

Review

Naturally occurring anxiolytic substances from aromatic plants of genus *citrus*

Pimenta, Flávia Cristina Fernandes^{1*}, Correia, Nadja de Azevedo², Albuquerque, Katy Lísias Gondin Dias², De Sousa, Damião Peregrino³, Da Rosa, Marine Raquel Diniz⁴, Pimenta, Martina Bragante Fernandes⁵, Diniz, Margareth de Fátima Formiga Melo⁶ and De Almeida, Reinaldo Nóbrega²

¹Departamento de Medicina Interna, Centro de Ciências Médicas, Universidade Federal da Paraíba, Brazil.

²Departamento de Fisiologia e Patologia, Centro de Ciências da Saúde, Universidade Federal da Paraíba, Brazil.

³Departamento de Fisiologia, Universidade Federal de Sergipe, São Cristóvão-SE, Brazil.

⁴Departamento de Fonoaudiologia, Centro de Ciências da Saúde, Universidade Federal da Paraíba, Brazil.

⁵Faculdade de Medicina Nova Esperança – PB, Brazil.

⁶Departamento de Ciências Farmacêuticas, Centro de Ciências da Saúde, Universidade Federal da Paraíba, Brazil.

Accepted 8 September, 2011

Currently, anxiety is one of the most common mental disorders affecting humanity and its prevalence is increasing. Anxiolytic substances occupy a prominent post in the ranking of the most utilized drugs by man. However, the anxiolytic drugs have an unfavorable risk/benefit ratio, especially benzodiazepines. Several medicinal plants have been used in traditional folk medicine for their anxiolytic or sedative properties. It is well reported in the literature that aromatic substances have the power to influence emotional states in humans. Several plants rich in essential oil have been used in the treatment of anxiety. In addition, a great number of essential oils are currently in use as aromatherapy agents to relieve stress and depression. These oils are considered a holistic complementary therapy utilized for increased comfort and reduce stress. For this reason, we performed a literature review used papers indexed in Elsevier Science Direct and PubMed a source of research. The dates were collected of reviewed studies from 2000 to 2011 using essential oils of genus *citrus* with anxiolytic effects in preclinical models and clinical studies. Ethnopharmacological data has confirmed the popular use of plant species of the genus *Citrus* with sedatives, hypnotics, tranquilizers and anti-epileptics activities to treat disorders of the central nervous system. Given these assumptions, this paper aims to describe the principal evidence in the literature about the use of essential oils of genus *citrus* with anxiolytic effects in preclinical models and clinical studies.

Key words: Genus *citrus*, anxiolytic effects, preclinical models, clinical studies of anxiety.

INTRODUCTION

Anxiety and medicinal plants

Anxiety includes a feeling of apprehension and fear characterized by physical symptoms such as palpitations, sweating and feelings of stress (<http://search.medicinenet.com>). It is known to man for thousands of years, being regarded as responsible for human survival on earth. Fear of attacks by predators

and mental anticipation of this possibility, characteristics of anxiety, allowed the man to adopt effective strategies to escape or coping allowing the preservation of the species (Schmitt and Kapczinski, 2004). It is recognized that some anxiety is necessary for performance of tasks cognitive being inadequate in exaggeration, as this will degrade performance. However, the distinction between normal and pathological anxiety state is not easy, when anxiety interferes with normal activities, it is pathological anxiety, which is considered an inappropriate response to a stimulus, because of its intensity or duration, being consensus on the psychiatric the need for medical

*Corresponding author. E-mail: flavia@yahoo.com.br. Tel+55-83-3216-7039. Fax: +55-3216-7094.

intervention when it is apparent disproportionate possible causes which can cause confusion and distortion of time perception and the meaning of events (Brandão, 2001). The pathological anxiety is most often a result of other psychiatric illness or not, being called secondary anxiety. However, when it is main or only manifestation clinical is classified of primary anxiety (Graeff and Brandão, 1999).

