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International Journal of Family & Community Medicine

Research Article

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Generalized anxiety: a systematic review *Passiflora incarnata* (passion fruit), *Matricaria recutita* (Chamomile) and *Melissa officinalis* (lemongrass)

Abstract

The goal was to Develop a systematic review of randomized clinical trials, Masked and controlled with or standard placebo drug on the safety and efficacy of *Passiflora incarnata* (passion fruit), *Matricaria recutita* (chamomile) and *Melissa officinalis* (lemon balm) to Generalized Anxiety Disorder treatment. The articles were fetched in PubMed, Scielo and Google Scholar date basis. Selected articles met the eligibility criteria That Were Evaluated and detailed in tables containing the authors, location, year, inclusion and exclusion criteria, results, verified by validated efficacy criteria for diagnosis and prognosis of GAD and the existence of interest conflicts. There were selected only 7 of the 1471 articles found. In studies with Passiflora incarnata, there was a significance of the Passiflora Compared to placebo effect and the standard drug, getting Decreased anxiety without inducing sedation. The study was conducted with Matricaria recutita, suggesting it may have mild anxiolytic effects in anxiety cases. Two studies were carried out with Melissa officinalis, one with interest conflicts, and another suggesting que its use may be adequate and secure. The conclusion is que was used to low sample size in the seven studies included, showing inconclusive results, the presence of conflicts of interest as well as several types of biases. Thus, the are scientific evidences insufficient to prove the efficacy and prescription guided by scientific evidence of phytotherapy these medicines for Generalized Anxiety Disorder.

Keywords: anxiety, phytotherapic and clinical trial, dry mouth, sweating, chills, tremor, vomiting, palpitations, and abdominal pain, pathological anxiety

Volume 3 Issue 5 - 2019

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Received: September 20, 2019 | **Published:** October 10, 2019

Abbreviations: GAD, generalized anxiety disorder; HPA, hypothalamic-pituitary-adrenal; DSS, cerebral protection system; HM, hypothalamus medial; SCI, behavioral inhibition system; SCP, periaqueductal gray; ACTH, Adrenocorticotropic hormone; BZD, benzodiazepines; DAS, dental anxiety scale

Introduction

The use of medicinal plants with healing purpose and treatment of diseases accompanying human societies since the beginning of its existence. Marques postulated that even with the globalization of the chemical industry and the use of synthetic drugs, products from medicinal plants still hold a share of the world market, 14 billion of an estimated $ 280 billion (about 5% of the world market pharmaceuticals). In Brazil, the estimated amount spent on herbal medicines is of the order of 300 million dollars, relatively low; representing approximately 4% of the total pharmaceutical market in the order of $ 7.4 million; when compared with the values of Europe and the United States in 2000, equivalent to 8.5 and 6.3 billion dollars respectively.[1,2] Generalized Anxiety Disorder (GAD) is among the disorders the most common currently found anxiety, approximately 12% of the population, according to the Institute of Psychiatry, Hospital das Clinicas, University of São Paulo, research conducted in 2011, which is almost 24 million Brazilians with pathological anxiety.[3] Among its symptoms include involuntary bodily manifestations such as dry mouth, sweating, chills, tremor, vomiting, palpitations, and abdominal pain. The most recommended herbal remedies for anxiety is kava (Kava), Passiflora incarnata, Valeriana officinalis, Ginkgo biloba, glauca Galphimia, *Melissa officinalis* (lemon balm) and *Matricaria recutita* (chamomile); allopathic drugs most commonly used to treat anxiety are Diazepam, Buspirone, Clonazepam, Sertraline, among others.[4,5] The aim of this study was to develop a systematic review on Randomized, controlled clinical trials with *Matricaria recutita* (camomile), *Melissa officinalis* (Lemon balm) and *Passiflora incarnata* (passion fruit) for Generalized Anxiety Disorder (GAD). The specific objectives of the study include identifying clinical studies on the efficacy and safety of *Matricaria recutita* (Chamomile), *Melissa officinalis* (lemon balm) and *Passiflora incarnata* (passion fruit) for the treatment of GAD; describe the characteristics of these herbal medicines and provide clinical evidence for the correct prescription and rationalized these herbal medicines. Despite the advances noted in treating GAD in recent years, it is estimated that less than 50% of patients suffering from total remission of symptoms.[6] So this review is justified by the fact that pharmacotherapeutic alternative may be required. And considering that herbal pharmaceuticals are freely available and can be directly linked to self-medication, prescription and use must be made safely, rational and guided by scientific evidence.

Methodology

Design

A systematic review of randomized, masked, placebo-controlled drug or standard was carried out on *Matricaria recutita* (camomile), *Melissa officinalis* (Lemon balm) and *Passiflora incarnata* (passion

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fruit). Articles were sought systematically to meet the eligibility criteria after that were reviewed and evaluated qualitatively. They included national and international articles published in PUBMED, Scielo and Google Scholar. The systematic literature study is a secondary, having the aim of gathering similar studies published or not, evaluating them critically, in their methodology and gathering them in a statistical analysis, meta-analysis. By condensing equivalent primary education of good quality is considered the best level of evidence for decision-making on issues of therapy.[7]

Definition of a structured research question in acronym format

In order to formulate the question that guides this research, it was decided to it structured in accordance with the acronym components peak, where each letter represents a component of the question. As the following Table 1: Thus, the definition of the components of the research question in PICO format helped to define the eligibility criteria for the selection of primary studies were included in this review.

