



Evaluation of the Effect of *Rosa damascena* Mill. Product on Constipation During Pregnancy: A Single-Arm Clinical Trial

Nafiseh Nili¹, Shahrzad Hadavand², Fatemeh Emadi³, Mohammad Gholami-Fesharaki⁴, Elham Emaratkar^{3*}

Abstract

Objectives: Constipation is one of the most common issues at the time of pregnancy. Traditional Persian medicine (TPM) has always emphasized the use of safe laxatives to relieve constipation during pregnancy. The present study aimed to investigate the effect of *Rosa damascena* Mill. products on constipation and the quality of life during pregnancy.

Materials and Methods: This is a single-arm clinical trial study on 35 pregnant women (14-34 weeks) with constipation diagnosed on the basis of Rome IV criteria in Tehran and Qom, Iran during 2018-2019. The consumption of *R. damascena* products was recommended daily for 4 weeks. Then, the severity of constipation and the quality of life were assessed via the Rome IV criteria and the World Health Organization (WHO) quality of life questionnaires (WHOQOL-BREF), respectively.

Results: This study was performed on 35 pregnant women (14-34 weeks). The consumption of *R. damascena* products decreased the score of Rome IV criteria (Mean 9.4 to 1.1) while increasing the frequency of bowel movements and improving the overall quality of life ($P < 0.001$). The predominant constipation signs, including straining, lumpy and hard stools, a sensation of incomplete evacuation, a sensation of anorectal obstruction, manual facilitation maneuvers, and less than 3 spontaneous bowel movements per week significantly improved after the consumption of *R. damascena* products ($P < 0.001$).

Conclusions: *Rosa damascena* products can effectively treat constipation and enhance the quality of life.

Keywords: Constipation, Pregnancy, *Rosa damascena* products, Traditional medicine, Persian medicine

Introduction

Pregnancy is one of the most sensitive physiological and emotional phases in women's life (1) during which they may suffer from several complications including constipation (2). It is reported that approximately 11%-38% of women experience constipation as a decrease in bowel movements and difficult evacuation. It is more common in women with a history of pre-pregnancy constipation and multiparous (3,4). Physiological and anatomical changes during pregnancy include elevated progesterone levels in the second and third trimesters, reduced motilin, decreased muscle tone, increased bowel movement period, and increased intake of intestinal water and drying of stools that lead to constipation (2,4,5). Constipation during pregnancy, which is evaluated via Rome IV criteria (3,6,7), is managed with the first line of treatments such as physical activity, increased fluid intake, dietary fiber volume, fruits and vegetables, and probiotic intake. Laxatives are considered as second-line treatment (6,8). The lack of peripheral absorption and no risk of fetal malformations make the short-term use of some laxatives safe with various side effects that may restrict

their consumption (3,4,6).

Due to the prevalence of constipation through pregnancy and the side effects of current treatments, it is necessary to investigate safe and healthy therapies. Over the past two decades, complementary and alternative medicines have been significantly employed worldwide (9). According to reports from the World Health Organization (WHO), almost 80% of the world's population is using traditional herbal medicine to diagnose, prevent, and treat diseases (10). Common pregnancy issues such as constipation are one of the main reasons for using herbal remedies (11).

From the perspective of traditional Persian medicine (TPM), as a complementary medicine, the use of safe laxatives has been emphasized for alleviating pregnancy constipation since it has an effective role in reducing the other complications of pregnancy. *Rosa damascena* Mill. (Rosaceae family) also known as *Damask Rose* (12,13), is one of the safest laxatives prescribed for constipation during pregnancy in TPM literature and has been introduced as an effective medicinal plant in strengthening and maintaining the fetus (3,14,15). *Damask Rose* has numerous pharmacological effects (12,16), and no report

Received 13 September 2019, Accepted 30 December 2019, Available online 11 February 2020

¹Department of Traditional Medicine, School of Medicine, Shahed University, Tehran, Iran. ²Department of Obstetrics and Gynecology, Mustafa Khomeini Hospital, School of Medicine, Shahed University Tehran, Iran. ³Traditional Medicine Clinical Trial Research Center, Shahed University, Tehran, Iran, Department of Traditional Medicine, School of Medicine, Shahed University, Tehran, Iran. ⁴Department of Biostatistics, Faculty of Medicine, Tarbiat Modares University, Tehran, Iran.

