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Can Plant Lectins be Alternatives to Treat Anxiety and Depressive Disorders?

Bárbara Raíssa Ferreira de Lima[1], Leydianne Leite de Siqueira Patriota[1], Lidiane Pereira de Albuquerque[2], Dalila de Brito Marques Ramos[3], Patrícia Maria Guedes Paiva[1], Emmanuel Viana Pontual[4], Michelle Melgarejo da Rosa[1] and Thiago Henrique Napoleão[1*]

[1]Departamento de Bioquímica, Centro de Biociências, Universidade Federal de Pernambuco, Recife, Pernambuco, Brazil.
[2]Departamento de Bioquímica e Farmacologia, Universidade Federal do Piauí, Teresina, Piauí, Brazil.
[3]Campus Amilcar Ferreira Sobral, Universidade Federal do Piauí, Floriano, Piauí, Brazil.
[4]Departamento de Morfologia e Fisiologia Animal, Universidade Federal Rural de Pernambuco, Recife, Pernambuco, Brazil.

Authors' contributions

This work was carried out in collaboration among all authors. All authors managed the literature searches, participated in discussion of the selected material, and contributed to the writing of the paper. All authors read and approved the final manuscript.

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ABSTRACT

Depression and anxiety disorder are the most common mental disorders worldwide and their treatments are combinations of pharmacological and psychotherapeutic approaches. Depression treatment depends largely on a pharmacotherapy that improves the transmission of monoamines in the brain. However, the drugs available have adverse reactions and do not contemplate positively all patients, which stimulates scientific research that seeks new molecules, including from natural sources. Lectins are proteins capable of binding reversibly and non-covalently to specific sugars. For example, it has been reported the antimicrobial, antitumor, antiparasitic, anti-

**Corresponding author: E-mail: thiago.napoleao@ufpe.br;*

inflammatory and antinociceptive activities of lectins. The ability of some lectins in modulating nociception and inflammation stimulated studies on the possible effects on processes that share some pathways and molecular agents, like depression and anxiety. Lectins isolated from plants showed antidepressant effects, which were demonstrated to be linked to activation of serotonergic, adrenergic, and dopaminergic systems as well as to inhibition of the glutamatergic system and L-arginine–NO–cGMP pathway. In view of their immunomodulatory properties, it is also suggested that lectins can ameliorate the inflammatory framework associated with depression. Anxiolytic effects were also reported and associated with modulation of GABAergic mechanisms, serotonergic system, and NO pathway. It should be taken in account that some lectins induced depressive-like behavior, associated with an neuroinflammatory action, as well anxiogenic action. Thus, it is important to use combinations of batteries for testing anxiety, depression, despair, and anhedonia behaviors in the studies with lectins. The mechanisms by which lectins exactly modulate depression or anxiety frameworks are still unclear but important windows had already been open by researchers and preclinical studies with lectins have indicated these proteins as candidates for alternative or complementary agents in therapies of depression and anxiety disorder.

Keywords: Anti-depressive effect; anxiolytic effect; anti-inflammatory action; plant bioactive proteins.

1. NTRODUCTION

The latest edition of the “Diagnostic and Statistical Manual of Mental Disorders” (DSM-V, 2013) classifies mental disorders in several groups, including mood disorders (e.g. depression) and anxiety disorders. According to the report "Depression and Other Common Mental Disorders: Global Health Estimates", released by the World Health Organization (WHO) in 2017, it is estimated that anxiety disorder affects 3.6% of the population worldwide, with characteristics as fear and apprehension that can become a generalized anxiety disorder, panic disorder, and different types of phobias. The symptoms can vary according to the degree of intensity, from mild to strong [1]. In Brazil, about 18 million people (9.3% of the population) suffer from anxiety disorder [2].

Depression is a chronic mental illness that can lead to physical and social interaction disabilities with a significant relationship with comorbidities and morbidities. Similar to anxiety disorder, depression also has a variability in the intensity of symptoms [3,4]. It is characterized by profound mood changes as well as by states of euphoria, irritability, insomnia, or hypersomnia, and even thoughts of death and suicide on a recurring basis [3,4,5]. It is often characterized by a constant feeling of sadness and lack of interest or pleasure in activities that were previously gratifying or pleasant (a condition called anhedonia) [6]. About 320 million people are affected by depression, around 4.4% of the world population [4,7]. In Brazil, this percentage reaches approximately 5.8% of the population [4]. Approximately 800,000 people die every year from depression-related suicide, which is the second leading cause of death in young people aged 15 to 29 [1]. Depression is complex and considered a product of biopsychosocial interactions. Currently, it is widely known that it is not caused by a single factor, but by a combination of several biological and environmental factors that can influence its appearance over the years [6,8]. Treatment for depression and anxiety disorders is a combination of pharmacological and psychotherapeutic approaches [3,9,10,11].

At the neurobiological level, depression is characterized by changes in the level of neurotransmitters – including serotonin, dopamine, and norepinephrine – and by functional and structural changes in brain regions, including the prefrontal cortex, amygdala, basal ganglia, and hippocampus [12,13]. The most recognized theory of depression is based on the monoaminergic hypothesis, which postulates that there is a reduced activity of neurotransmitters such as serotonin, norepinephrine, and dopamine in the brain of people with depression [6,8]. Consequently, therapy for depression depends largely on a pharmacotherapy that improves the transmission of monoamines in the brain. The therapy is similar for individuals with anxiety disorder, but in this case there is another factor, which is the neuronal stimulation factor, such as glutamate over-stimulation and reduced GABA stimulation [14].

