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Original Article

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Effect of *Rosa damascena* on the Severity of Depression and Anxiety in Postmenopausal Women: A Randomized, Double-blind, Placebo-controlled Clinical Trial

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Abstract

Background: Depression and anxiety as the most common psychological disorders reduce the quality of life in women during menopause.

Aim: Given the potential therapeutic properties of *Rosa damascena*, the present study aimed to investigate the effect of *Rosa damascena* on the severity of depression and anxiety in postmenopausal women.

Method: This clinical trial was conducted on 110 postmenopausal women in Tehran, Iran, during 2020. The participants in the intervention group received 500 mg dried *Rosa damascena* capsules, and the control group received placebo capsules three times a day (once every 8 hours) for 40 days. The data were collected using a demographic characteristics form, Beck's Depression Inventory, Spielberger's State-Trait Anxiety Inventory, and adverse effects questionnaire. Subsequently, the data were analyzed in SPSS software (version 19) through the independent t-test, chi-square, Mann-Whitney, and repeated measures tests.

Results: There was no difference in the mean score of depression before and 20 days after the intervention in the intervention group; however, this difference was significant 40 days after the intervention ($P<0.05$). The severity of anxiety differed significantly in the intervention group on days 20 and 40 post-intervention ($P<0.001$); however, these changes were not significant in the placebo group. The mean score of anxiety 20 and 40 days and depression 40 days after the intervention showed a significant difference between the two groups ($P<0.001$).

Implications for Practice: It seems that *R. damascena* has effects on postmenopausal depression and anxiety. Accordingly, menopausal women are recommended to use *R. damascena* as an efficient non-pharmacological intervention.

Keywords: Anxiety, Depression, Herbal medicine, Menopause, *Rosa damascena*

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Introduction

The transition from menstruation to menopause is a phenomenon that all women across the globe eventually go through (1). Menopause is the complete stop of menstrual periods because of the loss of ovarian activity (2). Although menopause is a natural and physiological phenomenon, the global trend of population aging, which results in a rise in the population of menopausal women, has turned women's health during the years surrounding menopause into a significant health issue (1). Menopause spans approximately one-third of a woman's life (3). Hormonal changes during menopause lead to physical and psychological complications (2, 4). Anxiety and depression, two common symptoms of menopause (5), are among the most important health issues worldwide (6), and as the most prevalent psychological disorders, they are associated with gynecologic complications that cause social, functional, and career disruptions (7).

Depression as a mental and psychological disorder is the most common psychological disorder in the world (8), affecting roughly one-fifth of women (9) with 21% and 12% prevalence in females and males, respectively (10). Women who are more exposed to hormonal fluctuations are more prone to depression. In menopause, these fluctuations will result in mood disturbances, thereby increasing the risk of major depressive disorder, such that the prevalence of depression is 15%-18% during menopause; however, this corresponding value is between 8% and 12% before it (11). Depression has recently been proposed as one of the most important health issues in postmenopausal women (12).

Women with postmenopausal depression have decreased estradiol and serotonin levels. These hormonal changes compromise the function of the nervous system. There is a positive correlation between the severity of menopausal symptoms and depression/anxiety (13). High levels of stress and anxiety exacerbate the symptoms of menopause. Undesirable life events, for instance, are correlated with more severe symptoms of menopause (14). The risk factors of depression symptoms during menopause include a history of depression, demographic characteristics (e.g., age, youth, race, and financial problems), psychosocial factors (e.g., undesirable life events and low social support), menopause symptoms (e.g., hot flashes, sleep disturbance, night sweats, sexual disorders, weight changes, and cognitive disorders), as well as anxiety and mood disorder symptoms associated with reproduction (e.g., postpartum or premenstrual depression symptoms) (15).