Table 1 Definition of a structured research question in PICO format for Systematic review of intervention studies Clinical Trial type

Acronym	Definition of the acronym	Components of a structured research question
P	*Patient or Problem* (Population	Individuals with Generalized Anxiety Disorder (GAD)
	interest)	
I	*Intervention*	Extract capsule or solution Matricaria
	(Intervention)	Recutita (Chamomile) or Melissa officinalis (lemon balm wort) or Passiflora incarnata (passion fruit).
Ç	*Comparison*	Placebo or use of an anxiolytic drug allopathic
	(Comparation)	
THE	*Outcome*	herbal effectiveness of the verification from the improvement in signs and symptoms of GAD
	(Desfecho- Prognosis)	

Criteria for inclusion of eligibility

I. The target population consists of adults regardless of gender, age and diagnosed with Generalized Anxiety Disorder;

II. Studies that performed randomized clinical trials, placebo-controlled masking allopathic or antianxiety drug.

III. Articles that support the efficacy of herbal medicine from the improvement of signs and symptoms of the disease based on questionnaires or validated criteria for diagnosis and prognosis of TAG.

Criteria for eligibility exclusion

I. Articles with experimental research in animal models or in vitro;

II. Studies that evaluated effects of these herbal remedies for insomnia, depression and other affective disorders and mood.

Search strategies

National and international documents were used dated from 1989. The search strategy prioritized the use of Decs descriptors and/or Mesh for the following search terms: "AND Anxiety AND Phytotherapic Clinical Trial" (Anxiety AND Phytoterapy AND Trial) " anxiety AND *Melissa officinalis* AND Clinical Trial "(anxiety AND *Melissa officinalis* AND Trial)," AND anxiety *Matricaria recutita* AND Clinical Trial "(anxiety AND *Matricaria recutita* AND Trial)," AND anxiety *Passiflora incarnata* AND Clinical Trial "(anxiety AND *Passiflora incarnata* AND Trial). The researchers devised a eligibility form which included the following: type of participants, place of study, inclusion and exclusion criteria, definition of the outcomes of interest, check the herbal effectiveness through questionnaires or validated criteria for diagnosis and prognosis of TAG, the existence of conflicts of interest. Thus were determined studies included or excluded from this review.[8] After this step, a flowchart of selection of items was drawn up for the systematic review. This flow chart includes an initial number of identified references. After that, it performed the screening phase, which removed references in duplicates and analyzed the full articles. Thus it was possible to perform the synthesis of qualitative studies.

Evaluation and interpretation of results

Each article has been revised, interpreted and evaluated. The results were listed in tables using the Microsoft Word 2013 program for discussion.

Herbal in clinical practice

Herbal uses and medicinal plants are part of the practice of folk medicine, constituting a set of traditions and knowledge that accompany generations, having the goal to aim at healing, prevention and treatment of diseases. The use of natural products with therapeutic indications was born with humanity. In the centuries of colonization, the use of medicinal plants for treating and curing diseases was given only by Indians and their shamans; the rest of the population used imported drugs, especially in Europe.[9,10] Oliveira and Hamilton came to the same conclusion that the plants are important sources of raw materials, representing the main medical material used by traditional medicine in their treatment practices. Its use is very old and in the past was the main therapeutic means known to treat population.[11,12] The Brazilian legislation and the Collegiate Board Resolution - 48/2004 number of DRC resemble the state that is the herbal medicine, whose active ingredient is a derivative of plant drug (extract, tincture, oil, wax, exudates, juice and others) obtained by technologically suitable processes, with exclusive use of vegetable raw materials, with prophylactic use, curative, palliative or diagnostic purposes. Not considered herbal medicine that product which, in its constitution, has isolated active substances, from any source, or associations of these with plant extracts. Herbal may contain excipients in addition to its active ingredients; if the plant material associated active substances are defined chemical standpoint, synthetic or isolated from plants, the final product is not considered a herbal medicine.[13,14]

Currently, it is remarkable the increase in the use of herbal medicines by Brazilian related to their customs and cultures. According to data obtained by the Foreign Commercial Department, in 1998 the sale of herbal medicines increased by 15% compared to only 4% of synthetic drugs. Herbal medicines compared with those obtained by chemical synthesis have some advantages, as low cost and reduced side effects, and are coming from plants.[15,16,17] "Herbal medicine, as

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an alternative or complementary medicine, is a social phenomenon in today's world, characterized by its biological interrelations, social, cultural and economic."[18] Medicinal plants can be sold in pharmacies and health food stores, according to Law No. 5,991/1973; while the products obtained from them, may be registered or registered with the National Health Surveillance Agency - ANVISA, such as food, cosmetics and herbal medicines. But only products registered as drugs may have therapeutic statements in their package inserts, packaging and advertising. According to ANVISA about 400 herbal medicines are with their valid records. This value change frequently, because the reality of the record is very dynamic, since the situation of the products is constantly modified. Every day, new drugs are launched and registered, while others lose their records, either by rejecting the renewal request and / or cancellation of previously granted registration, or by estoppel, which is characterized by the non registration renewal request within the legal time limit.[13]