The anxiety disorders include: panic disorder, obsessive compulsive disorder, post-traumatic stress disorder, social phobia, specific phobias and generalized anxiety disorder. Each of these anxiety disorders has its own distinct features, but they are all bound together by the common theme of excessive, irrational fear and dread (<http://search.medicinenet.com>).

As at present the etiologic factors responsible for anxiety and tension are not expected to decrease; there is a need for new anxiolytic drugs with less potential to induce adverse reactions. Some plants have been used for such purposes since ancient times. Today, the use of their extracts is gaining increased acceptance by both the medical profession and patients (Carlini, 2003).

In the treatment of anxiety employment of teas from various plants is common. Given the standard of effectiveness presented by currently available drugs for the treatment of anxiety, research is needed to identify new compounds (Gomes et al., 2009). In this context, natural products are a promising source for obtaining new molecules with pharmacological activity on central nervous system.

Moreover, research involving medicinal plants has been shown to be important in getting new chemicals that are potentially capable of becoming a drug. Medicinal plants are distributed throughout the world but are most abundant in tropical countries (Calixto, 2000). Unquestionably recognized on the world scenario the Brazilian flora is considered unique because of the immense variety of plant species. In this scenario, the Amazon is one of the most important sources of active compounds on the planet, for its diversity of species with therapeutic potential, making the prospects for the highly promising phytotherapy in Brazil (Vieira, 1992).

The modern man differs from other seasons by high consumption of medicines. However, the large supply of medicine does not solve the health problems of the majority of the population. According to World Health Organization, 80% of the population has no access to primary health care, because they are distant from health centers or lack resources to purchase prescription drugs (Akerle, 1993; Veiga, 2008). Thus, alternative therapies are a major form of treatment and medicinal plants the main form of therapy, and patients generally consider this form of treatment to be both safe and effective (Eisenberg et al., 2008; Mengue et al., 2001; Mendonça-Filho and Menezes, 2003; Carlini et al., 2006; Agra et al., 2007). Moreover, such ancient use of plants was a lead for scientists in their search for new substances endowed with therapeutic properties, it is estimated that nearly

25% of the modern drugs directly or indirectly originated from plants (Carlini, 2003). Several plants rich in essential oil has been used in the treatment of anxiety, among these stand out, orange, *Citrus sinensis* (Faturi et al., 2010), bergamot, *Citrus aurantium* (Carvalho-Freitas and Costa, 2002; Pultrini et al., 2006), lemon, *Citrus limon* (Ceccarelli et al., 2004). In addition, the essential oils are currently in use as aromatherapy agents to relieve stress and depression and have been used topically for their antibiotic and antiviral properties for years (Setzer, 2009; Cooke and Ernst, 2000).

ESSENTIAL OILS AND AROMATHERAPY

Essential oils have been defined as the volatile organic constituents of fragrant plant matter that contribute to both flavour and fragrance. Essential oils are extracted from plants primarily through the technique of steam distillation; they are consisting mainly of mono- and sesquiterpenes and phenylpropanoids, metabolites that confer their organoleptic characteristics. Brazil stands in the production of essential oil, along with India, China and Indonesia that are considered the world's largest producers. Brazil stands out mainly by the production of essential oils obtained especially the *Citrus* genus and the species *C. aurantium* L. is one of the most used (Bizzo et al., 2009). Currently in France, the purchase of essential oil is made only on prescription. In Britain and other European countries the essential oil has been used for massage, inhalation and skin application and are therefore considered a holistic complementary therapy utilized for increased comfort and reduce stress (Buckle, 2001). Several authors also report that the oils essences restore the emotional well-being, reduces depression, anxiety and stress (Louis and Kowalski, 2002; Edge, 2003; Kyle, 2006; Atsumi and Tonosaky, 2007).