In light of the prevalence of the noted complications, numerous remedies are available for the treatment of menopausal anxiety and depression. Hormone therapy is an effective treatment for reducing menopausal vasomotor symptoms and additional adverse effects. Nonetheless, hormone therapy has been shown to potentially cause an increased risk of breast cancer, cardiovascular diseases, and pulmonary embolism (16, 17). A number of other medications, except for estrogen, have also been used for the treatment of menopausal depression and vasomotor symptoms (18). Antidepressants and other psychotherapies must remain at the frontline of menopausal depression treatment. The existing data on different Serotonin Selective Reuptake Inhibitors (including citalopram, desvenlafaxine, duloxetine, fluoxetine, sertraline, and venlafaxine) indicate an adequate efficacy and tolerance in normal doses (15). Benzodiazepines are currently regarded as the principal method for the treatment of anxiety, and they are accompanied by adverse effects, such as rash and headaches (19). Due to the adverse effects of medications and hormone therapy, herbal medicines and supplements are extremely important in the treatment and management of menopause symptoms and adverse effects (20). Some of these medicines have been studied in terms of the effects of their isoflavone content on a number of behavioral states and psychological symptoms. Isoflavones have a chemical structure similar to that of estrogens and are thus classified as phytoestrogens (12).

Damask rose with the scientific name *Rosa damascena* (*R. damascena*), a member of the *Rosaceae* family, is one of the most important plants in Iranian traditional medicine (21) with a wide variety of chemical compounds, including flavonoid, glycosides, citronellol, geraniol, terpenes, anthocyanins, citric acid, malic acid, pectin, and carotenoids, as well as vitamins A, B1, B2, B3, C, and K (22). *R. damascena* extract decreases sympathetic activity and reinforces the parasympathetic system. It is additionally an antioxidant, antibacterial, antimicrobial, sedative, anti-depressant, and antiemetic agent; moreover, it regulates the appetite and menstrual bleeding, removes skin blemishes, and treats dry and itchy skin, gallstone, hepatitis, asthma, coughs, sexual dysfunction, hypoactive sexual desire disorder, headaches, and insomnia (23-25). The antidepressant mechanism of *R.damascena* operates through the stimulation of β-adrenergic receptors, inhibition of histamine H1 receptors, blocking calcium channels of tracheal chain, inhibition of KCl-induced contractions, and electrical stimulation

(23), as well as dopaminergic, adrenergic, and serotonergic mechanisms (26).

Given that chemical medications have harms and side effects, other solutions have been always sought that have effects similar to these agents without side effects. If the effects of these plants are proven, they can be used as non-chemical drugs. Much research has been conducted on the effects of *R. damascena* in animal models (27, 28); however, more human research is required for the use of this plant. A number of studies have examined the effectiveness of *R. damascena* on depression in patients without side effects (29, 30); nonetheless, no studies have investigated the effect of this plant on depression and anxiety in postmenopausal women.

Due to the limited studies on the therapeutic effects of *R. damascena* and owing to the increasing demand for non-medicinal treatments, and since women spend a third of their lives in menopause, it is very important to pay attention to their health and care issues. Accordingly, this study aimed to investigate the effect of *R. damascena* capsules on depression and anxiety in women during menopause.

Methods

This randomized, double-blind, placebo-controlled clinical trial was conducted on 110 post-menopausal women for six months in Tehran, Iran, during 2020. The sample size was estimated at 50 participants in each group using the formula of "comparison of two independent population means"(31) with α=0.05 and 80% power considering the 1.12 unit difference in the mean scores of depression and standard deviation of 2 based on a study performed by Tadayon et al (32).

Considering a 10% sample attrition in different levels, 55 persons were included in each group. First, a list of health centers affiliated to Shahid Beheshti University of Medical Sciences, Tehran, Iran, which had the most clients was prepared, and then two centers were selected using a simple random sampling method. In total, 110 postmenopausal women who were referred to these centers and met the inclusion criteria were selected using the available sampling method. The participants were then divided into groups A or B using the random number function in Excel software.

