



Comparison of the Effect of Lavender and Bitter Orange on Depression in Menopausal Women: A Triple-Blind Randomized Controlled Trial

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Abstract

Objectives: Menopause is an inevitable milestone and an important stage in every woman's life. This study aimed to compare the effects of lavender and bitter orange on depression in menopausal women.

Materials and Methods: This triple-blind randomized controlled clinical trial was conducted on 156 menopausal women in Urmia, Iran in 2015. Eligible women were allocated into 2 intervention groups and one control group with a ratio of 1:1:1 through the randomized block design. Intervention groups received 500 mg capsules containing only bitter orange or lavender flower's powder and control group received 500 mg starch capsules, all groups used capsules twice daily after breakfast and dinner for 8 weeks. Capsules were in the same appearance. Beck Depression Inventory was completed by the participants before and 8-week after the commencement intervention. The analysis was performed based on intention to treat approach.

Results: The one-way analysis of variance (ANOVA) analysis showed no significant difference in mean depression score in the three groups before the intervention ($P = 0.262$); however, the general linear model test adjusted for base line and confounding factors such as menopausal age and women age showed significant differences between the groups in the mean depression score after 8 weeks of treatment ($P < 0.001$). Bitter orange significantly reduced the mean depression score compared with the control group (adjusted mean difference [AMD], -2.88; 95% CI, -4.26 to -1.51). Lavender significantly reduced the mean depression scores compared with the control group as well (AMD, -3.01; 95% CI, -4.40 to -1.63). There was no significant between lavender and bitter orange groups after intervention ($P = 0.850$).

Conclusion: Considering the positive effect of bitter orange and lavender in reducing depression in menopausal women, they can be used as a complementary medicine in depressed patients.

Keywords: Depression, Menopause, Lavender, *Citrus aurantium*, Bitter orange

Introduction

Menopause is an inevitable milestone and an important stage in every woman's life (1) and a physiological event that occurs due to lack of ovarian activity and permanent cessation of menstruation and it is when 12 months have passed from the last menstrual period (2). Since one third of women's life is spent after menopause, there should be conditions for postmenopausal women to experience a life with high quality without pain, illness, and disability. Menopause is a natural and important stage of women's life that occurs between the ages of 45 and 55 and the average age for menopause is 50 (3,4). In developed countries, the average age at menopause is about 51 years, whereas in countries like India (5), Philippines, Pakistan and Thailand, it is reported to be 45-50 years (6). The average age of menopause in Iran was reported as 48.2 in 2011 (7).

The population of postmenopausal women is estimated to increase from 742 150 000 in 2010 to 1.2 billion until 2030, and the most of this enhancement will occur in developing countries (8). Decreased estrogen levels are as-

sociated with a wide range of menopausal symptoms, the most common vasomotor symptoms include hot flashes and night sweats (9). Symptoms such as irritability, anger and depression also aggravate at menopause (10).

In a study in 2013 in Pakistan, prevalence of depression in postmenopausal women was reported as 39.4% (1) and it was reported as 34.7% in postmenopausal women in Dezful, Iran (11). Reduced estrogen levels in menopause indicates that the cause of depression is related to female hormones (12). Depression can negatively affect social functioning and may cause loss of interest in enjoyable activities, sleep problems, loss of appetite or increased appetite, feeling of sadness, tiredness, low energy and even lead to suicide attempts (13).

Although medical treatment including hormone therapy and relaxation therapy are considered the first-line of treatment for depression, many women are not eligible to use them (14). Several potential side effects have been associated with hormone therapy including thromboembolism, gallstones, cerebral stroke, breast and endometrial



cancer (15). The use of tricyclic antidepressants and selective serotonin reuptake inhibitor to treat depression also has side effects such as anticholinergic effects, orthostatic hypotension and arrhythmia (16).

Lavender with the scientific name *Lavandula angustifolia* contains linalool, linalyl acetate, ocimene, camphor, caryophyllene oxide, tannins, coumarin, flavonoid and phytosterol (17) which have antidepressant (18), sedative, local anesthetic, dose-dependent anti-seizure (19), hypnotic (18), antioxidant and anti-anxiety (20) effects. Its linalool that affects the noradrenaline and dopamine levels and explains its antidepressant effects (21). This plant has been used in different studies without any certain reported side effects (22,23), only in some cases, nausea and vomiting (24) and skin dermatitis (25) had been observed in the case of topical use. Lavender has been confirmed by the World Health Organization (WHO) (26).

