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PHARMACOLOGICAL ASPECTS OF *CITRUS AURANTIUM* (RUTACEAE) IN ANXIETY DISORDERS: AN INTEGRATIVE REVIEW

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ABSTRACT

Anxiety is a mental disorder of high prevalence, being a topic of attention since the earliest historical records. In Brazil, it affects all life aspects of 9.3% of the population. Conventional treatments, which are most effective, can have adverse effects. Therefore, there is a significant increase in demand for alternative therapies which are less "aggressive" and cheaper, like phytotherapy. Among the numerous plants indicated for the treatment of anxiety, it is worth highlighting *Citrus aurantium* popularly known as "bitter orange" or "sour orange". Studies show the influence of its essential oils and plant extracts on the central nervous system, especially in the control of anxiety and depression. Although the use of plants, as a form of disease treatment and prevention, is an ancient practice, their indications are often based especially on popular knowledge. Thus, scientific evidence and studies are needed to ensure safety and efficacy in the use of plant species. Thus, the purpose of this study is to investigate the mechanism of action of *Citrus aurantium* in anxiety disorders. A bibliographical revision was carried out in health scientific databases using the descriptors "*Citrus aurantium*", individually and, combined with the following descriptors "anxiety", "central nervous system", "mental disorders" and "mechanism of action". Articles searched based on titles, abstracts, and year of publication (2010-2020), and those that did not address the anxiolytic effect of the species and/or its mechanism of action were excluded. We found 151 articles and considered for the review 16 articles that met the inclusion criteria. Although there are few works that study and prove the anxiolytic effect of *Citrus aurantium*, the vast majority of them only mention possible mechanisms of action. Analyzing the results reviewed, it was possible to observe that *Citrus aurantium* acts positively on anxiety, probably, as suggests the studies, through serotonergic pathway.

Keywords: Phytotherapy, *Citrus aurantium*, anxiety, essential oils.

INTRODUCTION

Anxiety is present in everyday life, being primarily a physiological mechanism of adaptive response to imminent internal or external danger, stress or some environmental stimulus, all of which happens due to an intrinsic defense system[1].

The mechanism of anxiety is associated with cortisol increased levels. This hormone's release process starts with the brain's circuitry responsible for fear and worry, the amygdala. This structure receives the stressful stimulus and activates the hypothalamic-pituitary-adrenal (HPA) axis, which induces the release of corticotropin-releasing hormone (CRH) and arginine vasopressin (AVP) from the hypothalamus. The CRH, then, binds to the pituitary's receptors and stimulates the release of adrenocorticotropic hormone (ACTH), which induces the Adrenal Glands secretion of Cortisol.

Negative feedback happens when these increased levels of glucocorticoids are detected by the hippocampus which inhibits the

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release of the CRH and, therefore, the HPA axis. As pathways that regulate the HPA axis activity operates, serotonin, which exerts a stimulatory influence on CRH, also stands out through receptor subtypes of 5-hidroxitriptamina (5-HT): 5-HT $_{1A}$, 5-HT $_{1B}$, 5-HT $_{1C}$ and 5-H $_{T2}$ receptor subtypes[1,2].

However, from the moment this response to stress becomes more frequent or more intense due to amygdala hyperactivity or damage to factors that regulate the activity of the HPA, such as decreased hippocampal response, it's known as anxiety disorder and can interfere in the individual's social, professional and academic life.[1].

According to the World Health Organization (WHO), the worldwide prevalence of anxiety disorder in 2017 was already 3.6%, being within the American continent 5.6% of the population[3] and among these, Brazil has not only the highest index on the continent, but among all countries in the world, with 9.3% of the affected population[4].

Drugs available for the treatment of anxiety disorders are diverse and include several classes of medications, which are currently the most prescribed medications in the world. However, due to the lack of direct and specific control in this area, the available resources are modulators of neurotransmitters that somehow - still not well explained - contribute to the improvement of disorders related to the HPA axis. Among them, the most used are benzodiazepines, whose action is based on the potentiation of gamma-aminobutyric acid (GABA) neurotransmitters, but despite their proven efficacy, their use for a long period of time can lead to a series of adverse reactions, such as possibility of tolerance, abstinence and dependence[1].

