

REVIEW ARTICLE

Investigating the Effect of Saffron on Anxiety, Fatigue, Labor Pain and Vaginal Childbirth: Review Article

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ABSTRACT

Saffron and its active ingredients were found effective in the management of pain due to neurological and inflammatory causes. Therefore, this study was conducted to evaluate the effect of saffron on anxiety, fatigue and pain during labor progress. In this review study, articles in Persian and English language indexed in reputable databases, including Irandoc, Iranmedx, SID, Google scholar, Magiran, Scopus, web of science and PubMed were searched. Articles that met the inclusion criteria were analyzed qualitatively. Out of 34040 studies, 6 articles were included. The mean score of anxiety and fatigue, active phase length score of the first and second stages of delivery were lower in the saffron consumer group compared to pharmacotherapy group. Saffron can increase cervical ripening in term pregnancies. Saffron had abortive effects. Saffron can be used as a facilitator of labour and a natural analgesic for labor pains.

Keywords: Saffron, Anxiety, Fatigue, Labor pain, Childbirth

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INTRODUCTION

Labor pain is one of the most well-known types of pain, and despite the existence of various ways to relieve pain, management of labor pain still remained a treatment challenge in most countries (1). Excessive pain in the mother stimulates the sympathetic nervous system and increases the release of epinephrine, norepinephrine, and cortisol, and ultimately slows labor and increases fetal and neonatal complications, labor fear, stress, and anxiety, which can affect labor process (2-4). Labor pain is one of the most important factors that encourages pregnant women to choose cesarean delivery (5). It was also reported that 93% of pregnant women feared labor, and nearly half of them reported high levels of anxiety (6). Caesarean section is performed in 65-50% of deliveries in Iran (7). All the currently used analgesic agents are associated with morbidity and even mortality (8). Systemic analgesics can cause nausea, vomiting, and drowsiness in the mother and respiratory depression at birth, drowsiness, and breastfeeding problems in the newborn (9). Furthermore, in mothers who receive painkillers shortly after delivery, pushing ability is reduced during active labor, which leads to maternal and neonatal complications. Therefore, identifying an analgesic drug with minimal side effects that can cause euphoria and sedation can be ideal in midwifery (9).

Based on the studies that have been performed till present, various medicinal plants were found to reduce labor pain. These plants have been used in traditional medicine. It seems that these medicinal plants can be a good alternative in this field. One of these plants is saffron, which has been widely mentioned in traditional medicine and modern studies for its sedative and analgesic effects (10). Saffron is plant of the *Crocus sativus* family and has long been used as a spice and medicine in a number of cultures. Saffron and its extract have been used in traditional medicine as a sedative, analgesic, and antiemetic. Spasm, anti-cramp, anti-depressant. Saffron has been also used as a medicine with hypnotic, anticonvulsant effects and has been used in the treatment of menstrual irregularities and some other disorders. In traditional Indian medicine (Ayurveda), saffron is considered as an adaptogen, a substance that increases body resistance to stresses including trauma, anxiety, and fatigue. Crocin, crocetin, and safranin are the main active ingredients in saffron (11). Crocin and safranin have shown to have anti-anxiety effects in light/dark transition test in rats (11). Prior to this study, Ahmadi et al. (2015) in Mashhad, Iran showed that prescription of oral saffron capsule at the beginning of the active phase of labor reduced fatigue and anxiety in the first stage of labor (12).

Therefore, to reduce labor pain not only alleviates pain, but also can reduce the adverse effects of physiological processes that cause anxiety and pain in mother and lead to maternal and fetal harm. It seems necessary that the side effects of analgesic chemicals lead to the choice of

medicinal plants. In recent years many researchers have studied alternative methods of pain relief, including the use of medicinal plants. Considering the local availability and indigenous uses of herbal medicines in different cultures and ethnicities of Iran provinces, the present study was designed and conducted with the aim of determining the effect of oral saffron administration on anxiety, fatigue, labor pain and vaginal delivery and to review clinical evidence regarding the effects of these agents considering sample size, reliability and precision of the studies.