*Corresponding Author: Elham Emaratkar, Tel: +989122511026, Email: E.EMARATKAR@gmail.com



Key Messages

- ▶ Constipation is a common complication during pregnancy.
- ▶ *Rosa damascena* products can effectively treat the constipation during pregnancy.
- ▶ It is mentioned and experienced in TPM as an effective and safe laxative in pregnancy.

exists regarding the adverse effects of therapeutic doses (17,18).

The laxative and stimulating effect of *R. damascena* on the intestines in recent in vivo studies (19-21), the omission of the side effects in routine consumption (3), convenient access and maintenance of this herb, and popular acceptance are important reasons behind the selection of *R. damascena* products. This research is important as, to the best of our knowledge, it is the first clinical trial to determine the impact of *R. damascena* products on constipation during pregnancy.

Materials and Methods

This study was a single-arm clinical trial to investigate the effect of *R. damascena* products on pregnancy constipation in Tehran and Qom during 2018-2019. The study comprised 35 pregnant women suffering from constipation referring to gynecologists in Tehran and Qom, Iran.

Having qualified based on the inclusion criteria, the participants of this study were visited in person. After providing the necessary explanations by the practitioner, the written informed consent form was obtained from the patients. In this study, the severity of constipation was assessed via the Rome IV criteria at three time points before entering the study and after the second and fourth weeks, and quality of life was assessed using the WHO quality of life questionnaire (WHOQOL-BREF) at two times, namely, before entering the study and after the fourth week. The variables of Rome IV (7) and WHOQOL-BREF questionnaire (22) were considered as the primary outcome. The constipation questionnaire was designed based on the ROME IV criteria (7), including 6 sections of straining, lumpy or hard stools, a sensation of incomplete evacuation, a sensation of anorectal obstruction, manual facilitation maneuvers, and fewer than 3 spontaneous bowel movements per week. The baseline information questionnaire including week and number of pregnancies, previous delivery, supplementation, and the like were initially completed for each patient.

The inclusion criteria were healthy pregnant women with constipation based on Rome IV criteria (7), being over 18 years and under 45 years old, presenting informed patient consent to participate in the study, being in their 14-34 weeks of pregnancy, consuming no medication to relieve constipation, and having no history of anorectal disease. On the other hand, patients were excluded from

the study in case of unwillingness to cooperate, drug sensitivity, pregnancy and midwifery problems (i.e., leaking amniotic fluid, preterm labor, placental abruption, and preeclampsia), the incidence of anorectal disease, and the use of other medications during the treatment.

Initially, 120 pregnant women were assessed for inclusion criteria, 48 of whom were enrolled in the study, and 35 of them completed the treatment to the end of the study (Figure 1).

According to Figure 1, 13 patients could not finish the treatment for different reasons including constipation treatment without medication (4 patients), personal issues (2 patients), ineffectiveness (2 patients), nausea (2 patients), flatulence (2 patients), and diarrhea and vomiting (1 patient). After selecting a group of 35 individuals, participants were asked to consume the *R. damascena* products based on equal instructions. In this study, *R. damascena* products were dissolved in 25 mL rose water and daily consumed by the patients half an hour after breakfast for 4 weeks. Due to the intestinal motility and bowel movements, patients were allowed to reduce their dose. There was no intervention in the lifestyle and diet. Patients were also asked to record and report to the researchers if they found any side effects of the drug.

Preparation of Medicine

First, *R. damascena* flowers were purchased from Kashan. The sample was authenticated at the herbarium of the Faculty of Pharmacy, Tehran University of Medical Sciences. The petals were separated, dried, and powdered, and 750 mg of the mentioned powdered was packaged with 1250 mg white rock candy. Then, 30 minutes after breakfast, the item was consumed with 25 cc of rose water.

Total Phenolic and Flavonoid Content Assay

The concentration of the phenolics content in the hydroalcoholic extract of the *R. damascena* preparation was determined via the spectrophotometric method and the Folin-Ciocalteu's reagent, NaHCO₃ solution, and gallic acid as the standard (23,24). Then, the content of phenolics in the extracts was expressed in terms of gallic acid equivalent (mg of GA/g of extract). Further, the spectrophotometry method via AlCl₃ solution and the catechin standard was conducted for the flavonoid content (24, 25). The content of flavonoids in the extracts was expressed in terms of the catechin equivalent (mg of CAT/g of the extract).

