



## Phytotherapy to control anxiety

*Phytotherapy in anxiety control*

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**Jackson Machado Silva**

### Summary

Anxiety is a psychic state of apprehension or fear caused by the anticipation of an unpleasant or dangerous situation. Its characteristics are physical and mental, when it is of great intensity and complications, it is also called panic syndrome. Therefore, the use of herbal medicines can be quite effective in anxiety, without causing adverse symptoms as expected, such as effects caused by conventional pharmacological treatments. In view of the above, the objective of this study will be the use of herbal medicines in anxiety, using drugs with anxiolytic activities in the treatment of anxiety, which has been experiencing growth as a treatment for anxiety in the last 5 years. This growth is due to its low cost, being an effective and culturally appropriate therapeutic option, aiming to obtain safety in its use by users of herbal medicine. Legislation was created in ANVISA, PNPIC, SUS AND PNPMF that govern the matter, seeking to regulate phytotherapy, expanding access to medicinal and herbal plants, guaranteeing safety and effectiveness for SUS users.

**Key words:**Anxiety; Low cost; Efficiency; Phytotherapy.

### Abstract

Anxiety is a psychic state of apprehension or fear brought about by the anticipation of an unpleasant or dangerous situation. Its characteristics are physical and mental, when it is in great intensity and intercurrentence, it is also called panic syndrome. Thus, the use of herbal medicines can be quite effective in anxiety, not causing adverse symptoms than expected, such as effects caused by conventional pharmacological treatments. In view of the above, the objective of this study will be the use of phytotherapy in anxiety, using drugs with anxiolytic activities in the treatment of anxiety, which has been growing as an anxiety treatment in the last 5 years. This growth is due to low cost, being an effective therapeutic option and culturally appropriate, aiming to obtain safety in its use by the users of herbal medicine. Legislation was created in ANVISA, PNPIC, SUS and PNPMF that govern the matter, seeking the regulation of phytotherapy, expanding access to herbal and phototherapeutic plants, guaranteeing safety and efficacy to SUS users.

**Keywords:**Anxiety; Low cost; efficiency; Phototherapy; Regulations.

## 1. Introduction

The use of herbal medicines has gained prominence in recent years as it is an effective, low-cost, culturally appropriate therapeutic option. Therefore, the National Policy for Integrative Practices (PNPIC) was published for the area of medicinal plants and herbal medicines in the National Health System (SUS), ordinance No. 971 of May 3, 2006, National Policy for Medicinal Plants and Phytotherapeutics (PNMPF), which aim to have more therapeutic options with access to medicinal plants and herbal medicines, with guarantee, safety and effectiveness for SUS users.

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Anxiety is a psychic state of apprehension or fear caused by the anticipation of an unpleasant or dangerous situation. The word "anxiety" comes from the Latin *anxietas*, which means "anguish", "anxiety", from *anxius* = "disturbed", "uneasy", from *anguere* = "to squeeze", "to suffocate". Anxiety is the great symptom of psychological characteristics that shows the intersection between the physical and psychic, since it has clear physical symptoms, such as: tachycardia (beating), sweating, tremors, muscle tension increased secretions (urinary and fecal), increased intestinal motility, headache (headache). When recurrent and intense, it is also called Panic Syndrome (acute anxiety crisis).

Specifically in the treatment of anxiety, herbal medicine can become a great alternative with true effectiveness. Evidence found in the literature regarding this type of alternative treatment. As an example, *Maticaria recoita*, *Passiflora incarnata*, *Valeriana officinalis*, *Kava-Kava*, *Melissa officinalis* and *Eritrina Mulungu* stand out as they prove to be good therapeutic options and are successfully used as an alternative treatment for anxiety disorders.

This study is intended for anyone who wishes to obtain information about herbal therapies and their effects in relation to the treatment of anxiety, based on the review of some previous studies that show the effectiveness of treatment with herbal medicines in controlling anxiety, it may bring or problematize the use of phytotherapy in anxiolytic treatment.

This is a bibliographic review based on research in books, digital magazines, dissertations and scientific articles. Materials relevant to the use of herbal medicines, their anxiolytic functions, advantages and

disadvantages found on secure websites and the Scientific Electronic Library Online ( *SciELO*).

## 2 Theoretical Framework

### 2.1 Herbal medicines

Phytotherapy or plant therapy is one of humanity's oldest therapeutic practices. It dates back to around 8,500 BC and has origins in both popular knowledge (ethnobotany) and scientific experience (ethnopharmacology). The term Phytotherapy derives from the Greek *therapy*, treatment, and *phyton*, vegetable, and concerns the study of medicinal plants and their applications in curing diseases.

Herbal medicines, like all medicines, go through **a series of research** to prove its effectiveness. Medicinal plants can be used in other ways, in the preparation of "teas".

