doi: http://dx.doi.org/10.11606/issn.1679-9836.v101i3e-183634 Rev Med (São Paulo). 2022 May-June;101(3):e-183634.

Review Article

Medicinal plants and herbal medications in mental health care in pandemic times: a literature review

Plantas medicinais e fitoterápicos no cuidado da saúde mental em tempos de pandemia: uma revisão da literatura

Ivan Justo de Mendonça Neto[1], Sabrina Santos Lourenço da Costa[1], Vinícius de Noronha Barboza[1], Clara Maria Germano Cidrack do Vale[1], Francisco Vitor Aires Nunes[2], Caio Augusto Martins Aires[2], Maiara de Moraes[2], Teresinha Silva de Brito[2*]

Mendonça Neto IJ, Costa SSL, Barbosa VN, Vale CMGC, Nunes FVA, Aires CAM, Moraes M, Brito TS. Medicinal plants and herbal medicines in mental health care in times of pandemic: a literature review / *Plantas medicinais e fitoterápicos no cuidado da saúde mental em tempos de pandemia: uma revisão da literatura.* Rev Med (São Paulo). 2022 May-June;101(3):e-183634.

ABSTRACT: Although the use of medicinal plants to treat health problems is traditionally accepted, this practice of Popular Medicine still finds resistance from health professionals, especially under the allegation of lack of scientific proof of its effects. During the COVID-19 outbreak, there was a significant increase in stress, anxiety and insomnia symptoms, and the use of plants and herbal medications emerged as a possible therapeutic alternative. The objective of this study was to conduct a literature review about the effectiveness of medicinal plants as an alternative and/or complementary therapy for anxiety and insomnia disorders. The main medicinal plants were selected from the Phytotherapeutic Formulary and Phytotherapeutic Memento of the Brazilian Pharmacopoeia, using the 'scientific name' and the terms 'anxiety' and 'insomnia' as descriptors between 2015 and 2020. 230 results were found and 42 studies were selected (27 in humans and 15 in animals). Anxiolytic effects have been demonstrated for *Cymbopogon citratus*, *Lavandula officinalis*, *Melissa officinalis*, *Passiflora incarnata* and *Valeriana officinalis*, as well as sedatives effects for *M. officinalis*, *P. incarnata* and *V. officinalis*. *Piper methysticum* only revealed a sedative effect and *Matricaria chamomilla* showed anxiolytic clinical efficacy. Consequently, the potential clinical application of these plants in the treatment of anxiety and insomnia symptoms is indicated, helping to reduce the psychological symptoms resulting from the COVID-19 pandemic. However, it is worth emphasizing the need to standardize methodological procedures and advance phytotherapy in the medical practice.

Keywords: Medicinal plants; Herbal medicine; Anxiety; Insomnia; COVID-19.

RESUMO: Apesar do uso de plantas medicinais para tratamento de problemas de saúde ser tradicionalmente aceito, esta prática da medicina popular ainda encontra resistência por profissionais da saúde, sobretudo sob a alegação da falta de comprovação de seus efeitos. Durante o surto de Covid-19, houve aumento significativo do estresse, sintomas ansiosos e insônia e o uso de plantas medicinais e fitoterápicos surge como uma alternativa terapêutica.

1. Medical student at *Universidade Federal Rural do Semi-Árido* – UFERSA, Mossoró, Rio Grande do Norte, Brazil. ORCID: Mendonça-Neto IJ - https://orcid.org/0000-0001-9028-3769; Costa SSL - https://orcid.org/0000-0002-7445-1512; Barboza VN - https://orcid.org/0000-0001-9427-5723; Vale CMGC - https://orcid.org/0000-0001-9128-1087. E-mail: ivan.neto@alunos.ufersa.edu.br, sabrina.costa15368@alunos.ufersa.edu.br, vinicius.barboza@alunos.ufersa.edu.br, clara.vale@alunos.ufersa.edu.br.

2. Professor of the Medical Course of the Health Sciences Department at *Universidade Federal Rural do Semi-Árido* - UFERSA, Mossoró, Rio Grande do Norte, Brazil.ORCID: Nunes FVA - https://orcid.org/0000-0001-6262-4087; Aires CAM - https://orcid.org/0000-0001-6577-374X, Moraes M - https://orcid.org/0000-0002-0602-4594, Brito TS - https://orcid.org/0000-0003-1713-9415. E-mail: vitor.nunes@ufersa.edu.br, caio.aires@ufersa.edu.br, maiara.moraes@ufersa.edu.br, teresinha.brito@ufersa.edu.br.

[*] **Correspondence**: Universidade Federal Rural do Semi-Árido, Departamento de Ciências da Saúde; Av. Francisco Mota, 572 - Bairro Costa e Silva – CEP 59625900 - Mossoró, RN – Brazil. E-mail: teresinha.brito@ufersa.edu.br.

O objetivo deste estudo foi realizar uma revisão da literatura sobre a eficácia de plantas medicinais como terapia alternativa e/ou complementar para transtornos de ansiedade e insônia. As plantas investigadas foram selecionadas a partir do Formulário de Fitoterápicos e Memento Fitoterápico da Farmacopeia Brasileira, sendo utilizados como descritores o nome científico da planta e os termos "anxiety" e "insomnia" com recorte temporal de 2015 a 2020. 230 resultados foram encontrados, 42 selecionados (27 em humanos e 15 em animais). Foi possível demonstrar efeitos ansiolíticos para as plantas capim santo (*Cymbopogon citratus*), lavanda (*Lavandula officinalis*), melissa (*Melissa officinalis*), maracujá (*Passiflora incarnata*) e valeriana (*Valeriana officinalis*) e sedativos para melissa, maracujá e valeriana. A kava-kava (*Piper methysticum*) demonstrou apenas efeito sedativo e a camomila (*Matricaria chamomilla*) apresentou eficácia clínica ansiolítica. Portanto, a potencial aplicação clínica dessas plantas é indicada para tratamento dos sintomas de ansiedade e insônia, ajudando a reduzir os sintomas psicológicos decorrentes da pandemia de Covid-19. Contudo, vale ressaltar a necessidade da padronização dos procedimentos metodológicos e avanço da fitoterapia na prática médica.

