REVIEW ARTICLE

GMJ.2017;6(4):281-90
www.gmj.ir

Received 2017-01-18
Revised 2017-04-10
Accepted 2017-04-17

A Review of Herbal Medicines for Nausea and Vomiting of Pregnancy in Traditional Persian Medicine

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Abstract

Nausea and vomiting of pregnancy (NVP) is one of the prevalent pregnancy complaints. This study was conducted to review the medicinal plants mentioned in Traditional Persian Medicine (TPM) for the treatment of NVP. A literature research was conducted on a number of main references of TPM, including the books of *al-Qanun fī al-Teb, Zakhireye Kharazmshahi, Tadbir-al-Habali al- Atfal al-Sabiban* and *Makhzan-al-Adviah*. Then, medicinal plants mentioned in TPM for treatment of NVP were determined and searched in electronic databases, including PubMed and Google Scholar to find studies that confirmed their efficacy. The search terms were ‘‘vomiting’’ or ‘‘nausea’’ or “emesis” and “pregnancy” and the name of each herb. Data were collected for the years 1990–2016. The findings included 10 plants. *Citrus limon* (Lemon), *Citrus medica L.* (Citron), *Cydonia oblonga* (Quince), *Elletaria cardamomum* (Cardamom), *Mentha spicata L*. (Spearmint), *Menatha piperita* (Mint), *Myristica fragrans Houtt* (Nutmeg), *Pistacia lentiscus Linn.* (Mastic), *Punica granatum L*. (Pomegranate), *Malus domestica Borkh* (Apple), and *Piper cubeba L*. are the most recommended medications for NVP. There is evidence in human studies for some of these medicinal plants (*Mentha Piperita L., Citrus limon, Elletaria cardamom, and Cydonia oblonga Mill*). The other mentioned herbs have not been evaluated during pregnancy. There is limited evidence to safely recommend these plants for NVP. Although some human studies have suggested the antiemetic effects of TPM remedies, their safety is not sufficiently documented in modern literature. Scientific studies on these medicinal plants during pregnancy are warranted to determine their safety.
[GMJ.2017;6(4):281-90] DOI: 10.22086/gmj.v0i0.809

Keywords: Nausea; Vomiting; Pregnancy; Traditional Medicine; Morning Sickness

Introduction

The prevalence of nausea is reported to be 50 - 80% and 50% for vomiting and retching during pregnancy [1]. Nausea and vomiting begin in the first trimester, at about 6-8 weeks’ gestation, peaking at about 9 weeks’ gestation and subsiding at about 12 weeks.

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Only a minority of women have symptoms after 20 weeks' gestation. Loss of working days, decreased quality of life, difficulty in child birth preparation, and decline in energy and fatigue are considerable stresses that women with nausea and vomiting of pregnancy (NVP) experience [2]. The pathophysiology is a combination of genetic, endocrine, gastrointestinal, environmental, and psychosocial factors. Although the exact causes of NVP are unknown, the level of human chorionic gonadotropin (hCG), placental prostaglandins, serotonin, estrogen and progesterone, size of the placental mass, thyroid dysfunction, increased leptin levels, immune system dysregulation, Helicobacter pylori infection, and gastrointestinal dysmotility may be involved [3]. The current anti-emetic drugs to control NVP can be classified as vitamins (B6, B1), anti-dopaminergic drugs, serotonin antagonists, antihistamines, anti-cholinergic drugs, promotility agents, and corticosteroids [4]. The side effects of current anti-emetic drugs have turned attention to the use of traditional medicines [5]. Some of these side effects include tardive dyskinesia with metoclopramide, headache, diarrhea, constipation, fatigue with ondansetron, sedation, and extrapyramidal symptoms with promethazine [3]. Traditional remedies are used by the people of a region for many years, indicating their efficacy and safety [6]. Traditional Persian Medicine (TPM), as one of the complementary/alternative medicine (CAM) methods, tries to offer simple and available recommendations for health maintenance and treatment of diseases in different groups of people (e.g., pregnant women). Medicinal plants are the most commonly used components of TPM medications [7]. Because of concerns related to the consumption of drugs in early pregnancy, natural remedies could be considered in this regard. The aim of the present study was to review the efficacy of medicinal herbs claimed to be effective in TPM for NVP.