In accordance with the Resolution of the Collegiate Board of Directors – RDC n°48/04 of ANVISA, Phytotherapeutic is defined as: Medicine obtained using exclusively active plant raw materials. It is characterized by knowledge of the effectiveness and risks of its use, as well as the reproducibility and constancy of its quality. Its efficacy and safety is validated through ethnopharmacological surveys of use, techno-scientific documentation in publications or phase 3 clinical trials. Herbal medicine is not considered to be one that, in its composition, includes isolated active substances, of any origin, nor their associations with extracts. vegetables (BRAZIL, 2004).

Phytotherapeutics are medicines obtained from medicinal plants. They are obtained using exclusively vegetable drug derivatives (extract, tincture, oil, wax, exudate, juice and others). It is not subject to registration as a herbal medicine, medicinal plant or its parts, after collection, stabilization and drying processes, and may be intact, erased, crushed or pulverized (ANVISA, 2017)

According to the Health Surveillance Secretariat, in its ordinance no.o.6 January 31, 1995:

Phytotherapeutic is "any medicine technically obtained and prepared, using exclusively vegetable raw materials for prophylactic, curative or diagnostic purposes, with benefit to the user. It is characterized by knowledge of the effectiveness and risks of its use, as well as for the reproducibility and constancy of its quality. It is the finished, packaged and labeled final product.

Pharmaceutical adjuvants permitted under current legislation may be used. Active substances from other origins cannot be included, and any active substances, even if of plant origin, isolated or even mixtures thereof, are not considered herbal products” (VALDIR; ANGELO, et al, 2005).

Plants contain active ingredients capable of curing various diseases and it was from the recognition of these therapeutic properties that modern allopathic medicine emerged. Medicinal plants are those capable of alleviating or curing illnesses and have a tradition of use as medicine in a population or community. To use them, you need to know the plant and know where to harvest it and how to prepare it.

Phytotherapeutics are also used as an alternative to the use of anxiolytics and antidepressants, as these can cause side effects and dependence. Phytotherapeutic medicines are those obtained with the exclusive use of active plant raw materials. Herbal medicine is not considered to be one that includes isolated, synthetic or natural active substances in its composition, nor their associations with plant extracts (BRASIL, 2004).

Herbal medicines used for anxiety are, like any other medicine, recommended by doctors and should not be used without a prescription (ANVISA, 2013).

According to information from Anvisa, all plant-based medicines, as well as any other medicine, can cause unpleasant reactions and even more serious health problems, special attention should be paid to children, the elderly and pregnant women. The use of herbal medicines associated with other medications is also a risk to the patient's health, especially if the doctor is unaware of their use (JÚNIOR; 2008).

## **2.2 History of herbal medicine**

The treatment of diseases with medicinal plants is present in several cultures around the world. The oldest known were found in prehistoric tombs dating back to 60 thousand years ago (VILLAS BOAS, 2004).

The use of medicinal plants is considered one of humanity's most widely used and oldest practices and is used to cure, prevent and treat diseases with biologically active compounds. (ANDRADE; CARDOSO; BASTOS, 2007).

One of the oldest uses was tobacco, which was quickly transferred to several civilizations. The story goes that since 3000 BC, in China, Emperor Sheng Nung experimented with the power of ginseng. It is noteworthy that this emperor also lived in China for 123 years. Emperor Huang Ti mentioned 252 plants in his “Canon of Herbs” (2,798 BC). One of the oldest herbaria can currently be found in Egypt, the Erbs papyri, which cataloged 125 medicinal plants and 811 recipes. The doctor Imhotep stood out in Egypt, who used medicinal herbs in his cures. In addition to healing, the Egyptians used plants in the famous method of preparing mummies, which to this day has not been fully revealed (MORAES BRAGA, 2011, p. 10).

The first records of herbal medicines were recorded in the period 2838-2698 BC with 365 herbs and poisons cataloged by the Chinese Shen Nung, and depended on two opposing poles to maintain the order of the herbarium as well: Left yang-light, sky and heat, and right ydarkness, earth and cold. (SCHENKEL; SIMON, 2001).

Hippocrates, called the “Father of Medicine”, created his work “Bodies *Hyprocathium*”, where, among other medical information, he pointed out the plant remedy and treatment for each disease. In the Christian era, a precious contribution was left by Pelácius, Nero's doctor, who carried out studies on more than 500 species of medicinal plants (MORAES BRAGA 2011, pg 10).

From the beginning of the 19th century, medicines of plant origin began to be studied scientifically. The first time that chemical and analytical methods were used to extract the active ingredient from a medicinal plant was for the isolation of morphine from opium (1803-1806). This made it possible to carry out pharmacological and toxicological studies on the effects of morphine in animals and humans (SCHOLTZ et al., 2000).

A few years later Pelletier and Caventou isolated strychnine (1818) and quinine (1820). In 1828 Wohler was the first to achieve organic synthesis, that of urea (FERRO, 2006).