Palavras-chave: Plantas medicinais; Fitoterapia; Ansiedade; Insônia; COVID-19.

INTRODUCTION

The epidemic by the new coronavirus, SARS-CoV-2, emerged in 2019 in Wuhan, China, to then become a pandemic affecting several countries, Brazil among them. Due to the growing number of cases, together with other entities, the World Health Organization (WHO) started to recommend physical distancing, social isolation and quarantine measures[1]. Such measures, linked to fear of COVID-19 and to the large amount of information about the virus in the media, acted as stress factors and exerted a major impact on the mental health of the population. Many individuals started to present anxiety symptoms such as palpitations and excessive fear, in addition to depressive symptoms such as lack of energy and sleep disorders such as insomnia[2].

Ettman et al.[3] reported a significant increase in depressive symptoms among American adults since the beginning of the pandemic, whereas Park and Park[4] indicated that family members of infected patients or individuals with suspected COVID-19 already present symptoms that can progress to chronic mental disorders, such as lack of energy, anger, anxiety and difficulty concentrating. In this context, Portella et al.[5] reinforced the importance of medicinal plants as an alternative to help prevent mental health problems during and after the COVID-19 pandemic. It is worth highlighting that medicinal plant-based drugs often act on several targets and are usually not related to chemical dependence, which is commonly observed with traditional anxiolytic drugs[6,7].

Brazil is the country with the highest number of Generalized Anxiety Disorder (GAD) cases in the world, with a prevalence rate of 9.3%[8] a rate of depression cases of approximately 4.1%[9], a concerning situation, as depression and anxiety are the fifth and sixth leading causes of work inability, respectively[10], and can be aggravated by the effects of the COVID-19 pandemic. Such scenario points to the need to conduct more studies on plants with soothing effects. Therefore, this study aimed at gathering diverse evidence from clinical and pre-clinical studies on the effectiveness of medicinal plants and herbal medications in the treatment of anxiety disorders and insomnia, especially in mental health care in pandemic times.

METHODS

Search criteria for the articles

A bibliographic research was conducted from October to November 2020 in the Medline/PubMed and LILACS databases. The descriptors used were the plants' scientific names and the terms "anxiety" and "insomnia", connected by the "AND" and "OR" Boolean operators (e.g. *Matricaria chamomilla* AND anxiety OR insomnia). For selection of the medicinal plants, the study included those identified in monographs found in the Phytotherapeutic Formulary[11,12] and/or the Phytotherapeutic Memento of the Brazilian Pharmacopoeia[13] with official indications for the treatment and/or prevention of anxiety symptoms and sleep-inducing activity. In this sense, eight medicinal plants were included in this study: *Matricaria chamomilla* L. (Chamomile); *Melissa officinalis* L. (Lemon Balm); *Lippia alba* (Mill.) N.E. Br. ex Britton & P. Wilson (Bushy Matgrass); *Lavandula officinalis* Chaix (Lavender); *Cymbopogon citratus* (DC.) Stapf (Lemon Grass); *Valeriana officinalis* L. (Valerian); *Passiflora incarnata* (Passion Fruit) and *Piper methysticum* G. Forst (Kava-kava).

Criteria to select the articles

The following inclusion criteria were used: study design/primary articles (pre-clinical, clinical or observational studies) that were fully available, published in the last five years (from 2015 to 2020) in English, Portuguese or Spanish, and addressing the soothing effect of the medicinal plants selected. The articles excluded were those repeated between the databases, as well as review studies or those that did not address the use of medicinal plants in the topic in question.

Data extraction

Data extraction was in charge of two reviewers. The data recorded on the collection spreadsheet included the following: author/date; plant species; common name; type of study; objective; usage and dosage of the plant; methods for assessing the soothing properties of the plants; main results and conclusions of the studies.

RESULTS

A total of 230 results were found in the databases: 220 studies in Medline/PubMed and 10 in LILACS. After reading titles and abstracts and applying the eligibility criteria, 52 articles were selected for full reading, of which 42 were included in the current study. The flowchart corresponding to selection and application of the criteria is presented in Figure 1.

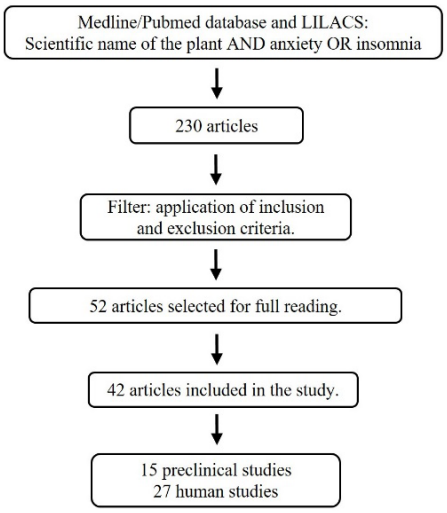

Figure 1. Methodology used in selection of the articles

The main effects of the medicinal plants included in the current review can be seen in Chart 1.

Chart 1. Main effects observed in the medicinal plants evaluated.