Search strategies

This literature research was conducted to investigate some important Persian medical and pharmaceutical manuscripts from the ninth to the eighteenth century CE. Medicinal herbs used for the treatment of NVP were extracted from the most famous TPM books including the *Canon* (*al-Qanun fī al-Teb*) of *Avicenna* (*Ibn Sina*, 980-1032 AD)[8], *Zakhireye Kharazmshahi of Jorjani* (*Hussain ibn Muhammad ibn Mahmoud ibn Ahmad Hussaini Jorjani,* 1042–1137 AD)[9], *Tadbir-al-Habali al- Atfal al-Sabiban of Albaladi* (*Ahmad ibn muhammad Albaladi* 990 AD), and *Makhzan-al-Adviah of Aghili Khorasani* (*Mir Muhammad Hussain ibn Muhammad Hadi Aghili Khorasani* 1843 AD). The words ''*Ghessyan* (nausea), *Ghey* (vomiting), *Tahavo* (Retch) and *Taghalobe naphs* (permanent nausea), *Tadbir Al-Havamel* or *Al-Habali* or *Abestan* or *Bardari* (Pregnancy)'' were searched in traditional Persian books mentioned above. These books are specified as traditional Persian references in medicine and pharmacy and are now used as references for the Iranian PhD program in traditional medicine. Moreover, side effects of these herbal medicines and their safety in pregnancy were considered through a search in Physician's Desk Reference (PDR) [10] and Botanical Safety [11]. The scientific names of the reported herbal drugs were confirmed using textbooks such as Popular Medicinal Plants of Iran [12]. PubMed, Google Scholar, Iran medex, and SID (the last two are Iranian databases) were searched using all scientific names of plants separately from 1990 to 2016. The inclusion criteria of the selected articles were any clinical and animal evidence of the efficacy and safety on treatment of NVP. The publications without available full texts, case reports, and older studies (before 1990) were excluded from the study. The literature search revealed 829 articles, of which 798 were excluded due to irrelevance, being repetitive, and lack of eligibility (Figure-1). Then, 31 articles were included after retrieving their full texts and methods. Three CTs met our inclusion criteria; their key data are listed in Table-1. The search terms were "vomiting" or "nausea" or "emesis" or" anti-emetic" and "pregnancy" or "pregnant" in the title and abstract, and the scientific name, common name, and Persian and traditional names of the above-mentioned herbs in the whole text. The included clinical articles were reviewed to extract the scientific name of the

plant, medicinal part, study design, number of patients, and duration of treatment (Table-1).

Results

The medicinal herbs mentioned for the management of NVP in TPM and all evidence confirming their efficacy are described individually. *Citrus limon* (Lemon), *Citrus medica L.* (Citron), *Cydonia oblonga mill* (Quince), *Elletaria cardamomum* (Cardamom), *Mentha spicata L.* (Spearmint), *Mentha piperta L.* (Mint), *Myristica fragrans Houtt* (Nutmeg), *Pistacia lentiscus Linn.* (Mastic), *Punica granatum L.* (Pomegranate), *Malus domestica Borkh* (Apple), and *Piper cubeba L* are the most commonly recommended medications for treatment of NVP (Table-1) [13-15]). There is evidence of efficacy for some of these medicinal plants (*Mentha Piperita L., Citrus limon, Elletaria cardamom*) in human studies [16-18] (Table-2).

1. Citrus limon (Lemon)

The lemon is a plant of the family Rutaceae [19]. It is known as "*Limoo*" and has been used as an efficacious remedy for NVP in TPM [20]. It is said to be cold and dry in nature. Lemon contains volatile oils, citric acid, flavonoids [10]. In a randomized clinical trial on 100 pregnant women, lemon essential oil and placebo were given to the intervention and control groups respectively to inhale as soon as they felt nausea, and the PUQE24 (24-hour Pregnancy Unique Quantification of Emesis) was used to assess them. The result was a statistically significant difference between the two groups in the mean score of the fourth day (P=0.017 and P=0.039, respectively) [16]. *Citrus Limon* could be administered as a supplement to enhance the efficacy of some antibacterial therapies (*anti H. pylori*) that are part of antiulcer treatment [19]. *Citrus limon* has been used as natural antiemetic [5]. No health hazards or side effects have been reported following the proper administration of designated therapeutic dosages [10].

