WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.453
Volume 14, Issue 10, 380-392. Review Article ISSN 2277–7105

TARGETING DEPRESSION: SYNERGISTIC MODULATION OF P2X7 RECEPTORS BY ALKALOIDS AND POLYPHENOLS

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Article Received on
26 March 2025,

Revised on 15 April 2025,
Accepted on 05 May 2025

DOI: 10.20959/wjpr202510-36665

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ABSTRACT

Depression, a complex and debilitating mental health disorder, continues to pose a significant global health burden. Current treatment approaches often exhibit limited efficacy and numerous side effects, necessitating the exploration of novel therapeutic approaches. Alkaloids and polyphenols are naturally occurring compounds found in various plant sources, and have individually demonstrated neuroprotective and mood-stabilizing properties. The P2X7 receptor, a ligand-gated purinergic receptor associated with neuroinflammation and synaptic dysfunction in depression, emerges as a crucial potential target for depression. By combining exploration interactions of alkaloids and polyphenols, this review aims to provide a comprehensive understanding of their combined effects on the P2X7 receptor intricately linked to the pathophysiology of depression. The elucidation of the synergistic effects of these natural compounds on neuroinflammation by modulating the P2X7 receptor opens a new way for the development of innovative therapeutic strategies for depression, with the potential to enhance treatment outcomes and improve the quality of life for individuals affected by this prevalent mental health disorder.

KEYWORDS: Depression, Neuroinflammation, NLRP3 inflammasome, P2X7 receptor, Polyphenols, Alkaloids.

INTRODUCTION

Depression is the most severe and predominant psychiatric disease worldwide. It is characterized by the presence of feelings of depression, sadness, anxiety, hopelessness, worthless, guilt, shame, and loss of interest or pleasure in almost all activities they enjoyed in their life.[1] It is clinically characterized by depletion of brain monoamine neurotransmitters, interfering glutamatergic transmission, and dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis along with oxidative stress.[2]

Recent findings indicate that neuroinflammation is a pivotal factor in the emergence and advancement of neurological disorders, including depression. Downstream mechanisms that mediate the connection between inflammation and symptoms of depression involve changes in dopaminergic, serotonergic, and noradrenergic neurotransmission and tryptophan metabolism.[3] Microglia, the principal resident immune cells in the brain, play a vital role in the neuroinflammatory processes linked to depression.[4] Inflammation results in elevated generation of reactive oxygen species, adversely affecting neurogenesis in the medial prefrontal cortex.[5] Activated microglia are considered indicative of neuroinflammation. Dysfunction in microglial activity and the release of inflammatory cytokines associated with neuroinflammation are implicated in the potential progression toward depression.[6]

The P2X7 ionotropic ATP-gated ligand gated purinergic receptor (P2X7R) is associated with an elevated susceptibility to developing depressive disorders.[7] As a member of the adenosine triphosphate (ATP)-gated cation channels distributed extensively in brain tissues, P2X7R plays a significant role in the modulation of pathology related to depression via neuroinflammation.[8] Dysregulation of the P2X7 receptor can lower levels of associated pro-inflammatory cytokines may impact tryptophan metabolism and elevate neuroprotective metabolites.[9]

NLRP3 present in neurons, astrocytes, and microglia, catalyzes inflammatory responses within the central nervous system (CNS), presenting a promising target for mitigating neuroinflammation in the treatment of depression.[10] Nucleotide-binding oligomerization domain-like receptors (NLRs), characterized by their nucleotide-binding structural domains and leucine-rich repeat proteins, constitute a family of pattern recognition receptors integral

to innate immune defense mechanisms.[11] Elevated concentrations of ATP activate the P2X7 receptor during neuroinflammation, and the activation of P2X7R is implicated in promoting NLRP3 activation by inducing mitochondrial dysfunction and generating reactive oxygen species (ROS).[12] The confirmed association between the activation of NLRP3 inflammasome and the development of depression underscores the significance of targeting this intricate molecular interplay for potential therapeutic interventions through manipulating the NLRP3 inflammasome.[13]

Contemporary investigations are exploring substitutes for conventional antidepressants to diminish unwanted side effects and enhance effectiveness. Phytoconstituents offer a broad research spectrum in the realm of antidepressant treatments. Secondary plant metabolites such as alkaloids, polyphenols, glycosides, saponins, and terpenoids demonstrated antidepressant effects. Many of these phytoconstituents were observed to enhance brain-derived neurotrophic factor (BDNF), serotonin, noradrenaline, and dopamine, contributing to their antidepressant actions. Additionally, some compounds exhibited antidepressant effects by inhibiting monoamine oxidase (MAO) activity and alleviating hypothalamic-pituitary-adrenal (HPA) axis overactivity.[14]