Among the effective interventions, phytotherapy has shown great prominence, being widely used to complement allopathic treatment[5]. For example, of the use *Citrus aurantium*, also called bitter orange or sour orange - a hybrid between *Citrus maxima* (Pomelo) and *Citrus reticulata* (Mandarin)[6].

In folk medicine, products derived from orange peel and/or dried fruit are used to treat health problems that affect various systems, such as gastrointestinal disorders, respiratory disorders, insomnia, stress, epilepsy, and anxiety[7].

Considering the increasing cases of anxiety disorders in Brazil and the cultural importance of medicinal plants as well as its relevance for maintaining the health of various communities, this review seeks to address the investigation of the mechanism of action of *Citrus aurantium* on anxiety disorders.

METHODS

A integrative review was carried out, seeking scientific evidence on the use of the *Citrus aurantium* in anxiety disorders. To synthesize the pharmacological aspects of *Citrus aurantium* a integrative review was elaborated, aiming to answer the following research question: How does *Citrus aurantium* work on anxiety disorders? For this purpose, healthcare related databases such as PUBMED/MEDLINE, ELSEVIER/SCIENCE DIRECT/EMBASE, LILACS and COCHRANE were used, and searched under the descriptors "*Citrus aurantium*", alone and combined with the descriptors "anxiety", "system central nervous", "mental disorders'' and "mechanism of action". Articles were first screened based on titles and abstracts, and those that did not meet the inclusion criteria were automatically discarded.

The inclusion criteria were: articles, monographs, dissertations and theses published in Portuguese and English languages; and articles published in full and indexed in databases that contain data on the subject; and published between 2010 and 2020. As exclusion criteria we used: original and review articles, monographs, dissertations and theses that do not address the medicinal aspects of the plant species; abstracts and expanded summaries of scientific events; articles that do not fit the theme in question; review articles; and articles that are repeated.

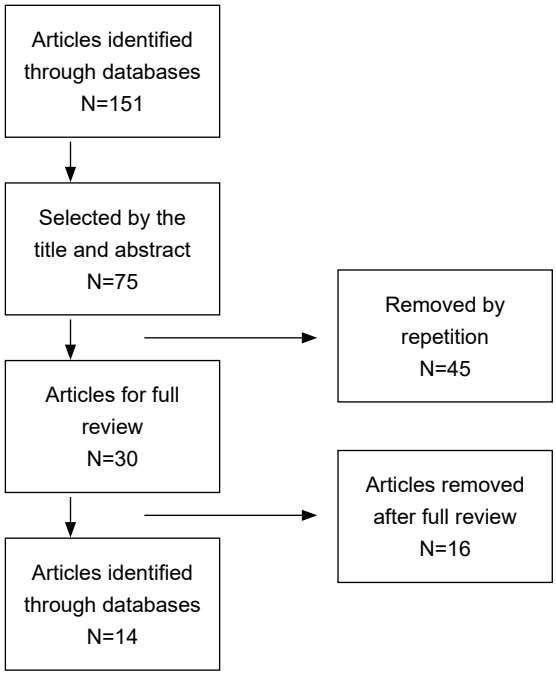

Figure 1: Flowchart outlining the protocol adopted in this review.

For data analysis, the questions and hypotheses of the articles, monographs, dissertations and theses, the experimental methods used, the results and their outcomes were highlighted, bringing the mechanisms of action in anxiety disorders, especially those that comprised clinical and pre-clinical trials.

RESULTS AND DISCUSSION

After searching, 151 articles were found, of which 16 were corresponding to the inclusion criteria, being 14 clinical or preclinical studies on the subject. Three of the preclinical studies using animal models administered the essential oils of the plant by inhalation, two by peritoneal injection and only one by oral route. The results are shown in Table 1.

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Table 1: Main characteristics of pré-clinical studies on the anxiolytic effect of *C. aurantium* in animal models.