R. damascena petals used in this research were obtained from Kashan farms in Iran, where the plant is widely cultivated. The plant was approved by one of the professors of the Pharmacognosy Department of the Faculty of Pharmacy, Shahid Beheshti University of Medical Sciences, Tehran, Iran. The flowers were dried in the shade and then turned into powder. Zero size empty capsules were purchased from "Gelatin Capsule Company, Iran" (registration number: 1156). The resulting powder in the laboratory of the Faculty of Pharmacy became 500 mg capsules. Placebo capsules (500 mg) were also prepared from dry bread powder in the same laboratory. The envelopes containing the *R. damascena* capsule and placebo were encoded by the pharmaceutical consultant (A&B). The researcher and participants did not know about these codes. Based on the group the participant was in, the envelope with the code related to that group was given to her. At the end of the research and after analyzing the data, the type of capsule in the envelopes was announced by the pharmacognosy consultant.

The objectives of the study were explained to the participants, and written consent was obtained from all of them. The inclusion criteria consisted of being a postmenstrual woman aged 45-60 years with no records or history of breast cancer, ovarian cancer, endometrial hyperplasia, abnormal vaginal bleeding, liver disease, hyperthyroidism, hysterectomy or oophorectomy, diabetes, known psychological diseases, allergy to spices and herbal medicines, smoking, drinking and using drugs, and consuming rose water or dried *R. damascena* extract. On the other hand, those who were taking hormonal and/or herbal medicines during the study period and showed adverse effects as a result of the administered medications, as well as the participants who failed the correct and regular medication adherence and were unwilling to continue the research were excluded from the study. It should be mentioned that the sampling was performed for six months.

The participants in the intervention group received 500 mg dried *R. damascena* extract capsules, and the control group received placebo capsules three times a day (once every 8 hours) for 40 days. The researchers regularly contacted the participants on the phone to stay vigilant for any possible complications during the intervention period.

Data were collected using a demographic characteristics form, Beck's Depression Inventory, Spielberger State-Trait Anxiety Inventory, and adverse effects questionnaire. The severity of anxiety and depression was measured at three intervals, once prior to the intervention, and then on days 20

and 40 post-intervention.

Beck's Depression Inventory is a 21-item questionnaire that is scored based on a Likert scale from 0 to 3, and its raw scores range from 0 to 63. Based on each subject's overall score, their degree of depression is then defined as mild (14-19), moderate (20-28), and severe (29-63) (33). In 2015, Hamidi et al. assessed the psychometric properties of this questionnaire and reported a convergent validity of 0.8 and reliability of 0.93 and 0.64 based on Cronbach's alpha and bisection methods (34).

The present study examined trait anxiety using Spielberger's State-Trait Anxiety Inventory, which has been designed with 20 items and is scored based on a four-point Likert scale of not at all=1, sometimes=2, often=3, and always=4. The overall score for each section ranged from 20 to 80 (35). In Iran, Mahram (1993) assessed the psychometric properties of this tool and reported validity values of 0.99 (state anxiety) and 0.95 (trait anxiety), and reliability values of 0.91 (state anxiety) and 0.91 (trait anxiety) using Cronbach's alpha (36). It should be mentioned that Forouzanmehr (2017) assessed the validity and reliability of this questionnaire and confirmed it (37).

The data obtained in this study were analyzed in SPSS software (version 19) using statistical tests, including the independent t-test, the chi-square test, and Mann-Whitney's test. The Kolmogorov-Smirnov test was also utilized for normality, and Mauchly's test of sphericity was employed in this study, all of which were valid (P>0.05). The repeated-measures test (ANOVA) was used for the intra- and intergroup comparisons before the intervention and on days 20 and 40 post-intervention. A p-value less than 0.05 was considered statistically significant.