In 1819, atropine was isolated from belladonna (*Atropa belladonna L.*), used in the treatment of diseases of the nervous system. In 1820, quinine, an antimalarial drug obtained from the bark of the Peruvian plant Cinchona sp., was isolated. In 1827, a French chemist isolated *salicin* from the *spirea* (*Filipendula ulmaria (L.) Maxim.*), and traditional medicine had, over the centuries, obtained the same effect from willow bark (*Salix alba L.*). In 1829, emetine from ipecac was isolated (*Psychotria ipecacuanha Mull*), a valuable emetic. In 1860, the

Cocaine is extracted from coca leaves (*Erithroxylum coca Lam*), a local anesthetic that made many surgeries possible. (CRF SP, 2016, p. 9).

In the 19th century, the industrial process of medicines grew, leaving behind healing processes using medicinal herbs. It is noteworthy that during the major world wars, with production focused on war material, large-scale industrial production was interrupted, a fact that again favored the use of medicinal herbs (MORAES BRAGA 2011 p. 11).

At the beginning of the century. XX, the philosopher Rudolf Steiner (1861 – 1925), together with Dr. Ita Wegman, led to the emergence of anthroposophic medicine which, in addition to the purely physical organization of man, considered by Academic Medicine, also includes three other organizations: the vital, the soul and the spiritual. The medicines typical of this form of Medicine are taken from the three kingdoms of nature, mainly the plant kingdom. In the same period, allopathic medicine (from the Greek *allos* + *pathos*, a method of combating illness by means contrary to their nature) still had plants as their main raw materials. (CRF SP 2016, p. 10).

In the 1950s until the 1970s, medicinal plants were marginalized due to the great impulse that organic chemistry promoted in allopathic medicine. However, from the 1980s onwards, they began to be valued again as a low-cost source of healing properties (MATOS, 1987).

With all the evolution of medicine in the 20th century, plants still have important therapeutic actions for maintaining health (SOUZA; FELFILI, 2006). With few conditions and lack of access to medicines, there are the main reasons for using plants for medicinal purposes. (VEIGA JUNIOR; PINTO, 2005).

Although great advances in allopathic medicine have been seen since the 20th century, the consumption of medicinal plants, based on family tradition, has become a widespread practice in popular medicine. Currently, many factors have contributed to the increased use of this resource, including the side effects resulting from the chronic use of industrialized medicines, the population's difficult access to medical care, the greater consumption of natural products, as well as the tendency to use of integrative medicine and holistic approaches to the concepts of health and well-being. Consequently, the assumption arises that medicinal plants as well as natural products do not present a health risk. This concept, without scientific basis, merely passed down from generation to generation, ends up offering serious

health risks for less enlightened people. This important fact is not considered by the population, leading to indiscriminate self-medication, aggravated by the lack of reliable information about the potential toxic effects even in combinations with commonly used medications (CRF SP 2016 p. 12).

In Brazil, the first references to medicinal plants are attributed to Father José de Anchieta and other Jesuits who came here during colonial times. They formulated recipes called “Boticas dos Colégios”, based on plants for the treatment of diseases. Several indigenous populations made insignificant use of these plants and even with the process of extinction of these peoples, they passed on a lot of information about the use of plants for medicinal purposes, which was certainly transmitted to European migrants and African slaves (LAMEIRA PINTO 2008 p. 22) .

When the Portuguese arrived in Brazil, they found Indians who used annatto (*Bixa orellana* L.) to paint and protect the body from insect bites and also to dye your ceramic objects. Father José de Anchieta, in his "Letters", tried to awaken his superiors to the richness of indigenous flora and medicine, but in vain. Scientists, rare exceptions, have not yet fully woken up to the richness that this Brazilian flora represents (BREVE 2008).

In the centuries of colonization, the use of medicinal plants to treat pathologies was the heritage of only the Indians and their shamans (DUNFORD, 2001). Knowledge of the powers of various herbs was acquired from generation to generation. With the arrival of European colonizers, this knowledge was also passed on to them, who explored the different regions of the country. In fact, the knowledge brought by Europeans, further encouraging the studies and use of herbs (MORAES BRAGA p.11).

According to Souza (1995). Popular medicine and specific knowledge about the use of plants are the result of a series of cultural influences, as the persistence of these groups in maintaining these teachings among their people is commendable. It is worth mentioning that natural plant-based medicines have had positive effects throughout history, with undeniable advantages, in the treatment of certain conditions.

In 1978, the World Health Organization officially recognized the use of herbal medicines. In Brazil, the policy on medicinal and herbal plants dates back to 1981 through Ordinance no. 212, of September 11, of the Ministry of Health which, in its item 2.4.3, defines the study of medicinal plants as one of the priorities of clinical research and, in 1982, the

Ministry of Health (PPPM/Ceme) launched the Medicinal Plants Research Program of the Medicines Center to obtain the development of an alternative and complementary therapy, with a scientific basis, through the establishment of herbal medicines, based on the real pharmacological value of herbal preparations. popular use, based on medicinal plants (FARMACOPEA BRASILEIRA, p.5).