Herbal medicines are regulated as conventional medicines in Brazil, requiring records and that have similar criteria of quality, safety and efficacy required by ANVISA for all medicinal products; ensuring that the population has access to safe, effective and proven. However, the use of medicinal plants and herbal medicines should be oriented so that its use does not cause health problems, such as therapeutic failure, severe adverse reactions, toxicity, among others. So it is necessary to make the sanitary control of, and public awareness of its possible risks, making it clear that the precautions to be taken with the use of herbal medicines are the same intended for other medicines. You should always seek information with health professionals, especially pharmacists, and inform your doctor the use of herbal medicine.[5,13] Arguably, medicinal plants and herbal medicines play an important role in therapeutic medicine, and is subject to the constant demand and the increasing use of these products by the population two factors could explain this fact, would be the first discovered the advances in science, which allowed the development of safe and effective herbal recognized with quality evidence; The second factor is the increasing search trend for less aggressive therapies aimed at the primary health care of the entire population. So the idea in the indication of the use of herbal medicine in human medicine, is not to replace existing drugs on the market, but increase the therapeutic option of health professionals, offering equivalent, effective drugs and registered with ANVISA, with the same therapeutic indications, and sometimes with additional information to existing.[9,14]

The medicinal plants has greatly contributed to the discovery and development of novel strategies of therapy, through their secondary metabolites; which are known to act directly or indirectly in the body, and may cause activation or inhibition of important molecular and cellular targets. From the popular and use their knowledge, they were discovered some drugs that are used in traditional medicine and can cite, salicylates and digitalis. Approximately 25% of prescribed drugs worldwide are of plant origin, and 121 active substances are used in therapy. Among the 252 basic or essential drugs selected by the World Health Organization - WHO, 11% of them are exclusively vegetable origin and a significant portion is composed of synthetic drugs, obtained from natural precursors. Mention may be made, for example, important drugs extracted from plants, such as digoxin, digitalis species obtained; quinine and quinidine obtained from species of Cinchona; vincristine and vinblastine obtained from Catharanthus roseus; atropine and scopolamine, of Atropa belladonna; morphine and codeine, of Papaver somniferum; among others.[10,14] Various scientific studies are being conducted with various herbal medicines already marketed or with only isolated plants, in order of effectiveness proof and verification of their possible effects. So gather such studies are important for making decisions when choosing a drug therapy to be prescribed.

Generalized anxiety disorder

Anxiety can be a normal reaction to destabilizing stimuli or that might frighten people. This reaction may occur with psychological symptoms such as apprehension, discomfort, different fears, and also physical symptoms such as tachycardia, increased respiratory rate, and blood pressure changes among others. It affects men and women of all age groups, however, women are twice as likely to have this disorder.[19] The Generalized Anxiety Disorder - GAD, is among the most common psychiatric disorders found in the general population, about 24% of health services by users, have the diagnosis of GAD. Although initially seen as a mild disorder, TAG today can be evaluated as a chronic disease associated with a relatively high morbidity, and high individual and social costs. It is one of the most under diagnosed psychiatric disorders, and rarely patients seek directly a mental health, choosing a general practitioner or physicians of different specialties. a complaint of vague physical symptoms predominate and that has the characteristics of a defined disease.[20,21] In Brazil, anxiety disorders have a high prevalence, with 9.5% to 17.5%, and potentially needy cases of assistance. These data, along with morbidity and high costs associated with these diseases; show that anxiety disorders are a group of major inconvenience to the individual and public health.

Generalized Anxiety Disorder in the anxiety occurrences fluctuate over time, but do not take place in the form of attacks or relate to certain situations, remain for days and for long periods of many months or years. The main complaint is the anxious anticipation or preoccupation, the person is most of the time worrying too much.[22] Addressing the question with a greater physiological range, Mackenzie anxiety is postulated that a state of brain function that occurs on activation of the hypothalamic-pituitary-adrenal (HPA) axis, causing symptoms neurovegetative such as insomnia, tachycardia, pallor, increased perspiration, muscle tension, tremor, dizziness, intestinal disorders, among others.[23] When some form of anxiety is felt, you feel fear and danger of sensations, the brain recognizes them and sends messages to a section of nerves called the autonomic nervous system. This system has two subsections, the sympathetic nervous system and the parasympathetic nervous system, which are directly related to control of the body's energy levels and their preparation for action. That is, the sympathetic nervous system is the system of fight-and-flight which releases energy and puts the body ready for action, providing the sensations felt in anxiety disorders such as dry mouth, chills, tremor, tachycardia, etc. while the parasympathetic system is the restoration that brings the body to its normal state.[24]

In recent decades there has been a significant advance in the science of the structure of the neural systems related to anxiety states. Different preclinical research showed that anxiety states would be related to animal welfare mechanisms before threatening stimuli or danger. These defensive behaviors involve two brain systems that would be included in anxiety: the Cerebral Protection System (DSS); consisting of a set of nervous structures arranged longitudinally formed by the amygdala, hypothalamus medial (HM) and periaqueductal gray (SCP); and behavioral inhibition system (SCI), whose main substrate septohipocampal neural system. The amygdala present in the SCD has nerve connections to the neocortex, functioning as sensory-emotional interface, analyzing and classifying the type and degree of stimulus.

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The result is passed to HM and MCP, which then selects and organizes the behavioral and physiological responses appropriate defense. HM is responsible for regulating the functioning of the pituitary that through secretion adrenocorticoprópico hormone (ACTH) stimulates adrenal glands to secrete glucocorticoids (such as cortisol), norepinephrine and epinephrine. Secretion by adrenocorticoprópico hormone (ACTH) stimulates adrenal glands to secrete glucocorticoids (such as cortisol), norepinephrine and epinephrine.[25] Secretion by adrenocorticoprópico hormone (ACTH) stimulates adrenal glands to secrete glucocorticoids (such as cortisol), norepinephrine and epinephrine.