Polyphenols, being naturally present compounds in plants, exhibit diverse biological activities. They can engage with reactive oxygen species (ROS), interrupting the chain reaction and thereby preventing oxidative damage to tissues.[15] Polyphenols possess the ability to modulate various inflammation mediators, such as the overproduction of reactive oxygen species (ROS) during oxidative metabolism, which can initiate the inflammatory cascade, resulting in the synthesis and release of pro-inflammatory cytokines via P2X7-NLRP3 axis.[16]

Alkaloids consist primarily of naturally occurring chemical compounds containing basic nitrogen atoms, which can be used in herbal medicine, and have recently demonstrated efficacy in treating mood disorders.[17] They can modulate neurotransmitters and their receptor systems within the central nervous system.[18] Alkaloids can reduce the neuroinflammatory response by inhibiting the activation of NLRP3 inflammasome and rescue neuronal deterioration by suppressing impairments in synaptic plasticity and neurogenesis.[19]

PATHOPHYSIOLOGY

Neuroinflammation plays a crucial role in the development of depression, influencing it through the regulation of immune factors, immune cell activation, neuron generation, synaptic plasticity, and neurotransmission.[20] Microglia, the primary resident immune cells in the brain, play a pivotal role in the development of depression. Activation of microglia in the presence of ATP molecules modulates neuroinflammation, synaptic plasticity, and the development of neural networks, all of which have an impact on depression.[21]

NLRP3 inflammasome in depression

One of these hypotheses is that inflammation and immunity are important factors affecting the occurrence and development of mood disorders. Neuroinflammation is caused by the excessive secretion of inflammatory cytokines in the brain and is considered one of the important mechanisms of depression.[22] The NLRP3 inflammasome exhibits elevated expression within innate immune cells, significantly contributing to the pathogenesis of depression.[23] Inflammasomes play crucial roles in innate immunity by triggering the activation of caspase-1, which, in turn, facilitates the maturation and secretion of interleukin-1 beta (IL-1β), along with the production of other relevant mature cytokines.[24] The mRNA expression levels of NLRP3 inflammasome and proinflammatory cytokines show a significant increase in the brains of mice experiencing depression induced by various factors such as reserpine, lipopolysaccharide, and chronic unpredictable mild stress (CUMS), etc.[25]

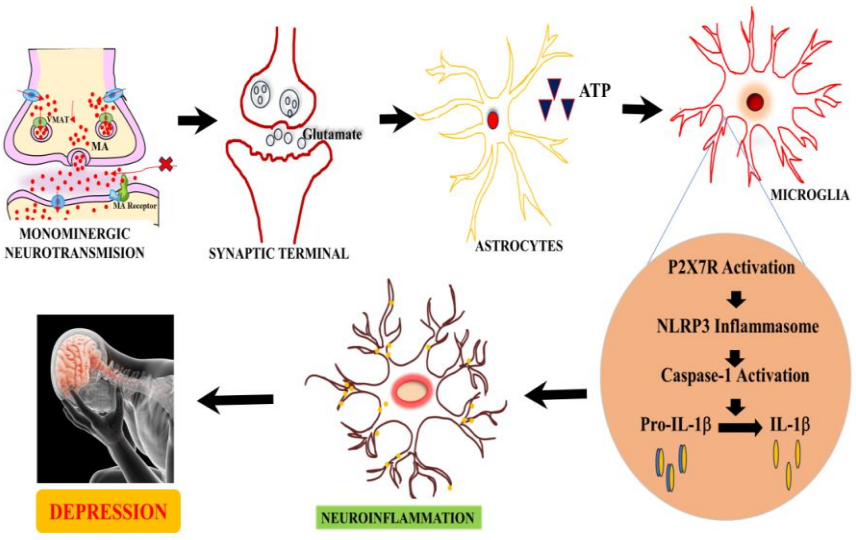

Fig 1: Pathophysiology of Depression associated Neuroinflammation (P2X7-NLRP3 Axis).