In 1990, Brazil instituted Law No. 8,080/90, which established the State's obligation to formulate and execute economic and social policies that guaranteed universal and equal access to health actions and services. In this context, the medicines policy was formulated with the purpose of guaranteeing the rational use and access of the population to medicines. Following this law, initiatives were intensified from the 1980s onwards, with the aim of strengthening herbal medicine in the SUS. The study of medicinal plants for clinical investigation was intensified (1981) and the Medicinal Plants Research Program of the Medicines Center was implemented (1982), which established the pharmacological value of preparations based on medicinal plants with the aim of including them in the National List of Essential Medicines (Rename). (TEIXEIRA, BARBOSA, p. 2)

In 2006, the Ministry of Health approved the National Policy on Medicinal Plants and Phytotherapeutics, through decree law no. TEIXEIRA, BARBOSA, p. 2), leading to the presence of herbal science in people's daily lives, combined with the fact that Brazil is the country that holds the largest share of the world's biodiversity, around 15 to 20% (TEIXEIRA, BARBOSA , p. 2).

The National Policy on Integrative and Complementary Practices in the SUS (PNPICS), from 2006, was the last measure of this policy cycle and proposed the inclusion of medicinal plants and phytotherapy, homeopathy, traditional Chinese medicine/acupuncture and social thermalism/crenotherapy in the SUS. This policy created the National List of Medicinal Plants and Phytotherapeutics and the provision of access to medicinal and herbal plants for SUS users (TEIXEIRA, BARBOSA, p. 3)

Since then, studies on medicinal plants, together with the increase in the population's knowledge and access to these medicines through the SUS, have led to the incorrect use of medicines, leading to the emergence of side effects.



### 2.3 Anxiety and herbal treatment

The origin of the word anxiety is derived from the German meaning narrowing or constriction. In Latin, its synonym would be *angustus*, which expresses discomfort or *angor* which means shortness of breath, oppression or even *angere* meaning constriction, suffocation, panic (NARDI, 2006).

Anxiety is characterized by discomfort derived from the anticipation of something unknown or strange, it is an unpleasant feeling of fear and apprehension. (ALLEN; LEONARD, 1995). May (1980) defined anxiety as a relationship between the person, the threatening environment and the neurophysiological processes resulting from this relationship. Thus, anxiety implies the occurrence of an aversive condition, some degree of uncertainty or doubt and some form of impotence of the organism in a given situation. Anxiety is considered normal when it corresponds to psychological and physiological responses, as a response from the body. It is considered pathological when they are exaggerated and do not correspond to the situation that triggers it, or when there is no specific object to which it is directed, or from the moment it brings harm to the person due to their behaviors and abstaining from important situations of the life. (ANDRADE, GORENSTEIN, 1998).

To differentiate normal anxiety from pathological anxiety, it is necessary to assess whether the anxious reaction is short-lived and whether it is related to the current stimulus or not. Anxiety disorders become a clinical condition when they are not derived from other psychiatric conditions, that is, when they are primary symptoms, when they are exposed to fear and do not constitute a set of symptoms that determine a typical disorder (BERNSTEIN; BORCHARDT; et al, 1996 ).

The manifestation of panic disorder is a set of manifestations of anxiety with a sudden onset and lasting ten minutes. Its typical symptoms are: Sweating, tremors, tachycardia, sensation of suffocation, among others. These manifestations usually appear without any prior warning, they arise from a greater level of anxiety when they are precipitated by contact with some type of situation (VERSIANI, 2008 p.3)

From a biological point of view, anxiety is a state of brain functioning that is linked to environmental contexts, related to reinforcing (or eliciting) events or cues associated with these events. This perception is compared with familiarities stored in memory and activates brain systems associated with the flight/fight system or brain control system.

defense. Different neurotransmission pathways are part of the mechanisms that mediate anxiety in this system, in particular, the GABAergic and serotonergic systems as well as the dopamine and neuropeptide systems, among others (BERNIK, 1999; GRAEFF, GUIMARÃES, 2000).

It is made up of emotional/behavioral and physiological factors. In the emotional aspect, the individual may manifest a feeling of fear, a feeling of insecurity, apprehensive anticipation, catastrophic thinking, an increase in the period of wakefulness or alertness. From a physiological point of view, anxiety is a state of brain functioning in which the hypothalamic-pituitary-adrenal (HPA) axis is activated, causing neurovegetative symptoms, such as insomnia, tachycardia, paleness, increased perspiration, muscle tension, tremor, dizziness, intestinal disorders, among others (MACKENZIE, 1989; ANDRADE, GORESTEIN, 1998; GIUNTINI, 2006).

Physiological factors play a fundamental role in anxiety disorders, but the influence of external factors such as socioeconomic conditions and family structure cannot be ignored. (CARLSON, 1998). Anxiety disorders are the most common in the entire population and their manifestations arise involuntarily, such as dry mouth, sweating, chills, tremors, vomiting, palpitations, abdominal pain and other biological and biochemical changes. (ANDRADE; GORENSTEIN, 2013).

