

Medicinal plants as a therapeutic alternative for Major Depressive Disorder (DMD)

Plantas medicinais como alternativa terapêutica para o Transtorno Depressivo Maior (TDM)

Plantas medicinales como alternativa terapéutica para el trastorno Depresivo Mayor (DMD)

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ABSTRACT

Objective: To review the antidepressant activity and mechanisms of action of plants that have antidepressant action. **Literature Review:** The use of plants for medicinal purposes has been used as an adjunct to the treatment of depression due to easy access by the population, few side effects and lower cost. Based on the studies, the plants St. John's wort, ground turmeric, anona and lavender have antidepressant potential for acting in different ways in depression, either by inhibiting the reuptake of serotonin or by modulation in the dopaminergic and serotonergic pathways. **Final Considerations:** From the studies of the mechanisms of action it was found that the plants studied can modulate the brain signaling pathways responsible for the patient's mood, with the reuptake of serotonin (inhibition of the serotonin transporter protein) the main mechanism of action shared between them. In addition, some of these plants can modulate not only the concentrations of serotonin in the synaptic cleft, but also dopamine. It is worth mentioning that, although these actions have been scientifically proven, much research is still needed to ensure the safe use of these agents as herbal medicines in the alternative or adjunctive treatment of depressive disorders.

Keywords: Depression, Medicinal plants, Treatment.

RESUMO

Objetivo: Revisar a atividade antidepressiva e mecanismos de ação de plantas que possuem ação antidepressiva. **Revisão Bibliográfica:** O uso de plantas para fins medicinais vem sendo utilizado como coadjuvante para o tratamento da depressão devido ao fácil acesso pela população, poucos efeitos colaterais e menor custo. Com base nos estudos as plantas Erva-de-São-João, Açafraão-da-terra, Anona e Lavanda possuem potencial antidepressivo por atuar, de maneiras distintas, na depressão seja por inibição da recaptação da Serotonina ou por modulação nas vias dopaminérgicas e serotoninérgicas. **Considerações Finais:** A partir dos estudos dos mecanismos de ação constatou-se que as plantas estudadas são capazes de modular as vias de sinalização cerebral responsáveis pelo humor do paciente, sendo a recaptação da serotonina (inibição da proteína transportadora da serotonina) o principal mecanismo de ação compartilhado entre elas. Além disso, algumas dessas plantas são capazes de modular não apenas as concentrações de serotonina na fenda sináptica, mas também de dopamina. Vale ressaltar que, embora essas ações tenham sido comprovadas cientificamente, muitas pesquisas ainda são necessárias para garantir o uso seguro desses agentes como fitoterápicos no tratamento alternativo ou coadjuvante dos transtornos depressivos.

Palavras-chave: Depressão, Plantas medicinais, Tratamento.

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RESUMEN

Objetivo: Revisar la actividad antidepresiva y los mecanismos de acción de las plantas que tienen acción antidepresiva. **Revisión Bibliográfica:** El uso de plantas con fines medicinales se ha utilizado como complemento del tratamiento de la depresión debido al fácil acceso de la población, pocos efectos secundarios y menor costo. Según los estudios, las plantas de hierba de San Juan, cúrcuma, anona y lavanda tienen potencial antidepresivo porque actúan de diferentes formas en la depresión, ya sea inhibiendo la recaptación de serotonina o modulando las vías dopaminérgicas y serotoninérgicas. **Consideraciones Finales:** A partir de los estudios de los mecanismos de acción se encontró que las plantas estudiadas son capaces de modular las vías de señalización cerebrales responsables del estado de ánimo del paciente, siendo la recaptación de serotonina (inhibición de la proteína transportadora de serotonina) el principal mecanismo de acción compartido entre ellos. Además, algunas de estas plantas son capaces de modular no solo las concentraciones de serotonina en la hendidura sináptica, sino también la dopamina. Vale la pena mencionar que, aunque estas acciones han sido científicamente probadas, aún se necesita mucha investigación para garantizar el uso seguro de estos agentes como hierbas medicinales en el tratamiento alternativo o coadyuvante de los trastornos depresivos.

Palabras clave: Depresión, Plantas medicinales, Tratamiento.

