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Therapeutic Effects of *Citrus aurantium* Components on Psychological States: A Systematic Review

Farkhondeh Aboualsoltani[1], Parvin Bastani[2*], Laleh Khodaie[3], Seyyed Mohammad Bagher Fazljou[1]

Abstract

Objectives: *Citrus aurantium* L., frequently known as the sour or bitter orange, is native to Asia and, nowadays, is widely cultivated in different regions such as the Mediterranean. Different parts of *C. aurantium* are consumed as an alternative medicine in some areas to treat some diseases, and various recent studies have proven the potential of this medicinal plant. This review examined the therapeutic effects of *C. aurantium* components.

Methods: Tactful and progressive search strategies were developed to determine the studies. To this end, a large number of databases were evaluated, including Cochrane Library, PubMed/MEDLINE, Scopus, and Google Scholar (2010 to April 2019). Finally, 12 clinical trial studies were selected for evaluation and analysis, and the JADAD scale was used to evaluate the quality of the papers.

Results: Of 546 papers found in the preliminary search, 12 clinical trials (1132 participants), which were written in English, were selected for structured reviews. The researches consisted of those which evaluated the therapeutic role of the plants in anxiety, depression, sleep quality, premenstrual syndrome, and menopausal symptoms.

Conclusions: The review of clinical trials brings some evidence that different components of *C. aurantium*, especially its flower have therapeutic effects on particularly psychological states like anxiety, depression, and insomnia and aromatherapy by the essential oil is considered as the most used method of prescription. Therefore, *C. aurantium* can confidently be used in various disorders which have these psychological aspects among their symptoms.

Keywords: *Citrus aurantium*, Bitter orange, Treatment, Therapeutic effects

Introduction

Citrus aurantium L. (Rutaceae) is widely recognized as a bitter orange native to Asia, but is extensively cultivated in different districts such as the Mediterranean (1). The fruit, flower, and other components of *C. aurantium* are the sources of phenolic and flavonoid-type compounds with distinct biological effects (2-4). *C. aurantium* flower has been traditionally used for gastric and nervous disturbances, gout, insomnia, nervous tension, and sore throat. In Chinese medicine, it is used for epigastric pain, vomiting, and anorexia. In addition, its peel is used for appetite loss and dyspepsia in addition to cough and colds. It has a moderate anti-spasmodic effect on the digestive system (1). In ancient Iranian medical books, different parts of the plant have been mentioned as the strengthener of the head and chest organs, as well as a carminative. Further, it is effective in catarrh and cough, and ameliorates itching, helpful in dystocia, and useful for palpitation and faintness. Furthermore, it is a facilitator of menstruation and causes cheerfulness, and the like (5,6). *C. aurantium* flower and flower oil mainly constitute of linalool, linalyl acetate, alpha pinenes, limonene, nerol, methyl anthranilate, limonoids, and flavonoids. Moreover, the essential constituents of its peels are limonene, nerol, geraniol, linalool, linalyl, neryl, geranyl, citronellyl acetate, methyl anthranilate, flavonoids, and furocoumarins (1). Additionally, *C. aurantium* has bioactive compounds that act as an antioxidant, anti-inflammation, anti-virus, and anti-cancer (7,8). It has been demonstrated that its analgesic effect is due to neroli and involving nitric oxide pathways (4).

Daily dosage for bitter orange peel and the extract is 4-6 g and 1-2 g, respectively. There is no health hazard or side effect when it is used properly in the range of therapeutic dosages. Elevated UV sensitivity is possible in light-skinned individuals and frequent contact with its volatile oil can cause erythema, swelling, and blisters (1).

In a study, the flavonoids of *C. aurantium* have demonstrated an inhibitory effect on adipogenesis (9). In addition, its flower extract has proven to have spasmolytic effects on the uterus of non-pregnant rats in an *in vitro* study (10). In another animal study conducted on rats, *C. aurantium* flower extract was able to improve cognition and memory damage induced by scopolamine (11). In some animal-based research, the essential oil of *C. aurantium* had anxiolytic effects and lowered anxiety-

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[1]Department of Iranian Traditional Medicine, School of Traditional Medicine, Tabriz University of Medical Sciences, Tabriz, Iran. [2]Women's Reproductive Health Research Center, Tabriz University of Medical Sciences, Tabriz, Iran. [3]Department of Phytopharmacy, School of Traditional Medicine, Tabriz University of Medical Sciences, Tabriz, Iran.
***Corresponding Author:** Parvin Bastani, Tel: +98 (0)411 3556 1653, Email: bastani@tbzmed.ac.ir

related behaviors in mice (12,13). Another animal study performed on zebrafish evidenced that the *C. aurantium* leaves extract has anticonvulsant effects and increases seizure latency induced by pentylenetetrazole (14). No adverse effect or health hazard was found at the therapeutic doses of *C. aurantium* plant (1,15).