The drugs most used as antidepressants are the selective serotonin reuptake inhibitors (SSRIs), norepinephrine reuptake inhibitors (NRIs), tricyclic antidepressants, and monoamine oxidase inhibitors [3,5,11]. However, these drugs have adverse reactions, such as drowsiness, fatigue, tremors, weight gain, and sexual dysfunction [15,16], and do not contemplate positively all patients, with a variation of 30% to 50% of individuals who do not benefit from the treatment [5,11]. This margin of non-benefited patients as well as the described adverse reactions lead to low adherence to treatment and, consequently, non-stabilization of symptoms [15,17]. Individual variations in the expression of receptors as well as in the release level of neurotransmitters may be behind the low response and even refractoriness to the pharmacotherapy. The central nervous system (CNS) takes time (about 2 weeks) to adapt the synthesis of neurotransmitters and receptors and many times the patient abandons treatment before that because he/she does not see immediate results. In turn, the adverse effects are related to the lack of specificity of the drugs and many of them end up giving side effects even before the pharmacological effect itself [18,19,20].

Carvalho et al. [21] described that important inflammatory genes were identified in circulating leukocytes in individuals with depression, in addition to high serum levels of pro-inflammatory cytokines like interleukins (IL) 6 and 8. Corroborating this finding, meta-analysis studies reported significant concentrations of pro-inflammatory cytokines, such as IL-6 and tumor necrosis factor (TNF), and an association between C-reactive protein and depressive conditions [22,23]. These reports stimulate the investigation of putative effects of anti-inflammatory agents on depression.

The context of the COVID-19 pandemic – comprising social isolation, uncertainties, the fear of losing loved ones and the economic recession – can make people even more vulnerable to anxiety disorder and depression [24]. Consequently, this scenario tends to raise or aggravate mental health problems, increasing the risk of suicidal behavior [25]. A strong impact of the pandemic on these statistics is expected in the coming years.

The limited success rate of conventional therapeutic approaches in depression and anxiety stimulates scientific research that seeks new molecules, including from natural sources, in order to increase the effectiveness of therapies and reduce adverse effects. In this review, we will approach the anti-depressive and anxiolytic effects of lectins, a special class of proteins broadly studied. Before this, we gathered some information about the animal models that have been used in preclinical studies to evaluate the efficacy of these proteins.

2. ANIMAL MODELS FOR STUDY OF ANXIETY AND DEPRESSION

Animal models with rodents have been improved over the years, in which cognitive and emotional aspects can be better evaluated, enabling research into models of anxiety and depression. Animal models provide a crucial way to examine neural circuits along with molecular and cellular pathways that can be critical in the pathogenesis of depression and are essential for the study of new drugs. However, no independent test or individual model is acceptable. Instead, combinations of batteries for testing anxiety, depression, despair, and anhedonia behaviors can be used to assess the occurrence and severity of depression. Using these assessments, a researcher may be able to study different aspects of depression in order to deepen knowledge and treatment as a whole [3].

Among the main tests to assess behavior similar to anxiety in animals, there are the open field test (OFT) and the elevated plus maze (EPM). The level of anxiety is determined by the OFT through the relation of time/entries in the periphery and center. A non-anxious rodent obeys a less curious exploitation profile, being more in the center of the apparatus [3,26]. The EPM is based on the fact that rodents tend to avoid open and brightly lit places, but at the same time they tend to explore new spaces. Thus, the proportion of these opposite stimuli is assessed [27]. The frequency of entries into the open and closed arms in the central zone and the total time spent in these zones are recorded. The increase in time spent in open arms indicates a lower degree of anxiety in the animal [28].

Among the most used behavioral tests to assess depression-like behavior, there are the Forced Swimming Test (FST), tail suspension test (TST) and the sucrose preference test (SPT) [29]. FST is the most used to evaluate the effects of antidepressants. For instance, a rat that is placed in water typically tries to escape. However, if it exhibits a depressive behavior, it will simply float

without attempting to escape until rescued [3]. This easily identifiable behavioral immobility has been described as the state of “despair” when the animal realizes that the escape is impossible and gives up. Antidepressants reduce the immobility time, which is used as the main predictor of antidepressant action [29,30].

The TST assumes that the animal will try to escape the stressful situation. After a while, the animal stops fighting, and immobility occurs; longer periods of immobility are signs of depressive behavior [27]. Consequently, it is proposed that substances with antidepressant activity decrease the animal immobility time in this test, without altering their locomotor activity [31].

On the other hand, SPT is based on the fact that normal rodents will exhibit a greater preference for water with dissolved sucrose instead of ordinary water. However, rodents with behaviors similar to depression will exhibit a reduced preference for the sweetened solution, which is indicative of a loss of interest in something that was previously satisfactory and pleasurable (an anhedonia framework) [29, 32]. The consumption or preference for sucrose decreases over weeks of exposure to chronic stress but it can be restored to normal levels by chronic treatment with antidepressant drugs [33].

The unpredictable moderate chronic stress model (UMCS) aims to chronically develop the depressive state in response to unpredictable stress stimuli and, consequently, reproduces the main symptoms observed in depressed patients, including decreased sugar consumption, weight and appetite loss, and decreased response to rewarding brain stimulation. In addition, factors such as an increase in the size of the adrenal gland can be observed, which is related to exposure to long periods of stress and hyperactivity of the hypothalamic-pituitary-adrenal axis and, consequently, an increase in circulating glucocorticoids [3].