P2X7-NLRP3 Axis: *Dysregulation of monoaminergic neurotransmission triggers the release of excessive glutamate (Glu) at the synaptic terminals of neurons. This, in turn, prompts astrocytes to release a substantial amount of adenosine triphosphate (ATP). In the microglia, P2X7 receptors become activated in response to elevated extracellular ATP levels, setting off cascade reactions that result in the production of cytokines and cause depression through neuroinflammation.* (Fig 1)

P2X7 receptor in depression

P2X7 receptors, members of the ligand-gated ion channel P2X subfamily within the purinergic P2 receptors, exhibit activation in response to elevated concentrations of extracellular adenosine 5′-triphosphate (ATP). The P2X7 receptor assumes a crucial role in innate immune response, primarily by modulating the expression of proinflammatory cytokines belonging to the IL-1 family.[26] In preclinical investigations, alterations in P2X7 receptor signalling have been implicated in the mediation of depression-like behaviors. For instance, the activation of hippocampal P2X7 receptors occurs in response to a substantial increase in extracellular ATP levels during episodes of acute immobilization stress. This activation, in turn, initiates the activation of NLRP3, subsequently resulting in the release of inflammatory cytokines.[27] Psychological stress and monoamine depletion have been associated with elevated extracellular ATP levels in the brain along with excessive glutamate release from the synaptic terminal, triggering the activation of P2X7 receptors by microglia. This, in turn, contributes to CNS neuroinflammation associated depression.[28]

POLYPHENOLS IN DEPRESSION

Polyphenols are secondary metabolites found in plants and have growing scientific attention due to their potential positive impact on human health. The increasing interest in polyphenols and other phenolic compounds in food stems from their recognized antioxidative properties. The consumption of polyphenols holds promise in offering protective benefits against neurological diseases, given their robust antioxidative nature.[29] Polyphenols like curcumin, quercetin, flavonoids, ferulic acid, resveratrol, rutin, etc., among others, present a promising adjunctive approach for both preventing and treating depression. This is attributed to the multifaceted potential of polyphenols to influence various pathophysiological pathways associated with depression.[30]

Curcumin: Curcumin demonstrated the capacity to suppress the production of reactive oxygen species (ROS) and inhibit the activation of the NLRP3 inflammasome, as evidenced

by reduced expression of NLRP3 and caspase-1. This inhibition subsequently led to a decrease in the secretion of interleukin-1β (IL-1β).[31] Moreover, curcumin effectively downregulated the mRNA expression of proinflammatory cytokines, including IL-1β, IL-6, and TNF-α. Additionally, it exerted inhibitory effects on NF-κB activation and suppressed the expression of P2X7 receptors, thereby mitigating NLRP3 inflammasome activation.[32]

Quercetin: Quercetin, a flavonoid sourced from plants like apples, berries, legumes, teas, and various fruits and vegetables, has demonstrated a notable ability to diminish neuroinflammation.[33] This is achieved through the modulation of brain-derived neurotrophic factor (BDNF) and inducible nitric oxide synthase (iNOS). Consequently, quercetin not only ameliorates depressive-like symptoms but also enhances psychologically rooted behaviors and addresses neurochemical alterations associated with a depressive state.[34]

Flavonoids: Flavonoids, natural polyphenols subject to extensive pharmacological scrutiny, have been investigated for their diverse properties.[35] The elevation in the expression levels of neurotransmitters, neurotrophic factors, and the promotion of neurogenesis in the brain are posited as potential mechanisms underlying their antidepressant effects.[36]

Ferulic acid: Ferulic acid, a phenolic acid abundantly found in numerous plants, exhibits a diverse array of biological effects, encompassing anti-inflammatory, anti-epileptogenic, anticancer, and antioxidant activities.[37] Ferulic acid mitigates stress-induced depression through its anti-inflammatory activity and regulation of the HPA axis.[38]

Resveratrol: Resveratrol, a polyphenol is predominantly found in grape skins, red wine, Japanese knotweed, and peanuts.[39] Its antioxidant and anti-inflammatory properties have been extensively researched, contributing to its recognition in the realm of natural compounds with its potential neuroprotective effects. Furthermore, Resveratrol has been implicated as a neuroprotective agent capable of fostering neurogenesis.[40] Studies using animal models of depression have demonstrated that resveratrol can enhance sucrose consumption in a dose-dependent manner. This suggests that resveratrol may play a role in mitigating the decrease in reward-seeking behavior often associated with depression, highlighting its potential as a therapeutic intervention in mood disorders.[41]