Effect	Medicinal Plants
Anxiolytic	Lemon Grass, Lavender, Lemon Balm, Passion Fruit and Valerian [a, b]
	Chamomile [b]
Sedative	Lemon Balm, Passion Fruit and Kava-kava [a]
	Lavender, Lemon Balm and Valerian [b]
Antidepressant	Lemon Balm [a, b]
	Lavender [a]
	Valerian [b]

a = Pre-clinical study; b = Clinical study

Of the 42 articles included in the study, 15 studies were pre-clinical and 27 were conducted in humans, of which 17 were double-blind randomized controlled clinical trials, two were single-blind randomized controlled clinical trials, two were crossed randomized controlled clinical trials, two were open randomized clinical trials, two were non-randomized pilot studies, and two were observational studies. Bushy matgrass (*Lippia alba*) was the only plant species about which no study had been found according the criteria adopted.

The methods used to the assess the soothing properties of the plants in the pre-clinical studies using experimental models with rodents mainly included assessing anxiety behaviors, social interaction and spontaneous motor activity[14], elevated plus maze and forced swim tests[15,16], open field test[17], time to sleep and duration of induced sleep[18,19], in addition to measurement of the melatonin blood levels[19,20]. In the models using zebrafish, anxiolytic activity was assessed through parameters related to the animals' mobility during light *versus* dark periods before and after being exposed to the derivatives of the plants studied[21-23]. Locomotive activity trials were also conducted in the models with fruit flies[24,25].

To assess efficacy of the plants investigated in the studies conducted with humans, various scientifically validated questionnaires and scales were used, with the following standing out: for the measurement of anxiety, the Hamilton *Anxiety Rating Scale* (HAM-A)[26-32] and the *State-Trait Anxiety Inventory* (STAI)[33,34]; the *Visual Analog Scale* (VAS) to assess pain or anxiety[34-38], the *Depression Anxiety and Stress Scale* (DASS-21)[39], and the *Dental Anxiety Scale* (DAS), proposed by Corah[40-42]. Antidepressant activity was assessed using mainly the *Hamilton Depression Rating Scale* (HDRS)[29,32] and *Beck Depression Inventory* (BDI)[28,29,43,44]. Regarding the evaluation of the sedative or sleep inducing effects, the most frequently used questionnaire was PSQI (*Pittsburg Sleep Quality Index*)[26,27,32,39,45]. The studies by Roh et al.[46] and Mineo et al.[47] differed from the others because they proposed to study changes in the brain circuits induced by the use of valerian by assessing electroencephalogram (EEG) and transcranial magnetic stimulation, respectively. Chart 2 presents a summary description of the studies selected.

Chart 2. General characterization of the scientific articles selected.

Reference	Plant species/ Common name	Type of study	Study objective	Usage/ Dosage
Goes et al.[33]	*Cymbopogon citratus* (DC.) Stapf LEMON GRASS	Double-blind placebo controlled randomized clinical trial	To assess the potential anxiolytic effect of *C. citratus* aroma in healthy patients subjected to an anxiogenic situation	Inhalation of *C. citratus* (BioEssência®) essential oil in acute form (3 or 6 drops)
Mendes-Hacke et al.[21]		*In vivo* pre-clinical study	To investigate the anxiolytic properties of *C. citratus* and its isolate compounds citral and geraniol in an anxiety model using zebrafish	Immersion for 10 minutes in a solution containing *C. citratus* hydroalcoholic extract (1, 3 and 10 g/L), essential oil, citral or geraniol (1, 5 and 10 mg/L).
Umukoro et al.[14]			To assess the potential anticonvulsant and anxiolytic effects of *C. citratus* extract in mice	Oral administration of *C. citratus* aqueous extract (25, 50 and 100 mg/kg), 60 min before the behavioral observations
Hasanzadeh et al.[48]	*Lavandula officinalis* Chaix LAVENDER	Open and controlled randomized clinical trial	To investigate the effects of application of cold, inhalation of lavender essential oil or their combination in pain and anxiety in patients during removal of chest tube after surgery	Inhalation of 1-2 drops of lavender essential oil contained in a cotton ball during 20 minutes.
Nasiri et al.[43]		Crossed placebo controlled randomized clinical trial	To evaluate the efficacy of inhaling lavender essential oil for insomnia in patients with diabetes	Inhalation of 3 drops of lavender essential oil contained in a linen cloth for 5 min during 4 weeks
Tugut et al.[34]			To compare anxiety levels in women subjected to gynecological examination before and after consultation treated with aromatherapy with lavender oil or placebo	Inhalation of lavender essential oil at 10% dispersed by a lamp in the gynecological examination room for 10-15 minutes
Seifritz, Schläfke, Holsboer-Trachsler[26]		Double-blind placebo controlled randomized clinical trial	To evaluate if the improvement in sleep quality attributed to Silexan® is due to its primary anxiolytic effect or to its secondary sedative effect	Oral administration of 80 mg Silexan® a day for 10 weeks
Abbaszade, Tabari, Asadpour[37]			To assess the anxiolytic effect of lavender in patients undergoing bone marrow biopsy	Inhalation of 3 drops of lavender essential oil at 10% contained in a cotton ball during 15 min
Kasper, Anghelesc, Dienel[27]			To assess the efficacy of Silexan® in reducing the anxiety levels and improving sleep quality	Oral administration of a slow-release gelatinous capsule containing 80 mg of Silexan® a day during 10 weeks
Bazrafshan et al.[44]		Single-blind controlled randomized clinical trial	To assess the effect of lavender tea on the mean levels of depression, trace-anxiety and state-anxiety in older adults	Oral administration of lavender infusion (2 g of plant drug) twice a day during two weeks
Karaman et al.[35]			To assess the effectiveness of aromatherapy with lavender on pain, anxiety, and satisfaction level associated with peripheral venous cannulation in patients subjected to surgeries.	Inhalation of 2 drops of lavender essential oil at 1% contained in gauze for 5 min before cannulation and during the procedure
Jaruzel et al.[36]		Pilot observational study	To assess the use of lavender adhesive on the variability of anxiety and vital signs during the preoperative period for breast surgery.	Lavender adhesive assessed every 15 min after placement of the adhesive up to the start of anesthesia for the surgery (nearly 58 min)
Velasco-Rodriguez et al.[49]		Crossed non-randomized pilot study	To analyze the effect of aromatherapy with lavender oil on the melatonin serum levels in older adults	Inhalation of 5 drops of lavender essential oil at 100% diluted in 20 mL of water and placed in a disperser during 30 min, 2 sessions a week for 4 weeks
Rahmati et al.[15]		*In vivo* pre-clinical study	To study the effects of lavender extract on memory loss, anxiety, and depressive behavior induced by scopolamine in rats	Intraperitoneal administration of lavender hydroalcoholic extract (100, 200 and 400 mg/kg) 30 min before administration of scopolamine during 12 days
Shady, Nair, Crannel[50]		Open non-randomized prospective study	To examine the effects lavender oil adhesives on patients hospitalized in a Hematology-Oncology unit	Adhesives containing 55 mL of lavender essential oil adhered to patients' clothes during 6-10 h a night during 3 months