According to DSM-IV (American Psychiatric Association, 1994) and ICD-10 (World Health Organization, 1982):

Anxiety disorders are classified into diagnostic categories, which are grouped into five groups of disorders: generalized anxiety disorder, panic disorder, obsessive-compulsive disorder, phobic disorders, and post-traumatic stress disorders.

Generalized anxiety disorders (GAD) are present daily for long periods and fluctuate over time, presenting themselves in the form of apprehensive expectations or exaggerated, morbid worry. Its symptoms are restlessness, tiredness, difficulty concentrating, irritability, muscle tension and insomnia. (DSM-IV, 1994). These are the most frequent mental disorders found in the clinic, even though it is seen as a mild disorder at its onset, GAD is a chronic disease associated with relatively high morbidity and high individual and social costs. (RAVEN PRESS, 1995 p.1349-59)

Panic disorder (PD) is characterized by the presence of sudden anxiety attacks accompanied by physical and affective symptoms, such as tremors, fear of dying, feelings of unreality, affecting a population of 3.5% in men and twice as many in men.

women throughout their lives. (FYER, 1999; MANFRO et al, 2002). PD begins with agoraphobia in which, in certain situations, the patient avoids being present for fear of suffering an attack. The situations and places are: tunnels, traffic jams, large open spaces, being alone, going out alone, thus becoming dependent on others and having their activities increasingly limited (DSM-IV, 1994).

Obsessive compulsive disorder (OCD) are images, thoughts and impulses that occur repetitively and that become uncontrollable by the patient, despite recognizing their abnormal nature. Compulsions often involve cleaning, checking and counting rituals. These obsessions emerge and become noticeable in adulthood and tend to worsen and take up an increasingly greater portion of the individual's time. (DSM-IV, 1994).

OCD symptoms significantly interfere with family life. The disease changes routines and requires adaptations to symptoms. It is common to restrict the use of sofas, beds, clothes, towels, crockery and cutlery, as well as access to certain areas of the house. Other typical symptoms are delays in the bathroom and excessive washing of hands, clothes and floors in the house. People with OCD usually force other family members to do the same, but exaggerated fears, excessive care and demands are not always understood or tolerated by others. In general, this difference causes arguments, friction, irritated demands not to interrupt rituals or participate in them, difficulties in leaving the house and delays that compromise leisure and routines. Not infrequently, attitudes and relationship difficulties lead to couples separating or being fired from jobs. (CORDIOLI, 2004, p. 9).

Social anxiety disorder (Phobia) presents itself in situations in which the person feels observed by other people and in contact with them, the patient suffers symptoms such as tremors, palpitations, sweating, difficulty concentrating, unlike panic attacks these symptoms appear in social situations. (DSM-IV, 1994; ICD-10, 1993).

In post-traumatic stress disorder (PTSD), the patient must have been through a real situation in which they felt exposed to danger, and for this reason they always feel threatened, provoking a response of fear, despair or terror. (AMERICAN PSYCHIATRIC ASSOCIATION, 2000.)

The etiological hypotheses of phobias point to dysfunctions in dopaminergic and serotonergic circuits, and stress-related disorders are involved in neuroendocrine aspects related to the hypothalamic-pituitary-adrenal axis, due to the reduction in basal cortisol levels and greater regulation of negative feedback. related to the decrease in serotonergic function, compromising the behavioral inhibition system, and the increase in dopaminergic function, facilitating hypervigilance, in addition to changes in

GABAergic, glutamatergic and noradrenergic systems interfering with emotional memory related to a traumatic event. (GRAEFF; HETEM, 2004)

Neurotransmitters are implicated in anxiety disorders because they participate in the modulation and regulation of defensive behaviors, among them are biogenic amines such as: norepinephrine, serotonin and dopamine, the amino acids  $\alpha$ -Amino-butyric acid- GABA, glycine, peptides as a release factor corticotropin, and steroids such as corticosterone. (RIBEIRO, 1999; GRAEFF, 2004)

Norepinephrine is a monoamine implicated in defense and anxiety due to patients affected by deficient noradrenergic levels with occasional increases in activity. Disorders caused by post-traumatic stress are those that present abnormalities of noradrenergic function. (RIBEIRO, BUSNELO et al. 1999)

Serotonin is considered fundamental in anxiety disorder, but its role in anxiety is still poorly understood. (GRAEFF; HETTEM, 2004). This neurotransmitter has both stimulatory and inhibitory activity, danger signals stimulate the defense system through the amygdala and activate serotonergic neurons located in the dorsal raphe nuclei, which is the periaqueductal gray matter that innervates the amygdala, therefore having an adaptive sense. Serotonin increases anxiety by acting on the amygdala and contains panic by acting on the periaqueductal gray matter. (RIBEIRO, BUSNELO et al. 1999)