The high level of anxiety can interfere with the development of different cognitive functions. Thus, people who suffer from anxiety disorder are more susceptible to the presence of cognitive deficits, such as attention, memory and executive functions. Through neuropsychological tests, it is possible to measure the performance and describe these possible changes. People with this disorder have difficulty focusing on specific objects or keep them in mind for a while, as well as concentration, due to its lack of focus ability. Thus, it is observed that high levels of anxiety impair performance on tasks that require attention; however, it is important to note that despite the anxiety affect efficiency (ability to perform well in a given task), can not affect the effectiveness (expected work).[26] In recent years, we have seen a major advance in the pharmacological treatment of anxiety disorders. The two main elements of treatment are the use of medicines in the medium and long term and/or cognitive behavioral psychotherapy. Patients need to be educated about the effects of drugs, especially undesirable; should be clear that drugs delongam weeks to induce the required therapeutic effects, unlike undesirable that manifest after the first pill. TAG currently has been characterized as a chronic disorder, and most often is associated with impairment of social, occupational and family. Until a few years, the only alternative for the treatment were benzodiazepines (BZD); however, since the insertion of buspirone, azapirona single (azaspirona, azaperone or azaspirodecanodiona) available in Brazil, the range of effective drugs in the TAG has been extended.[21,22]

The benzopiazepínicos has proven effective in symptoms of GAD, producing its effect rapidly, within minutes or hours, but have a lot of side effects like sleepiness, decreased reflexes while driving or handling dangerous machinery and ataxia and / or memory impairment at higher doses. The limitation on the use of benzodiazepines due to its ease to develop tolerance and dependence effects. Thus, one should opt for another class of drugs as we anticipate the need to use the medication for a longer time, or in patients who develop rapid tolerance and present propensity to addictions in general. It is also important to be alert and aware of the interaction with alcohol and other drugs. The benzodiazepines have similar efficacy varied, differentiating by their pharmacokinetic characteristics, such as time to onset of action or duration of effect.[20] Antidepressants serotonin reuptake inhibitors, such as, escitalopram, sertraline, fluoxetine or serotonin reuptake inhibitors and noradrenaliana, venlafaxine and duloxetine are the drugs of first choice for longer treatments TAG. The time to onset of action is time consuming and can be between two to four weeks, and have side effects that can disturb the patients. May present agitation or increased anxiety at the start of treatment, which can be ameliorated by association with benzodiazepines for a short period. The most frequently reported adverse effects are gastrointestinal disorders (nausea and diarrhea), sexual dysfunction, and rebound insomnia symptoms in abrupt interruption of prolonged use. The initial dose of the medication, if needed, can be adjusted after four weeks.[20] The treatment of generalized anxiety disorder and the use of drugs may be associated with psychotherapy, physical activities and use of tranquilizers food. Herbal medicines are used as an alternative to the use of tranquilizers and antidepressants, as these may cause various side effects and addiction.[3]

Herbal in generalized anxiety

Bezerra, Meireles Fernandes and Son are positioned similarly to say that the major therapeutic classes are more marketed herbal sedatives, anxiolytics, antidepressants and liver and digestive aids; may observe that the herbal medicines for treating anxiety disorder is one of the most sought, it fits in the class of sedatives, anxiolytics and antidepressants. Some factors might explain the rise in consumption of these products, as demand and interest in natural products, accessibility for low-income and efficacy in the treatment of diseases, as well as being remarkable, the advances in the scientific area that allowed the development admittedly safe and effective herbal medicines.[16] Wong Boon and Smith argues that there was an increase in recent decades in the marketing of herbal medicines indicated for mental disorders, causing mental health professionals, may have another treatment option. It is important to evaluate each herbal medicine with a similar approach to synthetic drugs, based on sound scientific evidence, ensuring an effective treatment based only on herbal medicines.[27] Different drugs from different therapeutic classes, have proven effective in the treatment of generalized anxiety disorder. However, all these substances have drawbacks, justifying the continued search for new anxiolytic substances; may name benzodiazepines which cause serious adverse reactions from sleepiness to dependence on the drug. Medicinal plants have great potential for the origin of new drugs, and a large number of herbal medicines is already sold in pharmacies.[4]

In this systematic review will be addressed three enough herbal medicines used in therapy for Generalized Anxiety Disorder, Matricaria recutita, *Melissa officinalis* and Passiflora incarnata. They were chosen due to lack of systematic reviews involving these herbal medicines in Brazil. The *Matricaria recutita* (Chamomile) is a native plant of the Mediterranean and southern Europe. Its therapeutic uses include antispasmodic action, digestive, antiseptic, anti-allergic, anti-inflammatory, anxiolytic, sedative, carminative, healing, soothing, refreshing and immunostimulant. The part of the plant to be used are flowers, floral chapters under infusion.[28]

Chamomile has drug interactions with anticoagulants such as warfarin, and may increase the risk of bleeding. With barbiturates, phenobarbital, and other sedatives, chamomile may enhance or prolong depressant action of the central nervous system. It may also reduce the absorption of iron ingested through foods or medicines. Some people may be sensitive to contain in its composition the Composite family, so people allergic to chrysanthemums, tasneiras or other members of this family are more likely to submit allergic reactions.[29,30]