Results

Out of 110 women who entered the study, six participants were excluded due to unwillingness and digestive problems. Eventually, 104 participants completed the study (Figure 1). The results showed
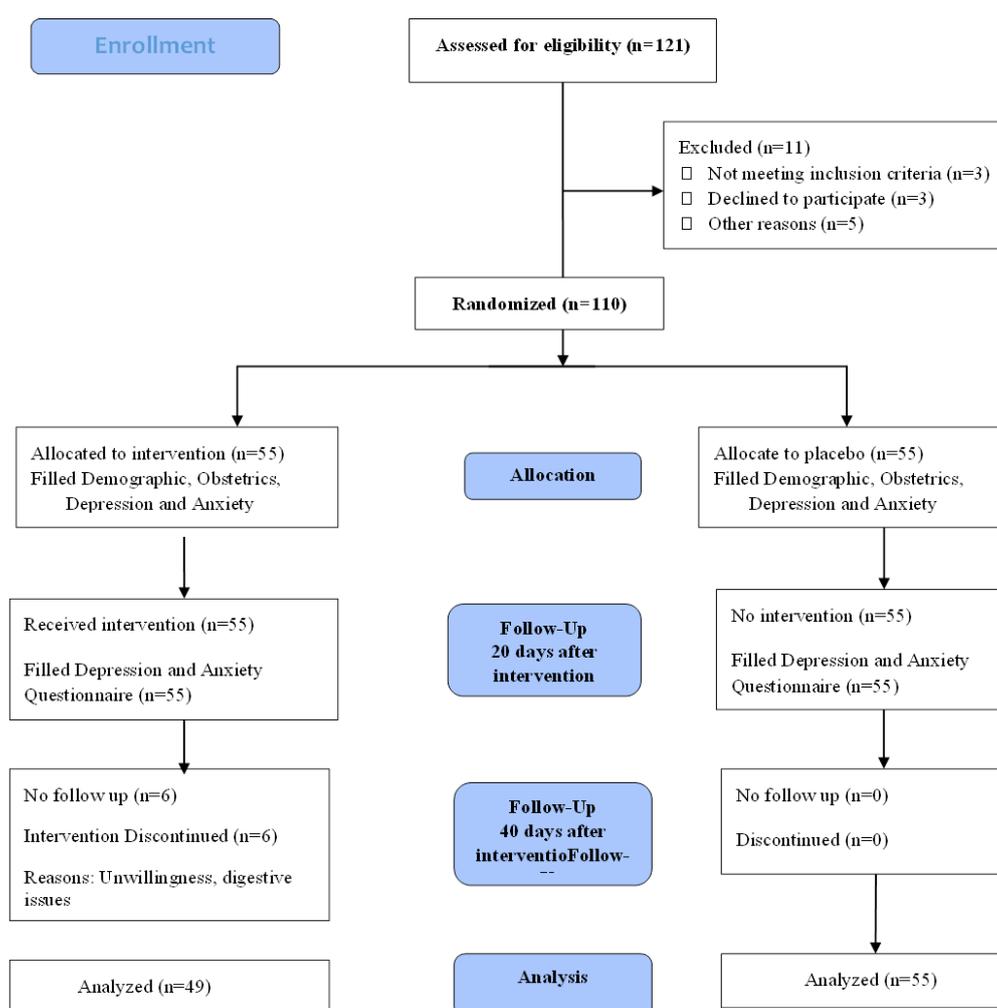

Figure 1. Consort Flow Diagram

Table 1. Comparison of some of the variables studied in the *R. damascena* and control (placebo) groups