2. Citrus medica L (Citron)

Citrus medica L is a plant of the family Rutaceae [21]. It is said to be cold and wet in nature [15]. *Citrus medica L*, known as "*Utroj*" in TPM, has been used for treatment of NVP [14, 20]. There is little information on the safety of *Citrus medica* fruit concentrated extract in pregnancy. To the best of our knowledge, no human studies have evaluated its effects on nausea.

Table 1. Clinical Studies On Plants Used for Treatment of NVP Mentioned in TPM

Scientific name	Medicinal part	number of patients,	Type of study	Treatment duration	Outcome
Citrus limon	Lemon essentials oil	100	Randomised, Double-blind clinical trial study	5 days	nausea and vomiting intensity
Elletaria Cardamomum	Cardamom powder	120	Randomised, double-blind clinical trial study	4 days	severity of NVP
***Mentha piperita* L**	Mint oil	67	Block-randomized method	18 days	severity of NVP
***Cydonia Oblonga* Mill**	Syrup of Cydonia oblonga (quince) fruit	60	Randomised, clinical trial study , not blinded	1 week	

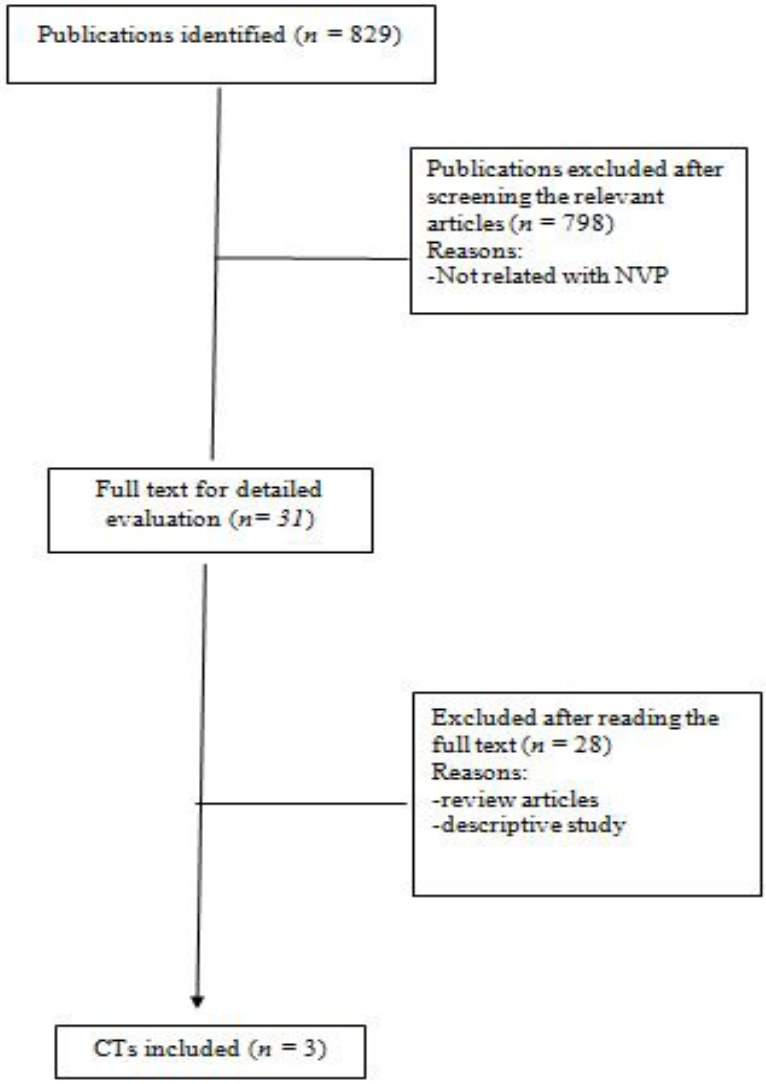

Figure 1- The process of including and excluding studies

3. Cydonia oblonga Mill (Quince)

The quince is a plant of the family Rosaceae [22]. *Cydonia oblonga*, known as "*Beh*", is another natural product used in TPM for treatment of NVP [14, 23, 13]. Persian physicians believed that roasted *Cydonia oblonga* Mill (Quince) was useful in treating nausea in pregnancy [20]. In addition, it protects the fetus from abortion and is used as an appetizer [15] . It is said to be wet and balanced in warm and cold in nature [15]. A clinical trial was carried out in Tehran, Iran on the effectiveness of *Cydonia oblonga* (quince) syrup for treatment of NVP. The results showed significantly decreased NVP in the group receiving quince syrup [24, 1]. No health risks or side effects are reported following the proper administration of designated therapeutic dosages [10].

4. Elletaria cardamom (Cardamom)

Cardamom is a member of the family Zingiberaceae [12]. Cardamom (*Elletaria cardamomum*), known as "*Hil*" or "*Hel*", has been used in TPM as a stomach tonic and for treatment of digestive complaints and NVP [20, 15]. It is said to be warm and dry in nature [15]. In a study by Pradier *et al*, a trial of a mixture of three essential oils (*Zingiber officinale, Elletaria cardamomum, and Artemisia dracunculus*) in the treatment of postopera-

