence interval was set at 95%.

### Results

35382 studies were found in the initial search, after removing the duplication, the title and abstracts of 10598 remaining articles were reviewed. After excluding irrelevant articles 12 studies were assessed for eligibility and six articles matched our eligibility criteria (Figure 1)<sup>[21-26]</sup>. Authors' names, years of publication, and sample size in the intervention and control group, type of intervention, outcomes, and results were extracted (Table 1). All six studies were considered of good quality based on Jadad scale scoring system (Table 1) and were included in systematic review and meta-analysis.

Six studies with a total sample of 346 pregnant women (173 in the intervention and 173 in the control group) were reviewed. The age range of participants was 18 to 38 and all participants were primiparous women. All of the studies were conducted in Iran.

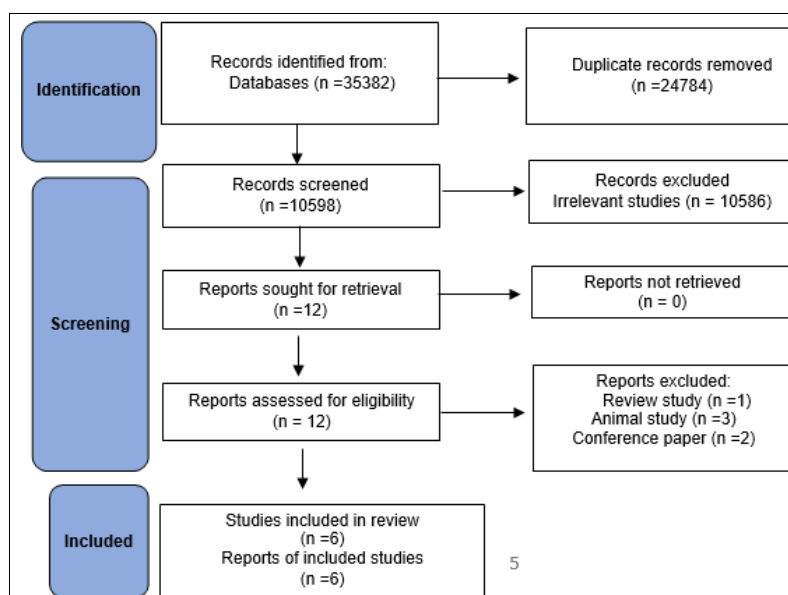


Fig 1: PRISMA Flowchart 2020

**Table 1:** Data extraction and quality assessment

	Author (year)	Sample size*		Type of intervention		Outcome Measure	Result	Jadad score out of 5
		intervention	control	intervention	control			
1	Ahmadi <i>et al.</i> (2017)	30	30	250mg saffron capsule	Placebo capsule	Labor pain, anxiety, length of 1 <sup>st</sup> and 2 <sup>nd</sup> and stages of labor, fatigue	1. ↓ of labor pain in the intervention group 2. ↓ in duration of the first and second stages of labor in the intervention group 3. ↓ in mean anxiety in the intervention group 4. Significant ↓ in mean fatigue in the intervention group	5
2	Ali-Akbari <i>et al.</i> (2020)	30	30	250mg saffron capsule	Placebo capsule	Bishop score, length of 1 <sup>st</sup> and 2 <sup>nd</sup> stages of labor	1. The Bishop's score was ↑ in the saffron group. 2. The average length of 1 <sup>st</sup> and 2 <sup>nd</sup> stages of labor in saffron group were shorter (not significant)	5
3	Darooneh <i>et al.</i> (2018)	30	30	250mg saffron capsule	Placebo capsule	Anxiety	The mean score of anxiety in the two groups was not significantly different	5
4	Ghaderi <i>et al.</i> (2019)	26	26	Saffron syrup (750mg saffron and 15g SS + 450ml water)	Placebo syrup (15g SS + saffron food coloring + 450ml water)	Length of 1 <sup>st</sup> , 2 <sup>nd</sup> and 3 <sup>rd</sup> stages of labor	↓ in duration of the 1 <sup>st</sup> , 2 <sup>nd</sup> and 3 <sup>rd</sup> stages of labor in the intervention group	5
5	Mohammadierad <i>et al.</i> (2018)	32	32	Saffron syrup (250 mg saffron and 65mg SS)	Placebo syrup (750mg saffron essential oil, 0.5g SS, and 1.25g sodium CMC.)	Labor pain, anxiety, length of 1 <sup>st</sup> , 2 <sup>nd</sup> and 3 <sup>rd</sup> stages of delivery	1. The mean score of anxiety in the two groups was not significantly different 2. No difference in the duration of the 1 <sup>st</sup> , 2 <sup>nd</sup> and 3 <sup>rd</sup> stages of labor between the two groups	5
6	Sadi <i>et al.</i> (2016)	25	25	250mg saffron capsule	Placebo capsule	Bishop's score, duration of the 1 <sup>st</sup> and 2 <sup>nd</sup> stages of labor	1. The Bishop's score was ↑ in the saffron group 2. No difference in the duration of the 1 <sup>st</sup> , and 2 <sup>nd</sup> stages of labor between the two groups	5

\*All the participants were primiparous women/SS: Sodium Saccharin

**Results from the systematic review**

Saffron had no significant effect on mothers' tiredness during labor, mode of delivery, APGAR score in first and 5<sup>th</sup> minute, need for painkillers, and cause of cesarean delivery [21, 23, 26].