Statistical Analysis

In this study, the descriptive statistics (i.e., mean, standard deviation, correlation, frequency, and ratio) and inferential statistics (i.e., paired t-test, repeated measure design, Friedman test, and Wilcoxon test) were used to determine whether or not the response variable was normal via the Kolmogorov-Smirnov test. Data were analyzed using SPSS, version 21. A *P* value of less than 0.05 was considered

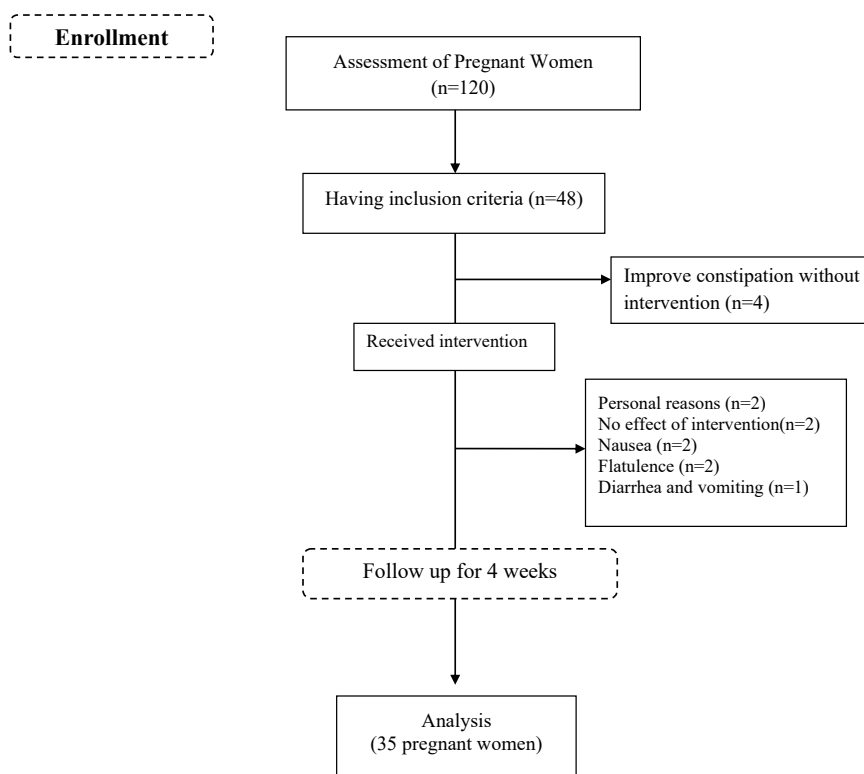


Figure 1. Follow up diagram.

statistically significant. In this study, the sample size was estimated as 30 individuals considering $\alpha = 0.05$, $\beta = 0.1$, and $d = 1$ and using the formula $n = 2 (Z_{\alpha/2} Z_{\beta})^2 / d^2$. Given the sample loss of 20%, 35 samples were considered in this study (26).

Results

Drug Analysis

Total phenols and flavonoid contents for *R. damascena* products were determined as follows 168 ± 15.9 mg gallic acid equivalent/g and 30.2 ± 3 mg catechin equivalent/g, respectively.

Treatment

In this study, 48 pregnant women with constipation were enrolled, 13 of whom did not remain until the end of the intervention (Figure 1). Table 1 presents demographic characteristics of the participants by age, education, number of pregnancies and previous deliveries, and a history of constipation and supplement use. Based on the information, most participants having a college education were housewives and experienced their first pregnancy. A history of constipation before pregnancy was reported in 69% of cases. The mean age of pregnant mothers was 27.6 years and their mean gestational age was 19.07 weeks.

Table 2 presents the mean and standard deviation (SD) of the total score of the Rome IV questionnaire with questions 1-6 and the frequency of bowel movements

before the intervention and 2 and 4 weeks after the intervention. Based on the reported information, *R. damascena* products decreased the Rome IV criteria score while increased the number of the frequency of bowel movements. On average, 2 weeks after the last dose of *R. damascena* products, patients required no more laxatives (mean = 14.08, SD= 9.78).