Bitter orange with the scientific name of *Citrus aurantium* belongs to the Rutaceae family and contains limonene, linalool, linalyl acetate, carotene, coumarin, flavonoid, pectin and p-synephrine (27). It has sedative (28), weight loss (28), hypnotic (29) and anti-anxiety (27) effects. Flavonoid and p-synephrine found in bitter orange has antidepressant effects (29).

Bitter orange with a dose of 975 mg (54 mg p-synephrine 6%) for 6 weeks in order to lose weight had not caused any particular side effect (30), while dermal use led to sensitivity to light (29). Bitter orange has been confirmed by US Food and Drug Administration (FDA) (27).

According to WHO report, in most countries because of herbal medicine's effectiveness, low risk and accessibility, there is an increasing trend toward consumption of complementary medicine for therapeutic reasons. In third world countries, majority of people utilize herbal medicine for treating their disease due to the lower cost of herbal plants (31).

No study has been conducted to compare the effect of these 2 medicinal plants on menopausal depression. Few studies have been conducted on the effect of bitter orange on depression (32), while study of the effects of lavender on depression has yielded contradictory results (24,33,34) and most studies have had an aromatherapy approach (32,33,35). Therefore, given the side effects of antidepressant drugs, popularity of complementary medicine and since one of the important responsibilities of midwives in primary care is the menopausal care, this study aimed to compare the effects of lavender and bitter orange on depression in menopausal women.

Materials and Methods

Study Design and Participants

This study was a triple-blind randomized controlled trial that was conducted on 156 menopausal women. The inclusion criteria were: The 45-60 years old women, with last menstruation of 1-6 years ago which started naturally, who get 14-28 from Beck depression score, without taking anti-depressant drugs, tobacco and alcohol, having phone number for follow-up, without history of asthma

and allergy to specific plants or citrus, lack of acute gastrointestinal problems declared by herself, Urmia residents, agreeing to participate in the study.

The exclusion criteria of the study were: Having to travel or change home during intervention, prior history of depression or any other mental disorder, unpleasant occurrences such as death of a family member during last three months, encountering events that caused depression, regular weekly exercise and use of other methods of traditional medicine.

G*Power (version 3.1.2) was used to determine the sample size. Based on the information in the study by Nikfarjam et al (34) $m_1 = 21.6$ (mean depression in their study), $m_2 = 18.36$ (considering at least 5% increase through our intervention), $sd_1 = sd_2 = 4.9$, $\alpha = 0.05$, $\beta = 0.2$, sample size was determined 47 women per group and finally regarding 10% sample loss, the final sample size was estimated as 52 participants for each group.

Sampling

Research setting included the gynecology clinics in Imam Reza and Fatemiyeh hospitals in Urmia, Iran. All menopausal women were assessed for eligibility criteria in the selected clinics through the convenience sampling method. Socio-demographic questionnaire and Beck Depression Inventory were completed by the participants. Score 28 or higher was indicative of severe depression, in which case, the subjects would be referred to the mental health service provider and excluded from randomization. Participants with a score of 14-28 in Beck Depression Inventory (mild to moderate depression) were included in the study.

Methodology, possible risks, potential benefits, and the nature of voluntary participation in the study were explained to the subjects. A checklist was also provided for the participants to record daily consumption of the capsules and possible side effects.

Randomization and Intervention

Allocation sequence was determined by computer random number table with blocks size of 3 and 6 and 1:1:1 allocation ratio. The women were randomly divided into 3 groups of bitter orange, lavender and placebo. Capsules contained only 500 mg of bitter orange or lavender flower's powder, while placebo capsules contained 500 mg starch. All capsules were similar in appearance and were prepared by Yashil Sahand Drug Incorporation in East Azerbaijan region, Iran. An opaque sealed envelope was given to each participant. Envelopes were numbered consecutively from 1 to 156 and prepared by non-involved person according to random sequence which contained the 120 lavender, bitter orange or placebo capsules for 8-week consumption.

The drugs were taken twice daily (after breakfast and dinner). In order to ensure about the administration of drugs, participants were followed up in weeks 2 and 6 via telephone. Participants, data collector and those assessing outcomes were blind in this research.

