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Potential action on the central nervous system of neroli oil extracted from *Citrus aurantium*

Potencial ação sobre o sistema nervoso central do óleo neroli extraído da *Citrus aurantium*

Acción potencial sobre el sistema nervioso central del aceite de neroli extraído de *Citrus aurantium*

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Abstract
The essential oil from *C. aurantium* has been widely studied due to its potential anxiolytic action on several receptors in the Central Nervous System (CNS). Although it presents variations in its phytochemical composition depending on its origin, we can highlight that many compounds remain present, such as linalool that demonstrated antagonistic activity on glutamatergic receptors, possible inhibitory action of noradrenaline and serotonin receptors, besides the ability to activate GABA receptors in association with some flavonoids present in the oil. It is globally known that the underlying pathology called anxiety influences worldwide as an antecedent of conflicting psychological and physical disorders, which are associated with various neuronal disorders. In this regard, the oil extracted from C. *aurantium* flowers shows a potential therapeutic application for the treatment of anxiety disorders. However, more studies are needed to elucidate its complete role on the CNS and to verify and prove its safety and efficacy profile.
Keywords: Linalool; *Citrus aurantium*; Volatile oils; Anti-anxiety agents.

Resumo
O óleo essencial da *C. aurantium* tem sido amplamente estudado devido a seu potencial ação ansiolítico e sobre diversos receptores do Sistema Nervoso Central (SNC). Apesar de apresentar variações em sua composição fitoquímica a depender da sua origem, podemos destacar que muitos compostos se mantêm presentes, como o linalol que demostrou atividade antagônica sobre receptores glutamatérgicos, possível ação inibitória da receptação de noradrenalina e serotonina, além disso, capacidade ativar receptores GABA em associação com alguns flavonoides presente no óleo. É de conhecimento global que a patologia subjacente denominada como ansiedade, influi mundialmente como antecedente de conflitantes transtornos psicológicos e físicos, os quais estão associados a diversos distúrbios neuronais. Diante do exposto o óleo extraído das flores de *C. aurantium* demonstra um potencial aplicação terapêutica para o tratamento de transtornos de ansiedade. Entretanto, faz-se necessário mais estudos para a elucidação do seu papel completo sobre o SNC e para que seu perfil de segurança e eficácia, possam ser verificados e comprovados.
Palavras-chave: Linalol; *Citrus aurantium*; Óleos voláteis; Ansiolíticos.

Resumen
El acero esencial de *C. aurantium* ha sido ampliamente estudiado por su potencial acción ansiolítica neroli sobre varios receptores del Sistema Nervioso Central (SNC). Aunque presenta variaciones en su composición fitoquímica dependiendo de su origen, podemos destacar que muchos compuestos siguen presentes, como el linalol que demostró

actividad antagonista sobre los receptores glutamatérgicos, posible acción inhibidora de los receptores de noradrenalina neroli serotonina, además de la capacidad de activar los receptores GABA en asociación con algunos flavonoides presentes en el aceite. Es mundialmente conocido que la patología subyacente llamada ansiedad influye en todo el mundo como antecedente de trastornos psicológicos neroli físicos conflictivos, que se asocian a diversas alteraciones neuronales. Por todo ello, el aceite extraído de las flores de *C. aurantium* muestra una potencial aplicación terapéutica para el tratamiento de los trastornos de ansiedad. Sin embargo, se necesitan más estudios para dilucidar todo su papel en el SNC para verificar i probar su perfil de seguridade i eficacia.
Palabras clave: Linalool; *Citrus aurantium*; Aceites volátiles; Ansiolíticos.