MATERIALS AND METHODS

Search Strategy

In the present study, Irandoc, Iranmedex, SID, Google scholar, Magiran, Scopus, web of science and PubMed databases were searched to find relevant studies. There was no time limit for the electronic search. The list of references in all related articles and reports was manually evaluated to find other possible sources.

In this review, the Persian keywords, including “saffron”, “anxiety”, “fatigue”, “labor pain”, “labor”, and English keywords, including “SAFFRON”, “LABOR”, “DELIVERY”, “Anxiety” and “stress”, were used to find subsets of papers related to the study research questions.

Article evaluation

The inclusion criteria were availability of full-text article, peer-reviewed clinical trial studies that assessed the effects of saffron on labor pain and anxiety and delivery in primiparous women. Exclusion criteria were low quality and studies that the effects of saffron on the desired outcomes were not assessed as the primary outcome.

The Jadad score was used for the quality assessment of the articles. This tool examines articles based on randomization method and procedure and the way blinding as performed and patient follow up. The minimum Jadad score is 1 and the maximum score is 5. Articles that were scored 3 or above were included in the study.

The identified studies were entered in Endnote software and duplicate publications were eliminated. Two reviewers performed the screening independently based on the inclusion and exclusion criteria. Then the included articles by each reviewer were compared and combined. In case of disagreement between the reviewers an external expert was contacted and decision was made in a meeting. In the next step the full text of the selected articles were obtained and the content of the articles were assessed for availability of the outcome parameters and quality. Data extraction was then performed by the initial two reviewers. The flowchart of the study is shown in Figure 1.

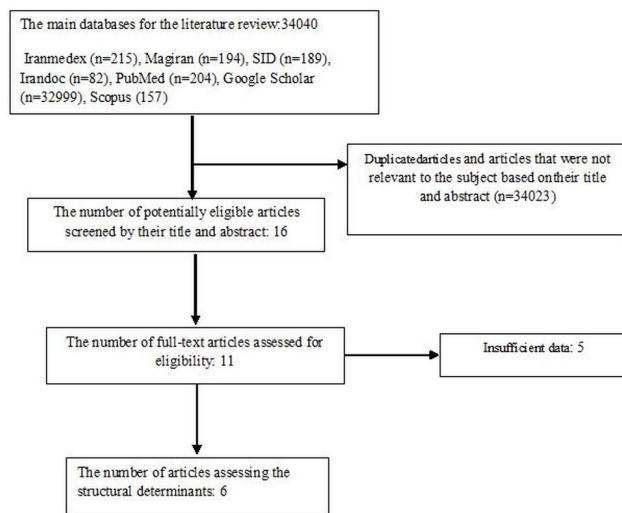


Figure 1: Flowchart of the study

RESULTS

In the first step, 34040 articles were found based on the search strategy. In the second step, 34,023 articles were excluded after reviewing the title and abstract and elimination of duplicate studies. Duplicate studies were defined as studies with similar title, author’s name, and journal. Eleven studies were excluded due to unavailable full text. In the third step, 6 full text articles were reviewed and evaluated qualitatively (Table I).

In a triple blind randomized controlled trial entitled “Study of the effect of saffron oral capsule on the severity of active pain in the first phase of labor” by Azhari et al. (2014), 60 pregnant women with labor pain who referred to the maternity ward of 17 Shahrivar Hospital in Mashhad, Iran were studied. Subjects were randomly assigned to intervention (250 mg saffron capsule) and control (placebo capsule) groups. At the onset of the active phase of delivery, one capsule (saffron or placebo, which were identified by a code by the manufacturer) was administered. Severity of pain was measured hourly until the end of the active phase of the first stage of labor using the visual analogue scale. Further doses of the capsules were administered every 2 hours (maximum 3 capsules) based on uterine contractions, fetal heart rate pattern and mother’s vital signs. The results of this study showed that the mean intensity of labor pain in the saffron group was 11.5% lower than the placebo group and this difference was statistically significant (P <0/001) (8).