Given the lower side effects and high acceptability of traditional and complementary medicine, which involves using medicinal plants, the general desire to use alternative and complementary therapies is increasing. Accordingly, this study was planned to determine the therapeutic effects of *C. aurantium* plant according to the scientific studies based on human clinical trials. It is hoped that this study sheds light on the effective use of the bitter orange and the different parts of the trees for treating diseases. Finally, the present study was done to gain knowledge about the therapeutic value of plant components and its aspects according to scientific evidence.

Methods

In this study, a systematic review was done on all research conducted regarding determining the therapeutic effects of *C. aurantium* from 2010 until April 2019. The detailed explanation of the applied methods for data extraction, as well as inclusion and exclusion criteria is as follows.

Literature Search

The data presentation in this work, including the determination of the problem under study, data collection, along with the analysis and interpretation of the findings was done based on the systematic study reporting system (i.e., PRISMA). The above-mentioned protocol was used as a criterion for searching the articles that were published from 2010 to April 2019. To access information requested from the studies related to our title, several English databases, including Cochrane Library, PubMed/MEDLINE, Scopus, and Google Scholar were searched by using some keywords such as "*C. aurantium*", "*Bitter orange*", "treatment", and "therapeutic effects".

Inclusion and Exclusion Criteria

English original human clinical trial papers related to the therapeutic effects of *C. aurantium*, were selected for the present study.

To maximize the search comprehensiveness, the list of sources for all articles related to the subject was handled in a handy manner to find other possible sources. The main inclusion criterion was human clinical trials that were written in English and examined the therapeutic effect of *C. aurantium* components. The most complete report would be chosen if there were multiple reports from a study. Further, the information in the abstract was used in cases where the full text of the article was not available, and if the abstract of the article did not provide enough information, that article was excluded from the study. To select the studies and extract data, the titles of all articles obtained by two of the contributors to the study and repetitive cases were removed and then the title and abstract of the remaining articles were carefully studied, followed by deleting the articles that had no criteria for entering this structured review. Finally, the full text of the probably related articles was examined and eligible articles were selected and separated from non-relevant items.

In general, 12 papers were found and analyzed based on inclusion and exclusion criteria. Data were collected based on study characteristics in addition to non-adherence measures, prevalence rates, and factors associated with non-adherence. The PRISMA guidelines were followed in performing this systematic review.

Data Extraction

To avoid subversion, the articles were extracted, and their quality was evaluated by two independent researchers. If the articles were not accepted, the reasons for refusing it were mentioned accordingly. In cases where there was a controversy between the two researchers, the review was done by a third person. In the next step, information about the selected articles included the name of the first author, the year and place of the study, the year of the publication, the sample size, the general characteristics of the samples, the type of the used intervention, the method of the plan, and the measure of the reported results in the study. For the quantitative-qualitative evaluation of the articles, a systematic review of the choice bias (random sequence generation and allocation concealment) implementation (the blindness of the participants and evaluators), diagnosis (statistical analysis blindness), the sample loss out of the study after randomization, and reporting (selective outcome report) were done and JADAD scale was calculated for each study. The information is depicted in Table 1.

Results

Overall, 546 articles were found in the initial search, and then 28 possible related articles were examined after reviewing the titles and abstracts and removing repetitive and non-related articles. Of these, 16 articles were omitted from the abstract because of the lack of access to the original article and the lack of sufficient information. Finally, 12 clinical trials were included in the study (Figure 1).