1. Introduction

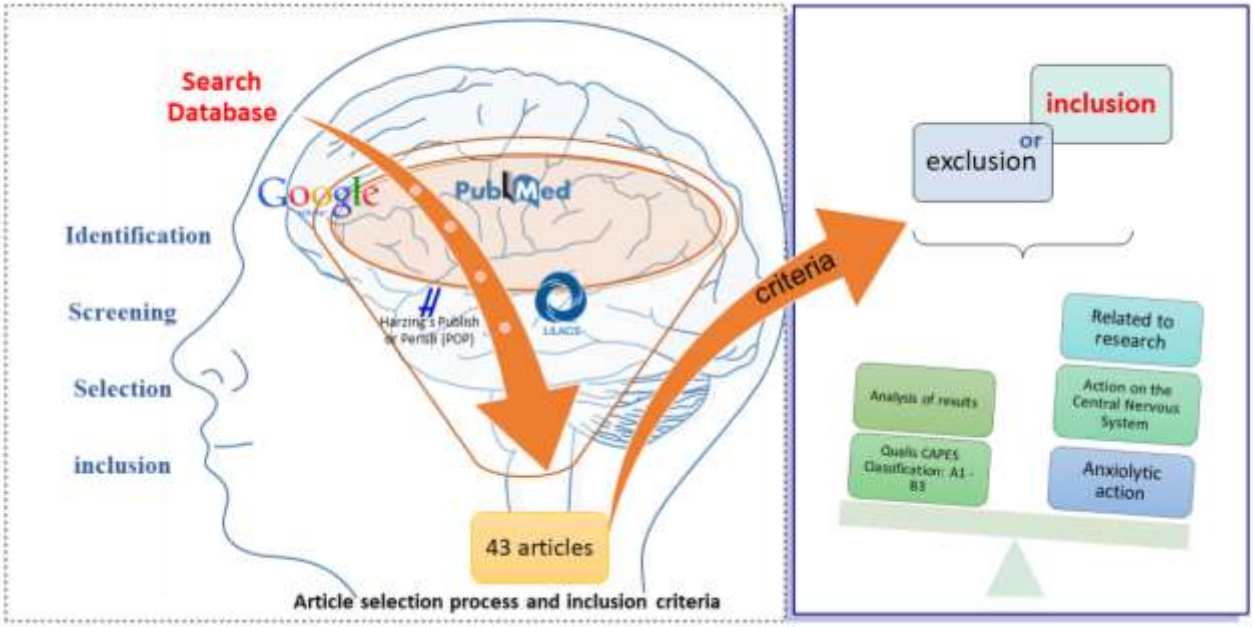
Essential oils are volatile substances that do not present viscosity and integrate the secondary metabolism of plants, produced in the leaves, roots, seeds, fruits, flowers and trunks, by secretory structures such as oil channels, among other specialized nuclei (Amravati & Suryawasnshi, 2011). Obtained through physical processes, they are composed of complex combinations of metabolites with reduced molecular mass, responsible for giving them organoleptic characteristics. Being able to be presented in isolated form, rectified, concentrated, mixed or deterpenated (Astani et. al, 2010), the essential oils can be extracted and isolated by hydrodistillation, steam distillation, extraction by organic solvents, extraction with supercritical fluid, enfloration or enfleurage and by cold pressing (Kobori & Jorge, 2005), being constituted mostly by monoterpenes, sesquiterpenes and phenylpropanoids (Akhlaghi, et al., 2011).

Among the hundreds of essential oils currently marketed, we have the oils extracted from the Bitter Orange tree (*Citrus aurantium*), a species of citrus fruit that belongs to the botanical family *Rutaceae* (Sousa et al., 2015). This is a particularly interesting tree as it alone is capable of producing three distinct types of essential oils, the PetitGrain which is the essential oil obtained from the leaves of the tree and the small buds of the green fruit, the neroli, which is the oil resulting from the distillation of the flowers of the plant and the Bitter Orange essential oil which is the essence obtained by cold pressing the peels of the ripe fruit. The essential oils extracted from the leaves, flowers and fruits of *C. aurantium* are composed of several bioactive compounds and, among the pharmacological activities already described for the essential oil of *C. aurantium*, one can mention possible anxiolytic and antioxidant effects (Fonsêca, et al., 2019). Preclinical studies also suggest that some essential oils, such as *C. aurantium* do not act by conventional mechanism, which may become the motivation for studies that can confirm and leverage a more current therapeutic class and different from the anxiolytics already available on the market, and thus may be an alternative to benzodiazepines. (Sousa et al., 2015).