GABA is found throughout the central nervous system, as it is a neurotransmitter with inhibitory action on serotonergic neurons in the dorsal and raphe nuclei. These inhibitory neurons function as controllers of the nervous system, guaranteeing its action. (GORESTEIN, POMPÉIA, 1999). Its role in anxiety is supported by the effectiveness of benzodiazepines in reducing anxiety, especially in generalized anxiety disorder. (SILVA, 2001)

Among the main treatments for anxiety disorder are the use of medication for a specific or even indefinite period of time and/or cognitive-behavioral psychotherapy. (KOBALK, GREIST et al 1998) To draw up a treatment plan, the diagnosis must be very comprehensive, as there are variations in different anxiety disorders. Blocking the main symptoms does not always result in significant improvement. (LIEBOWITZ; 1999)

The pharmacological resources available for the treatment of anxiety disorders are diverse and include the following classes of medications: benzodiazepines (such as diazepam, chlordiazepoxide and lorazepam), antidepressants (tricyclics: such as imipramine and amitriptyline; Selective serotonin reuptake inhibitors: such as fluoxetine and sertraline; Monoamine oxidase inhibitors: how

phenelzine and moclobemide and others), barbiturates (such as amobarbital and mephobarbital), carbamates (such as hydroxyfenamate and meprobamate), noradrenergics (such as clonidine and propranolol), antihistamines (such as hydroxyzine and cinnarizine) and others such as glutamic acid and buspirone (ALMEIDA, BARBOSA FILHO, 2006).

Benzodiazepines enhance the inhibitory effect of -aminobutyric acid (GABA), which is the main inhibitory neurotransmitter in the CNS. Benzodiazepine receptors are actually a subtype of GABA A receptor, and their activation by benzodiazepines facilitates the action of GABA, causing the opening of chlorine channels, the entry of chlorine into the nerve cell, and a decrease in nervous excitability. It is, therefore, an indirect action and is limited by the amount of GABA available (STAHL, 1997; BALLENGER, 1998).

All antidepressants affect the serotonergic (5HT) or catecholaminergic (dopamine or norepinephrine) systems of the central nervous system, either by blocking presynaptic reuptake, stimulating their release into the cleft, inhibiting their catabolism (MAOI) or by agonistic or antagonistic effects on receptors. The increase in the availability of these neurotransmitters in the synaptic cleft is immediate, but the clinical effect generally takes several weeks, and is correlated with another neurochemical effect: the downregulation of presynaptic autoreceptors, responsible for modulating the release of neurotransmitters in the cleft. synaptic. It is also important to note that the action of most receptors is linked to the G protein, a substance involved in a cascade of intracellular events related to protein synthesis, such as genetic transcription. It is postulated that through the prolonged action of antidepressants on receptors there would be a modulation of the G protein and other second messenger systems, and a change in the conformation of new receptors as they are synthesized, resulting in their desensitization, which could contribute both to the therapeutic action of antidepressants and to the development of tolerance to many of their side effects (STAHL, 1997; REID et al., 2001).

Buspirone is the first drug in the azapirone class and the only one of this class marketed in Brazil. It was synthesized in the 1970s and approved by the US Food and Drug Administration in 1986 (Andreatini et al., 2001; Caixeta, 1995). It is a non-benzodiazepine compound with anxiolytic properties (Santos et al., 2006) and without anticonvulsant, myorelaxant and hypnotic activity, and is therefore called anxiolytic (GOA; WARD, 1986). It also differs from benzodiazepines in that it does not cause depression in the Central Nervous System (CNS) (Lima et al., 2002).

The SSRIs, citalopram, fluoxetine, fluvoxamine, paroxetine, and sertraline are the result of rational research to find medications that are as effective as TCAs but with few tolerability and safety problems. SSRIs potently and selectively inhibit serotonin reuptake, resulting in potentiation of serotonergic neurotransmission. Although they share the main mechanism of action, SSRIs are structurally distinct.

with marked differences in the pharmacodynamic and pharmacokinetic profile. The potency of serotonin reuptake inhibition is varied, as is the selectivity for norepinephrine and dopamine. Sertraline and paroxetine are the most potent reuptake inhibitors. (Goodnick et al., 1998)

Several medications are used to treat anxiety, such as benzodiazepines, and they bring with them several side effects such as: dependence, sedation, amnesia, withdrawal syndrome and interactions with central nervous system depressant agents. (FAUSTINO et al., 2010).

Phytotherapy has been an alternative form of treatment for older pathologies and has been widely used by the population as they are opting for a treatment that is less aggressive to the body, they are looking for something natural, but like any medicine there are its dangers and interactions and it should always be guided by a professional. Herbal medicines used for anxiety are, like any other medicine, recommended by doctors and should not be used without a prescription (ANVISA, 2013a).

With the increase in the manipulation and sale of these “natural” anxiolytics, regulatory agencies have shown themselves to be more cautious in relation to medications that act on the Central Nervous System, such as Hypericum (Hypericum perforatum), Valeriana (Valeriana officinalis), Kava Kava (Piper methisticum). Those containing passion fruit (Passiflora incarnata) and Carmelite cider (Melissa Oficinallis L).