Akhlaghi et al conducted a randomized double-blind clinical trial to evaluate *C. aurantium* effects on preoperative anxiety. In this study, 60 candidate patients for minor limb operations were divided into two groups of 30 subjects each by computer-based randomization. One of the groups received 1 mL/kg *C. aurantium* blossom distillate and the other received 1 mL/kg saline solution oral two hours before the initiation of anesthesia. Anxiety was assessed before and after treatment using the Spielberger state-trait anxiety inventory (STAI-state) and the Amsterdam preoperative anxiety and information scale

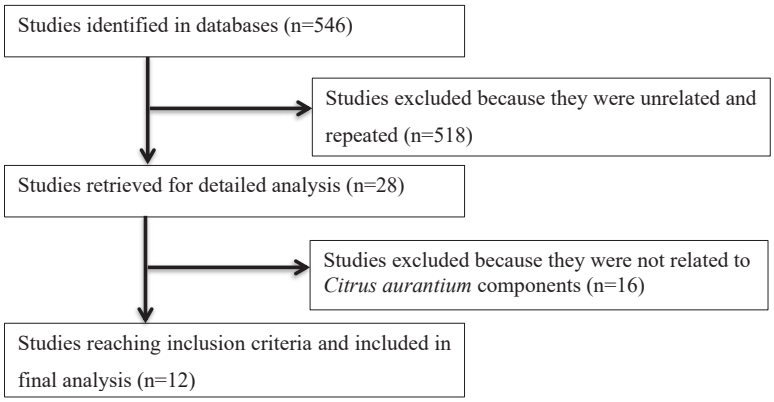

Figure 1. The Selection Process of Studies.

(APAIS) before the operation. The results showed that both STAI-state and APAIS scales decreased significantly in the *C. aurantium* blossom group compared to the saline solution group, which exhibited no considerable changes (16).

Similarly, Namazi et al performed a randomized clinical trial to identify the effect of aromatherapy with *C. aurantium* distillate oil on anxiety during the first stage of labor. Totally, 126 eligible pregnant women referred to the hospital for delivery were randomly allocated to

Table 1. Summary of Clinical Trials Reviewed in the Study

Author/ Reference	Participants	Condition Under Study	Experimental Group/Method of Prescription	Control Group/ Method of Prescription	Results	JADAD Score
Akhlaghi et al (16)	60 preoperative patients	Anxiety	*C. aurantium* blossom distillate /oral	Saline solution/oral	Significant anxiety reduction in the experimental group	4
Namazi et al (17)	122 pregnant women	Anxiety	*C. aurantium* blossom distillate/ inhalation	Saline solution/ inhalation	Significant anxiety reduction in the experimental group	3
Dehghan et al (18)	66 preoperative heart patients	Anxiety	*C. aurantium* EO/oral	Oxazepam pill/oral	Significant and statistically equal anxiety reductions in both groups	2
Pimenta et al (19)	42 hospitalized CML patients	Anxiety	*C. aurantium*. EO/inhalation	1. Saline solution/ inhalation2 .10 mg diazepam pill/oral	Significant anxiety reductions in the experimental group	1
Bakhsha et al (20)	80 female students	Anxiety	*C. aurantium*. EO/inhalation	Lavender EO/ inhalation	Significant anxiety reductions in both groups	2
Eslami et al (21)	90 cholecystectomy preoperative patients	Anxiety	1. *C. aurantium*. EO/inhalation 2. Lavender. EO/inhalation	Odorless oil/ inhalation	Significant anxiety reductions in both experimental groups	1
Chaves Neto et al (22)	51 participants (17 crack user and 34 non user)	Anxiety	*C. aurantium*. EO/ inhalation(both user and non-user groups)	Distilled water/ inhalation	Significant anxiety reductions in both experimental groups	1
Kamalifard et al (23)	156 menopausal women	Depression	1. 500 mg *C. aurantium* blossom/oral 2. 500 mg lavender flower/oral	500 mg Starch/oral	Significant depression reductions in both experimental groups	5
Maroufi et al (24)	78 patients with MDD	Depression	30_60 drops of *C. aurantium* concentrated water/oral	70-150 mg Imipramine/oral	Significant depression reductions in both groups	1
Choi et al (25)	63 postmenopausal women	Menopausal symptoms	1. 0.1% *C. aurantium* EO/ inhalation 2. 0.5% *C. aurantium* Eo/ inhalation	Almond oil/ inhalation	Significant menopausal symptom reduction in both experimental groups	4
Kamalifard et al (26)	156 menopausal women	Sleep quality	1. 500 mg *C. aurantium* blossom/oral 2. 500 mg lavender flower/oral	500 mg starch/oral	Significant improvement of sleep quality in both experimental groups	5
Heydari et al (27)	66 Female students	Premenstrual syndrome	0.5% *C. aurantium*. EO/ inhalation	Sweet almond oil/ inhalation	A significant decrease in overall and psychological symptoms in the experimental group	3