ALKALOIDS IN DEPRESSION

Alkaloids, a diverse group of naturally occurring chemical compounds, are characterized by the presence of predominantly basic nitrogen atoms. Research suggests that certain alkaloids have the potential to serve as natural antidepressants.[42] Alkaloids encompassing diverse classes including mitragynine, berberine, piperine, piperidine, vinca, β-carboline, lycopodium, etc., have been found to play constructive roles in mitigating the pathophysiology of various neurological diseases, including depression. These compounds exert their therapeutic effects by acting as modulators of monoaminergic neurotransmission influencing key neurotransmitters, such as serotonin, dopamine, and norepinephrine.[43] By modulating the levels and activity of these neurotransmitters, these alkaloids contribute to the regulation of mood, cognition, and emotional well-being.[44] Research suggests that the modulation of monoaminergic neurotransmission by alkaloids may enhance synaptic plasticity, neurogenesis, and neuronal survival, thereby providing a potential avenue for addressing the underlying mechanisms of depression and other neurological disorders.[45]

Berberine: Berberine is classified within the isoquinoline class of alkaloids, characterized by its distinct bitter taste and vibrant yellow color. This compound is renowned for its therapeutic applications in diverse Ayurvedic treatments.[46] It exerts various pharmacological effects on neurological diseases, including anti-inflammatory, antioxidant, and antidepressant properties, and generates anxiolytic, antidepressant, and anti-amnesic effects while showcasing promising potential in addressing drug addiction during treatment.[47] Berberine has been shown to inhibit neuroinflammation in the hippocampus, thereby exerting antidepressant effects. Additionally, it modulates the brain's biogenic amine and nitric oxide pathways, attenuates nerve damage dysfunction and improves immune dysregulation. Specifically, berberine disrupts the NLRP3 inflammasome, contributing to its antidepressant properties.[48]

Piperine: Piperine serves as the principal alkaloid present in long pepper (Piper longum) and black pepper (Piper nigrum), both belonging to the Piperaceae family reported to have the ability to inhibit monoamine oxidase enzyme and increase the level of monoamine neurotransmitter levels.[49] Piperine has been demonstrated to reduce both immobility time and plasma nitrite levels.[50] It also exerts a neuroprotective effect by inhibiting oxidative stress and modulating both monoaminergic and GABAergic pathways.[51]

Mitragynine: Mitragynine is an alkaloid found in the leaves of the Kratom plant (Mitragyna speciosa). Researchers have reported that mitragynine has mood-enhancing and anti-depressant-like effects.[52] Mitragynine appears to exhibit a lack of acute toxicity and does not seem to induce psycho-stimulant side effects associated with hyperkinesia in the brain. The potential antidepressant-like action of mitragynine may be attributed to its ability to restore levels of monoamine neurotransmitters, including serotonin, noradrenaline, and dopamine in mice.[53]

SYNERGISTIC EFFECT OF POLYPHENOLS AND ALKALOIDS

Emerging research underscores the potential of polyphenols and alkaloids as promising natural compounds with diverse pharmacological effects that could benefit individuals with a spectrum of neurological diseases. These include Depression, Alzheimer's disease, Parkinson's disease, Huntington's disease, stroke, aging-related conditions, multiple sclerosis, amyotrophic lateral sclerosis, and various other neurological disorders.[54] The synergistic impact of polyphenols in combination with alkaloids is known bioavailability enhancer. targeting the underlying mechanisms associated with the antidepressant effects, particularly involving the monoaminergic system.[55] Accumulating evidence indicates that employing a combination strategy presents several potential advantages, including minimizing the demoralizing impact of psychiatric effects associated with therapeutic failure in depressed patients. Additionally, it may contribute to reducing withdrawal syndromes and promoting a swifter and more effective clinical response.[56]

CONCLUSION

At times, polyphenols face challenges in oral bioavailability, hindered by rapid metabolism that limits their penetration into the brain. Enhancing the systemic absorption of these polyphenols has become a significant challenge, and a potential solution lies in their combination with alkaloids. The utilization of combined compounds can yield a synergistic effect on depression-like behaviors, offering a natural alternative in the prevention of psychiatric disorders with high efficacy and minimal side effects.

ACKNOWLEDGEMENT

We extend our heartfelt gratitude to all those who contributed to the completion of this review paper.

CONFLICT OF INTEREST: Nil.

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