Author	Species - Preparation - Administration route - Species - Anxiety model - Dose - Observed effect
Costa et. al., 2013	**Species =** *Citrus Aurantium*. | **Preparation =** *Citrus aurantium* essential oil. **| Administration route =** oral. | **Species -** Swiss mice, males. | **Anxiety model =** Light/Dark Box Test (LDB) , *Rotarod Test* (RRT), Forced Swim Test (FST). | **Dose =** Group 1: single dose of C. aurantium's EO (essential oil) administered 30 min. before LBD at 1, 5, 10 and 50 mg/kg; and 1 mg/kg diazepam (DZP) for the positive control. Group 2: 14 days repeated dose of EO at 1, 5, 10 mg/kg/day; and 10 mg/kg BUSP for the positive control. Group EO + FLU: 5mg/kg, p.o. of EO and 15 min. later, 2 mg/kg, i.p. of Flumazenil (FLU). Group WAY + EO: 0.5 mg/kg, of WAY100635 (WAY)i.p. and 15 min. later, 5 mg/kg, p.o. of EO. | **Observed effect =** After administering a single dose of 5mg/kg, was noted an increase of the time spent in the light compartment as well as the exploratory parameters, showing the anxiolytic effects of C. aurantium. Repeated treatment showed modification in the amount of time spent in the light compartment and the number of transitions and rearings. Acute or repeated treatments did not interfere with motor skill. In the group EO + FLU, the EO's anxiolytic effects were not affected, indicating that EO does not function through the GABAergic pathway. In the group WAY + EO, essential oils' effects were all reversed, suggesting that EO works through a serotonergic system.
Wolfenbüttel et al., 2017	**Species =** *Citrus aurantium.* | **Preparation =** *Citrus aurantium* essential oil. | **Administration route =** Inhalation. | **Species -** Albino mice, males. | **Anxiety model =** LDB, locomotor activity test, tail suspension test, MEL (Melatonin) and COR (Corticosterone) analysis. | **Dose =** Dispersion of 10% (v/v) C. aurantium leaves' EO in Tween 80 (TW - 1% v/v in distilled water). TW (1% v/v in distilled water) or 2.0 mg/kg of diazepam intraperitoneal or 20.0 mg/kg of imipramine (IM; i.p.) or saline solution (0.9% NaCl) as control solution. **| Observed effect =** LBD showed that 30 min. of mice's exposure to 10% C. aurantium EO did not produce anxiolytic or sedative effects. MEL or COR levels were not affected by C. aurantium inhalation.
Chaves Neto et al., 2020	**Species =** Citrus aurantium. | **Preparation =** C. aurantium and limonene associated with 2-hydroxypropyl-β-cyclodextrin (*Citrus/* β-CD). | **Administration route =** Inhalation. | **Species =** albino mice, males. | **Anxiety model =** EPM (Elevated Plus Maze), Open Field, RRT. | **Dose =** 1.0 g/kg, 250 mg/kg and 500 mg/kg of *Citrus*; 1.0 g/kg, 250 mg/kg and 500 mg/kg of *Citrus/*β-CD; 1.0 mg/kg of DZP. | **Observed effect =** In EPM after a single treatment with OE 1g/kg significantly increased the number of entries and permanence in the open arms of the maze when compared to the control groups. As for the Open Field, there was a significant timing increase for Grooming Time and Ambulatory time when compared to control group, but just a slight increase for the rearing time.
Saketi et al., 2014	**Species =** *Citrus aurantium.* | **Preparation =** *Citrus aurantium* essential oil. | **Administration route =** Intraperitoneal injection. | **Species =** albino mice, males. | **Anxiety model =** EPM. | **Dose =** Essential oil dissolved in olive oil at concentrations of 0.5% , 2,5% and 5% indiferente mices for five days; 2 mg/kg Fluoxetine for the positive control group and at the 5th day, 30 min before receiving EO in another group receiving the different concentrations of EO. | **Observed effect =** Both administration of OE or OE + FLU (Fluoxetine), increased the number of entries and the time spent in the open arms of the maze.
Khosravi et al., 2014	**Species =** *Citrus aurantium***. | Preparation =** *Citrus aurantium* essential oil. | **Administration route =** Intraperitoneal injection. | **Species =** Albino mice, males. | **Anxiety model =** EPM. | **Dose =** Essential oil dissolved in olive oil at concentrations of 0.5%, 2,5% and 5% indiferente mices for five days; 0.1 mg/kg DZP for the positive control group and at the 5th day, 30 min before receiving EO in another group receiving the different concentrations of EO. | **Observed effect =** Both administration of OE or OE + DZP demonstrated increased time in EPM, especially, the concentrations 2.5 and 5% of essential oil that showed significant increase in time spent in open arms compared when compared to control.