continue

Chart 2. General characterization of the scientific articles selected. *continuation*

Reference	Plant species/ Common name	Type of study	Study objective	Usage/ Dosage
Keefe et al.[30]	*Matricaria chamomilla* L. CHAMOMILE	Open placebo controlled randomized clinical trial	To analyze the effects of chamomile on the severity classifiers of Generalized Anxiety Disorder and its safety	Oral administration of chamomile capsules containing 500 mg of dry extract 3 times a day for 8 weeks
Mao et al.[28]		Double-blind placebo controlled randomized clinical trial	To assess the long-term use of chamomile to prevent the recurrence of Generalized Anxiety Disorder (GAD) symptoms	Oral administration of chamomile capsules containing 500 mg of dry extract 3 times a day for 26 weeks
Amsterdam et al.[29]		Open clinical trial	To examine the putative antidepressant effect of chamomile in individuals diagnosed with Generalized Anxiety Disorder with or without depression	Oral administration of chamomile capsules containing 500 mg of dry extract 3 times a day for 8 weeks
Haybar et al.[39]	*Melissa officinalis* L. LEMON BALM	Double-blind placebo controlled randomized clinical trial	To determine the effects of lemon balm on depression, anxiety, stress and sleep disorders in patients with chronic stable angina	Oral administration of 3 lemon balm capsules a day containing 1 g of extract during 8 weeks.
Heydari et al.[51]			To examine the effect of lemon balm on the psychological health of female adolescents	Oral administration of lemon balm capsules containing 600 mg of extract twice a day for 7 days of the menstrual cycle, during 3 cycles
Hajhashemi, Safaei[18]		*In vivo* pre-clinical study	To assess the hypnotic effect of *Coriandrum sativum*, *Ziziphus jujuba*, *Lavandula angustifolia* and *Melissa officinalis* on mice to select the most effective ones for a combined formula	Oral administration of lemon balm hydroalcoholic extract (200, 400 and 800 mg/kg) 1 hour before sleep induction
Ghazizadeh et al.[16]			To assess the effect of lemon balm on anxiety, depressive behavior, oxidative stress and apoptosis in mice	Oral administration of lemon balm hydroalcoholic extract (50, 75 and 150 mg/kg) for 14 days
Aman et al.[17]	*Passiflora incarnata* L. PASSION FRUIT	*In vivo* pre-clinical study	To evaluate the antinociceptive, anxiolytic and sedative activity of *P. incarnata* in a model of streptozotocin-induced diabetic neuropathic allodynia and vulvodinia in rats.	Oral administration of *P. incarnata* methanolic extract (150, 200 and 250 mg/kg) 30 min before allodynia induction
Guerrero, Medina[52]			To analyze the effect of *P. incarnata* extract on sleep in rats	Oral administration of *P. incarnata* hydroethanolic extract (500 mg/kg) for 7 days
Jawna-Zboińska et al.[53]			To evaluate the behavioral and neurochemical effects of long-term administration of *P. incarnata* in rats.	Oral administration of *P. incarnata* ethanolic extract (30, 100 or 300 mg/kg/day) for 7 weeks
Kim et al.[19]			To evaluate the sleep inducing effect of the *P. incarnata* extract in rodents.	Oral administration of *P. incarnata* hydroethanolic extract in a single dose (500 mg/kg or 250 mg/kg/day for 5 days
Kim et al.[54]			To evaluate the efficacy of repeated administration of *P. incarnata* on memory improvement in rodents	Oral administration of *P. incarnata* ethanolic extract (10, 50 or 100 mg/kg/day) for 3 days
Kim, Yi[20]			To evaluate changes in metabolic or behavioral patterns of *P. incarnata* extract in mice	Oral administration of *P. incarnata* ethanolic extract (500 mg/kg/day) for 5 days
Dantas et al.[40]		Double-blind controlled randomized clinical trial	To compare the effects of *P. incarnata* and Midazolam in controlling anxiety in patients undergoing extraction of the mandibular third molar	Oral administration of a *P. incarnata* tablet (260 mg) 30 min before the procedure
Rokhtabnak et al.[38]			To compare the sedative effect of preoperative melatonin and *P. incarnata* in patients subjected to elective surgeries	Oral administration of *P. incarnata* (1,000 mg) 1 h before the surgery
Lee et al.[45]			To investigate the effects of *P. incarnata* on polysomnographic sleep parameters in individuals with insomnia disorder	Oral administration of *P. incarnata* ethanolic extract (60 mg) for 2 weeks
Cunha et al.[41]		Triple-blind placebo controlled randomized clinical trial	To compare the effects of *P. incarnata*, *Erythrina mulungu* and Midazolam on anxiety control in patients subjected to extraction of the third molar	Oral administration of *P. incarnata* ethanolic extract (500 mg) 1 h before the procedure
Canella et al.[55]		Qualitative, exploratory and observational study	To explore the patients' experiences and perceptions about the use of *P. incarnata*	Oral administration of *P. incarnata* ethanolic extract, 9-10 drops a day for 6-8 weeks