Melissa officinalis (lemon balm) is originally from Europe and Asia. The essential oil of its leaves is widely used by the pharmaceutical industry for exhibit antioxidative properties, antiviral, antispasmodic, carminative, stomachic, diaphoretic, sedative, antidepressant, vermifuge and increases bile flow. The leaves are used in tea form, helping to aid digestion, acting as soothing and also in combating headaches, gas and intestinal cramps, viral infections (colds, herpes, mumps, chicken pox) and as an insect repellent when applied in the form of paste or cream. Clinical trials have studied the

articles were conducted with freeze-dried aqueous extract of Melissa officinalis.[31,32,33]

The balm may undergo interactions with other medications containing medicinal plants, especially with Kava (Piper methysticum). In general, *Melissa officinalis* interacts with the depressant of the central nervous system and thyroid hormones (may bind to thyrotropin). The most common adverse reactions are mild depression, drowsiness, loss of reflexes, allergy and / or contact dermatitis when used topically.[29,34] The Passiflora incarnata, known popularly as passion fruit, has sedative, antispasmodic, and anxiolytic properties. It is a plant native to southern North America, where its introduction occurred in the mid-1800s, by acceptance of the tea used by Indians and slaves in the southern region of the United States as a sedative and remedy for headache. In Brazil, the first reference to the passion was in 1587, popularly known as "herb yielding fruit."[35,36] The passion fruit has in its composition alkaloid fractions, indole derivatives as harmana, harmine; and flavonoídicas portions, vitexin, isvitexina. These fractions promote nonspecific depressant actions of the central nervous system, thus contributing to its therapeutic action, as a sedative and tranquilizer; consequently, can interact with hypnotics and anxiolytics, intensifying its effects. Based on animal research, the use of Passifora incarnata with alcohol or other sedative-hypnotic drugs may increase the intensity of drowsiness benzodiazepines such as lorazepam or diazepam, barbiturates such as phenobarbital, narcotics such as codeine, some antidepressants and alcohol. The use of this plant with monoamine oxidase inhibitor drugs (isocarboxazid, phenelzine and tranylcypromine) can cause an additive effect and naproxen.

Some studies even suggest that the use of Passifora incarnata with caffeine, guarana or ephedra can cause increased blood pressure. The most common adverse reaction is discomfort, but there are reports of allergic reactions, nausea, severe vomiting and tachycardia.[29,37]

Currently the Board Resolution - number of RDC 48/2004, allows the marketing and use of herbal medicines in Brazil, drug-free prescription, and therefore subject to prescription pharmaceuticals, according to RDC 586 of 2013[21] However, this requirement must be based on the best scientific evidence regarding the effectiveness and safety of herbal medicines to be prescribed. Pharmacists need to be aware of the indications and contraindications of these herbal medicines as well as possible side effects and potential drug interactions. You should also inform the patient the correct way to use and even accompany you during pharmacotherapy. This study therefore provides scientific data on clinical trials with *Matricaria recutita* (Chamomile) The three plants that have been studied and the results were summarized and evaluated qualitatively part of the Simplified Registration List of Herbal Medicines Resolution-RE 89, of March 16, 2004 / ANVISA, which reinforces the validation and verification of the sedative property of plants and its use as a herbal medicine.[38] In order to gather information on the effectiveness of herbal medicines, Passiflora incarnata, *Matricaria recutita* and *Melissa officinalis* this article conducted a systematic literature search of randomized controlled trials. Thus providing input for the practice of prescribing based on scientific evidence.[39]

Results

The search strategy resulted in 1,471 jobs that were analyzed by the title and abstract at first, and in some cases the full article, getting 7artigos who met all inclusion criteria. The plants used in these studies were: *Passiflora incarnata* (passion fruit), *Matricaria recutita* (camomile) and *Melissa officinalis* (lemon balm), and all the jobs included in this study are listed in the following (Table 2), (Table 3) and (Table 4), which shows and summarizes comparative manner works were selected randomized, blind or double-blind, compared with placebo or standard anxiolytic drug-allopathic (Figure 1).[40–42]

Table 2 Passiflora incarnata

Author (s) and date	Title	Design of research	Kind of Participants (Sample)	Inclusion criteria	Exclusion Criteria	Search results	Verification of Effective results	Conclusion Search	Conflicts
Kaviani et al.[47]	The efficacy of Passiflora incarnata in reducing dental anxiety in patients undergoing periodontal treatment	clinical trial, randomized, blinded, placebo-controlled	63 volunteers: 24 sex male and 39 female	Patients with moderate, high and severe anxiety, according to the Dental Anxiety Scale Corah (DAS)	Pregnant patients, under 18	Significant difference in anxiety levels before and after administration of Passiflora	DAS Corah scale, Chi Square, Tucky variance analysis and data were analyzed using SPSS software	The Passiflora incarnata administration as premedication significativamen- is effective in reducing anxiety you	-
Akhondzadeh et al.[43]	Passion fruit treatment of generalized anxiety: a double-blind randomized controlled pilot study Oxazepam	clinical trial, randomized, double-blind, controlled Oxazepam	36 volunteers	Patients diagnosed with TAG	Pregnant women and children under 18 years	Oxazepam, and Passiflora extract was effective in treating generalized anxiety	Manual criteria of the Diagnostic and Statistical of Mental Disorders (DSM-IV)	Passiflora is an effective drug for the management of GAD, and does not reduce the ability to work as Oxazepam	-
Movafegh et al[44]	preoperative oral route Passiflora incarnata reduces anxiety in patients surgery Outpatient: in study double- blind, controlled placebo	clinical trial, Double-Blind controlled by placebo-randomized. Were administered 500mg Passiflora before surgery corresponding to1,01mg of benzoflavona.	60 volunteers	It is between 25 to 45 healthy	Historydisorder Anxiety, user sedatives, painkillers and antidepressi you	Anxiety levels were lower with passiflora to placebo	Function dot Test trigger (DTT) and Test Replacement Digital symbol (DSST)	Passiflora reduces anxiety without induce sedation	-