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Results described in table 1 show that even though there were different administration routes used in animal models, it was possible to observe anxiolytic effects after contact with the essential oil (EO) of the *Citrus aurantium* L plant.

None of the studies mentioned above demonstrated adverse effects or these were not mentioned by the authors, considering tests performed by Costa et al.[8], Wolffenbüttel et al.[9] and Chaves Neto et al.[10] there was no impairment of locomotor activity even after administration of different doses of the EO.

Costa et al.[8], using one of the main components of the essential oils, limonene, demonstrated that application of this component did not imply a significant difference between experimental group and control group levels of anxiety. Therefore, this study suggests that its anxiolytic activity occurs through the interaction of biological compounds present in the species, and not by a single molecule. Table 2 shows the result and indication, as well as the route of administration of the clinical studies.

Supporting this evidence, previous studies have shown the effects of essential oils components: linalool and β-myrcene induces the release of acetylcholine; limonene application leads to a decrease in central nervous system activity; flavonoids leading to nervous system depression and antioxidant effect[11].

Results obtained by Costa et al.[8] and Saketi et. al.[11] suggests the 5-hydroxytryptamine$_{1A}$ (5-HT$_{1A}$) receptor as the main target by the essential oils components, thus affecting the serotonergic pathways. Costa et al.[8] comes to this conclusion after administering doses of *Citrus aurantium* essential oil in one experimental group and doses of *Citrus aurantium* essential oil combined with WAY100635 (WAY), a highly selective 5-HT$_{1A}$ receptor antagonist, in the other group, and then submitting this groups to the light-dark box test. As result, the experimental group that received only *Citrus aurantium EO* spent more time in the light chamber, when compared to the control group, and the group who received the combination with WAY actually had reversed all the observed effects. Saketi et al.[11] , in its turn, reinforced these conclusions by studying, through the EPM behavioral model, the interaction between *C. aurantium* and fluoxetine, a selective serotonin reuptake inhibitor. As results, was observed that not only the essential oils intraperitoneal injection increases the time in open arms, but, when co-administered with fluoxetine, shows a greater effectiveness, leading to the conclusion that EO has an activity that helps to modulate serotonin uptake into synaptic clefts, which may explain the demonstrated anxiolytic effects.

Khosravi et al.[12], on the other hand, inferred GABA$_A$ as the main target of *C. aurantium*'s components. The studies were conducted by administering only EO and EO combined with 0.1 mg.Kg^{-1} Diazepam (DZP) - a benzodiazepine drug, according to Silva[13], that operates intensifying the action of GABA by increasing its affinity - at concentrations of 0.5%, 2.5% and 5% for 5 days and then applying the EPM behavioral model. As results, it was observed that both EO alone and associated with DZP demonstrated an anxiolytic effect. Khosravi et al., (2014)[12] deduced that this anxiolytic action would work someway as benzodiazepines in the GABAergic pathway. However, Costa et al.[8], using EO combined with DZP with and without Flumazenil (FLU), a competitive DZP antagonist and, applying the LDB model, showed that all the anxiolytic effects of DZP were reversed in the presence of FLU, but when co-administered with OE, they did not interfere with its anxiolytic effects, leading to the conclusion that its mechanism of action is not associated with GABA-benzodiazepine complex.