**Cervical dilatation and augmentation:** Ahmadi *et al.* reported a higher mean in cervical dilatation in the intervention compared to the control group ( $p < 0.001$ ) (21), which suggests a reduction in the need for augmentation. However, in the study of Sadi *et al.*, there was no significant difference between the number of pregnant women that needed augmentation in the saffron and placebo group [26].

**Fetal descent rate:** One study reported a significantly faster fetal descent in the saffron group ( $p < 0.001$ ) [21].

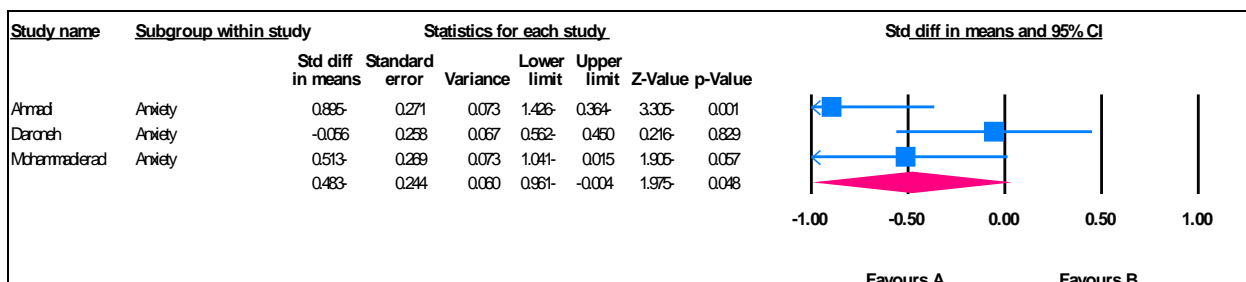
**Adverse effects:** Ahmadi *et al.*, Ghaderi *et al.*, and Sadi *et al.*

reported no maternal, fetal, and or neonatal adverse effects attributed to saffron [21, 24, 26]. In one study a pregnant woman in the intervention group reported lethargy, weakness, and redness in face and two participants in the control group reported palpation and nausea [22]. Another study reported that 17% of participants in intervention group and 11% in the control group had moderate to severe nausea [25].

**Results from the meta-analysis**

**Effect of saffron on anxiety during labor:** Results from 3 studies with a total sample size of 184, reported a significant decrease in anxiety levels in women in the intervention group (CI: -0.96- -0.004,  $p: 0.048$ ) (table 2) [21, 23, 25]. Studies were heterogeneous ( $I^2=60.48$ ,  $p: 0.08$ ) but results from Egger's and Begg's tests reported no significant publication bias (Egger's:0.22, Begg's: 0.11).

**Table 2:** Effect of saffron on anxiety during labor



**Effect of saffron on anxiety labor pain:** Based on results from Ahmadi *et al.*, and Mohammaderad *et al.*, studies, with a total sample size of 244, saffron does not have a significant effect on labor pain (CI: -1.19- -0.03, p: 0.066) [21, 25]. The studies were heterogeneous ( $I^2 = 63.57$ , p: 0.09).

**Effect of saffron on first stage of labor:** According to results from 5 studies, with a total sample size of 286, saffron reduced the duration of the first stage of the labor (CI: -0.80- -3.84,  $p < 0.001$ ) (Table 3) [21, 22, 24-26]. The studies were homogenous ( $I^2 = 22.93$ , p: 0.26).

**Table 3:** Effect of saffron on first stage of labor

Study name	Subgroup within study	Statistics for each study					Z-Value p-Value		Std diff in means and 95% CI
		Std diff in means	Standard error	Variance	Lower limit	Upper limit			
Ahmadi	Stage1	0.836	0.289	0.072	1.363	0.308	3.104	0.002	
Aliakbari	Stage1	0.574	0.283	0.089	1.091	-0.068	2.180	0.029	
Sadi	Stage1	0.338	0.289	0.083	0.964	0.167	1.380	0.168	
Mohammaderad	Stage1	-0.086	0.285	0.070	0.606	0.433	0.325	0.745	
Graderi	Stage1	0.730	0.280	0.078	1.339	0.241	2.821	0.005	
		0.535	0.139	0.019	0.807	0.262	3.847	0.000	

**Effect of saffron on second stage of labor:** 5 studies reported a significant reduction of the second stage duration in the intervention group (CI: -0.94- -0.13, p: 0.01) (Table 4)

[21, 22, 24-26]. Studies were heterogeneous ( $I^2 = 65.31$ , p: 0.02), (Egger's: 0.72, Begg's: 1.00).