INTRODUCTION

Major Depressive Disorder (MDD), a disease that affects more than 300 million people worldwide, has been considered a public health problem according to the World Health Organization (WHO). It is estimated that from 2020 it will become the second cause of disability in the world, according to a study published in 2018 by the WHO. The Diagnostic and Statistical Manual of Mental Disorders combined with the International Classification of Diseases and Related Health Problems, have the parameters for its diagnosis, which in most cases occurs as depressed mood, loss of interest or pleasure, changes in sleep and appetite. These symptoms are persistent, incapacitating the individual in several areas of life (RICE HC, et al., 2019).

About the etiology of depression, it is not possible to talk about just one cause, but about the interaction of several complex factors, which are genetic, biochemical, psychological, social and family. However, everyone turns to brain chemistry, interfering with the monoamine cycle, in which the main neurotransmitters are dopamine, norepinephrine and serotonin. Dopamine plays an important role in regulating the desire to seek rewards, in addition to the individual's ability to experience a sense of pleasure (CHESTER DS, et al., 2016). Norepinephrine, in turn, is related to the emotional improvement of memory (ROOZENDAAL B, et al., 2017). Serotonin is considered crucial for the development of the human and mammalian brain (ALBERT PR, et al., 2012).

Lafer B and Filho HPV (1999), pointed to some works that sought to demonstrate the influence of genetics on the etiology of depression, highlighting studies of a genetic-epidemiological character and those of molecular genetics, as well as hypotheses relating neurochemistry to the pathophysiology of the disease; among them are the dysfunction of brain monoaminergic systems and the desensitization of receptors. However, there has not yet been the identification of a gene or set of genes related to the development of depression, but the finding that there are specific variations in the segments of deoxyribonucleic acid (genetic polymorphisms) which increase the probability of the establishment of the pathology in individuals of the same family (ROT M, et al., 2009).

Stress factors, which are examples of environmental events, can cause physiological changes in the individual, contributing to the development of depressive disorders. Studies suggest a relationship between stress and changes in the hippocampus, the brain area associated with learning, memory and responses to stress. Thus, they assume stress as one of the biggest triggers for the appearance of depressive symptoms when considering the incidence of stressful events in periods prior to the onset of symptoms (JOCA SRL, et al., 2003). In addition, the context of early childhood is a determining agent about the ability to promote responses to stress in adulthood (ALBERT PR, et al., 2012).

Cultural factors can also contribute to the establishment of MDD, although there are few theories addressing its influence on this disorder. It is possible to observe the role of the socio-cultural context from studies by Martin D, et al. (2007) in women diagnosed with depression, who lived in a municipality marked by poverty, violence, and poor quality of life. The perception of these women about the causes of their disorder was related to external events, with a violent context inside and outside the home, unemployment, financial restrictions, loss of loved ones, restricted social ties, and little leisure.

The results of Cunha RV, et al. (2012) reinforce those found by Martin D, et al. (2007) relating major depression to demographic and socioeconomic factors, such as education and economic level. According to the authors, the higher occurrence of depression was associated with an increase in the age group and a decrease in education and income levels, as well as a higher prevalence in female participants, with a probability of occurrence of 2.38 times higher among women when compared to men. The depression can still strike more often people without partners and widowers.

Although almost half of patients suffering from MDD are treated by first-line antidepressant therapy, this does not manage the disorder effectively (FARAHANI MS, et al., 2015). It is a fact that conventional antidepressants are now considered the main treatment for this health problem, but they exhibit relevant side effects, especially those of the anticholinergic type, which are responsible for changes in psychic functions, and drug interactions. The adverse effect of these drugs involves anxiety, diaphoresis, tachycardia, tremor, sedation, insomnia, serotonin syndrome, parkinsonism, postural hypotension, blurred vision, among other aggravating factors. Therefore, alternative therapies, such as the use of medicinal plants and herbal medicines, compared to traditional ones, are necessary alternatives, since the absence or reduction of adverse effects through this is considerable (SUBRAMANIYAN V, et al., 2019).