Data Collection

Data was collected using a socio-demographic questionnaire and Beck Depression Inventory that were completed at baseline and 8 weeks after the commencement intervention. The socio-demographic questionnaire contained items on demographic information including: age, time passed since menopause, age at menopause, education, woman's and husband's occupation, and sufficiency of family monthly income for living expenses.

Beck Depression Inventory is one of the most suitable measures to reflect the state of depression. It includes 21 multiple choice questions on a four-point scale from 0 to 3 with a total score of 0-63 that was completed in 5-10 minutes. The menopausal women selected the choices that they had felt in the past 2 weeks. A score of 28 and higher was considered severe depression. Those with a score of 14-28 (mild to moderate depression) were enrolled in the study. This is a standard and approved questionnaire. Beck et al obtained a test retest reliability coefficient of 0.93 for the questionnaire. In a study on 125 students of Tehran University and Allameh Tabatabai University to evaluate the reliability and validity of BDI-II on Iranian population, a Cronbach alpha of 0.78 and test-retest reliability coefficient of 0.73 within 2 weeks were obtained (36).

Beck Depression Inventory was completed again by all participants 8 weeks after the commencement intervention. The day before the visit, a reminder phone call was made in order to completion of questionnaires.

Statistical Analysis

Data were analyzed using SPSS 22. Normality of the con-

tinuous variables was confirmed using the one-sample Kolmogorov-Smirnov test. The chi-square, trend chi-square test and Fisher exact test were used for categorical variables and one-way analysis of variance (ANOVA) was used for continuous variables to examine homogeneity regarding socio-demographic or background characteristics. ANOVA was used to compare the mean depression score at baseline between groups. General linear model adjusted for baseline and confounding factors such as menopausal age and women age was used for after the intervention. At all stages, the significance level was set to $\alpha = 0.05$ and all calculations were based on intention-to-treat analysis.

Results

The recruitment of participants and their follow-up were carried out from July 5, 2015 to November 21, 2015. All women who were available in this study were 400 people, but 244 were excluded as 190 women did not meet the eligibility criteria, and 54 were not willing to participate in the study. Finally, 156 menopausal women participated in the study. Fifty-two women were randomly assigned to each group. Four participants in the bitter orange group, 3 in the lavender group and 4 in the placebo group did not take the capsules. All 156 menopausal women completed the questionnaires at baseline and 8 weeks after the commencement intervention and were analyzed (Figure 1). There was no statistically significant difference among the 3 groups based on socio-demographic characteristics, except age at menopause ($P=0.029$) and women age ($P=0.011$) and the 3 groups were similar (Table 1).