3. LECTINS

3.1 Generalities

Lectins are defined as multidomain proteins of non-immune origin capable of binding reversibly and non-covalently to specific sugars, which can be free or present in larger structures forming glycoproteins and glycolipids. Interactions between proteins and carbohydrates are critical in many biological processes, such as: viral, bacterial, and parasitic infections; fertilization; cell growth and differentiation; and cancer metastasis. Lectins are unique in their ability to decipher the biological information encoded in the three-dimensional structure of sugars, called glycocode [34]. The lectins possess carbohydrate recognition domains (CRD), which can interact with carbohydrates through Van der Waals and hydrophobic interactions as well as hydrogen bonds [35]. Carbohydrate-binding specificity, requirements of additional functional groups and spatial configuration of CRDs are important aspects for the diversity of applications of lectins in chemical biology and drug research [36].

Lectins are produced by microorganisms, plants, and animals [37,38]. However, the largest number of known lectins are from the plant kingdom. Lectins are present in several organs like leaves, rhizomes, flowers, fruits, tubers, and seeds [39]. In plants, these proteins can act as reserve proteins, in defense against pathogens and predators, as carriers of plant hormones, in symbiotic interactions with microorganisms, and in cell recognition, for example [40]. Many plant lectins have been purified, characterized, and applied in studies in the areas of Agronomy, Medicine and Biotechnology. Lectins have shown antimicrobial [41], antitumor [42], and antiparasitic [43] activities, among others. They have also gained interest in pharmaceutical technology as active excipients to modulate the release of drugs [44].

3.2 Anti-inflammatory and Antinociceptive Activities of iectins

Plant lectins are promising molecules in the study of inflammatory processes. Assreuy et al. [45] suggested that anti-inflammatory effects of *Dioclea violacea* and *Dioclea guianensis* lectins result from the competitive blocking of glycosylated selectin binding sites in the membranes of leukocytes and/or endothelial cells. Lectins can also modulate immune response and its products by stimulating the release of pro- or anti-inflammatory mediators, for example [46,47].

Pires et al. [48] aimed to investigate the anti-inflammatory activity of *Lonchocarpus araripensis* lectin (LAL). In the dose of 10 mg/kg, LAL reduced carrageenan-induced paw edema in mice by about 77% and also slightly reduced vascular permeability. LAL also showed anti-

inflammatory effect against edemas induced by serotonin (5-HT), bradykinin (BK), and sodium nitroprusside. The preincubation of LAL with *N*-acetyl-D-glucosamine reversed the effect, indicating the involvement of its CRDs. It was also suggested that the effect depended on the inhibition of 5-HT, BK, prostaglandin E2, nitric oxide, TNF-α, and leukocyte rolling and adhesion. Santos et al. [49] demonstrated that the *Machaerium acutifolium* seed lectin (MaL) significantly decreased inflammation in the formalin test, inhibited cell migration in carrageenan-induced peritonitis, and blocked the formation of paw edema induced by carrageenan and dextran. *In vitro* studies in LPS-stimulated macrophages showed that MaL downregulated gene expression of pro-inflammatory cytokines, inducible nitric oxide synthase (iNOS) and TNF-α, while upregulated the anti-inflammatory IL-10 gene.

The antinociceptive potential is already described for plant lectins. A lectin isolated from *Canavalia grandiflora* seeds showed potential for new analgesic and anti-inflammatory therapies, as it was able to inhibit neutrophil migration and inflammatory hypernociception [50]. Another work reported that the *Lonchocarpus campestris* lectin (LCaL) presented antinociceptive effect in the formalin and acetic acid-induced writhing tests in mice; the authors verified that this lectin reduced inflammatory parameters, such as vascular permeability, neutrophil migration, paw edema and hypernociception induced by carrageenan [51]. The lectin purified from *Tetracarpidium conophorum* seeds (TcSL) showed significant inhibition of nociception as measured by paw licking time upon pain induction by formalin. TcSL also significantly reduced carrageenan-induced leucocyte migration to the peritoneum [52].

Campos et al. [53] studied the antinociceptive effect of *Bauhinia monandra* leaf lectin (BmoLL) in male Swiss mice and found that the analgesic effect of this lectin was attributed to both peripheral (through the inhibition of inflammatory mediators) and central (through the lectin-carbohydrate interaction and cellular receptors) mechanisms. The potent BmoLL anti-inflammatory and antinociceptive properties could explain the basis for the use of *B. monandra* in folk medicine in treating diseases associated with inflammation and pain.

A lectin from the green kelp *Caulerpa cupressoides* (CcL) inhibited the inflammatory nociception in the temporomandibular joint of male Wistar rats through the inhibition of TNF-α, IL-1β, cyclooxygenase-2 (COX-2) and intercellular adhesion molecule-1 (ICAM-1); the authors also found an effect independent of the cannabinoid and opioid systems [54]. AEL lectin, isolated from okra (*Abelmoschus esculentus*) seeds, reduced the hypernociception of the temporomandibular joint in male Wistar rats, depending on the central activation of δ and κ opioid receptors [55]. AEL was also able to reduce inflammatory hypernociception of the zymosan-induced temporomandibular joint in male Wistar rats through inhibition of TNF-α and IL-1β and dependently on the integrity of the heme oxygenase-1 (HO-1) pathway [56].

Depression and pain are closely correlated from the perspectives of both brain regions and the neurological function. The classical monoamine hypothesis proposes that depression may occur as a result of decreased availability of monoamine neurotransmitters, which in fact are also vital to the occurrence and development of pain. Thus, some antidepressants have been used to treat pain [57]. Some lectins that showed anti-depressant effect also displayed antinociceptive activity, as presented in the next section.