Health problems are caused by adverse reactions and ineffective therapy, therefore the use of medicinal plants and herbal medicines must be guided by a trained professional, ensuring that inappropriate use does not cause a severe adverse reaction. The population must be made aware of their risks, and it is important that sanitary control of natural products is carried out, given the widespread idea that natural products are not harmful to health. (CARVALHO et al., 2007).

#### **2.4 Herbal medicines with anxiolytic action**

Medicinal plants that can be used to treat anxiety are: Kava - Kava (Piper methysticum) figura 1, Passionflower (Passiflora incarnata) figure 3 and Valerian (Valeriana officinalis) figure 4. These are the plants most used for anxiolytic treatment and act in the CNS (FAUSTINO; ALMEIDA; ANDREATINI, 2010). All are found in the Simplified Registration of Herbal Medicines list of RE 89, dated March 16, 2004/ANVISA.

## 2.5 Kava-Kava (*Piper methysticum*)

James Cook (1768-1771) was possibly the first European to have contact with kava-kava. The botanical description was made for the first time by Johann G. Forster, who called it Piper, alluding to its spicy flavor and Methysticum, which would be a translation of the Greek word methu (intoxicating drink) (ALONSO, 1998).

During the years 1999 to 2002, kava-kava was on the list of the 10 best-selling herbal medicines in Brazil. This plant is indicated for the treatment of insomnia and anxiety (Figure 1), acting as a calming agent (JUSTO & SILVA, 2008b).

Figure 1: Kava-Kava Leaf



The part used is the dried rhizome (figure 2), which has a weakly aromatic odor and a slightly bitter taste. Chewing the kava-kava rhizome causes numbness in the tongue and salivation (JUSTO; SILVA, 2008b).

Figure 2: Rhizome



Source: Botanical Medicine, 2016.

Kava-kava extract, when acting on the central nervous system (CNS), provides a sensation of pleasure, alleviating feelings of fear. Peripherally, it acts as a potent local anesthetic, also exerting a protective effect against strychnine poisoning, being superior to all known non-narcotic antagonists (JUSTO; SILVA, 2008b). The pharmacological activity of kava-kava is due to kavalactones (also called kavapirones), kavaine, dihydrokavaine, mestisticin, dihydromestisticin and others. It has been proven that kava-kava has several effects on the CNS, including anxiolytic, sedative, anticonvulsant, local anesthetic, spasmolytic and analgesic activities; however, the exact mechanism of these events is unknown (JUSTO; SILVA, 2008b).

Kava-kava is made into a drink by crushing it using the dried rhizome, macerating it in cold water, then percolating the liquid. Extracts are prepared by extracting the plant drug with a mixture of ethanol and water, when extracts with approximately 30% active ingredient are desired. A mixture of acetone and water is used for more concentrated extracts, containing up to 70% of active ingredient (JUSTO; SILVA, 2008b).

The advantage of kava-kava's anxiolytic action is that it does not present the adverse effects of benzodiazepines such as impairment of cognitive functions, drowsiness, reduced motor coordination and dependence (JUSTO; SILVA, 2008b).

Kava Kava Herbarium has substances called *kavalactones* which alter some brain mechanisms, helping to relieve anxiety and insomnia. The onset of action of this medication occurs one hour after administration. The effects of the product are noticed after a brief period, and are intensified during the subsequent weeks. (HERBARIUM, 2014).

## 2.6 Passion fruit (*Passiflora Incarnata*)

According to ANVISA – National Health Surveillance Agency – Resolution RDC No. 48, of March 16, 2004, the therapeutic indication for passion fruit (*Passiflora incarnata*) is as a sedative.

For Gonçalves, 1996; Zatta, 1996; Biazzi, 1994; Panizza, 1997; Sartório, 2000, *Passiflora incarnata* is used internally and its leaves are indicated for headaches



of nervous origin, anxiety, menopause, insomnia, nervous tachycardia, spasmodic diseases, neuralgia, asthma, depressive states due to alcoholism, high blood pressure, fever, sedative, menstruation, palpitation, stress, vertigo, vomiting, hemorrhoids, rheumatism, skin inflammations, erysipelas, hysteria.

Passiflora incarnata has a substance called *benzoflavone*, with sedative characteristics. This drug is found in large quantities in passion fruit leaves and in smaller quantities in fruits, flowers, as shown in (figure 3) branches and trunk. So, if you want to relax, leave the juice aside and make some tea. Currently, a group of Indian scientists are studying replacing drugs normally prescribed for the treatment of depression with *benzoflavone*. (MENEZES, 2004).