Aromatherapy is defined as the use of essential oils extracted from plants to produce physiologic or pharmacologic effects through the sense of smell or absorption from the skin (Cooke and Ernst, 2000). The proponents of aromatherapy lay claim to an ancient tradition of herbal medicine practiced in countries such as Egypt and India thousands of years ago. However, the term was initially used by the French chemist Gattefossé in a book first published in 1936. It is now commonly administered by massaging into the skin, and the term aromatherapy usually implies massage with a range of aromatic plant extracts known as essential oils (Cooke and Ernst, 2000). Aromatherapy is employed for relief of pain, relaxation and anxiety reduction, and enhanced energy. Essential oils have been used to help women cope with labor pain, relieve chemotherapy side effects, enhance the rehabilitation of cardiac patients, promote restful sleep and to reduce post-surgical discomfort (Price and Price, 1999).

Despite aromatherapy's popularity, efficacy data are

scant and potential mechanisms are controversial. In 2001, Hirsch suggested that essential oils probably act like a drug or enzyme, such that particular odors should have very specific effects, a popular view among aromatherapy practitioners who prescribe certain odors for distinct health problems. For example, in a sleep study, lavender oil presented the first 2 min of every 10 min period for 40 min increased deep or slow-wave sleep compared to a control (distilled water) stimulus (Goel et al., 2005).

In view of the limitations of the more traditional approaches, attention was given to the use of complementary and alternative medicine as an adjuvant treatment. This form of therapy has been widely used. The complementary and alternative medicine refers to practices, approaches, knowledge, and beliefs incorporating plant, animal and mineral-based medicines, spiritual therapies, manual techniques, and exercise that are not presently judged to be part of conventional medicine (Hughes, 2008). This type of therapy adopts a holistic approach to medicine and indicates the treatment of the "whole" person by addressing their physical and mental. Thus, aromatherapy is a particular kind of complementary and alternative medicine widely used around the world for the management of depression or other stress-related disorders (Barnes et al., 2004; Komori, 2009).

GENUS *CITRUS* AND PRECLINICAL STUDIES

In recent years, research on the effects of aromatherapy using animal models has blossomed. Studies found that essential oils produced anxiolytic or antistress effects in rats and mice (Carvalho-Freitas and Costa, 2002; Komiya et al., 2006; Pultrini et al., 2006; Fukumoto et al., 2008; Gargano et al., 2008; Leite et al., 2008; Faturi et al., 2010). Among the many effects of essential oil, anxiolytic and antidepressant effects are very helpful for psychiatry and psychopharmacology, since combining the medicine and essential oil can reduce the dose of those medicines and essential oil may help prevent the side effects of the anxiolytic and antidepressant medicines (Cooke and Ernst, 2000). Since all clinically available anxiolytics and antidepressants have limited clinical efficacy because of their adverse side effects, such as the amnesic effect of benzodiazepine (Komiya et al., 2006). The search for new alternatives for treating these diseases is important.

In this context, plant species of the genus *Citrus* are used as sedatives, hypnotics, tranquilizers may be useful in treating disorders of the central nervous system. Among the species of this genus that can be useful in treating anxiety highlight the species *C. aurantium* L. This species belongs to the family Rutaceae is popularly known as "bitter orange" or "sour orange" (Santos et al., 1988; Sanguinetti, 1989) is native to Southeast Asia, India and China (Grieve, 1994). The parts most used for medicinal purposes by the population are the peel of fruit,

flowers and leaves. With respect to their effects on the central nervous system it is popularly used to cure insomnia, to treat nervousness, anxiety and hysteria, and the flowers are used as sedatives (Lehrner et al., 2000). Ethnopharmacological data has confirmed the popular use of *C. aurantium* L. as an alternative treatment of disorders related to CNS. This species has been used to treat anxiety, among other central nervous system disorders (Pultrini et al., 2006). The main compound present in the essential oil from peel of *C. aurantium* L. analyzed by gas chromatography is limonene 96.24% followed by myrcene 2.24%; (Leite et al., 2008). Pultrini and collaborators obtained similar results using analysis by gas chromatography coupled with mass spectrometer, the main compounds present in the essential oil from peel of *C. aurantium* L. is limonene (97.83%) and myrcene (1.43%). Both compounds have biological activity related with depression of central nervous system (Pultrini et al., 2006). Corroborating these results, Vale and collaborators demonstrated that mice treated with limonene or myrcene shown decrease in spontaneous activity, rearing and grooming in the open field test and were able to increase the barbiturate sleeping time (Vale et al., 2002).