In addition, the analysis of cortisol levels does not demonstrate significant changes in plasma contraction, even in the groups that received DZP (positive control) and negative control, indicating that the tail suspension test is not a suitable indicator for evaluating stress through cortisol dosage, leading to the hypothesis that it has no direct action on the HPA axis[9].

Table 2: Main characteristics of studies on the anxiolytic effect of *C. aurantium* in clinical trials.

Author	Intervention Group – Treatment - Principal endpoints - Observed effect - Adverse effect
Namazi et al., 2014	**Intervention Group =** Patients during the first stage of labor **| Treatment =** Gauze containing EO were placed every 30 minutes in the collar, patients were instructed to breathe normally | **Principal endpoints =** Data collected using a demographic and obstetric questionnaire, examination, fetal heart rate, and Spielberger questionnaire. The intensity of anxiety was measured after the intervention at dilations of 3-4 and 6-8 cm | **Observed effect =** Score according to (STAI) State-Trait Anxiety Inventory that aromatherapy with *C. aurantium* can reduce anxiety during labor | **Adverse effect =** No adverse effects were observed on patients or on the fetus.
Akhlaghi et al., 2011	**Intervention Group =** Preoperative anxiety | **Treatment =** Patients received flower of *C. aurantium* distilled orally 1mg.kg^{-1} | **Principal endpoints =** State-Trait Anxiety Inventory (STAI), Amsterdam Preoperative Anxiety (APAIS), and heart rate and blood pressure were used to assess anxiety after and before surgical intervention | **Observed effect =** The intervention group was significantly less anxious than the control group according to STAI and APAIS. No hemodynamic variables showed changes between groups | **Observed effect =** No adverse effects were observed

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Dehghan and Kalani, 2018	**Intervention Group =** Candidates for coronary artery implantation operation. | **Treatment =** Patients were divided into two groups. Three days before, they received *C. aurantium* and a control group received oxazepam. | **Principal endpoints =** In order to measure anxiety, the Spielberger questionnaire was applied 3 days before the operation and the following morning after surgery. | **Observed effect =** There was no difference between the groups, but in the group treated with *C. aurantium* the difference in scores before and after the intervention was significant, suggesting effects on the anxiety state.| **Adverse effect =** No adverse effects were reported.
Moradi et al., 2020	**Intervention Group =** Patients undergoing coronary angiography**. | Treatment =** The intervention was performed 60 minutes before angiography. Four millimeters of "aurantium acid" were dropped onto cotton and fixed to the collar of patients who were instructed to breathe normally for 15 to 20 minutes. **| Principal endpoints =** A demographic information questionnaire and vital signs observation were taken before the intervention. Twenty minutes after the intervention, the Spielberger questionnaire was applied. | **Observed effect =** After the intervention, the group that received the plant extract significantly decreased the mean anxiety score while in the control group there were no considerable differences when compared to the pre-treatment. **| Adverse effect** = No adverse effects were reported.
Pimenta et al., 2016	**Intervention Group =** Patients with chronic myeloid leukemia**. | Treatment =** The patients were divided into three groups, the first group was exposed to the EO of *C. aurantium* through diffusion by an electric dispenser, the second group received 10 mg of DZP orally (positive control) and the third was exposed to saline vaporization (negative control). | **Principal endpoints =** For the evaluations, systolic and diastolic pressure, heart and respiratory rate were measured and to assess the level of anxiety, STAI was applied, both before and after the procedure. | **Observed effect =** A decrease in systolic pressure was noted in the groups treated with OE and DZP, but in the diastolic pressure this effect only occurred with the EO, with no significant change in the groups treated with DZP and placebo. Only the group treated with EO observed a decrease in HR values. About STAI, the group treated with the EO showed significant differences, while the DZP and placebo groups did not show differences. | **Adverse effect =** No adverse effects were reported.
Chaves Neto, 2016	**Intervention Group =** Users in Crack Dependency Recovery. | **Treatment =** The patients were separated into three groups, control, EO user and EO non-user. The patients were exposed to the simulated public speaking test and all tests were performed before the stressful stimulus, during and at the end. | **Principal endpoints =** In order to assess anxiety measures, STAI, and mood analog scale were applied, as well as DBP, SBP, HR, extremity temperature and skin electrical conductance levels were verified. | **Observed effect =** Groups treated with EO had significantly lower scores on the STAI, there were no considerable variations in physiological measures between groups treated with EO and placebo. | **Adverse effect =** No adverse effects reported.
Farshad Khalili- et al., 2018	**Intervention Group =** post-menopausal women. | **Treatment =** The herbs *C. aurantium* and lavender were encapsulated and delivered to their groups, lavender, *C. aurantium*, and placebo, all containing 500 mg of herbs or placebo. The capsules were consumed twice a day for 8 weeks. **Principal endpoints =** STAI was applied to assess anxiety levels at the beginning and end of the study. **| Observed effect =** Differences were observed between the groups that received the herbal preparation when compared to the control group (8 weeks). No significant differences were observed between the groups that received bitter orange and lavender. **| Adverse effect** = Nausea (4.2%), palpitation (4.2%) and headache (2.1%).