In addition, the association between states of depression and pro-inflammatory cascades has been described. Cytokines are likely to play a role in the behavior of depression through a diverse set of mechanisms. Studies showing antidepressant effects of anti-inflammatory drugs and depressogenic effects of pro-inflammatory drugs in patients and rodents suggest a specific role for the immune system [58,59]. You et al. [60] reported that the levels of pro-inflammatory cytokines were positively regulated in rodents exposed to UMCS model while anti-inflammatory cytokines have been inhibited. In view of the capacity of some plant lectins to modulate nociception and inflammation, it has been hypothesized whether these proteins can have any effect on other processes that share some pathways and molecular agents, like depression and anxiety.

3.3 Lectins against Anxiety and Depression

Lectins isolated from plants have gained prominence in studies of neurobiological modulation, being promising biomolecules with

effects on the CNS, demonstrating responses that are involved in behavioral regulation, neuroplasticity, and neuroprotection [61]. These effects can occur through the interaction of these lectins with glycoconjugates present on the cell surfaces of the CNS, which act as cell regulators and are actively involved in the modulation of signal transduction [62]. Alternatively, lectins can have therapeutic effects on neurological disorders because they possess anti-inflammatory action, since neuropathies require complex signaling, and varied metabolic cascades for pathophysiological development [63,64,65,66].

The lectin from *Canavalia brasiliensis* seeds (ConBr), a glucose/mannose-binding protein, when administered by intracerebroventricular (i.c.v) route in Swiss mice, showed an antidepressant effect in FST model that was dependent on the activation of serotonergic (5HT1 and 5HT2 receptors), adrenergic (α1-adrenadrenergic receptor) and dopaminergic (D2 receptor) systems [67]. Rieger et al. [68] showed that ConBr administered centrally (i.c.v) in Swiss mice exerts an antidepressant-like effect in the FST assay by a mechanism involving inhibition of the glutamatergic system (NMDA receptors) and L-arginine–NO–cGMP pathway. It is interesting to mention that ConBr showed antinociceptive activity both peripheral and central, mediated by the opioid system and involving δ-and κ-receptors [69].

FTL (frutalin), α-D-galactose-binding lectin from *Artocarpus incisa* seeds, administered by intraperitoneal (i.p) injection in Swiss mice, presented an antidepressant-type effect in neurobehavioral models of depression (FST and TST). This effect was mediated by the glutamatergic system through NMDA receptors and the nitrergic pathway (L-Arginine/NO/cGMP) [66]. FTL was also reported to be able of reducing acute and neuropathic nociceptive behaviors in rodent models of orofacial pain, with action mediated by TRPA1, TRPV1 and TRPM8 receptors [70].

Araucaria angustifolia seed lectin (AaL), a *N*-acetyl-D-glucosamine-specific lectin, administered intraperitoneally, reduced locomotor activity of Swiss mice in the OFT test similar to diazepam, an anxiolytic drug. This anxiolytic effect was mediated by a GABAergic mechanism [71, 72]. DAL, a lectin isolated from the seeds of the *Dioclea altissima* with binding affinity to D-glucose or D-mannose, showed anxiolytic-like effect in the OFT and EPM tests when administered (i.p.) in Swiss mice. Its effect was mediated by the serotonergic and GABAergic systems as well as NO pathway [73].

Conversely, a lectin from seeds of *Vatairea macrocarpa* (VML) – a protein with galactose/N-acetyl-galactosamine binding specificity– produced a depressive-like behavior in the FST test when administered centrally (i.c.v) in Swiss mice, which was associated with an neuroinflammatory action [74]. In addition, the lectin FTL presented a possible anxiogenic-like effect observed in the EPM test when administered (i.p.). in Swiss mice [66]. Thus, it is important to use combinations of batteries for testing anxiety, depression, despair, and anhedonia behaviors in the studies with lectins.

Although the direct relation between central effects of lectins and other biological activities described for them is not clear in literature, some association can be suggested. For example, the antidepressant and antinociceptive effects of FTL were blocked with pre-treatment with L-NAME (a non-specific NOS inhibitor), suggesting involvement of the L-arginine-NO pathway in both effects [66, 75]. In contrast, the depressive-like effect of VML can be directly associated with its pro-inflammatory effect [74,76,77]. Table 1 describes a possible relation between the central effects of the lectins described here and other biological activities of them.

Table 1. Central effects of plant lectins and possible related biological activities

Lectin	Central effects	Other activities	Reference
Araucaria angustifolia seed lectin (AaL)	Anxiolytic	Anti-inflammatory	[71]
Artocarpus incisa seeds lectin (FTL)	Antidepressant and anxiogenic	Antinociceptive effect	[75]
Canavalia brasiliensis seeds lectin (ConBr)	Antidepressant	Antinociceptive	[69]
Vatairea macrocarpa seeds lectin (VML)	Depressive-like	Pro-inflammatory	[76, 77]