In 2002, Carvalho-Freitas and Costa demonstrated that the essential oil obtained from peel of *C. aurantium* L. showed anxiolytic activity after a single administration in mice, denoted by the increase in time spent in open arms of the elevated plus maze. The effects of the essential oil from *C. aurantium* L. it were evaluated in two other two experimental models: the light-dark box and the marble-burying test (Pultrini et al., 2006). Mice were treated acutely by oral route 30 min (single dose) or once a day for 15 days (repeated doses) before experimental procedures. In light-dark box test, single treatment with essential oil augmented the time spent by mice in the light chamber and the number of transitions between the two compartments. On the other hand, there were no observed alterations in the parameters evaluated in light-dark box after repeated treatment. In the marble-burying test, the essential oil significantly decreased the number of marbles buried after single and after repeated treatments.

Essential oils obtained from ripe fruit peels of *C. latifolia* and *C. reticulata* elicited anxiolytic and sedative effects. The limonene was the main compound in these essential oils, 58 and 90%, respectively. The essential oils were administered orally in mice, 30 min before each experimental procedure. Treatment with *C. latifolia* (1.0 and 1.5 g/Kg) and *C. reticulata* (1.5 g/Kg) significantly decreased the number of marbles buried in the Marble-Burying test. In the light/dark box test, 0.5 g/Kg of *C. latifolia* essential oil increased the time spent in light compartment. On the other hand, no effect was observed with the animals that were treated with *C. reticulata* of essential oil (0.25, 0.5 or 1.0 g/Kg). In addition, essential oils from *C. latifolia*, *C. reticulata* and *C. aurantium* were

Table 1. Preclinical studies of essential oils from genus *Citrus* and their effects on the central nervous system.

Herbs/essential oil	Effect	Species	Reference
Linalool	Anxiolytic, increased social interaction and decreased aggressive behavior	Mice	Linck et al. (2010)
<i>Citrus bergamia</i> oil	Anxiolytic	Rat	Carvalho-Freiras and Costa (2002), Pultrini et al. (2006), Saiyudthong and Marsden (2010)
<i>Citrus aurantium</i> oil	Anxiolytic, sedative and anticonvulsive	Rat Mice	Leite et al. (2008) Blanco et al. (2009)
<i>Cymbopogon citrates-Citrus</i> grass oil	Anxiolytic, sedative and Anticonvulsive	Mice	Faturi et al. (2010)
<i>Citrus sinensis</i> oil	Anxiolytic	Rat	Komiya et al. (2006)
<i>Citrus lemon</i> oil	Anti-stress, Sedative	Mice	Fukumoto et al. (2008)
<i>Citrus latifolia</i> and <i>C. reticulata</i> oil	Anti-stress and anxiolytic	Mice	Gargano et al. (2008)

effective in increased sleep duration induced by ether inhalation (Gargano et al., 2008).

Recently, Faturi et al. (2010) observed an anxiolytic effect of sweet orange (*Citrus sinensis*) aroma in rats. The main volatile component of *C. sinensis* is the limonene (97.66%). The animals were exposed to the orange odor (100, 200 or 400 μ l) for 5 min and were then immediately submitted to the behavioral tests. The animals that received (200 and 400 μ l) spent more time and entered more into the open arms than the control group. In addition, the group treated with 400 μ l also explored more the open arms than the group that was exposed to 100 μ l of essential oil. In the lit chamber of the light/dark paradigm, only the animals exposed to 100 and 400 μ l spent more time in the lit chamber than the control group. These results are summarized in Table 1. Park et al. (2011) found that limonene directly binds to the adenosine A_{2A} receptor, which may induce sedative effects. Moreover, results from an *in vitro* radioligand binding assay showed that limonene exhibits selective affinity to A_{2A} receptors. In addition, limonene increased cytosolic cAMP concentration and induced activation of protein kinase A and phosphorylation of cAMP-response element-binding protein in Chinese hamster ovary cells transfected with the human adenosine A_{2A} receptor gene. Limonene also increased cytosolic calcium concentration, which can be achieved by the activation of adenosine A_{2A} receptors. These results suggest that limonene can act as a ligand and an agonist for adenosine A_{2A} receptors.