2. Methodology

This is a systematic, qualitative review of the literature on the potential action of neroli oil on the central nervous system (Souza et al, 2010). The review is based on scientific articles that discuss the aspects of the essential oil, bioactivity and its phytochemical composition. The databases used were Google Academic, Pubmed, Lilacs and Harzing's Publish or Perish (POP) search tool, for which the following keywords were used: *Citrus aurantium*, essential oil, neroli, anxiolytic, Linalool. Among the criteria defined for the study were the identification, categorization and pre-selection of theses, inclusion of articles indexed in journals classified by Qualis CAPES as A1 to B3 and analysis of results pertinent to the theme. The selection included 43 articles, out of these, 23 referred to the bioactivity of the essential oil and its potential action on the Central Nervous System, 7 obtained and discussed its phytochemical composition and 13 dealt with the bioactivity of the neroli essential oil markers as detailed on Figure 1 below. Studies published in the last ten years (2011 to 2021) were included, since it was necessary to use basilar literature, articles published between 1990 and 2021 were also selected

Figure 1. Flowchart: Selection process and inclusion criteria of the scientific articles.



Source: Authors.

3. Results and Discussion

3.1 Activity of Neroli essential oil on the CNS.

C. aurantium L. var.amara, popularly known as Bitter Orange, became the object of studies because, it has in its chemical composition, flavonoids such as naringin, hesperidin and neohesperidin, flavones, flavonones, polimethoxylates, glycan peptides, coumarins such as meranzin and auraptene, tannic acid, limonoids and alkaloids such as synephrine, the aqueous extract of Zhi-Quiao, immature fruit of *C. aurantium*, thus presenting possible antidepressant, antioxidant and anxiolytic effect (Wu et al, 2015). Studies show that the genus *Citrus* (*Rutaceae*), to which *C. aurantium* belongs, presents a great variety of biological activities, which enables the application of this genus in numerous medicinal purposes (Shen, et al., 2017; Karimi et al., 2012; Yu et al., 2020; Rahnama et al., 2015; Golechha et al., 2011).

C. aurantium species has been widely studied due to its anxiolytic potential, possibly stimulated by the essential oil extracted from the flowers of this citrus fruit, also known as neroli oil, (Boussaada & Chemli, 2006). Its flowers are traditionally used to treat neurological disorders such as insomnia, epilepsy, hysteria (Rahnama S, et al., 2015). Several researches have suggested through analysis of bioactive compounds of Néroli essential oil, that among the remarkable action potentials coming from bitter orange oil, its antioxidant property also stands out (Zhao et al., 2012; Amravati & Suryawanshi, 2011; Astani & Schnitzler, 2010; Kobori & Jorge, 2005; Karimi et al., 2012; Goes, 2012; Franco-Vega, et al, 2015; Lin., et al, 2010).

In a study, Rahnama and colleagues, 2014, evaluated the anti-amnesic activity of *C. aurantium* during memory impairment induced by the cholinergic antagonist, scopolamine, through passive avoidance and Morris water maze tests with rodents, and it was possible to identify that the flower extract presents potential reducer of oxidative stress by inhibiting memory impairment, demonstrating reparative effects of behavioral and memory disorders produced by scopolamine, besides presenting possible promising effects in the treatment of Alzheimer's disease (Rahnama et al, 2015) .In a study using animal models, the essential oil extracted from *C. aurantium* flowers was administered to mice, where an effect on anxiety was observed due to a possible interaction with the GABAergic system, when compared with diazepam, a drug commonly used to

treat anxiety disorders. During the experiment it was observed that the animals submitted to the elevated cross test, both those treated with the control drug and those treated with the essential oil, showed a significant increase in the length of stay in the open arms. When the essential oil was applied simultaneously with diazepam, the results were even more significant, indicating a reduction in anxiety (Khosravi et al., 2014). Furthermore, additional studies have shown that essential oil can decrease or increase the responsiveness of nociceptors. This activity may depend on the baseline and level of neuronal excitability (Akhlaghi et al., 2011).