In view of the demand for less harmful and milder therapies for the individual's health in the face of MDD, mainly due to the increasingly significant occurrences of this disorder in society, based on the search for minimizing side effects arising from the consumption of conventional drugs, this study aims to describe the antidepressant activity found in some plant species relevant to Brazilian plant biodiversity, with an emphasis on the viability of their mechanisms of action against the biology of the central nervous system, as it is understood that in addition to treatment it is necessary to bring quality of life for the individual and the use of medicinal plants can help in this context by minimizing signs and symptoms, in addition to possible side effects.

LITERATURE REVIEW

Social vision of the use of medicinal plants

The use of plants with medicinal properties has been following humanity since its foundation, when drug intervention was still a distant idea. Nowadays, this practice is observable, mainly in the complementary or alternative form compared to conventional therapy, showing an increase in its viability in recent years, which occurs because its side effects are less drastic than those derived from isolated drugs, and which for many people is the only option for the treatment of the most diverse diseases (FERREIRA VF and PINTO AC, 2010; YUAN H, et al., 2016).

In Brazil, today the consumption and production of herbal medicines, which are pharmaceutical preparations obtained from vegetable raw materials, such as stems, leaves, and fruits, roots and seeds of plants with proven pharmacological effect, are accentuated, this fact occurs because the country has one of the largest plants biodiversities on earth, which is mostly concentrated in the North, Northeast and Midwest (SILVEIRA PF, et al., 2008; RODRIGUES TM, et al., 2012; MAZZARI A and PRIETO JM, 2014).

As a developing nation, 66% of the population does not have access to commercial medication, which corroborates to the growing demand for herbal medicines, whether due to outdated medical and pharmaceutical assistance or the precise cost of conventional drugs, in addition, these medicines are produced with less subsidies and more easily than the conventional ones and denoting a more significant storage period (SILVEIRA PF, et al., 2008; RODRIGUES TM, et al., 2012; MAZZARI A and PRIETO JM, 2014).

Phytomedicine is relative and growing, and there are many studies that have intensified this fact. It is possible to understand this through its applications in the treatment of skin lesions, metabolic syndromes, neoplasms and mental disorders, for example anxiety, depression and bipolar disorder. Among the Brazilian ethnobotanical variability, the following session will describe four species of plants with antidepressant properties that, although not all of them being native from Brazil, they can be grown in many regions of the country, which are: St. John's wort, saffron earth, annona and lavender (SARRIS J, 2007; DELFAN B, et al., 2014; SAFARZADEH E, et al., 2014; MALAZY TO, et al., 2015).

St. John's wort (*Hypericum perforatum*)

Hypericum perforatum (*H. perforatum*) is a perennial, erect herbaceous plant that reaches about 1 meter in height, belonging to the Hypericaceae family, originating commonly in regions of Europe, Asia, North Africa, and the United States. Also known as St. John's wort, hypericum or St. John's wort, *H. perforatum* is popularly used in tea consumption, for employing mechanisms of action in insomnia, headaches, weight loss and among others. Extracts of this plant have been used for some time due to its medicinal properties, presenting antioxidant, antibacterial, healing, antineuralgic, antifungal and antidepressant characteristics. However, it is its antidepressant effect that receives greater prominence in the academic-scientific scope, through the proof of this activity in many studies. The most used portions of the plant involve flowers and oils, which are sold in the form of powder, capsules, tablets, and teas in natural products houses (HENDERSON L, et al., 2002).

A study by Linde K, et al. (2008) with 5489 thousand patients involving comparisons with placebo and conventional antidepressants in relation to *Hypericum perforatum* extracts, showed that St. John's wort extract is more efficient than placebo in patients with major depression. Zirak N, et al. (2018) characterized the antidepressant potential of *H. perforatum* because of its most relevant active principles, that is hypericin and hyperforin, which are naphthodianthrones, being responsible for the antidepressant effect by inhibiting selectively the reuptake of serotonin. Furthermore, some authors have complemented the idea in question, stating that not only does serotonin have its synaptic reuptake inhibited by the activity of *H. perforatum*, but also norepinephrine and dopamine, which consist of other monoamine neurotransmitters in the brain, also important in the development of depression onset (ALVES ACS, et al., 2014).