GENUS *CITRUS* AND CLINICAL STUDIES

In a study by Lehner et al. (2000), dental patients,

exposed to the *C. sinensis* odour diffused in the waiting room before a dental procedure, female patients showed lower levels of state-anxiety compared to control patients, exposed to air only. Although, this effect was not observed in male patients.

In a controlled experimental study (Lehrner et al., 2005), patients were stimulated either with ambient odor of orange (*C. sinensis*) in a dentist's waiting room. These conditions were compared to a music condition and a control condition (with no odor and no music). The authors found that patients who were exposed to orange odor had a lower level of state anxiety, a more positive mood, and a higher level of calmness compared to the patients in the control condition and the patients that exposure to a music has a intermediate effect (Lehrner et al., 2005). It has been postulated that the effects of odors on stress are mediated through stimulation of the olfactory (Ceccarelia et al., 2004; Komori et al., 1995). Corroborating this assumption, citrus essential oil affected the release of monoamines from rat brain tissue, these results suggested that monoterpenes in citrus essential oils reach the brain and act on the neurotransmitter regulation system (Fukumoto et al., 2006). Recently, it was reported that flavors components in lemon essential oil, limonene (Saiyudthong and Marsden, 2010), gamma-terpinene and citral inhibited elevation of serum corticosterone levels and monoamine levels in brain on physical and psychological stress. These results suggest that limonene have a stress-alleviating effect. In addition, the presence of perillid acid, a limonene metabolite, was found at concentration of 1.5 to 2.5 μ g/ml in serum and 0.4 to 0.6 μ g/ml in brain tissue collected 3 h after intraperitoneal administration of lemon components (Fukumoto et al., 2008).

Table 2. Clinical studies of the essential oils of orange (*Citrus sinensis*).

Experimental design	Effect	Reference
35 patients were exposed to odor orange and the state anxiety was measured through questionnaires.	Reduced levels of state-anxiety in female.	Lehrner et al. (2000)
50 patients were exposed to odor orange and the state anxiety was measured through questionnaires.	Lower levels of state anxiety, more positive mood and a higher level of calmness.	Lehrner et al. (2005)
81 patients were exposed to odor orange and the state anxiety was assessed through questionnaires.	No effects on the anticipatory anxiety.	Toet et al. (2010)

On the other hand, Toet et al. (2010), investigated whether oranges and apple odor reduced anxiety in patients waiting for dental treatment in large dental clinics. While they were waiting for dental treatment, the participants were either exposed to the ambient odor of orange or apple, or they received no odor. Anxiety state, mood, and perceived level of pain of the participants were assessed using questionnaires. The results showed no effect on the anticipatory anxiety, mood or pain between the responses of patients in each of the three experimental groups. Because this study was conducted in a large dental clinics and studies of Lehrner et al. (2000, 2005) were carried out in a small dental office, in large practices there is a continuous coming and going of patients, and this may have provided the patients an additional source of distraction, thereby lowering their self-awareness and reducing their anxiety. These results are summarized in Table 2.

In conclusion, the use of essential oil of genus *Citrus* could be a great alternative since it has shown positive emotional effects in studies with humans and demonstrated anxiolytic and sedative effects in experimental models of anxiety.