continue

Chart 2. General characterization of the scientific articles selected. *continuation*

Reference	Plant species/ Common name	Type of study	Study objective	Usage/ Dosage
Wang et al.[22]	*Piper methysticum* G. *Forst* KAVA-KAVA	*In vivo* pre-clinical study	To assess the effects of acute and chronic exposures to kava-kava and kavalactones on anxiety, aggressiveness and sociability in adult zebrafish, as well as their neurochemical, neuroendocrine and genomic responses.	The fish were exposed to kava-kava aqueous extract (10, 20 and 50 mg/L) for 20 min or to kava-kava aqueous extract (5 mg/L) for 7 days
Sarris et al.[31]		Double-blind placebo controlled randomized clinical trial	To assess the efficacy and safety of kava-kava in the treatment of Generalized Anxiety Disorder	Oral administration of kava-kava standardized tablets (120 mg of kavalactones) twice a day for 16 weeks
Roh et al.[46]	*Valeriana officinalis* L. VALERIAN	Double-blind placebo controlled randomized clinical trial	To investigate the effects of valerian on functional brain connectivity in nonclinical volunteers suffering psychological stress.	Oral administration of a capsule containing valerian root ethanolic extract (100 mg) 3 times a day for 4 weeks
Mineo et al.[47]			To investigate the effects of valerian extract on cortical excitability in healthy adults	Oral administration of 3 capsules (300 mg) of valerian extract (900 mg in total) 1 h and 6 h before the experimental analysis
Farah et al.[42]			To assess the efficacy of valerian in controlling anxiety in patients during extraction of the third mandibular molar	Oral administration of a capsule containing valerian extract (100 mg) 60 min before the surgical procedure
Ahmadi et al.[32]			To evaluate the efficacy and safety of valerian in preventing the neuropsychiatric adverse events of Efavirenz in HIV-positive patients	Oral administration of a capsule containing powdered valerian root (530 mg) 1 h before sleep for 4 weeks
Torres-Hernandez et al.[23]		*In vivo* pre-clinical study	To establish an economical and accurate method to test the psychoactive efficacy of complex mixtures of crude plant extracts using zebrafish	Immersion in a solution containing valerian root extract (1-7 mg/mL) for 30 min before the experimental procedures
Choi et al.[24]			To assess the sleep promoting effect of valerian and lupulus, both isolated and combined, in fruit flies	Immersion in an agar-sucrose medium added with aqueous solutions of valerian extract (2-20 mg/mL) for 5 days
Jo et al.[25]			To evaluate the sleep enhancement activity of medicinal plants, including valerian, in a Drosophila model	Immersion in an agar-sucrose medium added with aqueous solutions of valerian extract (1-20 mg) for 5 days

The main results found in the articles selected according to the medicinal plants researched will be presented in the next topics.

***Cymbopogon citratus* - Lemon Grass**

The potential anxiolytic effect of *C. citratus* was addressed in three articles. Goes et al.[33] states that a brief inhalatory exposure to *C. citratus* essential oil in healthy patients subjected to an anxiogenic situation is able to promote anxiolytic effects immediately after administering the treatment (baseline anxiety levels), although there was no inhibition of the anxious response to the task. In animal models, Umukoro et al.[14] showed that *C. citratus* induced an anxiolytic effect and reduced spontaneous motor activity and social interaction through behavioral tests in mice. Using zebrafish, Mendes-Hacke et al.[21] showed a statistically significant reduction in anxiety, with probable involvement of the $GABA_A$ receptors.

***Lavandula officinalis* - Lavender**

Most of the studies with *L. officinalis* were conducted in humans; however, only three were double-blind controlled randomized clinical trials. Most of these studies showed statistically significant changes in the scores assessed, with a reduction in the anxiety rates and improvements in sleep duration and quality[15,17,26,27,34-37,43,44,48]. The exception was the study by Velasco-Rodriguez et al.[49], which only assessed changes in the melatonin serum levels, a hormone involved in sleep induction and that might be related to good sleep quality and duration. With regard to the effects of lavender on sleep, a study using herbal medication Silexan® indicates that, rather than a direct effect, the sedative effect of lavender is a secondary effect mediated by its anxiolytic action[26]. The clinical studies also showed analgesic[34,35,48] and antidepressant[44] effects. In the only pre-clinical study, Rahmati et al.[15] found a dose-dependent relationship in the reduction of anxious and depressive behaviors in rats.

***Matricaria chamomilla* - Chamomile**

Three studies were selected for *M. chamomilla*, all clinical trials[28,29,30]. Amsterdam et al.[29] showed a significantly greater reduction in the anxiety symptoms among patients diagnosed with anxiety disorder associated with depression when compared with patients only diagnosed with GAD. In addition, attenuation of the symptoms was shown in

patients with GAD, although with no change in the disease relapse risk[28]. Keefe et al.[30] noticed reductions in the anxiety symptoms, from severe and moderate to mild. It is worth highlighting that treatment with *M. chamomilla* for eight weeks[29] or 26 consecutive weeks[28] was considered safe, as no severe adverse effects were observed.