Note. EO: Essential oil; CML: Chronic myeloid leukemia; MDD: Major depressive disorder; *C. aurantium*: *Citrus aurantium*.

two groups (initially 63 subjects in each group by the table of random numbers). Furthermore, 4 cases of the *C. aurantium* group were eliminated from the study due to the vaginal bleeding and emergency cesarean section or unwillingness to cooperate with the study, followed by excluding 5 cases of the control group due to the fetal distress and emergency cesarean section or unwillingness to cooperate with the study. Two gauzes soaked in 4 mL of *C. aurantium* distillate and normal saline were stuck to the collar of each group, respectively. The level of anxiety was primarily measured using the Spielberger state-trait questionnaire and after the intervention at the dilatations of 3-4 and 6-8 cm. The results revealed that anxiety decreased significantly in the *C. aurantium* group compared to the normal saline group (17).

Likewise, Dehghan et al conducted research to compare the effect of *C. aurantium* and oxazepam on the preoperative anxiety of patients undergoing coronary artery implantation surgery. In this single-blind trial, 66 heart patients aged 40-56 were randomly allocated to two groups of 33 cases each. The patients in one of the groups received 10 mL (2 g) of *C. aurantium* essence daily starting three days before the operation and the other group received an oxazepam pill (10 mg) daily starting three days before the due date. However, 3 and 2 cases of the *C. aurantium* and oxazepam groups were excluded from the study because of the cancellation of operation, respectively. Then, the Speilberger questionnaire was used to measure the anxiety level of the patients before and after the intervention. According to the results, anxiety decreased in both groups by more decrease in the *C. aurantium* group which was not statistically significant. Thus, the level of anxiety in both *C. aurantium* and oxazepam groups decreased equally (18).

In another study, Pimenta et al evaluated the anxiolytic effect of *C. aurantium* essential oil (EO) in chronic myeloid leukemia patients. To this end, 42 hospitalized chronic myeloid leukemia (CML) patients were randomly divided into three groups of 14. Patients in one of the groups received 10 mg diazepam orally. The second group was exposed to 10 mL of *C. aurantium* EO which was spread in the space by an electric sprinkler. The third group was exposed to a vaporized saline solution. The duration of exposure was 30 minutes. Finally, the State-Trait Anxiety Inventory (STAI) and physiological measurements (i.e., blood pressure, along with cardiac and respiratory frequencies) were used to determine the anxiety level before and after the intervention. The results showed that the inhalation of the *C. aurantium* EO significantly decreased anxiety according to STAI and physiologic assessments compared to diazepam which just lowered diastolic pressure and placebo that had no effect (19).

Bakhsha et al also compared the effect of lavender and *C. aurantium* aroma on the anxiety of female university students. In this double-blind clinical trial, 80 female students were randomly and equally assigned to two groups. Prior to intervention initiation, the screening test, along with Sarason Anxiety Test Questionnaire was done and those with scores more than 12 were included in the study. One of the groups received the inhalation of the essence of lavender and the other group received the inhalation of the essence of *C. aurantium* for 60 seconds. For the persistency of the aromas, they were also applied to the forehead of the students by the applicator the night before the exam. The visual analogue score (VAS) scale ranging from 0 to 10 (indicating 0 and for no anxiety and extreme anxiety, respectively) was used before and 30 minutes after the intervention in order to evaluate anxiety. Moreover, hemodynamic status such as the heart rate and blood pressure were calculated before and after the intervention. The results showed that anxiety decreased significantly in both groups after the intervention. Additionally, the pulse rate significantly decreased after the intervention in both groups, but the decrease in diastolic blood pressure was only significant in the *C. aurantium* group. Eventually, the systolic blood pressure had no significant change in any of the groups (20).