Saadi et al. (2016) conducted a double blind randomized controlled trial entitled “Effect of oral consumption of saffron tablets on cervical readiness in pregnant women” in Bonab Martyrs Hospital. In this study, 98 pregnant women without labor pain with gestational age of 41 to 39 weeks with a Bishop score below 4 and no indication for cesarean section and willing to

Table 1: Characteristics of the reviewed articles

Author, year	Title	Subjects	Tools	Sample size	Intervention	Results	Quality score
Azhari, 2014	Evaluation of the effect of oral saffron capsules on pain intensity during the active phase of labor	nulliparous women	Visual Analogue Scale	60	Intervention: 256 mg saffron capsules Control: placebo capsule	mean overall pain intensity was 85.9±8.4 in the intervention group and 97.4±2.9 in the control group	4
Sheno Ghaderi, 2019	The Effect of Honey Saffron Syrup on Labor Progression in Nulliparous Women	nulliparous women	partogram form	90	Intervention: 1. saffron syrup prepared with honey and 2. saffron syrup prepared with sugar Control: placebo every two hours orally	duration of the first, second and third phases of labor after intervention was shorter in both intervention groups compared to the placebo group Only the duration of the first stage of labor was shorter in the honey saffron syrup group compared to the sugar saffron syrup group	5
Sadi, 2016	Effect of saffron (Fan Hong Hua) on the readiness of the uterine cervix in term pregnancy: a placebo-controlled randomized trial	nulliparous women	Bishop's score	50	Intervention: three 250mg saffron capsules Control: placebo pills in 24 hours	The Bishop's score was significantly higher in the intervention group 20 - 24 hours after saffron administration	5
Ahmadi, 2015	The effect of oral capsules of saffron on anxiety and fatigue during the first stage of labor	nulliparous women	spectrograph form, Visual Analogue Scale for Anxiety and fatigue	60	Intervention: 250 mg saffron capsules Control: placebo	Mean anxiety score of saffron group was lower than that of the placebo group. The mean fatigue score in the Saffron group was significantly lower than that of the placebo group	4
Mohammadierad, 2018	Effect of Saffron with or Without Date Sugar on Intensity of Pain and Anxiety During Labor in Primiparous Females: A Randomized, Controlled Trial	nulliparous women	visual analogue scale every one hour	96	Intervention: 1. 80 mL oral syrup of saffron (250 mg) plus date juice (65 g) 2. saffron (250 mg) plus artificial sugar (165 mg sodium saccharin and 420 mg sodium carboxymethyl cellulose) Control: placebo every two hours for maximum three doses (240 mL).	The differences were only statistically significant at the saffron plus date juice group	5
Darooneh, 2018	Effects of saffron capsule on labor anxiety in primiparous women: a clinical double-blind randomized controlled trial	primiparous women	Spielberger Anxiety Inventory	60	Intervention: 250mg saffron Control: placebo per night for 3 nights.	The mean score of anxiety at baseline and at admission were not significantly different between groups. In both groups, there was no significant difference in mean anxiety score between baseline and admission in maternity ward	4

perform vaginal delivery were allocated in two groups. Within 24 hours, subjects received three 250 mg tablets of saffron or placebo every 8 hours. Cervical ripening was assessed using the Bishop score. The results of the study showed that the mean Bishop score at 20-24 hours after the initiation of the intervention or other medical interventions for any reason in the saffron group was significantly higher than the placebo group (13).

In a study by Ahmadi et al. (2015) the effects of saffron on fatigue and anxiety in the first stage of labor was examined. In this study, 60 primiparous women were randomly assigned to two groups including saffron at a dose of 250 mg and placebo. One saffron or placebo capsule was administered at the initiation of the active phase of labor and continued every two hours to the maximum of three capsules. Fatigue and anxiety was measured was assessed once at the beginning of the study, and then every two hours until the end of the first stage of labor using a visual scale. The results of this study showed that saffron could reduce anxiety and fatigue during labor (14).