The anxiolytic activity of neroli oil was observed in a randomized clinical trial in pregnant women, which compared the levels of anxiety presented during childbirth after administration of neroli oil by inhalation, against the levels of anxiety recorded in a control group; it was possible to observe that aromatherapy with essential oil of the flower proved to be efficient (Namazi et al., 2014). Pimenta and colleagues, 2016, reinforce the findings of other articles, by postulating that the use of aromatherapy with essential oil of *C. aurantium* produces anxiolytic effect (Pimenta et al., 2016).

The results observed in the elevated cross maze, open field, Rotarod (rotatory bar test) and convulsion tests, during the study of the anxiolytic and sedative effects of *C. aurantium*, suggest that its ethnopharmacological uses as a sedative and hypnotic is plausible, given the activity of this citrus as a central nervous system (CNS) depressant, concluding that it is feasible to identify the active compounds responsible for the biological activity of the plant, for use in projects of new molecules with sedative and anxiolytic action (Carvalho-Freitas et al, 2002).

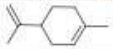
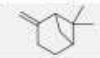
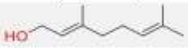
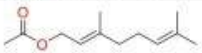
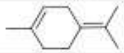
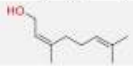
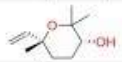
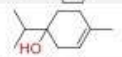
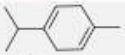
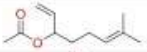
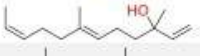
3.2 Identification of bioactive compounds present in the oil.

Through the quantitative and qualitative determination obtained by hydrodistillation of C. aurantium flowers, using methods such as Chromatography with Mass Spectrometry (GC-MS) and Gas Chromatography (GC), several authors have succeeded in identifying the chemical components of the essential oil neroli, however, given the economic importance and therapeutic potential of *C. aurantium*, it is worth noting that due to its origins and distinct forms of cultivation, A great variation in the phytochemical composition of this citrus fruit can be identified. (Ammar, et al, 2012; Boussaada & Chemli, 2006; Dosoky & Setzer, 2018).

By using the referential of five distinct literatures that describe the phytochemical composition of the neroli essential oil from four different nationalities, it was possible to obtain satisfactory results for the confirmation of the main bioactive groups present in the extract, through the analytical methods Gas Chromatography coupled to Mass Spectrometry (GC-MS) and Gas Chromatography with Flame Ionization Detector (GC-FID). The authors identified and quantified the molecules that added up to 84 different actives contained in neroli oil from Turkey, Morocco, Greece, and Tunisia. However, of these, only 17 compounds were equally present in more than one study (Jeannot et al., 2005; Ammar, et al, 2012; Boussaada & Chemli, 2006; Acar et al., 2021; Sarrou et al., 2013).

Table 1, summarizes the most relevant components that were verified with the same incidence by the authors previously mentioned, using as standard the same method of extraction, and obtaining the chemical composition:

Table 1. Main bioactives present in neroli essential oil extracted from Bitter Orange Blossom (*C. aurantium* L. var. *amara*).