The flavonoids, that are secondary metabolites contained in *Hypericum perforatum*, represent at about 2% to 4% of the total constituents of the plant extract. In addition, the glycosylated derivatives of quercetin, some types of flavonoids, are also responsible for antidepressant activity. A study performed by Butterweck V, et al. (2000) with an extract with high content of flavonoids showed that these molecules are able to inhibit the monoamine oxidase (MAO) and catechol-O-methyl transferase (COMT), enzymes responsible for the degradation of monoamines, such as serotonin and dopamine; thus, this plant can contribute to the enhancement of these neurotransmitters in the synaptic cleft, positively influencing the mood, anxiety and depression (BUTTERWECK V, et al., 2000).

Therefore, St. John's wort can be considered a medicinal plant with potential to treat depression disorders, by influencing directly in the monoamine system and balancing brain chemistry and can thus be used in conjunction with other drugs that lead to improvement in the condition major depression (MAHER AR, et al., 2016).

Turmeric (*Curcuma longa*)

Curcuma longa (*C. longa*) is an herbaceous plant belonging to the Zingiberaceae family of subtropical climate from Asian origin, but also found in parts of the Brazilian flora. Also known as turmeric and yellow ginger, *C. longa* is used in the manufacture of cosmetics, food products such as mustard sauce, cheese, butter, drinks and preservatives. Yet, It is used for therapeutic purposes and the most used parts are the rhizome, fragmented stem or underground and can be ingested in fresh or dry forms (SANTIAGO VS, et al., 2015).

Its main essential active element is the curcumin, a compound that has been recognized and used in many forms because of its several health benefits, presenting antiseptic, anti-inflammatory, and antioxidant properties. Yet, it has been used popularly to treat metabolic syndromes, hyperlipidemia, arthritis, anxiety, and depression. The antidepressant activity has shown satisfactory results when compared to conventional medicines, since it presented performance comparable to fluoxetine in preclinical trials (SANMUKHANI J, et al., 2013, LEE G and BAE H, 2017).

Xiang QN, et al. (2017) in a study involving 377 volunteers, demonstrated that curcumin-treated patients exhibited a significant improvement in depression onset when compared to placebo-treated ones, without notification of adverse reactions. This component showed to be safe, tolerable, as well as efficient in the face of depressive patients. However, deeper randomized clinical trials with more volunteers are still required, as well as more studies of toxicity and safety to well elucidate the mechanism of action of curcumin, however, studies performed previously demonstrated that the antidepressant effect occurs by modulation of the monoamine system.

Kocaadam B and Sanlier N (2017) demonstrated that curcumin, when administered through bilateral olfactory bulbectomy, exhibit a modulating action on neurotransmitters such as norepinephrine, dopamine and especially serotonin, blocking the reuptake of these molecules and increasing their concentrations in the synaptic cleft, therefore, acting on the pathophysiology of depression and improving the mood of experimental animals. Although bulbectomy is not related to depression, the present study showed that curcumin is able to modulate the concentration of serotonin through blockade of the reuptake protein in the serotonergic neurons.

In an experimental model with Wistar Kyoto rats (putative depression model) carried out by Hurley LL, et al. (2013), the antidepressant potential of curcumin was observed in a model of non-induced depression. In addition to modulating serotonin levels, for example, in this study it was possible to observe that curcumin also showed activity at the levels of the Brain Derived Neurotrophic Factor (BDNF) in the hippocampus region; this protein, when its expression is increased, has antidepressant action because it increases neurotrophic activity in the brain, improving the mood of experimental rats.

In this way, several studies allow us to suggest saffron as a potential alternative treatment for depressive disorders, because it presents action not only in the monoamine system, but also in other proteins important for the regulation of the brain chemistry and mood, being of great importance for the treatment of Major Depressive Disorder, as it can help in improving the main symptoms.

Anona (*Annona cherimola*)

The *Annona cherimola* (*A. cherimola*) is an arboreal plant, of the Annonaceae family, which reaches up to seven meters, originating in places with tropical or subtropical climate, such as the Andean regions of South America, also found abundantly in Brazilian biodiversity. *Annona cherimola* is also known as nona and anona, it is popularly used in the consumption of culinary dishes, in the production of drinks, jellies, infusions and cosmetics. The chemical composition of the plant is basically phenolic compounds, such as phenolic acids, tannins, stybenes, coumarins and flavonoids; the extract of this plant already was demonstrated to produce antioxidant, antibiotic, antiinflammatory, antibacterial, anticancer and relaxing effects. The antidepressant activity was shown to be linked mainly with the alkaloids, such as anonaine, lyriodenine and norruciferin in experimental models of depression (PRASAD GJ, et al., 2017; PERVIZ S, et al., 2016).