In the study by Mohammadi Rad et al. (2016) the effect of saffron syrup with or without date sugar was assessed on the severity of pain, anxiety and the duration of the active phase of Labor. Primiparous women (n=96) who referred to Tabriz Social Security Hospital at the beginning of the active phase of delivery entered the study. Subjects were assigned to three groups; 80 ml oral syrup containing saffron and date sugar (60 g), saffron (250 mg) and artificial sweetener (165mg) and placebo using random block sampling. The results of this study showed that saffron syrup + date sugar reduced the severity of pain, anxiety and duration of labor in primiparous women and can be used for this purpose. However, based on the results of this study, the effects of saffron + artificial sweetener could not be judged (15). In a study entitled "Evaluation of Escape Essential Effects or Selected Hydroalcoholic Extracts from Iranian Medicinal Plants including Saffron and Hourglass on Straight Muscle Contractions" by Sadraei et al. (2003), 188 micrograms of estrogen per kilogram of body weight was administered to mice one day before testing. The uterus was excised on the day of the test and was

kept in a tissue bath containing tyrode's solution gassed with O₂. Uterine isotonic contractions were induced by injecting 48 nM of potassium chloride and 320 nM acetylcholine. Subsequently, a mixed solution of plants including passion flower, barberry, and saffron were injected. They found that plants including saffron and passion flower aggravated aberrant uterine activity induced by potassium chloride and may play a role in miscarriage or preterm delivery (16).

In a study by Ghaderi et al. (2019) the effect of honey saffron syrup was assessed on the progression of labor in women. Subjects were randomly divided into three equal groups based on the inclusion criteria. The first group received saffron syrup prepared with honey, the second group received saffron syrup prepared with sugar and the placebo group received placebo. Administration was performed orally every two hours. The mean duration of labor in both intervention groups was significantly lower than the control group ($p < 0.001$). The duration of the first phase of delivery was significantly shorter in the saffron honey syrup group compared to the saffron syrup group ($P = 0.016$). Consumption of saffron syrup with honey reduced the duration of the first, second and third stages of labor (17).

In the study by Darooneh, et al. (2018), the effect of saffron capsule on labor anxiety was assessed in primiparous women. Subjects were randomly assigned to the intervention group, who received 259 mg saffron per night, and control group, who received placebo. The intervention duration was 3 nights. The study revealed no significant difference between groups in terms of anxiety at baseline based on the Spielberger State-Trait Anxiety Inventory (STAI) questionnaire ($p=0.99$) and at admission for delivery ($p=0.83$). No significant difference was observed in the changes in anxiety score from baseline to time of admission between groups (18). None of the studies reported serious side effects including abortion.

DISCUSSION

The aim of this study was to review the effect of oral saffron capsule on anxiety, fatigue, labor pain and vaginal delivery. In recent decades, steps have been taken to alleviate or reduce labor pain. Majority of the included studies in this review revealed the effectiveness of saffron in reducing the duration of labor, delivery and factors affecting the length of labor.

Regarding the effects of saffron on anxiety, the findings of the current review showed that oral saffron administration was effective in reducing anxiety in three studies (14, 15, 19), while in one study, anxiety was not affected by saffron administration (18). The reason for the different findings of the studies might be due to the use of different assessment tool (visual analogue scale vs STAI) in the studies and also the difference in the stages

of labor. While Darooneh et al. (2018) studied anxiety at the time of admission to maternity ward (18), other researchers assessed anxiety at different delivery phases (14, 15, 19).