The mean (SD) of participants' age in lavender, bitter

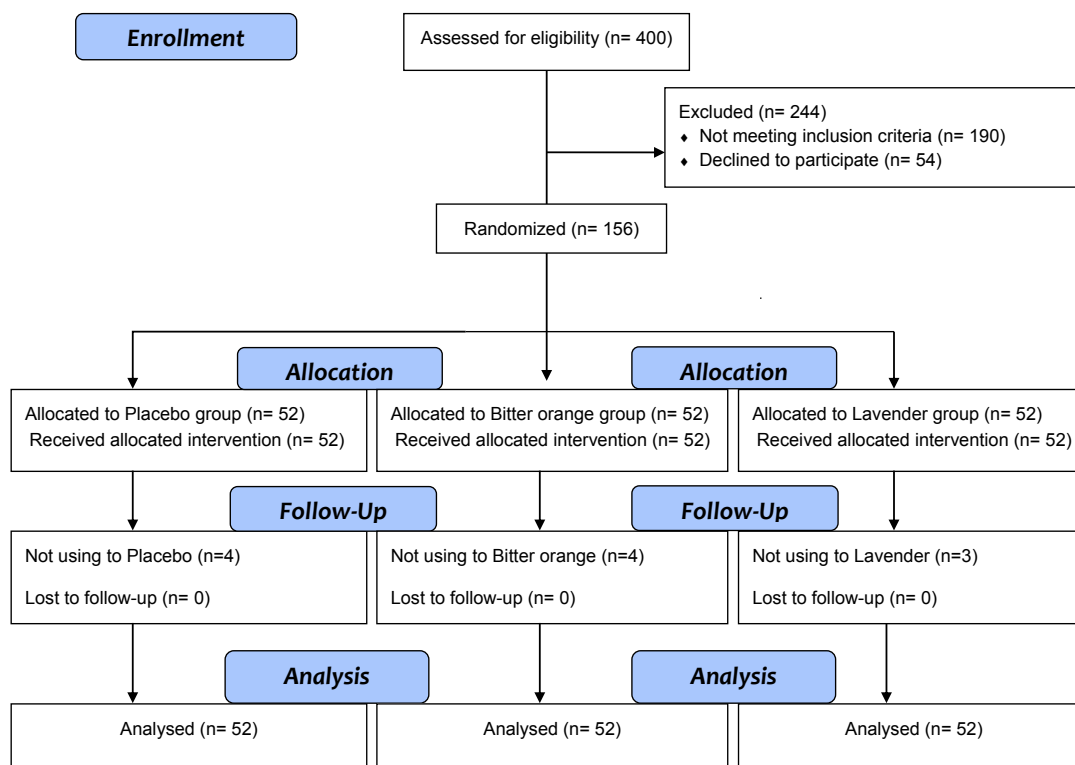


Figure 1. Flowchart of the Participants Through Each Stage of the Trial.

orange and control groups was 54.21 (3.86), 53.65 (3.55) and 52.12 (3.49), respectively. The results of other socio-demographic characteristics of the 3 groups are presented in Table 1.

The general linear model analysis showed that difference in mean score of depression was statistically significant among groups after intervention adjusted for baseline values and confounding factors. Before the intervention, the mean (SD) depression score in the groups receiving lavender 20.82 (4.30), bitter orange 21.38 (4.33) and the control group was 20.01 (4.13) and there was no statistically significant difference between the groups ($P=0.262$). The mean (SD) depression score was 14.07 (3.41) in the lavender group; 14.48 (4.24) in the bitter orange group; and 16.78 (4.16) in the control group 8 weeks after the intervention, showing a statistically significant difference between the groups ($P<0.001$).

Significant differences were observed between the group receiving lavender and the control group (adjusted mean difference [AMD], - 3.01; 95% CI, -4.40 to -1.63) and between the group receiving bitter orange and the control group (AMD, -2.88; 95% CI, -4.26 to -1.51). No statistically significant difference was found between the group receiving bitter orange and the group receiving lavender after the intervention (AMD, 0.12; 95% CI, -1.21 to 1.47) (Table 2).

Paired t test showed a significant difference in depres-

sion scores after the intervention compared to baseline in the lavender (mean difference [MD], 6.75; 95% CI, 5.50-7.99), bitter orange (MD, 6.90; 95% CI, 5.91-7.89) and the control groups (MD, 3.23; 95% CI, 2.04-4.41) (Figure 2).

In total, 83.4% of the participants in the bitter orange group, 83.7% in the lavender group, and 43.8% in the control group reported a good recovery. The group receiving bitter orange reported the highest satisfaction (79.2%).

The frequency of side effects reported by the menopausal women in the bitter orange group was as follows: nausea (4.2%), palpitations (4.2%) and headache (2.1%), in the lavender group included nausea (8.2%), palpitations (4.4%) and headache (4.1%) and in the control group included nausea (10.4%), palpitations (2.1%) and headache (6.3%) (Table 3).

Discussion

Findings suggested the effectiveness of administration of 500 mg bitter orange and lavender twice daily for 8 weeks in reducing the menopausal women's depression. Our results are consistent with those reported by the double-blind study conducted by Akhondzadeh, which aimed at comparing lavender tincture and imipramine in the treatment of mild to moderate depression on 48 outpatients aged 18 to 45 years visiting Roozbeh outpatient clinic in Tehran and showed that the combination of imipramine and lavender tincture was more effective than

Table 1. Demographic Characteristics of the Participants in Control and Intervention Groups