Phytochemical Composition (%)								
Authors/year of publication								
Bioactive Groups	Component	Sarrou, *et al.*, 2013	Ammar *et al.*, 2012	Jeannot *et al.*, 2005	Boussaada and Chemli, 2006	Acar *et. al.*, 2021	Average (%)	
Monoterpenes	Linalool	29,14 ± 0,38	-	60	34,4	27,41	30,19	
	Limonene	12,04 ± 0,16	27,5	-	10,9	-	10,16	
	β-Pinene	19,08 ± 0,18	-	-	5,2	-	4,856	
	α-Terpineol	4,56 ± 0,05	6,66	-	6,66	3,26	4,228	
	Geraniol	4,31 ± 1,43	0,3	7	4,2	0,64	3,29	
	Geranyl Acetate	2,59 ± 0,04	-	0,2	3,4	10,21	3,28	
	Sabinene	2,01 ± 0,20	0,5	-	4,1	-	1,322	
	α-Terpinolene	0,47 ± 0,01	0,3	-	0,3	-	0,214	
	Nerol	0,83 ± 0,02	-	3,5	1,4	-	6,808	
	linalool cis-oxide	-	-	5	0,1	-	1,02	
	trans-linalool oxide	-	-	3	0,2	-	0,64	
	Terpinen-4-ol	-	0,4	1,5	0,6	-	0,5	
	γ-terpinene	0,36 ± 0,01	0,3	-	0,2	-	0,172	
Esters	Linalyl Acetate	3,88 ± 0,40	-	-	11,3	42,77	11,59	
	Methyl anthranilate	0,19 ± 0,00	1,2	6	-	-	1,478	
Sesquiterpenes	(E) - Nerolidol	1,76 ± 0,03	17,5	-	0,4	-	3,932	
	(E) - Farnesol	5,14 ± 0,02	8	-	-	-	2,628	

Source: Authors.

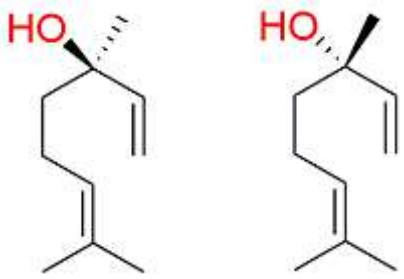
As seen in Table 1, among the major bioactive groups of the oil, the presence of monoterpenes, esters and sesquiterpenes was observed. Among these, linalool stands out as the compound with the highest average percentage (30.19%), since Sarrou, et al., 2013, during quantification, determined 26 possible actives, corresponding to 99.44% of the essential oil, with the components linalool and limonene being the most prevalent, with proportions of 29.14% and 19.08%, respectively (Sarrou et al., 2013). According to Boussaada and Chemli, (2006) the Neoli oil, also presents in its chemical composition, Linalool as the component of highest concentration, being approximately 34.4%, among the other 25 components that were also found during the analysis. Acar et al., 2021 had Linalyl Acetate (42.77%) as the main compounds identified, being the most prevalent chemical constituent followed by linalool (27.41%) and geranium acetate (10.21%), also found limonene dioxide (3.50%). Jeannot et al., 2005, identified eighteen compounds in the essential oil confirming that linalool is its major constituent as it has minimum concentration 40% and maximum concentration 60%. In contrast, Ammar and collaborators, 2012, investigated the constituents of the oil extracted in Tunisia, concluding that approximately 27.5% corresponded to Limonene, one of the most common monoterpenes in nature, followed by a-terpineol (14%). Sesquiterpene compounds constituted 30.2% of the total essential oil: (E)-nerolidol (17.5%) was the major component of this fraction followed by (E, E)-famesol (8%) and neroli-elemene (3.4%). while no significant amount of linalool was detected in the neroli oil from Tunisia. On the other hand, Limonene, the main component in the quantification of Ammar et al. (27%).

Thus, after careful analysis of the analytical findings, it is essential to stress the strong argument that linalool, the monoterpene identified with the highest prevalence, is possibly responsible for the anxiolytic action among the group of molecules present in the essential oil of the Neroli flower.