tive nausea and vomiting showed that 75% of cases had a favorable outcome [25]. A double blind randomized clinical trial was performed on 120 pregnant women and capsules containing 500 mg cardamom powder and placebo were administered three times a day half an hour before meals. The PUQE24h was used to evaluate the outcome. The frequency and duration of nausea and the frequency of vomiting significantly decreased in the cardamom powder group (P<0.0001) [18]. A randomized trial of aromatherapy with patients who reported nausea in the post anesthesia care unit showed that the number of antiemetic medications requested was significantly reduced after aromatherapy with ginger or a blend of the essential oils of ginger, spearmint, peppermint, and cardamom versus saline [26].

5. Mentha spicata L (Spearmint) and Mentha piperta L (Mint)

Mint is a plant in the family Lamiaceae [12]. The leaves of mint known as "*Na, na*" have also been used as an effective drug in the treatment of NVP [14, 13, 23]. It is said to be warm and dry in nature [15]. In a double blind RCT, the effect of aromatherapy with pure mint essential oil versus placebo was evaluated in 60 pregnant women with NVP. For 4 consecutive nights, before sleep, a bowel of water containing 4 drops of pure mint essential oil was placed on the floor near the beds of subjects in the case group while 4 drops of normal saline was used in the control group. The Visual Analog Scale (VAS) was used for assessment. The result showed a decreasing trend (especially in 4th night) in the mint and an increasing trend in the control group. The severity of nausea within 7 days after the intervention had a decreasing trend in both groups; however, the intensity was lower in the mint than saline group but the difference was not significant (P=0.14) [17]. In a randomized double-blind clinical trial, 200 patients with chemotherapy-induced nausea and vomiting (CINV) were randomly assigned into four groups to receive *M. spicata* or *M. piperita*. The treatment and placebo groups received essential oils of *M. spicata, M.piperita*, or a placebo, while the control group continued with their previous antiemetic regimen. The patients received their normal antiemetic regimen plus spearmint and peppermint capsules (containing two drops of each essential oil and filled with sugar) every four hours. The capsules were administered 30 minutes before the patients received their chemotherapy treatment, again four hours after the first capsule and finally, four hours later at home. It was concluded that there was a significant reduction in the intensity and number of emetic events in the first 24 hours with *M. spicata* and *M. piperita* in both treatment groups (P< 0.05) when compared with the control group [10]. Due to the highly concentrated nature of peppermint leaf essential oil, until further safety data is available, internal use during pregnancy should only be under the supervision of a qualified healthcare practitioner [11]. No teratogenic effects of the compound menthol were observed in mice fed 190 mg/kg, rats fed 220 mg/kg, hamsters fed 400 mg/kg, or rabbits fed 430 mg/kg [11].