Table3 Matricaria recutita

Author (s), Date and Location	Title	Design of research	Kind of Participants (Sample)	Inclusion criteria	Exclusion criteria	Search results	Verification of effective results	Conclusion Search	Conflicts of interest
Amsterdam et al[45]	A double-blind, randomized, placebo-controlled oral Matricaria recutita: therapy for generalized anxiety disorder	clinical trial, randomized, double-blind, placebo-controlled	sample size of 61 adult participants. A group of 28 participants received chamomile extract and the control group with 29 participants received placebo lactose.	Over 18 years and a diagnosis of generalized anxiety	current diagnosis of major depressive disorder, bipolar disorder, panic, phobia, kidney failure, cancer	57 patients participated in the study; 1 withdrew after taking the first dose of chamomile, 1 for noncompliance and two by the presence of adverse events. A significant reduction in anxiety compared to placebo	Hamilton Anxiety Scale (HAM-A) and IV - DSM criteria	First controlled clinical trial with chamomile for generalized anxiety. Results suggest that may have anxiolytic activity in some patients with mild anxiety	-
Mao et al[45,46]	Chamomile prolonged therapy for generalized anxiety disorder: a randomized protocol, double-blind and placebo-controlled.	clinical trial, randomized, double-blind, placebo-controlled initially performed for 4 weeks and continued for 26 weeks. Use Chamomile Extract in a ratio of 4: 1 containing 1.2% apigenin. The daily dose of 1.500 mg was divided into 3 capsules. The placebo Lactose monohydrate contained.	180 subjects with moderate to severe anxiety disorder	Individuals diagnosed with anxiety, 18 years	Users you antidepressi-medicines, res estabilizado-of humor, tranquilizers	Search still did not get a result, it will take 12 months of study; with the ultimate goal to check the increase of time to relapse of anxiety during therapy discontinued in each treatment with chamomile and placebo	The analyzes will be performed using the latest version of STATA, DSM-IV criteria, Hamilton Anxiety Scale (HAM-A)	Conduct a long-term study with chamomile to check the recurrence time for anxiety during treatment	-

Table 4 Melissa officinalis

Author (s) and date	Title	Design of research	Kind of Participants (Sample)	Inclusion criteria	Exclusion criteria	Search results	Verification of effective results	Conclusion Search	Conflicts of Interest
Alijaniha et al[47]	Heart throb of relief with Melissa officinalis leaf extract: double-blind, placebo controlled, randomized effectively and safely	clinical trial, randomized, double-blind, placebo-controlled. They were administered for 14 days Melissa 500mg twice daily or placebo.	71 adult participants	Adults suffering from benign palpitations, ie only symptoms of GAD	pregnant women, infants	16 patients were lost to follow-on study. 55 patients completed during 14 days of treatment, a reduction of frequency of symptoms	Visual Analogue Scale (VAS) - self-report questionnaire, and the General Health Questionnaire to check the secondary symptoms as anxiety and insomnia	lyophilized aqueous extract of M. officinalis may be suitable and safe for the treatment of benign palpitations	-
Cases et al[48]	Test pilot of Melissa officinalis leaf extract in the treatment of volunteers who suffer from anxiety disorders	randomized pivotal trial. All volunteers were treated with the drug Cyracos®, 600 mg daily, divided into two doses, one in the morning and another at night.	20 volunteers: 6 sex male, 14 female between 18 to 70 years	Anxiety Disorder Diagnosis and sleep disorders	Pregnancy, lactation, you antidepressi-consumption, sedatives, diabetes, asthma, schizophrenia	All volunteers were treated with Cyracos®, with a significant improvement of anxiety and insomnia associated with anxiety	DSM-IV criteria and Hamilton Anxiety Scale (HAM-A)	Cyracos® presented breakthrough results showing that its treatment can be beneficial to humans suffering from disorders anxiety and insomnia	Cyracos ® hidroalcóli-co extract of Melissa leaf with higher rosmarinic acid 7%

Citation: RibeiroSevero A, Ilva AL, Filho EJSDO. Generalized anxiety: a systematic review *Passiflora incarnata* (passion fruit), *Matricaria recutita* (Chamomile) and *Melissa officinalis* (lemongrass). *Int J Fam Commun Med.* 2019;3(5):200–208. DOI: 10.15406/ijfcm.2019.03.00158