Personal Data		Intervention N=49	Control N=55	P-Value
		No. (Percent)	No. (Percent)	
Age (Years)	45-48	2 (1.4)	6 (10.9)	
	48-51<	15 (30.6)	7 (12.7)	
	51-54<	10 (20.4)	13 (23.6)	P=0.54*
	54-57<	10 (20.4)	12 (21.8)	
	57-60	14 (24.5)	17 (30.9)	
	Mean and SD	53.20 (4.18)	53.71 (4.30)	
Marital Status	Non-Married	5 (10.2)	9 (16.4)	P=0.35**
	Married	44 (89.8)	46 (83.6)	
Education Level	Primary	13 (26.5)	21 (38.2)	
	High School, Diploma	25 (51)	27 (49.1)	P=0.12***
	College	11 (22.4)	7 (12.7)	
Occupational Status	Housewife	49 (89.1)	41 (83.7)	P=0.41**
	Employed	6 (10.9)	8 (16.3)	
Pap Smear Records	Yes	27 (55.1)	30 (54.5)	P=0.99**
	No	22 (44.9)	25 (45.5)	
Sports Activity	Yes, Daily	20 (40.8)	21 (38.2)	
	Yes, Weekly	15 (30.6)	19 (34.5)	P=0.91**
	None	14 (28.6)	15 (27.3)	
Duration of Menopause (Years)	1-5	30 (61.2)	31 (56.3)	
	5-9<	11 (22.4)	15 (27.3)	
	9-13<	7 (14.3)	5 (9.1)	P=0.54*
	13-20	1 (2)	4 (7.3)	
	Mean and SD	4.47 (3.94)	4.96 (4.25)	

* Independent T-test,   ** Chi-squared,   *** Mann-Whitney

that the majority of the participants in the intervention and control groups were in the age range of 48-51 and 57-60 years, respectively. In addition, the majority of the participants in these groups were housewives with high school education and diploma. Of all the demographic variables were examined, and no significant difference was observed between the two groups in this regard. Table1 tabulates some of the studied variables in the study. This study used the repeated measures ANOVA with two factors, including time (at baseline on days 20 and 40) and group (i.e. the intervention group versus the placebo group). Considering the significant interaction of time and group, these variables were compared separately in each group at three-time points. The two groups of intervention and control did not differ in terms of depression before and 20 days after the intervention; however, 40 days after the intervention, the difference in the mean depression score was significant between the two groups ($P<0.05$).

The severity of anxiety differed significantly in the intervention group before the intervention, as well as 20 and 40 days after intervention ($P<0.05$), and there was no significant difference between anxiety and depression scores in the control group at the same time (Table 2). The assessment of the potential adverse effects of the intervention showed that six subjects in the intervention group had developed gastrointestinal adverse effects, including nausea and diarrhea.

Table 2. Scores of depression and anxiety, before intervention, as well as 20 and 40 days after intervention in the *R. damascena* and control groups

	Time 1	Time 2	Time 3	P-value*		
				Time	Group	Time×group
Anxiety score				<0.001	<0.001	<0.001
R. damascena group (n=49)	45.14±10.14	40.02±8.52	35.67±7.41	<0.001**		
Control group (n=55)	47.76±7.56	47.05±7.38	48.40±6.68	0.39**		
P-value***	0.14	<0.001	<0.001			
Depression score				<0.001	0.10	<0.001
R. damascena group (n=49)	18.31±10.36	15.08±8.66	12.16±7.23	<0.001**		
Control group (n=55)	17.47±8.12	17.84±8.32	17.22±7.91	0.86**		
p-value***	0.65	0.10	0.001			

Data are presented as mean±SD
Time 1: Before intervention
Time 2: 20 days after intervention
Time 3: 40 days after intervention
*Obtained from the two way repeated measures analysis of variance
** One way repeated measures analysis of variance
***t-test (between two group)

Discussion

The results of the present study showed that *R. damascena* had positive effects on the improvement of depression and anxiety in postmenopausal women. The anti-depressant effects of *R. damascena* have been shown in animals. An animal study was conducted in Turkey to examine the effects of *R. damascena* essential oil and its steam inhalation on decreasing the oxidative toxicity of induced depression in rats. The results showed that the two main compounds of *R. damascena* affected the serotonin-dopamine receptors of the central nervous system, and by increasing antioxidants and decreasing lipid peroxidase, reduced the oxidative stress and treated depression (27).