6. Myristica fragrans Houtt (Nutmeg)

Nutmeg is a plant of the family Myristicaceae [12]. Nutmeg (*myristica fragrans*), known as "*joze bavva*", has been used in TPM as a digester, stomach tonic, and antiemetic [15] and for the treatment of NVP [20]. Nutmeg has been used as a carminative, antiemetic, spasmolytic, and anti-inflammatory agent. Moreover, nutmeg has been used for flatulence, diarrhea, nausea, and vomiting [27]. The activities of *Myristica fragrans* Houtt. seed on H. pylori - induced gastritis in albino rats have been proved [28]. Nutmeg has been used by many women to induce menstruation or abortion, although the literature suggests that nutmeg is not efficacious as an abortifacient [11]. An increase in maternal and fetal heart rate was observed in a pregnant woman who consumed cookies containing an excessive amount of nutmeg. The baby was delivered healthy at term [11]. Animal studies have provided conflicting results, with no adverse effects of the essential oil at doses up to 400 mg/kg in rabbits but some abnormalities in rats who administered 300 mg/kg of nutmeg [11]. An animal study indicated that after giving of mace to lactating mice, physiological effects were observed on both mothers and

nursing offspring. Thus, its use is not recommended during pregnancy except under the supervision of a qualified healthcare practitioner [11]. No health hazards or side effects are reported following the proper administration of designated therapeutic dosages [10]. To the best of our knowledge, no human studies have evaluated its effects on nausea yet.

7. Pistacia lentiscus Linn. (Mastic)

Oleogum resin of Pistacia lentiscus (*P. lentiscus*) known as "*Mastaki*" is an efficacious remedy for the treatment of NVP in TPM [14, 20]. It is a resin obtained from the mastic tree, a plant of the family Anacardiaceeae[12] . The medicinal part is the resin. Resins and volatile oils are the components of the mastic tree [10]. In TPM, It is said to be hot and dry in nature [15]. According to the Persian literature, *Pistacia lentiscus* Linn. relieves gastric inflammation, increases appetite, and is a carminative [29, 15]. Mastic gum is effective in eradication of *H. pylori* infection both *in vitro* and in vivo [30]. No health hazards or side effects are known to the proper administration of designated therapeutic dosages [10]. We found no human studies evaluating its effects on NVP.

8. Punica granatum L. (Pomegranate)

The omegranate is a plant of the family Lythraceae [31]. *Punica granatum L.* is known as"*Anar*" [15]. It is said to be cold and wet in nature. One way to treat NVP in TPM is keeping pomegranate seeds and mint in the mouth [23, 13]. One clinical trial evaluated the effects of pomegranate and spearmint syrup on NVP [32]. In TPM, pomegranate sauce is used to alleviate nausea [15]. A small number of studies have reported that pomegranate can treat H. pylori infection [33]. No health hazards are reported following the proper administration of designated therapeutic dosages [10].

9. Malus domestica Borkh (Apple)

The apple is a plant of the family Rosaceae. It is known as "*Tofah*" in TPM [15]. The apple has been used in TPM as an appetizer, stomach tonic, and antiemetic, and also for the treatment of NVP [14]. No human studies have evaluated its effects on NVP.

10. Piper cubeba L. (Cubeb)

Piper cubeba L. (PICL), a plant in the family Piperaceae, is a carminative, stomach tonic, and antiseptic [34]. *Piper cubeba L.*, known as "*kobabeh*", is another natural product used in TPM for NVP [20]. It is said to be warm and dry in nature [15]. The constituents of this fruit (alkaloids, glycosides, tannins, and flavonoids) are known to possess potent antioxidant activities and can be used as natural antioxidants [35]. There is no information on the safety of cubeb during pregnancy [11]. No health hazards or side effects have been reported following the proper administration of therapeutic dosage [10]. No human studies have evaluated its effects on NVP.