***Melissa officinalis* - Lemon Balm**

Four studies included in the current review evaluated the soothing effects of *M. officinalis*. The pre-clinical studies showed the dose-dependent sleep-inducing effect of lemon balm hydroalcoholic extract, similar to that of Diazepam, reducing time to sleep initiation and increasing sleep duration, in addition to reducing anxiety and depressive behavior[16,18]. In addition to that, lemon balm extract inhibited oxidative stress and apoptosis pathways in the prefrontal cortex and hippocampus of mice[16].

Heydari et al.[51] selected 100 participants diagnosed with premenstrual syndrome and noticed improvements in the symptoms related to anxiety, sleep disorders and social function disorder. The authors considered treatment with *M. officinalis* as a good alternative to the use of synthetics psychotropic drugs, with the possibility of being used to treat anxiety, insomnia and depression. In turn, Haybar et al.[39] studied the effects of this plant on fighting against psychosomatic symptoms in patients with stable angina, observing an improvement in the anxiety, depression, stress and sleep scores when compared to the control group.

***Passiflora Incarnata* - Passion Fruit**

The effects of *P. incarnata* were evaluated in various types of studies, both in animals and in humans, totaling 11 studies selected. The sedative effect of *P. incarnata* was evaluated in animal models, noticing an increase in total sleep time[52], in addition to increased eyelid closure time and immobility in rodents[19] and a sleep-inducing effect[17,53]. In turn, the assessment of the anxiolytic effect revealed that rodents treated with *P. incarnata* presented lower anxiety levels[17,53] and significantly reduced levels of corticortrophin-releasing hormone and glucocorticoid receptors[53]. In the study by Aman et al.[17], the anxiolytic and sedative activity of passion fruit was similar to that of Diazepam. Treating animals with *P. incarnata* extract also led to an increase in the brain-derived neutrophic factor[54] and in the melatonin blood levels[19,20], as well as an improvement in memory[53,54].

In humans, the sedative effect of *P. incarnata* was only assessed in one study[45], where a significant increase was observed in total sleep time in the participants who used the extract. However, sleep efficiency was not statistically different between the *P. incarnata* and placebo groups. On the other hand, an observational study conducted by Canella et al.[55] presented favorable results to the use of *P. incarnata* due to its anxiolytic effect, reported by six of the eight participants. The anxiolytic effect of *P. incarnata* was also assessed in patients subjected to extraction of the third molar and to elective surgeries. In extraction of the third molar, the anxiolytic action of *P. incarnata* was similar to that of Midazolam and superior to that of the placebo[40,41]. In elective surgeries, pre-treatment of patients with *P. incarnata* reduced anxiety in a similar manner to that of melatonin and exerted a sedative effect lower than that of melatonin, although its action caused fewer side effects[38].

***Valeriana officinalis* - Valerian**

Seven studies evaluated the effects of *V. officinalis*, most of them being clinical trials. The plant induced a significant anxiolytic and relaxing effect during extraction of the third molar in humans and, contrary to Midazolam, no adverse effects such as blood pressure reduction or retrograde amnesia were observed, although valerian was less effective than Midazolam[42]. Valerian was also able to reduce suicidal thoughts and improve sleep and anxiety in a study conducted with 51 HIV-positive patients using Efavirenz, a medication that causes adverse psychiatric effects[32].

In studies using rest EEG and TMS in humans, valerian extract showed anxiolytic capacity through changes in the brain circuits and reduced intracortical facilitation[46,47].

In the pre-clinical experimental studies involving animal models, valerian extract did not induce any significant sedative effect in zebrafish, although it was able to reverse the effects of Pentylenetetrazole, an anxiogenic agent[23]. In fruit flies, valerian extract was able to reduce locomotive activity, showing a sedative effect[24,25].

***Piper methysticum* - Kava-kava**

Only two studies evaluating the effects of *P. methysticum* were included in this review: one was a clinical trial and the other, a pre-clinical trial. Sarris et al.[31] assessed the efficacy of *P. methysticum* aqueous extract against GAD in a study involving 171 patients, although this extract did not show to be effective for this condition. In a study conducted with zebrafish, Wang et al.[22] observed reductions in all the parameters and associated this finding with a dose-dependent sedative effect. Both studies assessed the risk for herb-induced liver injury and, although the patients in the clinical study who received *P. methysticum* presented more frequent anomalies in the liver function tests, no participant met the criteria for herb-induced liver injury. Consequently, the studies considered *P. methysticum* as relatively safe for chronic use.

DISCUSSION

The current article gathered diverse evidence on the anxiolytic and/or sedative effects of eight commonly used plant species, either in the form of medicinal plant preparations (extracts, infusions, essential oils) or of

traditional phytotherapy medications or products. In a qualitative study, Rosa et al.[56] observed that the main therapeutic action investigated in the use of herbal medications in Primary Health Care was the soothing effect for the treatment of anxiety symptoms. Meanwhile, the authors reported failures in dissemination of the results of studies to medical professionals, showing the need to increase the number of studies such as the current one, in order to gather diverse scientific evidence on the phytotherapy practice.

As the plants selected in the current approach are recommended by the Brazilian Ministry of Health for the treatment or as a complementary therapy for anxiety and sleep disorders[11–13], it is important to highlight the large number of clinical trials identified, as these studies (comparative, double-blind and randomized), are considered the gold standard to verify the efficacy of medications[57]. However, there is still resistance from the professionals to prescribe and use these plants, which is partially explained by the limited integration between popular and scientific knowledge[6], as well as by the failure in including content on phytotherapy in medical curricula[56,58].