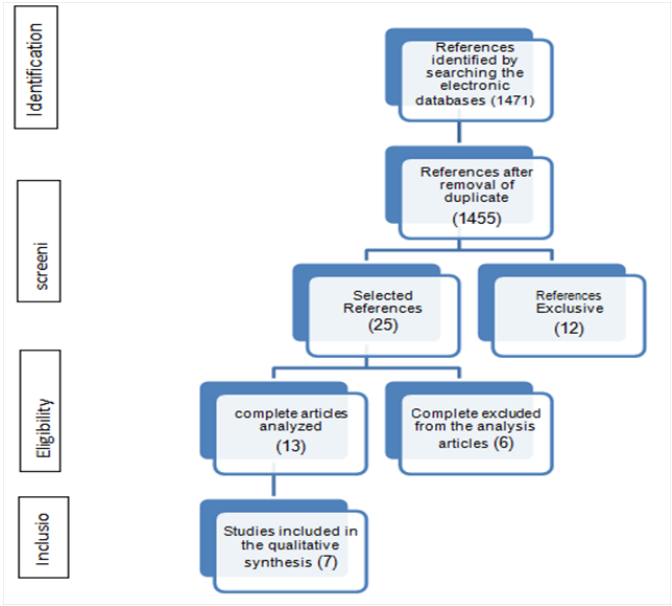

Figure 1 Selection of flow of the articles included in the systematic review final analyses.

Passiflora incarnata (Passion fruit)

In their study, Kaviani and collaborators in 2013, they evaluated the efficacy of *Passiflora incarnata* in reducing anxiety in patients undergoing periodontal treatment. The sample size was 63 participants of both sexes, including because they have some kind of anxiety according to the Dental Anxiety Scale Corah (DAS). They were randomized into 3 groups, and the group 1 was administered the extract of passion the night and in the morning 90 minutes before the procedure. In participants in group 2 was administered placebo in the same way. As for the group 3 was not administered or drug or placebo and therefore control group. Anxiety is a significant difference in the group treated with 1 Passiflora, compared to placebo treated groups and control was observed. In the placebo group and the control group was not any noticeable difference. Therefore, the authors concluded that the passion administration as premedication is significantly effective in reducing dental anxiety. In the second study by Akhondzadeh et al.,[43] conducted in 2001, there was a trial of Passiflora extract controlled Oxazepam for the treatment of Generalized Anxiety participated 36 volunteers diagnosed with TAG using the criteria of the Diagnostic Manual and Statistical of Mental Disorders (DSM-IV). Patients were allocated randomly, with 18 patients treated with Passiflora and 18 patients treated with oxazepam, for 4 weeks. The authors concluded that the Passiflora is an effective drug for generalized anxiety disorder and has a low incidence of reduced work capacity compared with Oxazepam. In the third study Movafegh et al.,[44] Conducted in 2008, analyzed the reduction of anxiety in patients in preoperative cases of outpatient surgery, 60 healthy volunteers were divided into two groups, one of control- placebo and the other with Passiflora. In one group were administered 500 mg Passion Flower 90 minutes before surgery, each tablet containing at 1,01mg of Benzoflavona; similarly placebo was administered to another group, being identical in appearance to the tablet the active form. There was a significant difference in anxiety in Passiflora group compared to the placebo group. The authors stated that the Passiflora reduces anxiety without inducing sedation.

Matricaria recutita (Chamomile)

The only trial included in this systematic review was done by Amsterdam et al.[45] and colleagues in 2009. The sample size was 61 participants, but only 57 participants completed the survey, eight of them discontinued treatment before completing the trial: two per presenting adverse effects in three or withdrawn consent, lost to follow up two and one for non-compliance of the regimen. A group of 28 participants received chamomile extract and a control group of 29 participants received placebo lactose monohydrate. The therapeutic regimen occurred similarly in both groups: in the first week, each participant received a 220mg capsule of chamomile or lactose. In the second week it increased to two tablets daily. By the third week, and those who had a reduction of ≤ 50% in ham- score A (Hamilton), was instituted three capsules. Similarly, in the fourth week for four capsules. Regarding the fifth week, and those who had other ≤50% reduction in HAM-A score, increased to five capsules a day. This procedure continued until the ending of the eighth week. The measurements of responses to therapy were made after the second, fourth, sixth and eighth weeks. The authors said that the findings suggest that the results Matricaria has modest anxiolytic effect in patients with mild anxiety. In the second study led by Mao et al.,[46] in 2014, analyzed a study protocol on the Chamomile for Generalized Anxiety. Where 180 patients diagnosed with moderate to severe anxiety, they received Chamomile extract once daily for 8 weeks. Those who have had good response remained the same treatment for another four weeks. After this period began to double-blind, placebo treating or Chamomile, once a day for over 26 weeks. The study has not yet obtained a result; it will be required 12 months of testing, with the ultimate goal of verifying the increase time to relapse of anxiety throughout the therapy. And the results were not published until this review.

Melissa officinalis (Lemongrass)

The first study was conducted by analysis Alijaniha et al.,[47] in order to verify the relief of heart palpitation with *Melissa officinalis* leaf extract. 71 patients were enrolled, but only 55 completed the study being conducted in a group of Melissa 500mg twice daily, and the other group was given placebo for 14 days. The authors concluded that the aqueous extract of *Melissa officinalis* may be suitable and safe for the treatment of benign palpitations, as the group tested with Melissa, a reduction of symptoms. The second study conducted in 2011 by Cases et al.,[48] Was funding the Cyracos® drug (hydroalcoholic extract of Melissa leaves and rosmarinic acid than 7%) analyzing its effectiveness in the treatment of volunteers who suffer from anxiety disorders. Participated 20 volunteers of both sexes, aged 18-70 years, with some anxiety disorder and sleep. They were administered two doses of the medicament Cyracos®, 600mg daily, one in the morning and evening for 15 days. A significant improvement in the symptoms was noted. The results showed that this treatment may be beneficial to patients with anxiety disorders and insomnia.