In addition, Eslami et al conducted a study to compare the effect of aromatherapy with lavender (Lavandula angustifolia Miller) and *C. aurantium* extracts on the anxiety of candidate patients for laparoscopic cholecystectomy. In this randomized clinical trial, 90 patients undergoing laparoscopic cholecystectomy were randomly allocated to three equal groups after screening with the Spielberg questionnaire. Patients in one of the groups received 2 drops of *Lavandula* essence on a tissue to inhale for 20 minutes from a 20-cm distance. The second group received *C. aurantium* essence on a tissue to inhale for 20 minutes from a 20-cm distance. The third group received the inhalation of placebo (an odorless oil) on a tissue for 20 minutes from a 20-cm distance. The results of the Spielberg questionnaire demonstrated that the state and trait anxiety significantly decreased in both *Lavandula* and *C. aurantium* groups (although no significant difference was found between the two groups) compared to the placebo group. Thus, aromatherapy with *Lavandula* and *C. aurantium* essences equally and significantly decreased the anxiety level in cholecystectomy preoperative patients (21).

Similarly, Chaves Neto et al reported the anxiolytic effect of *C. aurantium* in crack users. This randomized clinical trial was performed on 51 volunteers consisting of two experimental groups and one control group (n=17 each). The experimental groups included non-users and crack users during abstinence, respectively. Further, the control group encompassed the non-users of the crack. None of the groups were internal to therapeutic communities. The non-user subjects of the experimental group and the subjects of the control group were randomly selected from the general population. Furthermore, the crack user subjects of the experimental group included male subjects with chemical dependence to crack and internally

abstinent, who had been hospitalized to quit the drug. As regards the intervention, 2 drops (0.1 mL) of *C. aurantium* EO in 1.9 mL of distilled water with an emulsifier (Tween 80 at 12%) was given to the subjects of the experimental groups as inhalation with the electric nebulizer. The subjects of the control group received the same procedure with only distilled water nebulization. The simulated public speaking method was used to induce anxiety in the subjects of the three groups. Then, the Spielberg questionnaire was used to assess the psychological aspect of anxiety. Moreover, the physiological measurements of temperature, blood pressure, and heart rate were made during the specific phases of the experiment. The groups had similar levels of anxiety at the baseline phase. The results of psychological anxiety measures by the Spielberger questionnaire and Humor Analog Scale (both with the same results) showed that both experimental groups receiving *C. aurantium* EO had significant anxiety control compared to the control group in the stressor phase. Only the non-user EO group represented significant anxiety control in the during phase. At the final phase, all three groups had similar measurements with no significant difference. The evaluation of physiological measures revealed no significant difference between the groups unless in the DF of the experiment, there was a statistically significant systolic blood pressure decrease in the non-user EO group compared to the control group (22).

Additionally, Kamalifard et al evaluated the effect of lavender and bitter orange flower on depression in menopausal women. In this triple-blind randomized controlled trial, 156 menopausal women were randomly and equally allocated to two intervention groups and one control group by a block design. Intervention groups received 500 mg capsule of lavender flower or 500 mg capsule of bitter orange flower and the control group received 500 mg of starch twice daily for 8 weeks. All capsules were similar in appearance. Beck Depression Inventory questionnaire was filled out by participants before and after the intervention. The results showed that both lavender and bitter orange flower significantly reduced depression compared to the control group (23).

In their study, Maroufi et al compared the effect of *C. aurantium* and imipramine on the treatment of the major depressive disorder. In this randomized single-blind clinical trial, 38 major depressive disorder (MDD) patients received *C. aurantium* concentrated water 30-60 drops daily for 12 weeks. The other group consisted of 39 MDD patients who received 70-150 mg imipramine daily for 12 weeks. Then, the structured clinical interview and Beck Depression Inventory were used for evaluating depression before and after the intervention. The results demonstrated that the mean Beck score and thus depression decreased significantly in both groups although there was no significant difference between the two groups (24).