Furthermore, based on the obtained data, using the *R. damascena* product significantly reduced the straining, lumpy or hard stools, a sensation of incomplete evacuation, a sensation of anorectal obstruction, and manual maneuvers to facilitate while significantly increasing the frequency of spontaneous bowel movements per week.

Table 3 provides the mean and SD of the quality of life score and its subscales before and 4 weeks after the intervention. Based on the obtained information, *R. damascena* products significantly affected the total score of the quality of life and the three subscales of the quality of life, namely, physical, mental, and environmental health.

Discussion

The prevalence of functional constipation in pregnant women is greater compared to the general population as a common medical issue (1). Similar to rising chronic diseases including osteoarthritis, rheumatoid arthritis, diabetes, and chronic allergies, constipation significantly affects the quality of life (27).

To the best of our knowledge, this is the first clinical

Table 1. Frequency Distribution and Percentage of Variables in Study Participants

Discrete variables		Number	Percent
Previous delivery	Gravid ones	19	54.3
	Natural childbirth	11	31.4
	Cesarean section	5	14.3
Education	Undergraduate	2	5.7
	Diploma	14	40.0
	Master	15	42.9
	Bachelor	4	11.4
Job	Housewife	28	80.0
	Employed	7	20.0
Constipation before pregnancy	Yes	24	68.57
Iron intake	Yes	16	45.71
Acid folic intake	Yes	24	68.57
Calcium intake	Yes	2	5.71
Multivitamin intake	Yes	10	28.57
Vitamin D intake	Yes	21	60.00
Continuous variable		Mean	SD
Age of participants	Year	27.6	5.0
Pregnancy age	Week	19.07	5.95
Number of Pregnancy	Number	2.1	1.3

trial to investigate the effect of *R. damascena* products on pregnancy constipation. The results showed that *R. damascena* products could significantly treat constipation based on Rome IV criteria ($P < 0.001$) by increasing the frequency of bowel movements ($P < 0.001$). The main symptoms of constipation, including the straining, lumpy or hard stools, sensation of incomplete evacuation, sensation of anorectal obstruction, manual maneuvers to facilitate, and spontaneous bowel movements per week were significantly treated after the consumption of *R. damascena* products ($P < 0.001$).

In a retrospective clinical trial, the efficacy and safety of polyherbal laxative Laxisen, including *Rosa damascena*, *Cassia senna*, *Ficus hispida*, *Vitis vinifera*, *Terminalia chebula*, *Operculina terpepethum*, and *Convolvulus scammonia* were investigated on 35 patients. For the acute constipation of 2 weeks and the chronic constipation of 6

weeks, this laxative significantly increased the frequency of bowel movements in patients. Statistically, it improved straining, difficulty during defecation, and the sensation of incomplete evacuation. No side effects were observed in patients and all patients had a laxative period of up to 7 days after the last visit. The results of this study verified the safety and efficacy of Laxisen in the treatment of constipation (28).

As a laxative, *R. damascena* products had the same effect as Laxisen. However, Laxisen is never recommended because of its harmful ingredients in pregnancy (18). *R. damascena* products are safe and effective during pregnancy (14, 15). On average, patients did not need other laxatives within 2 weeks after using *R. damascena* products.

The results of a clinical trial of 60 pregnant women with constipation based on Rome III criteria demonstrated that the consumption of probiotic yogurt is more effective than normal yogurt in increasing the frequency of bowel movements. The symptoms of constipation (e.g., straining, a sensation of anorectal obstruction, and the use of facilitation maneuvers) were significantly improved in both groups. Conversely, the sensation of incomplete evacuation significantly decreased with probiotic intake. However, the mental and physical quality of life did not differ significantly between the two groups (29).

In addition to revealing constipation, the consumption of *R. damascena* products had a significant effect on the quality of life. The quality of life score increased significantly after 4 weeks under the scales of physical, mental, and environmental health. There was no significant change in social health, but the consumption of *R. damascene* products has a significant effect on the overall quality of life.

Rosa damascena can help treat constipation and have positive effects on the quality of life in light of TPM. Accordingly, it can strengthen and protect the fetus (14,15), an observation which definitely requires more investigations.