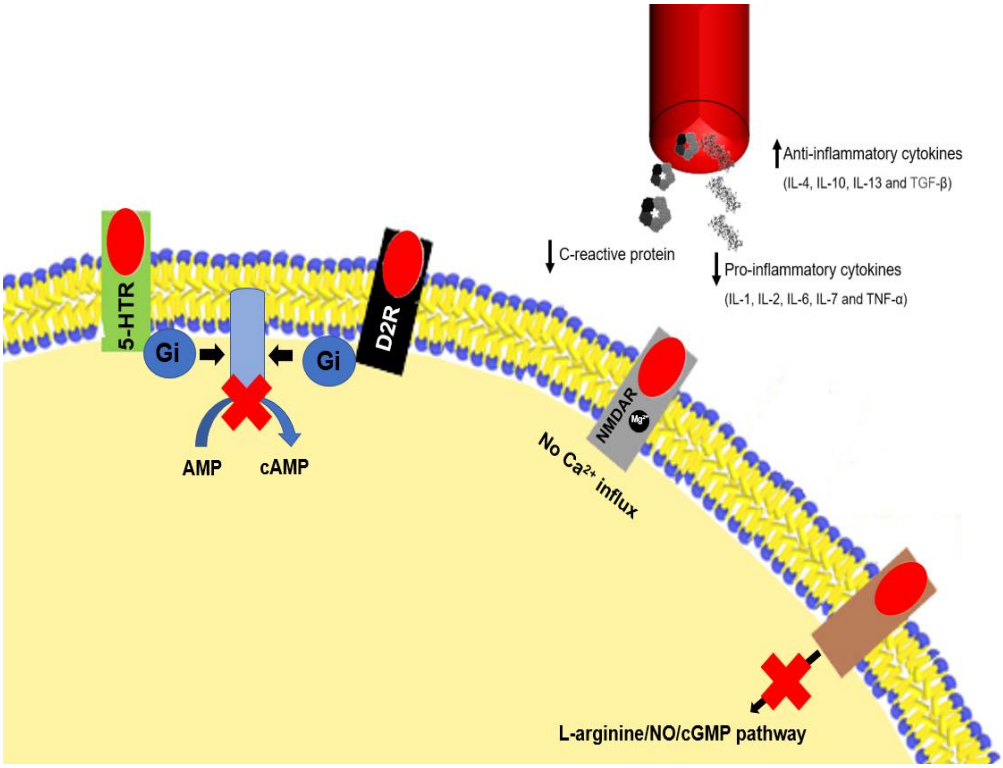

Fig. 1. Hypothetical mechanisms of antidepressive effects of lectins. The lectin (red circle) can bind directly to serotonergic (5HT1 and 5HT2 receptors) and dopaminergic (D2 receptor) receptors or can stimulate the binding of the ligand neurotransmitter, activating these systems. The stimulation of 5-HTR and D2R leads to activation of inhibitory G proteins (Gi), decreasing the activity of adenylyl cyclase. Lectin can also bind to NMDA receptors or prevent the binding of glutamate to them, which leads to blockage of Ca^{2+} influx through the receptor pore channel, inhibiting glutamatergic system. In addition, lectin can inhibit the activation of L-arginine–NO–cGMP pathway. In view of their immunomodulatory properties, lectins can ameliorate the inflammatory framework associated with depression by reducing the circulating levels of pro-inflammatory cytokines and C-reactive protein

4. CONCLUSION

Previous works have shown the anti-inflammatory and antinociceptive activities of lectins as well as some reports on antidepressant activity. The mechanisms by which lectins can modulate depression or anxiety frameworks are still unclear but it has been hypothesized that these proteins can act on the molecular basis of these pathologies: the monoaminergic system. Thus, pathways associated to serotonergic, adrenergic, dopaminergic, and glutamatergic systems have become of interest by researchers in order to understand the lectin physiological effects in depression and anxiety. In addition, possible correlations between the modulation of inflammatory responses and antidepressant and anxiolytic effects of lectins should gain attention in the next years. In summary, important windows had already been open by researchers and preclinical studies with lectins have indicated these proteins as candidates for alternative or complementary agents in therapies of depression and anxiety disorder.