It is believed that the flavonoids present in the plant species are mainly responsible for the pharmacological activities. These constituents, in synergism with the alkaloids also present in the plant, promote non-specific depressant actions on the Central Nervous System (CNS), thus contributing to the sedative and tranquilizing action. Recently, studies pointed to the *benzoflavone* tri-substituted as responsible for the sedative and anxiolytic effects of the plant species. The proposed mechanism of action for this molecule would be the inhibition of the aromatase enzyme, a member of the cytochrome P-450 family, responsible for the conversion of testosterone to estrogen. This inhibitory effect would restore normal testosterone levels, which, at low levels, would be the cause of symptoms such as anxiety and insomnia. However, ongoing studies attempt to fully elucidate the mechanism of action of this molecule in the CNS (HERBARIUM, 2013).

Figure 3: Passion Fruit, Fruit and Flower.



Source: Cria saúde, 2016.

## 2.7 Valerian (*Valeriana Officinalis*)

It is indicated for the treatment of sleep disorders associated with anxiety, moderate sedative, mood disorders such as depression, attention deficit disorder, hyperactivity and antispasmodic. (Alexandre RF et al. 2005).

Valerian extractions are carried out by immersing the dry root or rhizome of the plant as shown in (figure 5) in a solution (water, ethanol and water or methanol and water), followed by centrifugation and drying to extract and concentrate the plant components. According to the American Herbal Pharmacopoeia, the extraction of valerenic acid requires at least 30% alcohol and the extraction of valpotriatos requires 70% alcohol (HERBALIST, 1999).

Its active components are: Gamma amino butyric acid (GABA), a neurotransmitter related to the sedative effects of this herb; Valeric acid; Alkaloids: actinidine, catinine, isovaleramide, valerianine and valerine; Volatile oil containing active sesquiterpenes (acetoxyvalerenic acid, valerenic acid); Valepotriates, non-glycoside esters, mainly acevaltrate, isovaltrate and valtrate.

The chemical composition of Valerian varies according to the subspecies, variety, age of the plant, growing conditions, age and type of extract (WORLD HEALTH ORGANIZATION, 1999). Valerian root contains more than 150 identical components, including bicyclic monoterpenes (valpotriates – valtrate and dihydrovaltrate), volatile oils (valeranone, valerenal and valerenic acids), sesquiterpenes, lignans and alkaloids.

Free amino acids are also present, such as gamma-aminobutyric acid (GABA), tyrosine, arginine and glutamine (HADLEY PETRY, 2003).

**Figure 4: Valerian Flower**



## 2.8 Valerian (*Valeriana Officinalis*)

It is indicated for the treatment of sleep disorders associated with anxiety, moderate sedative, mood disorders such as depression, attention deficit disorder, hyperactivity and antispasmodic. (ALEXANDRE et al. 2005).

Valerian extractions are carried out by immersing the dry root or rhizome of the plant as shown in (figure 5) in a solution (water, ethanol and water or methanol and water), followed by centrifugation and drying to extract and concentrate the plant components. According to the American Herbal Pharmacopoeia, the extraction of valerianic acid requires at least 30% alcohol and the extraction of valpotriatos requires 70% alcohol (HERBALIST, 1999).

Its active components are: Gamma amino butyric acid (GABA), a neurotransmitter related to the sedative effects of this herb; Valeric acid; Alkaloids: actinide, catinine, isovaleramide, valerianine and valerine; Volatile oil containing active sesquiterpenes (acetoxvalerenic acid, valerenic acid); Valepotriates, non-glycoside esters, mainly acevaltrate, isovaltrate and valtrate.

The chemical composition of Valerian varies according to the subspecies, variety, age of the plant, growing conditions, age and type of extract (WORLD HEALTH ORGANIZATION, 1999). Valerian root contains more than 150 already identified components, including bicyclic monoterpenes (valpotriates – valtrate and dihydrovaltrate), volatile oils (valeranone, valerenal and valerenic acids), sesquiterpenes,

lignans and alkaloids. Free amino acids are also present, such as gamma-aminobutyric acid (GABA), tyrosine, arginine and glutamine (HADLEY PETRY, 2003).

### Final considerations

Phytotherapy in general has been growing as a therapeutic option and studies have demonstrated its effectiveness and ability to treat diseases with fewer side effects compared to conventional pharmacological treatments.

Based on the review of some previous studies, herbal medicine has been widely used as a therapeutic alternative for anxiety disorders, and *Matricaria Recutita*, *Passiflora Incarnata*, *Valeriana Oficinalis*, *Kava-Kava*, stand out as the main herbal anxiolytics used.

Anxiety is a psychic state of apprehension or fear caused by the anticipation of an unpleasant or dangerous situation and its manifestations appear as tachycardia, tremors, sweating, and pharmacological resources are used for its treatment, such as benzodiazepines, antidepressants, selective serotonin reuptake inhibitors. These drugs bring several side effects such as: Dependence, sedation, amnesia, among others.

For this reason, medicinal plants have been chosen by the population because they are a less aggressive treatment and because they are natural, but just as conventional medicines have their dangers, herbal medicine also has its reactions and interactions, so its use must be guided by the doctor. professional.

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