Discussion

The etiology of NVP in TPM can be due to effusion and accumulation of inappropriate substances in the stomach and stomach weakness is one of the factors of this etiology. Treatment consists of removing inappropriate substances from the stomach and decreasing their production as well as stomach strengthening [36]. Masters of TPM have always paid attention to the role of nutrition in preventing and treating diseases. For treating nausea in pregnancy, it is recommended to eat food that are light and easy to digest, apply lifestyle modifications, and use some medicinal plants and their preparations [37]. Astringent (*Ghabiz*) agents, which have the ability to tan the stomach and preserve its tonicity, are one of the treatments for stomach weakness [38]. *Punica granatum L*. (pomegranate), *Cydonia oblonga mill* (quince), and *Pistacia lentiscus Linn*. (mastic) are examples of astringent medicines that have been repeatedly mentioned in TPM resources for their effect on stomach tanning [15]. Fragmenting (*Moghattia*), stubbing (*Mohallil*), and tendering (*Mollatif*) agents are necessary for removing soft waste materials around the stomach villi [38] and are found in medicinal plants such as *Citrus limon* (lemon), *Mentha spicata L*.(spearmint), and *Mentha piperta L*. (mint)[15]. Removing excess humidity and gas from the

stomach with some herbal drugs such as *Mentha spicata L*. (spearmint), and *Mentha piperta L.* (mint) strengthens the stomach. [38, 15].

Sour (*Hamiz*) products such as *Citrus limon* (lemon) are good appetizers in TPM resources that are used to remove thick humors from the stomach, strengthen the stomach, and prevent vomiting [38]. Some euphoric (*Mofarrih*) agents such as *Malus domestica* Borkh (apple) and *Elletaria cardamomum* (cardamom) can strengthen the whole body including the stomach because of their good smell [15, 38]. Although the safety and the mechanism of action of herbal products have always been a matter of concern, attention has been paid to traditional medical systems and herbal medicines because of their few side effects and increasing failure of current drugs [39, 40]. In this study, 10 medicinal plants belonging to 8 families used as antiemetic drugs for NVP in TPM were evaluated. These medicinal plants were assessed from the perspective of traditional and herbal medicine and new studies in this field were reviewed. The main limitation of this study is the lack of relevant studies in databases. There were only four studies on pregnant women that reported the safety of *Mentha piperita L* (mint), *Citrus limon* (lemon), *Elletaria cardamom* (cardamom), and *Cydonia oblonga mill* (quince). Long-term use of traditional medicines may indicate their efficacy, but it is recommended to conduct scientific studies to confirndnm their efficacy and safety [6]. Scientific studies on these medicinal plants during pregnancy are required to determine their safety.

Conclusion

Iranian philosophers and scientists have taken rational steps based on the observations. They believed that three basic steps, i.e. lifestyle modification, nutrition and medicinal herbs, had great effects on NVP treatment. Therefore, this study can provide valuable information on the clinical use of herbal medicines in NVP and prepares the ground to investigate their potential medicinal use.

Acknowledgements

This research is part of the ongoing PhD thesis of Dr. Shahrbanoo Abdolhosseini at the School of Traditional Medicine, Kerman University of Medical Sciences.

Conflict of Interest

We declare that we have no conflict of interest.

Table 2. Medicinal Plants Used for Treatment of NVP Mentioned in TPM

Scientific name	Family	TPM name
Citrus limon	Rutaceae	*Limoo*
Citrus medica L.	Rutaceae	*Utroj*
Cydonia oblonga Mill	Rosaceae	*Beh, Safarjal*
Ellataria cardamomum	Zingiberaceae	*Hil*
Mentha piperita, M spicata L.	Lamiaceae	*Na na*
Myristica fragrans Houtt	Myristicaceae	*Jose bavva*
Piper cubeba L.	Piperaceae.	*Kobabeh*
Pistacia lentiscus L.	Anacardiaceae	*Mastaki*
Punica granatum L.	Lythraceae	*Anar*
Malus domestica Borkh	Rosaceae	*Tofah*

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