A variety of studies have shown the laxative effect of *R. damascena* and its stimulatory effect on bowel

Table 2. Mean and Standard Deviation of the Scores of Criteria 1 to 6 of the ROME IV Questionnaire Before, 2 and 4 Weeks After the Intervention

The Scores of Criteria 1 to 6 of the ROME IV Questionnaire	Before Intervention		2 Weeks After Intervention		4 Weeks After Intervention		P Value
	Mean	SD	Mean	SD	Mean	SD	
Straining (range 0-4)	1.86	1.17	0.17	0.38	0.31	0.53	<0.001
Lumpy or hard stools (range 0-4)	1.83	1.10	0.11	0.32	0.17	0.38	<0.001
Sensation of incomplete evacuation (range 0-4)	1.91	1.15	0.31	0.47	0.31	0.53	<0.001
Sensation of anorectal obstruction (range 0-4)	1.46	1.22	0.11	0.32	0.23	0.49	<0.001
Manual Maneuvers to facilitate (range 0-4)	0.94	1.19	0.06	0.24	0.06	0.24	<0.001
Fewer than 3 spontaneous bowel movements per week (range 0-4)	1.43	1.69	0.00	0.00	0.03	0.17	<0.001
Criteria ROME IV overall score (range 0-24)	9.4	4.8	0.8	0.9	1.1	1.3	<0.001
Frequency of bowel movements within a week	3.7	2.5	8.0	2.9	8.4	3.1	<0.001

Table 3. Mean and Standard Deviation of Quality of Life Score and its Subscales Before and 4 Weeks After Intervention

Quality of life score	Before Intervention		4 Weeks After Intervention		Difference	P Value
	Mean	SD	Mean	SD		
Physical health (range 7-35)	22.6	4.0	24.3	3.8	1.7	0.014
Psychological health (range 6-30)	19.7	3.6	20.9	2.5	1.2	0.021
Social relationships (range 3-15)	11.0	2.1	10.9	2.0	-0.1	0.727
Environmental health (range 8-40)	28.9	3.9	30.0	3.7	1.1	0.004
Total quality of life score	89.66	11.02	94.09	9.74	4.43	0.008

movements. Two studies investigated the laxative and stimulatory effects of *R. damascena* in rats. According to the results of one study, *R. damascena* significantly increased the amount of stool water and its frequency. It also significantly increased the volume of jejunal content compared to placebo. According to this study, by the mechanism of osmotic infiltration into the intestines, *R. damascena* functions as a laxative (20). *R. damascena* extracts had a dose-dependent stimulating effect on the ileum smooth muscle in rats. For constipation treatment, *R. damascena* electrolyte secretion and gastrointestinal smooth muscle contractions may be effective (30).

These laxative and stimulating effects have also been verified by other studies on guinea pigs, rabbits, and dogs. Affecting acetylcholine receptors and ileum contractions in guinea pigs, *R. damascena* can be considered as a mild laxative (31). Moreover, in the rabbit jejunum and guinea pigs ileum, it significantly increased the range of basal contractions which can be used to treat gastrointestinal movement dysfunctions (19). *R. damascena* is a dose-dependent laxative in dogs, thus causing diarrhea at 90 mg/kg low doses. During the intervention, there are no side effects, its laxative effect has been successfully performed, and it can also have a therapeutic value (21). No significant adverse events were observed in our study during the use of *R. damascena* products except for mild nausea, mild flatulence, and mild diarrhea in limited cases that did not disturb patient ingestion.

The use of herbal medicine during pregnancy has been varied across Europe, America, and Australia. In general, 7%-45% of pregnancy and constipation during pregnancy are treated by herbal remedies (11, 32) because herbs are believed to be safe medication for the fetus although there is insufficient evidence of the safety of herbal products during pregnancy (10). Given the changing the US Food and Drug Administration (FDA) approach in 2015 and replacing oral reports on the safety of medicines and products during pregnancy with the conventional classification, reports on plant and drug safety in Traditional Medicine sources are more valuable (3). It is recommended that clinical studies be designed on the basis of these sources since healthcare providers must advise pregnant mothers.

Further studies on the safety and efficacy of *R. damascena* products in pregnancy are recommended because of the numerous pharmacological effects of *R. damascena*

products. It can be used to relieve other problems of pregnant women by proving the safety of this product in pregnancy. Clinical trials can also be performed to design other drug forms of this product which are easier to use.