3.3 Linalool activity on the CNS.

The monoterpene linalool, as represented by Figure 2, is a volatile basic constituent of terpenic essential oils (Quintans-Júnior, 2013) , which has been characterized, through in vivo and in vitro studies, by its great potential for action on the most diverse biological activities, such as vasodilation (Siqueira, 2014) , sedation and anesthesia (Heldwein, 2014) , antimicrobial (Yang, 2014) , anxiolytic (Tankam, 2013; Linck, 2010) , antinociceptive (Batista, 2008) , anticonvulsant and in glutamatergic transmission (Brum, 2001).

Figure 1. chemical structures of (-)-Linalool and (+)-Linalool, respectively.



Source: Authors.

Through the studies carried out by Elisabetsky et. al., 1995a, b, 1999, it was observed that Linalool administered intraperitoneally, possesses a dose-dependent sedative effect besides, having shown, through neurochemical analyses, a potential of action on the glutamatergic system (Elisabetsky et al., 1995a; 1995b; 1999). The function of glutamatergic transmission on the possible anticonvulsant effect of Linalool was investigated by measuring its effects on [3H] Glutamate

binding in the Central Nervous System (CNS) membranes of rats, subsequently it was verified through analysis that Linalool has a dose-dependent inhibitory effect on the aforementioned binding. The result obtained was compared with the mechanism of action of Phenobarbital, a CNS depressant, which, by potentiating the GABA pathway and antagonizing the glutamatergic pathway, is used as an anticonvulsant. Importantly, it was also able to significantly inhibit [H3] Glutamate binding. Also, in order to determine which subtypes of glutamatergic receptors were involved, non-specific agonist markers were added to the incubation medium and after further evaluation, suggested that Linalool is able to interact with all the investigated receptor subtypes (NMDA, KA, AMPA, ACPD and Quisqualate) (Elisabetsky, 1995a).

Therefore, considering that glutamate is the main brain excitatory neurotransmitter and that the reduction of its activation in the CNS reflects an anxiolytic profile (Carobrez, 2003), it was possible to verify that, by behaving similarly to the control drug in the aforementioned study, linalool was able to block glutamatergic receptors and consequently reduce episodes of convulsion and anxiety.

Linck and collaborators reported in a study published in Phytomedicine journal, with the objective of analyzing its effects on anxiety, social interaction, and aggressive behavior among mice of linalool when administered by inhalation. Another experiment compared the effects of this monoterpene in relation to the administration of diazepam, however, when submitted to the light/dark transition test (this test was developed to evaluate the anxiolytic effects of benzodiazepine drugs, using a situation of conflict between the natural tendency of animals to explore and the initial tendency to avoid what is unfamiliar), the results show a significant increase in the time of social interaction and also an increase in the latency of the first attack, a decrease in the number of attacks and their duration, meaning that linalool had results that were compatible with the profile of anxiolytic drugs on mice (Linck, et al, 2010) .

The investigation of another possible mechanism of linalool and β-pinene was reported by Schildkraut, who analyzed the monoaminergic route, since clinical and experimental evidence suggests that the main neurochemical process of depression is the impairment of monoaminergic neurotransmission with the simultaneous decrease of noradrenaline and/or serotonin (Schildkraut, 1995). For this analysis, imipramine, a tricyclic responsible for inhibiting the reuptake of noradrenaline and serotonin, was used as a positive control, thus promoting an increase in the concentration of these neurotransmitters in the CNS, with Linalool and β-pinene, which were administered to mice and which, in turn, were subjected to the Forced Swim Test. It was observed that both linalool and imipramine decreased the immobility time, when compared to the negative control group. It is suggested that these monoterpenes act on the serotonergic pathway, since the administration of the serotoninergic antagonist drug reversed the antidepressant effect of linalool and, therefore, it is believed that these receptors are involved in the mechanism of action (Guzmán-Gutiérrez et al., 2015). Since hypofunction of the adrenergic system is implicated in the pathophysiology of depression, there is evidence that the α1 and α2 receptors, also participate in the mechanism of action of antidepressant agents (Millan, 2004; Bourin et al, 1991). For this reason, during the experiments, the guinea pigs were pretreated with yohimbine, which was able to reverse the effect of linalool, suggesting then that the α2 adrenergic receptors are involved in the antidepressant mechanism of linalool (Guzmán-Gutiérrez et al, 2015).