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COMPETING INTERESTS

Authors have declared that no competing interests exist

REFERENCES

1. World Health Organization (WHO). Depression and Other Common Mental Disorders: Global Health Estimates. WHO; 2017. Accessed 10 October 2020. Available: https://www.who.int/publications/i/item/depression-global-health-estimates.
2. World Health Organization (WHO). Depression. WHO; 2020. Accessed 10 October 2020. Available: https://www.who.int/health-topics/depression
3. Wang Q, Timberlake MA, Prall K, Dwivedi Y. The recent progress in animal models of depression. Prog Neuro-Psychopharmacol Biol Psychiatry. 2017;77:99-109.
4. Pan American Health Organization (PAHO). Depression. PAHO; 2020. Accessed 17 October 2020. Available:https://www.paho.org/en/topics/depression
5. Nestler EJ, DiLeone MBRJ, Eisch AJ, Gold SJ, Monteggia LM. Neurobiology of depression. Neuron, 2002;34:13-25.
6. Fakhoury M. Revisiting the serotonin hypothesis: implications for major depressive disorders. Mol Neurobiol. 2016;53:2778-86.
7. Gracioli, J. Brasil vive surtos de depressão e ansiedade. Jornal da USP; 2018. Accessed 17 October 2020. Available:https://jornal.usp.br/atualidades/brasil-vive-surto-dedepressao-e-ansiedade/
8. Albert PR, Benkelfat C, Descarries L. The neurobiology of depression-revisiting the serotonin hypothesis. I. Cellular and molecular mechanisms. Philos Trans R Soc Lond B Biol Sci. 2012;367:2378-81.
9. Kamenov K, Twomey C, Cabello M, Prina AM, Ayuso-Mateos JL. The efficacy of psychotherapy, pharmacotherapy and their combination on functioning and quality of life in depression: a meta-analysis. Psychol Med. 2017;47:414-25.
10. Ménard C, Hodes GE, Russo SJ. Pathogenesis of depression: Insights from human and rodent studies. Neuroscience. 2016;321:138-62.
11. Planchez B, Surget A, Belzung C. Animal models of major depression: drawbacks and challenges. J Neural Transm. 2019;126:1383-408.
12. Fakhoury M. New insights into the neurobiological mechanisms of major depressive disorders. Gen Hosp Psychiatry. 2015;37:172-7.
13. Dai L, Zhou H, Xu X, Zuo Z. Brain structural and functional changes in patients with major depressive disorder: a literature review. PeerJ. 2019;7:e8170.
14. Bueno SC. Avaliação da captação de glutamato no hipocampo ventral de ratos submetidos ao labirinto em cruz elevado. Dissertação (mestrado) - Universidade Federal de Santa Catarina, Centro de Ciências Biológicas, Programa Multicêntrico de Pós-graduação em Ciências Fisiológicas, Florianópolis; 2011.
15. Papakostas GI. Tolerability of modern antidepressants. J Clin Psychiatry. 2008;69:8-13.
16. Nabavi SM, Daglia M, Braidy N, Nabavi SF. Natural products, micronutrients, and nutraceuticals for the treatment of depression: A short review. Nutr. Neurosci. 2017;20:180-94.
17. Apaydin EA, Maher AR, Shanman R, Booth MS, Miles JN, Sorbero ME, et al. A systematic review of St. John's wort for major depressive disorder. Syst Rev. 2016;5:148.
18. Labermaier C, Masana M, Müller MB. Biomarkers predicting antidepressant treatment reponse: how can we advance the field? Dis Markers. 2013;35:23-31.
19. Martins-de-Souza D, Maccarrone G, Ising M, Kloiber S, Lucae S, Holsboer F, Turck CW. Blood mononuclear cell proteome suggests integrin and Ras signaling as critical pathways for antidepressant treatment response. Biol Psychiatry. 2014;76:15-7.
20. Souza AEC, Itano LSC, Rodrigues RMS, Pereira RP, Barbosa FK. Os efeitos dos antidepressivos no organismo. UNILUS Ensino e Pesquisa. 2015;12:146.
21. Carvalho LA, Bergink V, Sumaski L, Wijkhuijs J, Hoogendijk WJ, Birkenhager TK, Drexhage HA. Inflammatory activation is associated with a reduce glucocorticoid receptor alpha/beta expression ratio in monocytes of inpatients with melancholic major depressive disorder. Transl Psychiatry. 2014;4:e344.
22. Dowlati Y, Herrmann N, Swardfager W, Liu H, Sham L, Reim EK, Lanctôt KL. A meta-analysis of cytokines in major

depression. Biol Psychiatry. 2010;67:446-57.
23. Smith KJ, Au B, Ollis L, Schmitz N. The association between C-reactive protein, interleukin-6 and depression among older adults in the community: a systematic review and meta-analysis. Exp Gerontol. 2018;102:109-32.
24. Golberstein E, Wen H, Miller BF. Coronavirus disease 2019 (COVID-19) and mental health for children and adolescents. JAMA Pediatrics. 2020;174:819-20.
25. FIOCRUZ. Saúde Mental e Atenção Psicossocial na Pandemia COVID-19: Suicídio na pandemia COVID-19. FIOCRUZ; 2020. Accessed 17 October 2020. Available:https://www.arca.fiocruz.br/bitstream/icict/41420/2/Cartilha_PrevencaoSuicidioPandemia.pdf
26. Denenberg VH. Open-filed behavior in the rat: what does it mean? Ann N Y Acad Sci. 1969;159:852-9.
27. Teegarden S. Behavioral phenotyping in rats and mice. Mater Methods. 2012;2:122.
28. Carola V, D'Olimpio F, Brunamonti E, Mangia F, Renzi P. Evaluation of the elevated plus-maze and open- field tests for the assessment of anxiety- related behaviour in inbred mice. Behav Brain Res. 2002;134:49-57.
29. Belovicova K, Bogi E, Csatlosova K, Dubovicky M. Animal tests for anxiety-like and depression-like behavior in rats. Interdiscip. Toxicol. 2017;10:40-3.
30. Porsolt RD, Le Pichon M, Jalfare M. Depression: a new animal model sensitive to antidepressant treatments. Nature. 1977;266:730-2.
31. Steru L, Chermat R, Thierry B, Simon P. The tail suspension test: a new method for screening antidepressants in mice. Psychopharmacology. 1985;85:367-70.
32. Klein DF. Endogenomorphic depression: a conceptual and terminological revision. Arch Gen Psychiatry. 1974;31:447-54.
33. Willner P. The chronic mild stress (CMS) model of depression: History, evaluation and usage. Neurobiol. Stress. 2017;6:78-93.
34. Wiederschain GY. Glycobiology: progress, problems, and perspectives. Biochemistry. 2013;78:679–96.
35. Sharon N. Lectins: carbohydrate-specific reagents and biological recognition molecules. J Biol Chem. 2007;282:2753–64.
36. Cecioni S, Imberty A, Vidal S. Glycomimetics versus multivalent glycoconjugates for the design of high affinity lectin ligands. Chem Rev. 2015;115:525-61.
37. Singh RS, Walia AK, Kennedy JF. Structural aspects and biomedical applications of microfungal lectins. Int. J. Biol. Macromol. 2019;134:1097–107.
38. Preetham E, Lakshmi S, Wongpanya R, Vaseeharan B, Arockiaraj J, Olsen RE. Antibiofilm and immunological properties of lectin purified from shrimp *Penaeus semisulcatus*. Fish and Shellfish Immunol. 2020;106:776–82.
39. Ingale AG, Hivrale AU. Plant as a plenteous reserve of lectin. Plant Signal Behav. 2013;8:e26595.
40. Delatorre P, Silva-Filho JC, Rocha BAM, Santi-Gadelha T, Nóbrega RB, Gadelha CAA, et al. Interactions between indole-3-acetic acid (IAA) with a lectin from *Canavalia maritima* seeds reveal a new function for lectins in plant physiology. Biochimie. 2013;95:1697-703.
41. Silva PM, Moura MC, Gomes FS, Trentin DS, Oliveira APS, Mello GSV, et al. PgTeL, the lectin found in *Punica granatum* juice, is an antifungal agent against *Candida albicans* and *Candida krusei*. Int. J. Biol. Macromol. 2018;108:391-400.
42. Patriota LLS, Ramos DBM, Silva YA, Santos ACLA, Araújo MTMF, Brito JS, et al. *Microgramma vacciniifolia* frond lectin (MvFL) exhibits antitumor activity against sarcoma 180 in mice. Phytomedicine Plus. 2021;1:100013.
43. Castanheira L, Souza DLN, Silva RJ, Barbosa B, Mineo JR, Tudini KA, Rodrigues R. Insights into anti-parasitism induced by a C-type lectin from *Bothrops pauloensis* venom on *Toxoplasma gondii. Int J Biol Macromol. 2015;74:568-74.*
44. Juan LL, Recio VG, López PJ, Juan TG, Cordoba-Diaz M, Cordoba-Diaz D. Pharmaceutical applications of lectins. J Drug Deliv Sci Technol 2017;42:126-33.
45. Assreuy AM, Martins GJ, Moreira EE, Brito GA, Cavada BS, Ribeiro RA, et al. Prevention of cyclophosphamide-induced hemorrhagic cystitis by glucose-mannose binding plant lectins. J Urol 1999;161:1988-93.
46. Araújo LCC, Aguiar JS, Napoleão TH, Mota FV, Barros AL, Moura MC, et al. Evaluation of cytotoxic and anti-