Assessing the efficacy of medicinal plants in general is a complex task, as the chemical composition of the herbal preparations depends on several factors, such as genetic and environmental differences, quality of the soil, differences in the plant parts used, time of harvest and preparation methods, among others[59]. This complexity in preparation of the plants' extracts hinders development of evidence-based phytotherapeutic products[60]. Therefore, it is difficult to produce standardized extracts with reproducible chemical compositions and, thus, with reproducible pharmacological activities, especially when the extracts are produced by different manufacturers[59,61,62].

In the current review, it is also noted that six plant species (lemon grass, lavender, lemon balm, passion fruit, chamomile and valerian) presented anxiolytic effects confirmed in the clinical trials analyzed. The exception was kava-kava (*P. methysticum*), which presented a sedative effect and a reduction of the anxiety levels in an animal model but did not show any anxiolytic effect in the only clinical trial evaluated. Such result can be justified by the plant's low tolerability, which limits the dose to be employed[63], as well as by the complexity of the pharmacological treatment for GAD, as efficacy of the recommended drugs is highly variable[64]. Although recent reviews have shown inconsistent long-term results with regard to the efficacy of kava-kava in the treatment of anxiety, this plant represents an option for non-pathological anxiety[64,65] and is officially indicated for the treatment of mild to moderate anxiety symptoms in the short-term (1-8 weeks of treatment)[11].

Modulation of the GABaergic system is one of the main mechanisms responsible for the anxiolytic effects of synthetic medications[67] and it also mediates the anxiolytic effects of the plants analyzed[9,33,43,52,67]. According to the National Health Surveillance Agency (*Agência Nacional de Vigilância Sanitária*, ANVISA), chamomile (*M. chamomilla*) has been recommended for sedative and anxiolytic purposes[13]. However, only its anxiolytic effects were evaluated in the studies selected[28-30]. A pre-clinical research study conducted by Avallone et al.[68] revealed the pharmacological effects of chamomile mediated by modulation of the GABAergic system, highlighting flavone apigenin as one of the active ingredients, which acts as a benzodiazepine receptor ligand with anxiolytic activity. In turn, Yamada et al.[69] observed that chamomile oil vapor modulated secretion of the adrenocorticotropic hormone in mice, suggesting that it was one of the action mechanisms of chamomile in reducing anxiety.

In vitro studies have already shown the anxiolytic activity of lemon balm (*M. officinalis*) aqueous and methanolic extracts through increased GABA levels due to inhibition of GABA-transaminase, an enzyme responsible for degrading the GABA neurotransmitter and a target in the therapy for anxiety, epilepsy and other related neurological disorders[17,70]. In the current review, the efficacy of lemon balm extract was shown after several days of use[16,18]. However, Aldave et al.[71] obtained significantly positive results immediately after the first administration of lemon balm ethanolic extract in children who subsequently underwent dental treatments, showing the acute anxiolytic effect attributed to the plant. Corroborating these findings, in a double-blind randomized trial using lemon balm extract and placebo, acute use of lemon balm (600 mg) led to a significant increase in self-reported calmness and to a reduction in the alert state in individuals by means of a defined-intensity stressor simulation test[72].

Passion fruit (*P. incarnata*) is an important medicinal plant in herbal medicine to treat anxiety or nervousness, GAD, symptoms of opioid abstinence, insomnia, neuralgia and seizures, among others conditions[73]. Its main constituents include alkaloids such as chrysin, flavonoids like isovitexin and *schaftoside*, and phenolic compounds[74]. The anxiolytic activity of passion fruit was also postulated from modulation of the GABAergic system through inhibition of GABA uptake and modulation of the GABA receptor complex[53,75,76].

In the current review, two clinical trials assessed the anxiolytic efficacy of Silexan®, an oral preparation of lavender (*L. officinalis*) oil capsules. The results obtained by Woelk and Schlafke[77] showed that Silexan® effectively improves generalized anxiety in a way comparable to benzodiazepine Lorazepam, a traditional anxiolytic that acts by potentiating the inhibitory action of the GABA neurotransmitter, corroborating these studies. However, the anxiolytic and antidepressant effects attributed to the lavender essential oil and its main components, such as linalool, can also be attributed to an antagonism in the glutamate N-methyl-d-aspartate (NMDA) receptor and to

inhibition of the serotonin transporter (SERT)[78].

Valerian (*V. officinalis*) is officially indicated as a moderate sedative and hypnotic, and in the treatment of anxiety-related sleep disorders; in addition, it is commonly used in the form of standardized herbal medicationss[13]. In the current review, it stood out as the plant with the highest number of double-blind randomized controlled clinical trials, four in total, in which its anxiolytic and sedative actions were evidenced[32,42,46,47,79,80]. Awad et al.[70] showed that valerian stimulated the activity of glutamic acid descarboxylase (GAD), an enzyme that participates in the formation of GABA and exerts an influence on the brain levels of GABA and its neurotransmission, revealing a probable mechanism involved in its pharmacological properties.

The anxiolytic potential of lemon grass (*C. citratus*) was also analyzed in the studies selected, and the study by Mendes et al.[21] showed the involvement of the $GABA_A$ receptors in the anxiolytic action mechanism of this plant. In fact, participation of the $GABA_A$ receptors in the soothing effects of lemon grass had already been previously reported[81].