3.4 Identification of flavonoids present in the oil and their activity on the CNS.

As well as previously identified monoterpenes, a study published by the journal of chemistry Melecules, verified through liquid chromatography and mass spectrometry the presence of naringin, hesperetin and nobiletin among the flavonoids that make up bitter orange flowers (Yu et al, 2020).

A study using kainic acid to induce seizures in rats concluded that naringin can prevent cognitive impairment and may be useful as an adjuvant in antiepileptic therapy (Golecha et al., 2011). Additionally, research on the neuroprotective effects of

citrus flavonoids, showed that hesperetin is able to stimulate receptors that activate signaling pathways for neuroprotection, and is also shown to be effective in inducing proteins that contribute to cognition and intervene in oxidative stress (Hwang et al., 2012) . Nobiletin, a polymethoxylated flavonoid with the ability to cross the blood-brain barrier, has been shown to be a potentially therapeutic active for dementia (Rahnama, 2015).

Classified in distinct sets of structures, citrus flavonoids can be subdivided into three main groups, which include flavanones, glycosidic flavones and polimethoxyflavones (Manthey et al, 2001), and these may present neuroprotective and even neuro-suppressive activity, as observed in a study using the administration of 5,7-di-OH-flavone intracerebroventricular in mice, it was possible to verify that some flavonoids, such as chrysin, present affinity with peripheral benzodiazepine receptors, suggesting possible ligands for benzodiazepine receptors (Medina et al., 1990).

4. Final Considerations

Anxiety disorders are characterized by several conditions and symptoms, which are felt uniquely by each individual, being the result of a multifactorial disorder on the biochemical pathways of the body, making it one of the most incident disorders today. Since several neurotransmitters are part of this complex mechanism responsible for the behaviors that classify the spectrum of anxiety in humans, the search for an effective and safe treatment for patients has been widely investigated, mainly through the research of natural compounds available for consumption by the population. Thus, despite the different methodologies applied to the study of *Citrus aurantium*, showed its promising action on the CNS and its possible mechanisms of action in multitargets, since anxiety disorders are associated with several neuronal pathways, it is believed, that this plant derivative is promising for treatment.

The main oil marker identified was the bioactive compound linalool, being attributed to the compound the antagonist activity, as it competes with glutamatergic receptors, preventing the binding and therefore the activation of glutamate at brain level, resulting in decreased excitability and possibly anxiety. On the other hand, it is known that this compound may also behave similarly to drugs that block noradrenaline and serotonin receptors and to those that act on GABA receptors. Additionally, the flavonoids present in the oil can also suppress the CNS in synergy with linalool, causing sedation due to its ability to bind to GABA receptors, presenting similar effects to benzodiazepines (Brum et al., 2011; Marder et al., 2001).

We emphasize that the essential oil of *C. aurantium* flowers has a high pharmacological capacity among which we can highlight its potential anxiolytic action. Despite this, it is necessary to emphasize that more specific research should be conducted for a complete elucidation of its role on the CNS, safety and efficacy can also be verified and proven, besides serving as a platform for the development of new drugs and herbal medicines. Another important point is the pre-clinical toxicological tests that allow the determination of adverse effects and the risk of exposure to neroli oil for humans, identifying its toxicokinetic profile, complying with requirements by regulatory agencies such as ANVISA in Brazil, European Agency of Medicines (EMA) or regulatory agency of the United States the Food and Drug Administration (FDA).

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