Limitations of the Study

The present study contained a number of limitations, including the sensitivity of pregnant mothers and their concerns toward participating in the research project on the consumption of *R. damascena* products and the restricted use of *R. damascena* products in pregnant women under 14 weeks due to common problems during this period such as nausea and vomiting. Finally, the other limitation included difficulties with the follow-up of participants during the intervention due to the specific conditions of pregnant mothers.

Conclusions

According to the results, *R. damascena* products are therapeutically effective for the improvement of constipation in the pregnant women and accordingly improving their quality of life. Having no side effects in therapeutic doses, it can be recommended to help pregnant women with their constipation problems since it is mentioned and experienced in TPM as an effective and safe laxative in pregnancy.

Authors' Contribution

Study design and article preparation: All authors, intervention and data collection: NN, statistical analysis: M.GF. All authors read and approved the final format of manuscript.

Conflict of Interests

Authors declare that they have no conflict of interests.

Ethical Issues

This study was approved by the Medical Ethics Committee of Shahed University in 2018 and coded as IR.SHAHED.REC.1397.038. It was also registered and approved at the Iranian Clinical Trial Registration Center with the code of IRCT20190427043388N1.

Financial Support

This article was supported with the financial support of Shahed University, School of Medicine.

References

- Shi W, Xu X, Zhang Y, Guo S, Wang J, Wang J. Epidemiology and risk factors of functional constipation in pregnant women. *PLoS One*. 2015;10(7):e0133521. doi:10.1371/journal.pone.0133521
- Casanova R. Beckmann and Ling's Obstetrics and Gynecology. Lippincott Williams & Wilkins; 2018.