REFERENCES

- Agra MF, França PF, Barbosa-Filho JM (2007). Synopsis of the plants known as medicinal and poisonous in Northeast of Brazil. *Rev. Bras. Farmacogn.*, 17: 114-140.
- Akerele O (1993). Summary of WHO guidelines for assessment of herbal medicines. *Herbal Gram*, 28: 13-19.
- Barnes PM, Powell-Griner E, McFann K, Nahin RL (2004). Complementary and alternative medicine use among adults: United States 2002. *Sem. Integr. Med.*, 2: 54-71.
- Bizzo HR, Hovell AMC, Rezende CM (2009). Essential oils in Brazil: general aspects, development and prospects. *New Chem.*, 32: 588-594.
- Blanco MM, Costa CARA, Freire AO, Santos JJG, Costa M (2009). Neurobehavioral effect of essential oil of *Cymbopogon citratus* in mice. *Phytomedicine*, 16: 265-270.
- Brandão ML (2001). Emotional behavior. In *Psychophysiology*. New York: Atheneu, 126-149.
- Calixto JB (2000). Efficacy, safety, quality control, marketing and regulatory guidelines for herbal medicines (phytoterapeutic agents). *Braz. J. Med. Biol. Res.*, 33: 179-189.
- Carlini EA (2003). Plants and the central nervous system. *Pharmacol. Biochem. Behav.*, 75: 501-512.
- Carlini EA, Rodrigues E, Mendes FR, Tabach R, Gianfratti B (2006). Treatment of drug dependence with Brazilian herbal medicines. *Rev. Bras. Farmacogn.*, 16: 690-695.
- Carvalho-Freitas MIR, Costa M (2002). Anxiolytic and sedative effects of extracts and essential oil from *Citrus aurantium* L. *Biol. Pharm. bull.*, 25: 1629-1633.
- Ceccarella I, Lariviera WR, Fiorenzania P, Sacerdote P, Aloisi AM (2004). Effects of long-term exposure of lemon essential oil odor on behavioral, hormonal and neuronal parameters in male and female rats. *Brain Res.*, 1001: 78-86.
- Cooke B, Ernst E (2000). Aromatherapy: a systematic review. *Br. J. Gen. Pract.* 50: 493-496.
- Eisenberg DM; Davis RB, Ettner SL, Appel S, Wilkey S, Van RM, Kessler RC (2008). Trends in alternative medicine use in the United States, 1990-1997: results of a follow up national survey. *J.A.M.A.*, 280: 1569-1575
- Faturi CB, Leite JR, Alves PB; Canton AC, Teixeira-Silva F (2010). Anxiolytic-like effect of sweet orange aroma in Wistar rats. *Prog. Neuropsychopharmacol. Biol. Psychiatry*, 34: 605-609.
- Fukumoto S, Morishita A, Furutachi K, Terashima T, Nakayama T, Yokogoshi H (2008). Effect of flavour components in lemon essential oil on physical or psychological stress. *Stress Health*, 24: 3-12.
- Fukumoto S, Sawasaki E, Miyake Y, Yokogoshi H (2006). Flavor components of monoterpenes in citrus essential oils enhance the release of monoamines from rat brain slices. *Nutr. Neurosci.*, 9: 73-80.
- Gargano AC, Almeida CCAR, Costa M (2008). Essential oils from *Citrus latifolia* and *Citrus reticulata* reduced anxiety and prolong ether sleeping time in mice. *Tree For. Sci. Biotechnol.*, 2: 121-124.
- Goel N, Kim H, Lao RP (2005). An olfactory stimulus modifies nighttime sleep in young men and women. *Chronobiol. Int.*, 22: 889-904.
- Gomes NGM, Campos MG, Orfão JMC, Ribeiro CAF (2009). Plants with neurobiological activity as potential targets for drug discovery. *Prog. Neuropsychopharmacol. Biol. Psychiatry*, 33: 1372-1389.
- Graeff FG, Brandão ML (1999). Anxiety. *Neurobiology of mental illness*. 5ed São Paulo: Lemoseditorial, 135-178
- Grieve M (1994). *A Modern Herbal*. London: Tiger Books International, P. 601.
- Hirsch AR (2001). Aromatherapy: art, science, or myth? In: Weintraub, MI (Ed.), *Alternative and Complementary Treatment in Neurologic Illness*. Churchill Livingstone, Philadelphia, PA. 128-150. <http://search.medicinenet.com>
- Hughes BH (2008). How should clinical psychologists approach complementary and alternative medicine? Empirical, epistemological, and ethical considerations. *Clin. Psychol. Rev.*, 28: 657-675.
- Komiya M, Takashi T, Harada E (2006). Lemon oil vapor causes an anti-stress effect via modulating the 5-HT and DA activities in mice. *Behav. Brain Res.*, 172: 240-249.
- Komori T (2009). Effects of lemon and valerian inhalation on autonomic nerve activity in depressed and healthy subjects. *Int. J. Essent. Oil Ther.*, 3: 3-8.
- Lehrner J, Eckersberger C, Walla P, Pötsch G, Deecke L (2000). Ambient odor of orange in a dental office reduces anxiety and improves mood in female patients. *Physiol. Behav.*, 71: 83-86.