Choi et al performed a study to assess the effect of *C. aurantium* EO inhalation on menopausal symptoms, stress, and the estrogen level of postmenopausal women. In this double-blind randomized controlled trial, 63 menopausal women were randomly allocated to three groups (two intervention groups and one control group) by the random number table. One of the intervention groups with 22 participants received 0.1% *C. aurantium* EO dissolved in the almond oil in the bottles containing 1 mL of Neroli oil of *C. aurantium*. They were asked to pure the content of each bottle onto a pad twice daily (10 AM and 10 PM) and inhale it for 5 minutes from a 30-cm distance for 5 days. The other intervention group with 19 participants received the same procedure with 0.5% Neroli oil of *C. aurantium*. In addition, the control group with 22 participants received the same procedure but took the almond oil instead of *C aurantium* EO. The participants completed the Menopause-Specific Quality Of Life (MENQOL) questionnaire before and after the intervention. Further, the sexual desire and stress scale were controlled by VAS, blood pressure, pulse rate, serum cortisol, and serum estrogen levels measured before and after the intervention. The results revealed that the physical domain score of MENQOL and sexual desire improved significantly in both intervention groups who received *C. aurantium* EO compared to the control group who received the almond oil. On the other hand, systolic blood pressure significantly decreased in the intervention group who received 0.5% Neroli oil. Both intervention groups had significantly lower diastolic blood pressure compared to the control group and experienced significant improvement in serum cortisol and estrogen levels. Accordingly, the *C. aurantium* EO significantly ameliorated menopausal symptoms, increased sexual tendency and reduced blood pressure, and finally, improved serum cortisol and estrogen concentrations in postmenopausal women (25).

Kamalifard et al conducted a study to compare the effect of lavender and bitter orange flower on sleep quality in postmenopausal women. In this randomized triple-blind controlled trial, eligible postmenopausal women were randomly allocated to three groups of 52 participants each by the computer using the random number table with a block design (two intervention groups and one control group). The intervention group received 500 mg capsule of lavender flower or 500 mg capsule of bitter orange flower, and the control group received 500 mg of starch twice daily for 8 weeks. The appearance and odor of all capsules were the same. The Pittsburg Sleep Quality Inventory questionnaire was filled before and after the intervention. The results revealed that both lavender and bitter orange flower significantly improved sleep quality compared to the control group (26).

In another study, Heydari et al aimed to determine the effect of aromatherapy with *C. aurantium* blossom EO on premenstrual syndrome (PMS). In this randomized

triple-blind clinical trial, 168 female university students completed the Premenstrual Symptoms Screening Tool (PSST) and General Health Questionnaire (GHQ). Then, 66 of the initial participants who had a score of over 20 on PSST questionnaire (moderate and severe PMS) were selected and assigned to two intervention and control groups (each including 33 participants) by simple randomization. The intervention group received ten drops of 0.5% *C. aurantium* EO, which was administered on an eye pad for inhalation from a distance of 30 cm for 5 minutes twice daily, starting 5 days before menstruation for two successive cycles. The control group received the same procedure but the sweet almond oil drop was used instead of *C. aurantium* EO. They completed the PSST and GHQ questionnaire after five days in their menstrual period. The results indicated that PMS overall symptoms significantly decreased in the *C. aurantium* EO group compared to the control group. There was no significant change in physical symptoms and the social function between the two groups, but the decrease of the psychological symptoms was significant in the *C. aurantium* EO group compared to the sweet almond oil group (27).

Discussion

In the reviewed papers, anxiety was the most studied condition in 7 papers. Aromatherapy with the EO was the most prescribed method and *Citrus aurantium* flower was the most used part of the plant. The other groups received distilled water (Inhalation), a saline solution (oral and inhalation methods), lavender EO (Inhalation), odorless oil (Inhalation), oxazepam (oral), and diazepam (oral). In all 7 studies, there has been a considerable decrease in anxiety in *C. aurantium*, lavender, oxazepam, and diazepam groups, but no significant decrease of anxiety observed in distilled water, saline solution, and odorless oil groups (16-22).

Two studies evaluated depression which was the second most studied condition. In one of the studies, the oral prescription of *C. aurantium* flower powder, along with the oral prescription of lavender flower powder was compared with oral starch. In the second study, the oral prescription of *C. aurantium* concentrated water was compared with oral imipramine. In both studies, a significant depression reduction occurred in the groups who received *C. aurantium* blossom powder, *C. aurantium* concentrated water, lavender flower powder, and imipramine with no significant differences in between, but there was no significant reduction in depression in the starch-taking group (23,24).

Sleep quality, menopausal symptoms, and PMS were the third studied condition with 1 paper for each (25-27).

In the study regarding menopausal symptoms, aromatherapy by 0.1% and 0.5% *C. aurantium* EOs was compared with aromatherapy by the almond oil. The results indicated a significant reduction in menopausal symptoms in *C. aurantium* EO aromatherapy groups although there was no significant change of symptoms in the almond oil group.