It was previously shown that smelling saffron for 20 minutes reduced the level of the blood cortisol hormone in women (20). On the other hand, Mirzaei et al. (2015), reported a significant relationship between reducing blood cortisol levels and reducing the level of anxiety during labor in primiparous women (19). The results of previous studies on the active ingredients of saffron, including Crocin and saffronal, documented their anti-anxiety effects (21). In this regard, Hosseinzadeh et al. (2009) examined the anti-anxiety and hypnotic effects of saffron aquatic extract on mice. They showed that saffron and its aquatic extract have anti-anxiety and hypnotic effects (22). It has been stated that the effect of saffron is similar to diazepam and that saffron produces its effects has anti-anxiety, analgesic and muscle relaxant effects like benzodiazepines (22). The analgesic effects of saffron was previously shown in one human study and several animal studies (23, 24). Reducing maternal anxiety can prevent the release of stress hormones. Based on the findings of the mentioned study, saffron seems to be a suitable agent in reducing anxiety and fatigue during labor without any side effects on the mother and fetus.

Regarding the effects of saffron on duration of labor, the findings of the current review showed that the duration of labor and readiness for vaginal delivery achieved to a greater extent due to saffron administration compared to placebo (13, 17). Only one study assessed the effects of saffron on fatigue during delivery in the current review, and found that the mean fatigue score was significantly lower in the saffron group compared to the placebo group. With the onset of labor pain and increase in the level of stress hormones, the physiological indicators, including respiratory rate and heart rate, increase, leading to decreased energy and increased fatigue (25). Saffron has long been used in traditional medicine as an axytotic agent (21, 26). Saffron exposure at doses as high as 10 grams (in saffron farm workers) or continuous exposure to lower doses of saffron have been found to induce abortion in human and animals (27-29). The possible effect was hypothesized to be due to the effect of saffron of uterine muscle. In another study on pregnant women at 40 weeks gestation, administration of 250 mg of saffron for 3 consecutive nights resulted in increased cervical ripening compared to placebo (30). Therefore, saffron may shorten the duration of labor through the induction of uterine muscle contraction.

Regarding the effects of saffron on anxiety, the findings of the current review showed that saffron reduced pain in both the reviewed studies that assessed pain (8, 15). In a study on laboratory male rats, it was found that saffron ethanolic extract has the ability to inhibit the acute

phase of pain induced by formalin, due to the safranal content of saffron. The inhibition of inflammation and pain by the alcoholic extract of saffron and its important components in the second phase of the formalin test may be due to either the inhibition of cyclooxygenase enzyme, the main enzyme that produces prostaglandin, or the glucocorticoid hormone-like effects of extract components, that stimulate the release of adrenal cortex hormones (23). It is believed that in the chronic phase of the formalin test, prostaglandin pathways are activated, which can be inhibited by inhibiting of the synthesis of prostaglandins (31). Increased production of prostaglandins in the active phase of labor can increase pain through increased uterine contractions (32). It has been suggested that the anti-inflammatory effect of saffron extracts are due to their flavonoid, tannin, anthocyanin, alkaloid and saponin contents. Saffron can also be effective in reducing pain due to its tannins content (33).

The strength of the current review was the inclusion of all studies with different languages from different countries in the search. Furthermore, this study included studies with high quality based on the Jadad quality assessment tool.

One of the limitations of the current review was lack of studies with large sample sizes on the effects of saffron on delivery outcome, pain and anxiety in pregnancy. The heterogeneity in the study methods, duration of administration and outcome assessment prevented us from performing a meta-analysis. Although the quality of the studies were acceptable, combining the findings in terms of pain relief was hard due to the mentioned heterogeneity. It is therefore suggested that studies with larger sample sizes be conducted using reliable assessment tools in order to better identify the effects of saffron on the outcome measures.

CONCLUSION

According to the findings of the current review, saffron might be able to reduce pain during delivery but has an acceptable effect on reducing anxiety and length of delivery in primiparous women. The findings of the current study suggests saffron as a suitable analgesic and oxytocic agent in primiparous women but there is a need for further studies with a better design.

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