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Moslemi et al., 2019	**Intervention Group =** Acute Coronary Syndrome. | **Treatment =** Patients were separated into two groups that received the aroma of *C. aurantium* in liquid paraffin or Food Grade. In liquid paraffin (placebo), each group at the time of the intervention received a gauze soaked in the respective solution, placed in the collar, under guidance to breathe normally for 20 minutes. | **Principal endpoints = Before** and after the intervention, the STAI was applied to verify the levels of anxiety. | **Observed effect =** The scores before the intervention between the groups did not show any differences, but afterwards a significant difference was observed between the group that received *C. aurantium*. | **Adverse effect** = No serious side effects were reported.

Table 3 summarizes the main characteristics of volunteers in clinical trials. Altogether, these nine studies investigated the anxiolytic effects of *C. aurantium* extracts in different conditions considered stressful and, consequently, a trigger for anxiety.

Namazi et al.[14] showed the anxiolytic efficacy of aromatherapy with the EO of *C. aurantium* in a group of Iranian women in the first stage of labor, as a method a clinical trial was applied, randomized into two groups of pregnant women. Before the application of aromatherapy, both groups had their anxiety levels measured through the Apgar score at baseline levels, which showed no statistically significant difference between the intervention and placebo groups, after 3-4cm and 6-8cm dilation when a significant decay was already observed in the group that received treatment with the EO. This study shows not only the effectiveness of aromatherapy with *C. aurantium*'s oil, but also a simple and non-invasive way of intervention to reduce anxiety during labor.

Table 3 Characteristics of volunteers in clinical trials.

Study Name	Number of Patients	Age (years)	Study design
Anxiolytic effect of *Citrus aurantium* L. in patients with chronic myeloid leukemia	20	45 ± 5	Randomized Controlled Study
Effect of aromatherapy with orange essential oil on salivary cortisol and heart rate in children during dental treatment	30	6 - 9	Randomized Controlled Clinical Trial
Effects of *Citrus aurantium* L. essential oil on anxiety levels in crack users	51	27.33 ± 4	Randomized Controlled Clinical Trial
Citrus aurantium flower and preoperative anxiety	60	C 32.40 ± 11.72 P 29.33 ± 9.55	Randomized, Double-blind Design
Comparison between the effect of *Citrus aurantium* and Oxazepam on reoperative anxiety of patients who are candidates for coronary artery implantation surgery	66	40 - 56	Single-blind Trial
Citrus aurantium essential oil relieves anxiety in patients with coronary angiography	80	30 -75	Double-blind Controlled Randomized Clinical Trial
Citrus aurantium oil aromatherapy during the early stages of labor	113	C*26.6 ± 3.41 P*26.43 ± 3.22	Randomized Clinical Trial
Citrus aurantium aroma for anxiety in patients with acute coronary syndrome	140	56.72 ± 11.38	Placebo-controlled and Double-blind Trial
Comparison of the effects of lavender and sour orange in postmenopausal women	156	53.65 ± 3.55	Randomized controlled and Triple-blind Clinical Trial

* C = Control; P = Practice.