In a study performed by Vázquez MM, et al. (2012), the effect of *Annona cherimola* on depression was tested in mice by administering the extract of aerial parts of the plant. The evaluation was through the forced swimming test, in order to understand the mechanism of action of the alkaloids present in the extract. The results showed that there was the potentiation of the antidepressants imipramine and clomipramine, when used synergistically with the extract; after performing high-performance liquid chromatography on brain samples from animals treated and not with the extract, there was an increase in monoamine levels, mainly dopamine and serotonin (and their metabolites). This result suggests that the constituents of the plant act by increasing the serotonergic signaling, possibly through the inhibition of the serotonin transporter protein, inhibiting reuptake.

Although there are not many specific studies on the mechanism of action of *Annona cherimola*, existing studies suggest that the constituents of the plant act on the serotonin transporter protein. Scientific evidence has shown that these molecules work by improving the cell signaling of the monoamine system in the brain, interfering and increasing the synapses responsible for the animal/patient's mood. From the above, it is understood that the plant can be an ally in the treatment for depression because it contributes by improving the patient's quality of life.

Lavanda (*Lavandula angustifolia*)

Lavandula angustifolia (*L. angustifolia*) is a plant of the Lamiaceae family, with small perennial shrubs, which grows in regions of Mediterranean climate, blooming in spring and summer. Also known as lavender, it is marketed due to its mild aroma and flavour, being commonly used in the production of cleaning and culinary products. Besides that, it is also used for medicinal purposes due to its anti-inflammatory, bactericidal, antifungal, antibiotic, analgesic, antirheumatic, detoxifying, diuretic, hypotensive, healing and antidepressant properties (ADAMUCHIO LGI, et al., 2017).

From a study that consisted of evaluating the effects of the interaction of *Lavandula angustifolia* essential oil with MAO-A (Monoamine oxidase A), SERT (Serotonin transporter), GABAA (gamma-aminobutyric acid) and NMDA (N-methyl D-Aspartate) receptors in adult male Sprague Dawley rats, López V, et al. (2017) demonstrated that lavender essential oil exhibited dose-dependent specificity for NMDA receptor (IC₅₀ of 0.04 µl/mL). In addition, oil components, such as lavender and linalool, also tested, bind to SART (Serotonin Transporter), inhibiting it. From this, it was observed that the oil exerts pharmacological anxiolytic and antidepressant effects through the modulation of both dopaminergic and serotonergic pathways, improving the signaling. This study also showed that the oil has no specificity for GABAA.

In another study, carried out from the induction of stress in mice, it was demonstrated that the essential oil of *Lavandula angustifolia* acted by decreasing stress and depression from the acute administration (200 mg/kg) of the essential oil. In addition, it reversed the social aversion, increasing the interaction between the mice, acting as an antidepressant agent. In that study, it was not possible to point out the mechanism that led to the demonstrated effects (CAPUTO L, et al., 2018).

The literature that demonstrates the exact mechanism of action of *Lavandula angustifolia* still remains little known, however, the antidepressant effects have already been demonstrated in some studies with animals and humans, which makes this plant as a potential candidate for the development of new drugs to treat MDD, either as a main therapeutic alternative or co-adjuvant treatment, thus helping to improve the patient's quality of life.

FINAL CONSIDERATIONS

Depression, today, is characterized as the disease of the century since its incidence is increasing in society. Conventional treatments are based on the use of isolated antidepressants and psychotherapy seeking the balance of brain chemistry through, mainly, the modulation of the serotonergic pathway, to improve the patient's mood. In this scenario, the use of medicinal plants appears as a therapeutic alternative for treatment with the reduction of side effects and treatment of depression through the action of different chemical compounds present in the structure of plants. In this study, four species of plants were presented, which have already been shown to be able to modulate the brain signalling pathways responsible for the patient's mood, with serotonin reuptake being the main mechanism of action shared between them.

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