inflammatory activities of extracts and lectins from *Moringa oleifera* seeds. PLoS ONE. 2013;8:e81973.

47. Souza MA, Carvalho FC, Ruas LP, Ricci-Azevedo R, Roque-Barreira MC. The immunomodulatory effect of plant lectins: a review with emphasis on artinm properties. Glycoconj J. 2013;30:641–57.
48. Pires AF, Rodrigues NVFC, Soares PMG, Ribeiro RA, Aragão KS, Marinho MM, et al. A novel N-acetyl-glucosamine lectin of *Lonchocarpus araripensis* attenuates acute cellular inflammation in mice. Inflamm Res. 2016;65:43–52.
49. Santos ALE, Júnior CPS, Neto RNM, Santos MHC, Santos VF, Rocha BAM, et al. *Machaerium acutifolium* lectin inhibits inflammatory responses through cytokine modulation. Process Biochem. 2020;97:149–57.
50. Nunes BS, Rensonnet NS, Dal-Secco D, Vieira SM, Cavada BS, Teixeira EH, et al Lectin extracted from *Canavalia grandiflora* seeds presents potential anti-inflammatory and analgesic effects. Naunyn-Schmiedeberg's Arch Pharmacol. 2009;379:609-16.
51. Pires AF, Bezerra MM, Amorim RMF, Nascimento FLF, Marinho MM, Moura RM, et al. Lectin purified from *Lonchocarpus campestris* seeds inhibits inflammatory nociception. Int J Biol Macromol. 2019;125:53–60.
52. Oladokun BO, Omisore ON, Osukoya OA, Kuku A. Anti-nociceptive and anti-inflammatory activities of *Tetracarpidium conophorum* seed lectin. Scientific African. 2019;3:e00073.
53. Campos JKL, Araújo CSF, Araújo TFS, Santos AFS, Teixeira JA, Lima VLM, et al. Anti-inflammatory and antinociceptive activities of *Bauhinia monandra* leaf lectin. Biochimie Open 2016;2:62-8.
54. Rivanor RLC, Val DR, Ribeiro NA, Silveira FD, Assis EL, Franco AX, et al. A lectin fraction from green seaweed *Caulerpa cupressoides* inhibits inflammatory nociception in the temporomandibular joint of rats dependent from peripheral mechanisms. Int J Biol Macromol. 2018;115:331–40.
55. Alves SM, Freitas RS, Val DR, Vieira LV, Assis EL, Gomes FIF, et al. The efficacy of a lectin from *Abelmoschus esculentus* depends on central opioid receptor activation to reduce temporomandibular joint hypernociception in rats. Biomed Pharmacother. 2018:101:478-84.
56. Freitas RS, Val DR, Fernandes MEF, Gomes FIF, Lacerda JTJG, Gadelha TS, et al. Lectin from *Abelmoschus esculentus* reduces zymosan-induced temporomandibular joint inflammatory hypernociception in rats via heme oxygenase-1 pathway integrity and TNF-α and IL-1β suppression. Int Immunopharmacol. 2016;38:313-23.
57. Sheng J, Liu S, Wang Y, Cui R, Zhang X. The link between depression and chronic pain: neural mechanisms in the brain. Neural Plast. 2017;2017:9724371.
58. Tubbs JD, Ding J, Baum L, Sham PC. Immune dysregulation in depression: Evidence from genome-wide association. Brain Behav Immun. 2020;7:100108.
59. Colasanto M, Madigan S, Korczak DJ. Depression and inflammation among children and adolescents: A meta-analysis. J Affect Disord 2020;277:940-48.
60. You Z, Luo C, Zhang W, Chen Y, He J, Zhao Q, et al. Pro- and anti-inflammatory cytokines expression in rat's brain and spleen exposed to chronic mild stress: involvement in depression. Behav. Brain Res. 2011;225:135-41.
61. Araújo JRC, Coelho CB, Campos AR, Moreira RA, Monteiro-Moreira ACO. Animal galectins and plant lectins as tools for studies in neurosciences. Curr Neuropharmacol. 2020;18:202-15.
62. Yagi H, Kato K. Functional roles of glycoconjugates in the maintenance of stemness and differentiation process of neural stem cells. Glycoconj J. 2017;34:757-63.
63. Russi MA, Vandresen-Filho S, Rieger DK, Costa AP, Lopes MW, Cunha RM, et al. ConBr, a lectin from *Canavalia brasiliensis* seeds, protects against quinolinic acid-induced seizures in mice. Neurochem Res. 2012;37:288–97.
64. Nascimento APM, Knaut JL, Rieger DK, Wolin IAV, Heinrich IA, Mann J, et al. Anti-glioma properties of DVL, a lectin purified from *Dioclea violacea*. Int J Biol Macromol. 2018;120:566-77.
65. Leal RB, Pinto-Junior, VR, Osterne VJS, Wolin IAV, Nascimento APM, Neco AHB, et al. Crystal structure of DlyL, a mannose-specific lectin from *Dioclea lasiophylla* Mart. Ex Benth seeds that display cytotoxic effects against C6 glioma cells. Int J Biol Macromol. 2018;114: 64-76.