**Table 4:** Effect of saffron on second stage of labor

Study name	Subgroup within study	Statistics for each study					Z-Value p-Value		Std diff in means and 95% CI
		Std diff in means	Standard error	Variance	Lower limit	Upper limit			
Ahmadi	Stage2	1.079	0.276	0.076	1.621	0.537	3.904	0.000	
Aliakbari	Stage2	0.618	0.284	0.070	1.136	-0.100	2.337	0.019	
Sadi	Stage2	0.145	0.286	0.082	0.706	0.416	0.506	0.613	
Mohammaderad	Stage2	0.010	0.285	0.070	0.509	0.529	0.038	0.970	
Graderi	Stage2	0.877	0.282	0.080	1.430	0.323	3.105	0.002	
		0.540	0.209	0.043	0.949	0.131	2.589	0.010	

**Effect of saffron on third stage of labor:** Saffron has no significant effects on the duration of third stage of labor (CI: -1.08- -0.31, p: 0.28), according to the results from 3 studies with 176 participants [22, 24, 25]. Also the studies were heterogeneous ( $I^2 = 80.87$ , p: 0.005) but no publication bias was observed (Egger's: 0.15, Begg's: 1.00).

**Effect of saffron on Bishop score:** In two studies with 110 samples, Ali-Akbari *et al.*, and Sadi *et al.*, reported a higher bishop score in women's who consumed saffron (CI: 0.28- 1.07, p: 0.001) (Table 5), ( $I^2 = 27.33$ , p: 0.24) [22, 26].

**Table 5:** Effect of saffron on Bishop Score

Study name	Subgroup within study	Statistics for each study					Z-Value p-Value		Std diff in means and 95% CI
		Std diff in means	Standard error	Variance	Lower limit	Upper limit			
Aliakbari	Bshp	0.885	0.271	0.073	0.364	1.426	3.305	0.001	
Sadi	Bshp	0.422	0.298	0.089	0.162	1.007	1.417	0.155	
		0.681	0.200	0.040	0.288	1.074	3.399	0.001	

**Discussion**

Current data suggests saffron reduces labor anxiety. Anxiety during labor activates the sympathetic nervous system, which results in spasm of veins and reduction of blood flow to the uterus, it also increases serum levels of epinephrine which can prolong labor stages through decreasing uterine contractions force [6, 7, 23]. Several studies indicated that saffron has an anxiolytic effect [21, 27, 28]. But Daroneeh *et al.* (2018) reported no significant effect [23]. The exact mechanism by which

saffron works as an anxiolytic drug is yet unknown but there are some theories that suggest components such as crocin and safranal play an important role [23, 28, 29]. Like in Iran, saffron is used in traditional Indian medicine as an enhancer of the body's resistance to stress and anxiety [30, 31]. The study of Hosseinzadeh *et al.* (2009), showed that saffron extract and safranal have anti-anxiety effects on rats [32]. In the study of Fukui *et al.* (2011), smelling saffron for 20 minutes reduced the level of cortisol in women's blood [33]. Also, in the study

of Mirzaei *et al.* (2015), reported a significant relationship between lower cortisol levels and reduced anxiety during childbirth in nulliparous women [34]. Some studies also report a smooth muscle relaxing and antispasmodic effect related to saffron, which may help in anxiety reduction [14, 35].

Daroneeh *et al.* (2018) reported a reduction in labor pain, but the results of our meta-analysis did not support this finding [23]. Pain reduction was also reported in dysmenorrhea due to saffron consumption, but its mechanism of action is not clear [36]. It may be related to the smooth muscle relaxing effect of saffron [14]. It is also mentioned in Avicenna's book "The Canon of Medicine" that saffron acts as a sedative and joyful medicine and can be used orally for women suffering from labor pain to facilitate and accelerate childbirth [16, 25].

Even though as previously mentioned, saffron has a relaxing effect on smooth muscle, some animal studies stated that saffron may act as auterotonic agent, even the essence caused premature labor in rats [29, 37, 38]. Saffron essence on mice and Indian pigs can induce estrogenic effects and stimulate uterine contractions which seem to involve both neurological and myogenical mechanism [39]. Historically saffron was used to induce abortion, and one study reported a higher prevalence of miscarriage in women who worked in saffron fields, which can be due to theuterotonic effect of saffron [16, 40]. According to the results of our meta-analysis saffron shortens the first and second stages of labor, these findings may be due to saffron's effect on uterine contractions.

There are not enough data about the safety of saffron in labor and delivery.

**Limitation:** Due to the small body of studies that investigate the effect of saffron on labor and delivery, and variation in the type of intervention (capsule or syrup), consumption duration, and dose of saffron in these studies, results from this meta-analysis cannot be generalized to the general population of pregnant women.

### Conclusion

Results from our systematic review and meta-analysis suggest that saffron (capsules or syrups) has a positive effect on anxiety during labor, bishop score, and duration of the first and second stages of the labor. But no significant effect was observed on labor pain and the third stage of labor. Further studies with the purified components of saffron are needed.

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