Characteristics	Placebo (n = 52)	Lavender (n = 52)	Bitter Orange (n = 52)	P Value
	No. (%)	No. (%)	No. (%)	
Age (y) ^a	52.12 (3.49)	54.21 (3.86)	53.65 (3.55)	0.011 ^b
Menopausal Age ^a	48.00 (6.72)	50.35 (3.37)	49.90 (3.23)	0.029 ^b
Time passed from menopause ^a	3.25 (1.37)	3.87 (1.40)	3.75 (1.46)	0.065 ^b
Female education				0.134 ^c
Primary	13 (25)	20 (38.5)	31 (59.6)	
Secondary	10 (19.2)	13 (25)	7 (13.5)	
High school	7 (13.5)	5 (9.6)	4 (7.7)	
Diploma and University	22 (42.3)	14 (26.9)	10 (19.2)	
Number of children				0.104 ^d
0-2	26 (50)	19 (36.5)	15 (28.8)	
3-4	23 (44.2)	23 (44.2)	28 (53.8)	
5 and more	3 (5.8)	10 (19.2)	9 (17.3)	
Use hormone medicine				0.535 ^e
Yes	1 (1.9)	3 (5.8)	4 (7.7)	
No	51 (98.1)	49 (94.2)	48 (92.3)	
Job				0.161 ^e
Housewife	44 (84.6)	47 (90.4)	48 (92.3)	
Employed	5 (9.6)	1 (1.9)	0 (0)	
Retired	3 (5.8)	4 (7.7)	4 (7.7)	
Income				0.639 ^c
Sufficient	22 (42.3)	21 (40.4)	19 (36.5)	
Relatively Adequate	20 (38.5)	19 (36.5)	27 (51.9)	
Inadequate	10 (19.2)	12 (23.1)	6 (11.5)	

^a Data were presented as mean (standard deviation).

^b One-way analysis of variance (ANOVA).

^c Chi-square test.

^d Linear-by-Linear chi-square.

^e Fisher exact test.

Table 2. Comparison of Total Score of Depression Before and After Intervention by Study Groups

Total Score of Depression	Baseline Mean (SD) ^a	P ^d	8 Weeks After Intervention Mean (SD)	P ^e
Bitter orange (n= 52)	21.38 (4.33)		14.48 (4.24)	
Lavender (n= 52)	20.82 (4.30)	0.262	14.07 (3.41)	<0.001
Placebo (n= 52)	20.01 (4.13)		16.78 (4.16)	
Comparison of Between the Groups	MD (CI 95%) ^b	P	Adjust MD (CI 95%) ^c	P
Bitter orange with Lavender	0.55 (-1.41 to 2.53)	0.783	0.12 (1.21 to 1.47)	0.850
Bitter orange with Placebo	1.36 (-0.61 to 3.34)	0.234	-2.88 (-4.26 to -1.51)	<0.001
Lavender with Placebo	0.80 (1.16 to 2.78)	0.599	-3.01 (-4.40 to -1.63)	<0.001

Number of participants in each group was 52 before and after intervention.

^a Mean (standard deviation).

^b Mean difference (95% CI).

^c Mean difference (95% CI) adjusted for the baseline values and the confounding factors included menopausal age and women age).

^d One-way analysis of variance (ANOVA) was used for comparison of the baseline scores.

^e General linear model for comparison of the follow-up scores.

imipramine alone (24).

In a clinical trial on 80 outpatients referred to psychiatric clinic of Hajar hospital in Sahrekord, Iran, Nikfarjam et al concluded that lavender had positive therapeutic effects in patients with depression and had improved the patients, which is consistent with the findings of the present study. In that study, the control group received 20 mg citalopram tablet with 2 glasses of water and rock candy as a placebo twice daily, while the intervention group, in addition of 20 mg citalopram, received 5 g of dried lavender shoot twice daily in the form of decoction in the morning and evening with rock candy for 8 weeks (34).

In a study on adult male mice, Mahmoodi et al reported antidepressant effects of bitter orange extract, which is consistent with our findings (37).

Choi et al carried out a double-blind study to evaluate the effect of inhalation of bitter orange essential oil with concentrations of 0.1 and 0.5 on symptoms of menopause and estrogen levels in 63 menopausal women for 5 days and reported that bitter orange essential oil reduced the menopausal symptoms such as depression, insomnia, and stress; however, estrogen levels remained unchanged. Results are consistent with those of the present study (32).

Itai et al conducted a study to determine the effects of inhalation aromatherapy with lavender and Hiba on anxiety and depression of 14 dialysis patients for 6 weeks and showed that Hiba aroma significantly reduced anxiety and

depression in patients, and lavender aroma resulted in a significant decrease only in the anxiety levels, which is inconsistent with the present study (38).