3. Zareian MA, Nejatbakhsh F, Tabarrai Arani M. Importance and methods of treating pregnancy constipation in conventional medicine and comparison with traditional medicine. *Iran J Obstet Gynecol Infertil.* 2017;19(40):19-32. doi:10.22038/ijogi.2017.8444
4. Trottier M, Erebara A, Bozzo P. Treating constipation during pregnancy. *Can Fam Physician.* 2012;58(8):836-838.
5. Burkman RT, Berek & Novak's gynecology. *JAMA.* 2012;308(5):516-517. doi:10.1001/jama.308.5.516
6. Rungsiprakarn P, Laopaiboon M, Sangkomkarn US, Lumbiganon P, Pratt JJ. Interventions for treating constipation in pregnancy. *Cochrane Database Syst Rev.* 2015(9):CD011448. doi:10.1002/14651858.CD011448.pub2
7. Sood R, Ford AC. Diagnosis: Rome IV criteria for FGIDs--an improvement or more of the same? *Nat Rev Gastroenterol Hepatol.* 2016;13(9):501-502. doi:10.1038/nrgastro.2016.110
8. Zahoor S, Babar ME, Javed MM, Hussain T. Constipation in pregnancy: causes and remedies. *Prog Nutr.* 2018;20(1 Suppl):305-311. doi:10.23751/pn.v20i1-S.5788
9. Schunder-Tatzber S. European Information Center for Complementary and Alternative Medicine (EICCAM) gestartet. *Schweiz Z Ganzheitsmed.* 2010;22:90. doi:10.1159/000310540
10. John LJ, Shantakumari N. Herbal medicines use during pregnancy: a review from the Middle East. *Oman Med J.* 2015;30(4):229-236. doi:10.5001/omj.2015.48
11. Kennedy DA, Lupattelli A, Koren G, Nordeng H. Herbal medicine use in pregnancy: results of a multinational study. *BMC Complement Altern Med.* 2013;13:355. doi:10.1186/1472-6882-13-355
12. Nayebi N, Khalili N, Kamalinejad M, Emtiaz M. A systematic review of the efficacy and safety of *Rosa damascena* Mill. with an overview on its phytopharmacological properties. *Complement Ther Med.* 2017;34:129-140. doi:10.1016/j.ctim.2017.08.014
13. Amin G. The Most Common Traditional Medicinal Plants of Iran. Tehran: Tehran University of Medical Sciences; 2005:184. [Persian].
14. Aghili M. Kholase al-hekmah. Qom: Esmailian; 2006:933.
15. Arzani MA. Mofarreh al-gholob. Tehran, Iran: Almaee. 2012:356.
16. Mahboubi M. *Rosa damascena* as holy ancient herb with novel applications. *J Tradit Complement Med.* 2016;6(1):10-16. doi:10.1016/j.jtcm.2015.09.005
17. Hashem Dabaghian F, Taghavi Shirazi M, Amini Behbahani F, Shojae A. Interventions of Iranian traditional medicine for constipation during pregnancy. *J Med Plants.* 2015;14(53):58-68.
18. Gruenwald J, Brendler T, Jaenicke C. PDR for Herbal Medicines. Thomson, Reuters; 2007.
19. Heshmati Moghaddam MR, Dolati K, Rakhshandeh H. Cholinergic and histaminergic effects of the aqueous fraction of *Rosa damascena* extract in guinea pig ileum and rabbit jejunum. *Asian J Biol Sci.* 2013;6(1):67-75. doi:10.3923/ajbs.2013.67.75
20. Arezoomandan R, Kazerani HR, Behnam-Rasooli M. The laxative and prokinetic effects of *Rosa damascena* Mill in rats. *Iran J Basic Med Sci.* 2011;14(1):9-16. doi:10.22038/ijbms.2011.4948
21. Abbaszadeh M, Kazerani HR, Kamrani A. Laxative effects of *Rosa damascena* Mill in dogs. *J Appl Anim Res.* 2010;38(1):89-92. doi:10.1080/09712119.2010.9707162
22. Krzepota J, Sadowska D, Biernat E. Relationships between physical activity and quality of life in pregnant women in the second and third trimester. *Int J Environ Res Public Health.* 2018;15(12). doi:10.3390/ijerph15122745
23. Marinova D, Ribarova F, Atanassova M. Total phenolics and flavonoids in Bulgarian fruits and vegetables. *J Univ Chem Technol Metall.* 2005;40(3):255-260.
24. Hajjheydari MR, Yarmohammadi ME, Izadi P, et al. Effect of *Nepeta bracteata* Benth. on allergic rhinitis symptoms: a randomized double-blind clinical trial. *J Res Med Sci.* 2017;22:128. doi:10.4103/jrms.JRMS_316_17
25. Beketov EV, Pakhomov VP, Nesterova OV. Improved method of flavonoid extraction from bird cherry fruits. *Pharm Chem J.* 2005;39(6):316-318. doi:10.1007/s11094-005-0143-7
26. Skubisz MM, Tong S, Doust A, et al. Gefitinib and methotrexate to treat ectopic pregnancies with a pre-treatment serum hCG 1000-10,000 IU/L: Phase II open label, single arm multi-centre trial. *EBioMedicine.* 2018;33:276-281. doi:10.1016/j.ebiom.2018.06.017
27. Belsey J, Greenfield S, Candy D, Geraint M. Systematic review: impact of constipation on quality of life in adults and children. *Aliment Pharmacol Ther.* 2010;31(9):938-949. doi:10.1111/j.1365-2036.2010.04273.x
28. Sheikh ZA, Khan AA, Nawaz A, Zahoor A, Khan SS, Usmanghani K. Development and clinical evaluation of polyherbal laxative laxisen. *J Pharm Pharm Sci.* 2014;2(2):63-70.
29. Mirghafourvand M, Homayouni Rad A, Mohammad Alizadeh Charandabi S, Fardiazar Z, Shokri K. The effect of probiotic yogurt on constipation in pregnant women: a randomized controlled clinical trial. *Iran Red Crescent Med J.* 2016;18(11):e39870. doi:10.5812/ircmj.39870
30. Sadraei H, Asghari G, Emami S. Effect of *Rosa damascena* Mill. flower extract on rat ileum. *Res Pharm Sci.* 2013;8(4):277-284.
31. Dolati K, Rakhshandeh H, Shafei MN. Effect of aqueous fraction of *Rosa damascena* on ileum contractile response of guinea pigs. *Avicenna J Phytomed.* 2013;3(3):248-253.
32. Cuzzolin L, Francini-Pesenti F, Verlato G, Joppi M, Baldelli P, Benoni G. Use of herbal products among 392 Italian pregnant women: focus on pregnancy outcome. *Pharmacoepidemiol Drug Saf.* 2010;19(11):1151-1158. doi:10.1002/pds.2040

© 2021 The Author(s); This is an open-access article distributed under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/4.0>), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.