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Pimenta et. al.[19] demonstrated through physiological parameters that the EO has an action on autonomic excitability, however the results obtained by Chaves Neto et. al.[20] in crack users contradict this result as they did not find significant differences between the groups regarding heart rate and diastolic pressure after applying the SPS.

Findings described by Dehghan and Kalani[17] in their study with patients who were candidates for coronary artery implantation and used Oxazepam as a positive control, showed not only that there was a decrease in anxiety levels in the group that received 1 mL of *C . aurantium*, but also that the decay in the group that received Oxazepam was not significant, despite both being effective in controlling preoperative anxiety. These results collaborate with those found by Pimenta et al.[19] who used STAI and physiological measures such as blood pressure and heart and respiratory rate, in three groups that received DZP, EO and saline as, respectively, positive control, analyte and negative control or placebo. As results, it was noted that the use of the *C. aurantium* OE led to a decrease in STAI-S points while there was no significant decay in the placebo and DZP groups. These findings allow us to hypothesize that *C. aurantium* EO is not only effective but also sometimes more efficient than currently prescribed drugs.

LIMITATIONS

The results from the current review need to be interpreted cautiously due to some limitations. Although there are studies that describe the anxiolytic effect of *Citrus aurantium*, not all address its exact mechanism of action, mostly just mentioned, and even when investigated, sometimes there are contradictions between the results.

CONCLUSIONS

The studies analyzed in this integrative review showed that *Citrus aurantium* acts positively on anxiety.

Regarding the pharmacological mechanism, after analyzing the results, it is possible to suggest that the probable mode of action of Citrus aurantium is the interaction with serotonergic receptors, subtype 5-HT 1A, instead of GABA receptors.

Due to some limitations, further research should be carried out to provide more insights into the relation between *Citrus aurantium* and anxiety disorders.

REFERENCES

1 - Braga JEF. Pordeus LC, Silva ATMC, Pimenta FCF, Diniz MFFM, Almeida RN. **Pathological anxiety: neural bases and advances in the psychopharmacological approach**. Rev Bras Ciênc Saúde. 2010;14(2):93–100

2 - Owens MJ, **Nemeroff CB. The ole of HLC in the pathophysiology of affective disorders.** John Wiley & Sons, New York, 1993. (Laboratory and Clinical Studies, 172).

3 - Organização Mundial de Saúde-OMS. **Depression and other common mental disorders: global health estimates** [Internet]. Geneva: WHO; 2017[cited 2017 Nov 04]. Available from: http://apps.who.int/iris/bitstream/10665/254610/1/WHO-MSD-MER-2017.2-eng.pdf

4 - Fernandes MA, Vieira FER, Silva JS, Avelino FVSD, Santos JDM. **Prevalence of anxious and depressive symptoms in college students of a public institution**. Rev Bras Enferm.2018;71(suppl 5):2169-2175.

5 - Bortoluzzi MM, Schmitt V, Mazur CE. **Herbal effect of medicinal plants on anxiety: a brief review**. Research, Society and Development. 2020 1;9(1): e02911504.

6 - USDA United States Department of Agriculture (USDA), Natural Resource Conversation Service (NRCS), 24 September 2013. **The PLANTS Database**. http://plants.usda.gov National Plant Data Team, Greensboro, NC 27401–4901 USA.

7 - Mannucci C, Calapai F, Cardia L, Inferrera G, D'Arena G, Di Pietro M, et al. **Clinical Pharmacology of Citrus aurantium and Citrus sinensis for the Treatment of Anxiety**. Evidence-Based Complementary and Alternative Medicine. 2018:1–18.

8 - Costa CARA, Cury TC, Cassettari BO, Takahira RK, Flório JC, Costa M. **Citrus aurantium L. essential oil exhibits anxiolytic-like activity mediated by 5-HT1A-receptors and reduces cholesterol after repeated oral treatment.** BMC Complement Altern Med. 2013;13(1):42.