Discussion

From this systematic review was possible to verify the existence of many pre-clinical studies evaluating the anxiolytic effect of the three herbal fetched, but few controlled trials have been performed. According Faustino, Andreatini Almeida and randomized clinical studies with masking at least double blind comparative and are considered the gold standard for assessing the efficacy of drugs enabling a better result of the experimental drug tested. The advantage

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of this method is to have the possibility of benchmarking in each group tested, assessing the correct effectiveness of the study drug, with a drug already used in the market, and/or placebo, checking their significance.[4] A major difficulty in conducting research is the possible chemical herbal phyto variation even between plants of the same species. The way in which each was processed interferes with the result, so that two herbal medicines that have the same active product may have different qualities and therefore are not deemed equivalent therapeutic. So the ideal is to work with the standardization of extracts, inhibiting this type of problem. Were included in this systematic review, three studies of clinical trials with Passiflora incarnata, all carried out in Iran. Two of these studies were compared with placebo, one done by Movafegh and collaborators in 2008, and another conducted by Kaviani[47] and only done by Akhondzadeh[43], compared to a current standard drug for anxiety disorder, a benzodiazepine, Oxazepam. These studies found a relative significance of the Passiflora effect compared to placebo and a standard drug, may obtain as a result of decreased anxiety without inducing sedation, unlike what happens when you make use of benzodiazepines.

The number of volunteers in randomized studies was established as unimpressive to prove the efficacy of herbal medicines. Faustino, Almeida and Andreatini argue that they are necessary at least 40 patients per group, so as to generate results with significantly proven; and there was the number of participants in any study assessed.[4] Therefore, it was not possible to consider how relevant the results of the included items as the number of volunteers was inadequate, allowing possible random as well as systematic bias. In clinical trials chamomile, only two were found in the literature articles made or proposed to do this clinical trial phytotherapy. One of them held by Amsterdam and colleagues in 2009 in Medicine, University of Pennsylvania Unit suggests that recutita Matricaria may have anxiolytic activity in some patients with mild anxiety to moderate, however the same article states that more trials should be conducted. Based on this, a research protocol developed by Mao and colleagues with the participation of Amsterdam in 2014, intended to make a new clinical trial on the same research department. This research will involve 180 patients with disorder of moderate to severe anxiety, classified by DSM-IV criteria and the Hamilton depression scale, in which a group of participants will receive Chamomile extract in the ratio of 4: 1 containing 1.2% apigenin and daily dose of 1.500 mg to be divided into 3 capsules and one group will receive placebo. The mechanism of action of flavonoids and apigenin contained in chamomile extract, were observed in preclinical studies by Marder and Paladini and Zanoli, Avallone and Baraldi. These studies have demonstrated the role of these substances in benzodiazepine receptors (the activation of GABAergic) as well as the neurotransmitter dopamine, serotonin and noradrenaline. Therefore, the exact pharmacodynamic has not yet been elucidated.[40,41]

In view of the fact that the effectiveness of chamomile extract has not yet been confirmed, since only one paper on clinical trial that fulfilled the inclusion of this review criteria, it is concluded that these results are insufficient to justify the prescription and the use of this herbal medicine. For herbal Melissa officinalis, two clinical studies were included, the first held in Italy in 2011, for Cases and employees, and funding for the drug Cyracos® (hydroalcoholic extract of Melissa leaves and rosmarinic acid than 7%). It was evaluated its efficacy and safety in participants, which for the authors had a beneficial result in controlling anxiety and insomnia. But we cannot take as a basis, and, as was funded by Cyracos®, there may be conflicts of interest and possible bias of bias. In the second study, conducted in Iran for Alijaniha and collaborators in 2015, the effectiveness of Melissa in relieving palpitations was assessed, with the withdrawal of 16 participants, and was not addressed the reason for withdrawal of this pharmacotherapy, of enrolled considerations in this section, it is important to point out, in a very concise and succinctly points that were essential in the analysis undertaken, such as the presence of a few participants in clinical trials, small number of studies, the presence of conflicts of interest, so these facts justify the results were insufficient to justify the use and prescription of these herbal medicines. Limitations of this review include the small number of potentially eligible articles and which were available in the scientific literature. There was also an impossibility of meta-analysis, due to inequality of methodologies carried out in clinical trials. Thus, this research highlights the need for further clinical trials with well defined methodologies and in order to verify the effectiveness of these three herbal medicines in the treatment of Generalized Anxiety Disorder.

Final considerations

This systematic review concluded that randomized clinical trials conducted with masking and controlled for the three herbal of interest (Passiflora incarnata, *Melissa officinalis* and Matricaria recutita) were insufficient to these drugs in the treatment of Generalized Anxiety Disorder. The results showed that were used a low sample size of participants, showed inconclusive results, the presence of conflicts of interest, various types of biases, moreover only seven studies were eligible for review. Thus, the scientific evidence is insufficient to prove the effectiveness and thus the prescription of these herbal medicines for TAG.

Acknowledgments

None.

Conflicts of interest

The author declares there is no conflict of interest.

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