According to the study of sleep quality, one group of menopausal women received *C. aurantium* blossom powder, the other group received lavender flower powder, and the control group received starch orally. The results revealed that both *C. aurantium* blossom and lavender flower powders improved sleep quality significantly and statistically equally while there was no significant improvement in sleep quality in the starch group.

In the study of PMS, one group received aromatherapy by 0.5% *C. aurantium* EO and the other group received aromatherapy with the sweet almond oil. The results showed a significant overall reduction and a decrease in the specifically psychological symptoms of PMS in the *C. aurantium* EO group, but there was no significant decrease in the PMS symptoms of the sweet almond oil group.

Anxiety is a distressful event that causes feelings of uncertainty and vague hazard. This mental state, which is experienced many times, is accompanied by symptoms such as tightness in the chest and throat, difficulty in breathing, palpitations, confusion, psychological disturbances, and sweating. The low levels of anxiety can lead to a person's domination over the environment and increase his awareness of potential threats. However, intense anxiety disrupts one's behavior and prevents his logical response (28).

Depression is also one of the most annoying problems of public health, which is accompanied by notable weakness, comorbidity, fragile health, and mortality (30). It has 12 months prevalence of 6.6% and a lifetime prevalence of 16.2% (31). The major depressive disorder is diagnosed by the presence of five out of nine DSM-5 criteria for at least two weeks. One of the symptoms must be depressed mood or anhedonia (32). Further, depression is a heterogeneous disorder that appears with psychological, behavioral, and physiological symptoms (32).

Sleep is a regular, repetitive, and reversible physiological event in which the individual experiences a decrease in consciousness, a relative loss of skeletal muscle tone, and a significant increase in the threshold of the response to external stimuli and more than one-third of the human life span are allocated to sleep. Therefore, any disturbance in the quantity, quality, or pattern of sleep can have a significant negative effect on the performance, as well as the physical and mental health of the individual (26). On the other hand, insomnia is the risk factor for other medical problems such as depression, hypertension, and cardiac diseases (33). Sleep disorder is one of the fundamental symptoms of depression, and sometimes, the most causative annoyance for seeking help (34). Depression and sleep disturbance are also common symptoms of menopause (35).

PMS consists of physical, cognitive, affective, and behavioral symptoms, occurring during the luteal phase

of the menstrual cycle and soothes a few days after the initiation of menstruation. Moreover, anxiety and depression are prevalent conditions in those suffering from PMS (36). Additionally, anxiety, depression, and sleep disorders are highly prevalent and comorbid psychiatric disturbances (37). The World Health Organization has stated an increase in the use of traditional, complementary, and alternative medicine among people all over the world (38).

According to this systematic review, the most studied conditions for *C. aurantium* therapeutic roles are psychological disturbances like anxiety and depression or menopausal and premenstrual symptoms, which have prominent psychological aspects in their wide spectrum of manifestations.

Conclusions

Considering the side effects of conventional medicine in treating psychological conditions such as anxiety, depression, and sleep disturbances and regarding the public general tendency toward complementary and alternative medicine, herbal products with proven positive effects can be used for the management of these disorders. In this review, it seems that the specific *Citrus aurantium* flower as the aromatherapy plant can have significant therapeutic effects on conditions like anxiety, depression, and sleep disturbances with no reported side effects or health risks. Regarding the significant side effects of chemical drugs routinely used for treating these disorders, the current review gives promising evidence that the use of *C. aurantium* flower is highly effective in managing the above-mentioned conditions with no known side effects. Therefore, it can be considered for the treatment of mild to moderate forms of the diseases confidently. However, due to limited studies regarding various therapeutic effects of different components of *C. aurantium*, it is recommended that more human clinical trials be carried out to evaluate diverse conditions using different components of *C. aurantium* and varied methods of application with various dosages. The present study has some limitations. This study reviewed articles from 2010 onwards while not including those published in this regard before that time period. In addition, this review investigated the therapeutic roles of all components of *C. aurantium*. However, separate evaluation of each plant component will yield more accurate results, which was not applicable for the authors of this review due to the limited papers in the field.

Conflict of Interests

The authors declare that there is no conflict of interests.

Ethical Issues

This study was approved by the Ethics Committee of Tabriz University of Medical Sciences under the ethical code of IR.TBZMED.REC.1397.105.

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