9 - Wolffenbüttel AN, Zamboni A, Becker G, dos Santos MK, Borille BT, de Cássia Mariotti K, et al. **citrus essential oils inhalation by mice: behavioral testing, gcms plasma analysis, corticosterone, and melatonin levels evaluation**. Phytotherapy Research. 2018;32(1):160–9

10 - Chaves G, Andrade HHN de, Braga JEF, Quintans LJ, Almeida RN de, Diniz M de FFM. **Non-clinical study of the anxiolytic effect of Citrus aurantium L. essential oil in an inclusion complex with 2-hydroxypropyl-ß-cyclodextrin**. Brazilian Journal of Basic and Applied Pharmaceutical Sciences. 2021;41, 705-717

11 - Saketi S, Bananej M, Jahromy MH**. Effect of citrus aurantium l. Essential oil and its interaction with fluoxetine on anxiety in male mice**. JBBS. 2014;04(07):285–90.

12 - Khosravi M, Khakpour S, Adibi L, Jahromy MH. **A study of the effect of citrus aurantium l. essential oil on anxiety and its interaction with gabaergic pathways in male mice**. JBBS. 2014;04(10):470–6.

13 – Silva SRF. **Farmacocinética do Diazepam** [master thesis on the internet]. Porto: Universidade Fernando Pessoa, 2013 [cited 2022 Feb 9]. Available from: http://hdl.handle.net/10284/3978

14 - Namazi M, Amir Ali Akbari S, Mojab F, Talebi A, Alavi Majd H, Jannesari S. **Aromatherapy with citrus aurantium oil and anxiety during the first stage of labor**. Iran Red Crescent Med J. 2014;16(6).

15 - Akhlaghi M, Shabanian G, Rafieian-Kopaei M, Parvin N, Saadat M, Akhlaghi M. Citrus aurantium blossom and preoperative anxiety. Rev Bras Anestesiol. 2011;61(6):707–12.

16 - Jafarzadeh M, Arman S, Pour FF. **Effect of aromatherapy with orange essential oil on salivary cortisol and pulse rate**

in children during dental treatment: A randomized controlled clinical trial. Adv Biomed Res. 2013;2(1):10.

17 - Dehghan K, Kalani Z**. Comparison of the effect of citrus aurantium and oxazepam on the preoperative anxiety of patients candidate for coronary artery implantation operation**. J. Res Med Dent SCI. 2018;6(2): 1-5.

18 - Moradi K, Ashtarian H, Danzima NY, Saeedi H, Bijan B, Akbari F, et al. **Essential oil from citrus aurantium alleviates anxiety of patients undergoing coronary angiography: a single-blind, randomized controlled trial**. Chin J Integr Med. 2021;27(3):177–82.

19 - Pimenta FCF, Alves MF, Pimenta MBF, Melo SAL, Almeida AAF de, Leite JR, et al. **Anxiolytic effect of citrus aurantium l. On patients with chronic myeloid leukemia: anxiolytic effect of citrus aurantium l.** Phytother Res. 2016;30(4):613–7.

20 - Chaves Neto G, Braga JEF, Alves MF, de Morais Pordeus LC, Santos SG dos Scotti MT, et al. **Anxiolytic effect of citrus aurantium l. In crack users**. Evidence-Based Complementary and Alternative Medicine. 2017:1–8.

21 - Farshbaf-Khalili A, Kamalifard M, Namadian M. **Comparison of the effect of lavender and bitter orange on anxiety in postmenopausal women: A triple-blind, randomized, controlled clinical trial**. Complementary Therapies in Clinical Practice. 2018; 31:132–8.

22 - Fluoxetine hydrochloride: **drug leaflet for health professional**. Eurofarma, 2016. Available at: -https://cdn.eurofarma.com.br//wp-content/uploads/2016/09/Bula_Cloridrato_Fluoxetina_Profissional.pdf

23 - Moslemi F, Alijaniha F, Naseri M, Kazemnejad A, Charkhkar M, Heidari MR. citrus aurantium aroma for anxiety in patients with acute coronary syndrome: a double-blind placebo-controlled trial. The Journal of Alternative and Complementary Medicine. 2019;25(8):833–9.