It is worth emphasizing that, within the time frame analyzed, no study was selected involving medicinal species *L. alba*, popularly known as bushy matgrass, a species native to the Atlantic Forest[82]. This plant is widely used in Brazil[83] and is indicated in the Herbal Medicines Formulary as a mild anxiolytic and sedative[11]; however, the need to conduct controlled clinical trials to validate its clinical efficacy in the context of mental health is highlighted.

Despite showing the anxiolytic and/or sleep-inducing effect of most of the plants evaluated, the current review highlights that, in spite of consistent pre-clinical evidence, not all clinical studies showed anxiolytic and/or sedative efficacy for the plants investigated. The main experimental models were developed in rats, mice, flies, and zebrafish, which were mostly subjected to previously induced stress to subsequent assess the effect of the plant species. The main limitations of these studies involved the difficulty approaching anxiety, as animal models are not able to completely reproduce the physiological, physiopathological or behavioral characteristics found in humans[80,84,85]. In addition to that, it is important to consider that, when administered in humans, the plant constituents are significantly metabolized via enzymatic and hepatic processes, being biotransformed into new chemical structures. Thus, it is not always possible to extrapolate the diverse evidence of the pre-clinical trials to clinical efficacy in human beings[61].

In the clinical studies, the most common administration route was oral, through capsules containing the extract of the plant species or through infusions, in addition to modalities such as aromatherapy and massage therapy. The oral route is more convenient due to practicality and safety[86]; it also stands out as the main administration route for homemade preparations of medicinal plants in the form of infusions or decoctions[87]. However, the studies with *C. citratus* and *L. officinalis* used aromatherapy with essential oil. Nevertheless, it is important to highlight the difficulty standardizing doses in these studies, which mostly adopted drops as a unit of measurement, varying from 2 to 6 drops, with time measured in minutes, varying from 5 to 30 minutes.

In addition, in the clinical studies the anxiolytic and sedative effects were mainly measured by means of scales and questionnaires, which are assessment instruments susceptible to subjectivity[88]. It is important to highlight the significant variety of instruments used, in addition to the different methodologies and parameters, which hinders comparing the various studies analyzed. It is also worth noting the significant variability of what would be considered as "chronic exposure", varying from 4 weeks[89] to 16 weeks[31]. A probable explanation could be related to the time that each active ingredient of the different plants takes to accumulate to the point of maintaining its concentration stabilized within a therapeutic window in the period between doses[90].

Despite the aforementioned limitations, one of the factors that motivate the search for new anxiolytics is the concern with the adverse effects of the current drugs[57], which can be evidenced by the relevant prevalence of patients with anxiety disorders who use medicinal plants and herbal medications, accounting for more than 20% of these subjects[91]. Although herbal medications are not free from undesired effects and drug interactions, they are not usually associated with chemical dependence[6]. In this sense, the clinical studies selected that evaluated the occurrence of adverse events during the treatment with medicinal plants point to their safety[27,31,42,79]. It is important to note the study by Ozturk and Kalyaci[92], which analyzed safety of *P. incarnata* in pregnancy and identified neonatal death and other complications during childbirth. The authors emphasize that the fact that herbal medications are natural products does not mean that they are always safe, especially during pregnancy.

Therefore, the current study emphasizes that, despite the limitations in validation of the pharmacological properties of medicinal plants in the mental health context, phytotherapy stands out as an integrative and complementary practice supported by diverse scientific evidence, with the possibility of assisting in the reduction of anxiety and insomnia symptoms.

Progress in the field of Medicinal Plant Pharmacology depends on standardized trials that explore various fields, such as the following: the neurochemical pathways specifically implied in the pathogenesis of psychiatric disorders and the respective medicinal plants and herbal medications that are known to affect these pathways, the polymorphisms of P450 cytochrome and P-glycoprotein

that affect metabolization of the active constituent of the phytotherapy medication, and the epigenetic differences affected between individual active constituents *versus* whole extracts[61]. It is therefore expected that the main challenges in research in the phytotherapy area for the validation of popular knowledge are overcome based on good quality scientific evidence.

CONCLUSIONS

The current review showed the anxiolytic effects to the following medicinal plants: lemon grass (*C. citratus*), lavender (*L. officinalis*), lemon balm (*M. officinalis*), passion fruit (*P. incarnata*) and valerian (*V. officinalis*), as well as the sedative effects to lemon balm, passion fruit and valerian, which were evidenced both in pre-clinical and clinical studies. Plants such as kava-kava (*P. methysticum*) only had their sedative effect evidenced in a pre-clinical study, whereas chamomile (*M. chamomilla*) presented clinical anxiolytic efficacy. In addition, antidepressant effects were reported for lavender and lemon balm in the pre-clinical studies, as well as for lemon balm and valerian in the clinical studies. It is therefore emphasized that the medicinal plants analyzed may be especially useful in the treatment of anxiety and insomnia symptoms by assisting in the reduction of the psychological symptoms resulting from the COVID-19 pandemic; however, investments are necessary to better standardize the research studies in the area of phytotherapy.

Acknowledgments: To *Universidade Federal do Semi-Árido* (UFERSA) and to the Extension and Culture Dean's Office (*Pró-Reitoria de Extensão e Cultura*, PROEC) (UFERSA) for their financial and institutional support.

Authors' participation: *Mendonça-Neto IJ, Costa SSL, Barboza VN, Vale CMGC*: conception of the study; bibliographic review; data search, analysis and interpretation; and preliminary writing of the manuscript. *Nunes FVA, Aires CAM, Moraes M, Brito TS*: conception of the study; data interpretation; critical intellectual review; and final writing of the manuscript. All the authors took part in final approval of the manuscript for publication.

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Received: March 26, 2021
Accepted: April 12, 2022