In a double-blind study conducted to determine the effects of inhalation aromatherapy on anxiety and depression of 313 patients treated with radiation, Graham et al reported that lavender aromatherapy did not significantly reduce the anxiety and depression levels (39). The findings are inconsistent with the present study. The inconsistency between our study and these 2 studies may be due to the differences in number of samples, medication dose, and the administration method (in most studies, lavender has been used for aromatherapy).

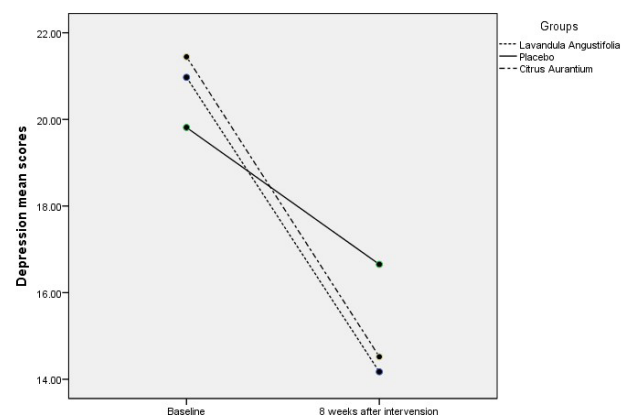
Our findings showed that lavender and bitter orange impose no serious health risk, and side effects are mild and transient, which is consistent with the findings reported by Mahmoodi et al (37) and Akhondzadeh et al (24).

Effects of lavender can be attributed to its active substances and their effects on a various neurotransmitters involved in depression. The effects of this plant on gamma-amino-butyric acid (GABA) have been proved, and therapeutic effects of this plant can be due to the role and involvement of GABA in the development of mood disorders (40). Linalool content of lavender affects the nor-

Table 3. The Frequency of Adverse Events by Study Groups

Adverse Events	Bitter Orange	Lavender	Placebo
	(n = 48) No. (%)	(n = 49) No. (%)	(n = 48) No. (%)
Nausea	2 (4.2)	4 (8.2)	5 (10.4)
Vomiting	0	0	0
Palpitations	2 (4.2)	2 (4.1)	1 (2.1)
Headache	1 (2.1)	2 (4.1)	3 (6.3)
Others ^a	2 (4.2)	0	4 (8.4)

^a Abdominal pain, bloating, stomach pain.

**Figure 1.** Total Depression Score Among Groups.

adrenaline and dopamine levels, justifying its antidepressant effects (21). Also, lavender can affect the enzymes, channels and ion receptors leading to brain stimulation, relief anxiety, and anti-depression effects and improve blood flow to the brain (20). Flavonoids found in bitter orange have numerous pharmacological effects including inhibition of oxidation of lipoproteins with low molecular weight, prevention of platelet aggregation and immune cells stabilization; therefore, it is used in the treatment of mental disorders such as depression, allergies and viral infections (41). These seem to justify our findings.

Our study shows that lavender and bitter orange do not have serious risk for health and reported side effects were mild and transient, so we can easily use them in future studies.

A limitation of this study was that participant's responses were considered correct and honest that researcher was not able to verify the responses. The strengths of this study include the random allocation of subjects to avoid selection bias and the use of blinding method to reduce the risk of bias in data collection.

Although many studies have been conducted on depression, few studies have been conducted on the effects of medicinal plants on depression in menopausal women. Therefore, generalization of the results requires further investigations due to the lack of studies in this area.

It is suggested that above medications to be used in men or among other age groups. It is also recommended to consider the effect of other medicinal plants on the depression of postmenopausal women.

Conclusion

Considering the positive effect of bitter orange and lavender in reducing depression in menopausal women, they can be used as a complementary medicine in depressed patients. However, no statistically significant difference was found between the group receiving bitter orange and lavender 8 weeks after beginning of intervention in terms of depression.

Ethical Issues

The Research Ethics Committee of Tabriz University of Tabriz Medical Sciences approved the study protocol (code: 1394.98). Also, it was registered at Iranian Registration Clinical Trial website (identifier: IRCT201504236582N11). Written informed consent was obtained from eligible women.

Conflict of Interests

The authors have no conflict of interest to declare.

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