66. Araújo JRC, Júnior JMAM, Damasceno MBMV, Santos SAAR, Vieira-Neto AE, Lobo MDP, et al. Neuropharmacological characterization of frutalin in mice: Evidence of an antidepressant-like effect mediated by the NMDA receptor/NO/cGMP pathway. Int J Biol Macromol. 2018;112:548-54
67. Barauna SC, Kaster MP, Heckert BT, Nascimento KS, Rossi FM, Teixeira EH, et al. Antidepressant-like effect of lectin from *Canavalia brasiliensis* (ConBr) administered centrally in mice. Pharmacol Biochem Behav. 2006;85:160-9.
68. Rieger DK, Costa AP, Budni J, Moretti M, Barbosa SGR, Nascimento KS, et al. Antidepressant-like effect of *Canavalia brasiliensis* (ConBr) lectin in mice: evidence for the involvement of the glutamatergic system. Pharmacol Biochem Behav 2014;122:53-60.
69. Pires AF, Assreuy AMS, Lopes EAB, Celedônio NR, Soares CEA, Rodrigues NVFC, et al. Opioid-like antinociceptive effects of oral administration of a lectin purified from the seeds of *Canavalia brasiliensis.* Fundam Clin Pharmacol. 2011;27:201-9.
70. Damasceno, MBMV, Melo Júnior JMA, Santos, SAAR, Melo LTM, Leite LHI, Vieira-Neto AR, et al. Frutalin reduces acute and neuropathic nociceptive behaviours in rodent models of orofacial pain. Chemico-Biol Interact 2016;256:9-15.
71. Santi-Gadelha T, Gadelha CAA, Aragão KS, Oliveira CC, Mota MRL, Gomes RC, et al. Purification and biological effects of *Araucaria angustifolia* (Araucariaceae) seed lectin. Biochem Biophys Res Commun. 2006;350:1050-5.
72. Vasconcelos SMM, Lima SR, Soares PM, Assreuy MAS, Sousa FCF, Lobato RFG, et al. Central action of *Araucaria angustifolia* seed lectin in mice. Epilepsy Behav. 2009;15:291-3.
73. Araújo JRC, Campos AR, Damasceno MBMV, Santos SAAR, Ferreira MKA, Moreira RA, et al. Neuropharmacological characterization of *Dioclea altissima* seed lectin (DAL) in mice: evidence of anxiolytic-like effect mediated by serotonergic, GABAergic receptors and NO pathway. Curr Pharm Des. 2020;26:3895-904.
74. Gonçalves FM, Freitas AE, Peres TV, Rieger DK, Ben J, Maestri M, et al. *Vatairea macrocarpa* lectin (VML) induces depressive-like behavior and expression of neuroinflammatory markers in mice. Neurochem Res. 2013;38:2375-84.
75. Damasceno MBMV, Júnior JMAM, Santos SAAR, Melo LTM, Leite LHI, Vieira-Neto AE, et al. Frutalin reduces acute and neuropathic nociceptive behaviours in rodent models of orofacial pain. Chem Biol Interact. 2016;256:9-15.
76. Alencar NM, Assreuy AM, Alencar VB, Melo SC, Ramos MV, Cavada BS, et al. The galactose-binding lectin from *Vatairea macrocarpa* seeds induces in vivo neutrophil migration by indirect mechanism. Int J Biochem Cell Biol. 2003;35:1674-81.
77. Alencar NMN, Assreuy MAS, Havt A, Benevides RG, Moura TR, Sousa RB, et al. *Vatairea macrocarpa* (Leguminosae) lectin activates cultured macrophages to release chemotactic mediators. Naunyn Schmiedebergs Arch Pharmacol. 2007;374:275-82.

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