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

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**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.

**Article Information**

DOI: 10.9734/AIR/2020/v21i1130274

Editor(s):
(1) Prof. Jaime Salvador Moysén, Universidad Juárez del Estado de Durango, Mexico.

Reviewers:
(1) Mahalaxmi Mohan, MGV’s Pharmacy College, India.
(2) Shalam M. Hussain, Qassim University, Saudi Arabia.

Complete Peer review History: http://www.sdiarticle4.com/review-history/64637

Received 25 October 2020
Accepted 30 December 2020
Published 31 December 2020

**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-
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 [3,4,10]. 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 (NRTIs), 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 Lectins

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-
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 brasilensis 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-adrenergic 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 centrally (i.c.v) 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**

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

ACKNOWLEDGEMENTS

The authors express their gratitude to the Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq) for research grants (407192/2018–2) and fellowships (LCBBC, PMGP and THN) as well as to the Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES; Finance Code 001) and the Fundação de Amparo à Ciência e Tecnologia do Estado de Pernambuco (FACEPE; IBPG-1712–2.08/16) for financial support.
COMPETING INTERESTS

Authors have declared that no competing interests exist.

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