- Lehrner J, Marwinski G, Lehr S, Jöhren P, Deecke L (2005). Ambient odors of orange and lavender reduced anxiety and improve mood in a dental office. *Physiol. Behav.*, 86: 92-95.
- Leite MP, Fassin Jr J; Baziloni EMF, Almeida RN, Mattei R, Leite JR (2008). Behavioral effects of essential oil of *Citrus aurantium* L. inhalation in rats. *Braz. J. Pharmacogn.* 18: 661-666.
- Linck VM, Da SAL, Figueiró M, Caramão EB, Moreno PRH, Elisabetsky E (2010). Effects of inhaled Linalool in anxiety, social interaction and aggressive behavior in mice. *Phytomedicine*, 17: 679-683.
- Mendonça-Filho RFW, Menezes FS (2003). Study of medicinal plants by the population of Ilha Grande, RJ. *Rev. Bras. Farmacogn.*, 13: 55-58.
- Mengue SS, Mentz LA, Schenkel EP (2001). Use of plants medical Pregnancy. *Rev. Bras. Farmacogn.*, 11: 21-35.
- Park HM, Lee JH, Yaoyao J, Jun HJ, Lee SJ (2011). Limonene, a natural cyclic terpene, is an agonistic ligand for adenosine A(2A) receptors. *Biochem. Biophys. Res. Commun.*, 404: 345-348.
- Price S, Price L (1999). *Aromatherapy for Health Professionals*. Vol.2 Churchill Livingstone.
- Pultrini AM, Galindo LA, Costa M (2006). Effects of the essential oil from *Citrus aurantium* L. in experimental anxiety models in mice. *Life Sci.*, 78: 172-175.
- Saiyudthong S, Marsden C (2010). Acute effects of bergamot oil on anxiety-related behaviour and corticosterone level in rats. *Phytother. Res.*, 25: 858-862.
- Sanguinetti EE (1989). *Plantas que Curam*. 2nd ed., Rígel, Porto Alegre.
- Santos CAM, Torres KR, Leonart R (1988). "Medicinal Plants (herbarium, flora et scientia)", 2nd ed., Icon, Sao Paulo.
- Schmitt R, Kapczinski F (2004). Anxiety disorders. In: Graeff FG.; Hetem LAB, Anxiety disorders. New York: Atheneu, pp. 265-283.
- Setzer WN (2009). Essential oils and anxiolytic aromatherapy. *Nat. Prod. Commun.*, 4(9): 1305-1316.
- Toet A, Smeets MAM, Van DE, Dijkstra D, Vanden RL (2010). Effects of pleasant ambient fragrances on dental fear: comparing apples and oranges. *Chem. Percept.*, 3: 182-189.
- Vale TG, Furtado EC, Santos Jr JG, Viana GSB (2002). Central effects of citral, myrcene and limonene, constituents of essential oil chemotypes from *Lippia Alba* (Mill.) N.E. Brown. *Phytomedicine*, 9: 709-714.
- Veiga JVF (2008). Study of the consumption of medicinal plants in the North Central Region of the State of Rio de Janeiro: acceptance by health professionals and method of use by the population. *Rev. Bras. Farmacogn.*, 18(2): 308-313.
- Vieira LS (1992). *Phytotherapy Amazon: Handbook of medicinal herbs (God's pharmacy)*. 2ed. St. Paul: Agron. Ceres, p. 347.