As proposed by Esfandiari et al. (2018), the flavonoid content of *R. damascena* extract as an antioxidant plays a major role in the treatment of mood disorders, such as depression. Furthermore, the ester, ketone, aldehyde, and terpene compounds in *R. damascena* stimulate the olfactory cortex and trigger many psychological effects (29). The effect of *R. damascena* on the central nervous system in mice has shown anti-depressant and anti-anxiety properties (28). In the same line, Farnia et al. (2015) found that *R. damascena* essential oil improved depression symptoms (30). It seems that the flavonoid in *R. damascena* which contains free-radical antioxidant compounds affects the central nervous system and can be a suitable herbal supplement in the treatment of psychological disorders, including depression. Studies demonstrated that its aroma helped improve postpartum depression, anxiety and psychosomatic complications, as well as memory function (24, 25, 27).

Informed by the results of the present study, the intergroup comparisons revealed that after the consumption of *R. damascena* capsules, the mean anxiety score differed significantly in the *R. damascena* group, compared to the control group. Owing to its terpene, glycoside, flavonoid, and anthocyanin content, *R. damascena* boasts anti-inflammatory, antiseptic, anticonvulsant, antidepressant, anxiolytic, and analgesic properties and is effective against central nervous system disorders (21). This finding conforms to the results derived from other studies.

Similarly, Khairkhah et al. (2014) showed that *R. damascena* oil reduced anxiety in women in the first stage of labor. It seems that the stimulation of tactile sensation using aromatic essential oils increases the production of neurotransmitters, and the excitation of the olfactory system reduces the sympathetic nerve activity, induces relaxation, and subsides anxiety symptoms, which are associated with two components of *R. damascena*, namely citronellol and 2-phenyl ethyl alcohol (38).

In line with these findings, another study conducted by Hamedanian et al. (2018) on the effects of *R. damascena* aromatherapy on the severity of anxiety in the first stage of labor in nulliparous women revealed a reduction in anxiety levels since by stimulating the olfactory tract, aromatherapy affected

the hypothalamus, thereby reducing the secretion of corticotropin-releasing hormones. As a result, adrenocorticotropin secretion from the pituitary is decreased, which in turn, triggers a drop in cortisol secretion from the adrenal gland, and consequently, a decline in anxiety during labor (39). Other studies demonstrated that *R. damascena* affected the central nervous system by decreasing sympathetic while increasing parasympathetic activities. The compounds present in *R. damascena*, such as geraniol and citronellol, can facilitate GABA inhibitory neurotransmitters. The flavonoid in *R. damascena* can also bind to GABA receptors and can therefore act as neuromodulators to exert their antidepressant, anxiolytic, and sedative effects (40).

Depression and anxiety reduce the quality of life of women during menopause, and due to the side effects of drugs and hormone therapy, herbal medicines and supplements are always very important for people in the treatment and management of menopausal symptoms and complications. Studies have shown that women have a strong desire for complementary medicine treatments and the use of herbs (20). Some research has been performed to investigate the effects of *R. damascena* on depression; however, the strength of our study is that it was conducted on postmenopausal women, a population group that has not been investigated so far. One of the limitations of the present study was the use of herbal medicine for 40 days, which makes it impossible to claim its effectiveness in long-term use. In addition, our patients were not followed up after the intervention period. The results of the study of long-term effects with a larger sample size can be better generalized. It is suggested to conduct more research on more populations to investigate the efficacy and safety of treatment with *R. damascena*. It is also suggested to compare the effect of *R. damascena* with other chemical drugs.

Implications for Practice

Oral consumption of *R. damascena* capsules during menopause reduces depression and anxiety levels in women without triggering any noteworthy adverse effects. It seems that the use of *R. damascena*, which is popular among people, can reduce the use of chemical drugs and their side effects in postmenopausal women. To access more results, further research is recommended to be conducted on this plant.

Acknowledgments

Conflicts of Interest

The authors declare that there is no conflict of interest regarding the publication of this study.

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