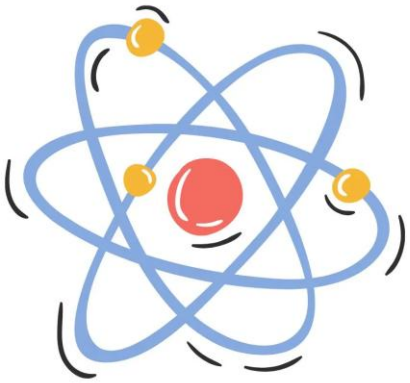

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INHIBITION OF P2X7R-DRIVEN NLRP3 INFLAMMASOME ACTIVATION BY *Dalbergia sissoo* IN EXPERIMENTAL ALZHEIMER'S DISEASE

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Abstract: *Alzheimer's disease (AD) is a progressive neurodegenerative disorder presenting memory loss, cognitive decline, synaptic dysfunction and irreparable neuronal damage. It is the most common dementia disorder in the world, and a major public health problem. Although much research has been done into this, no pharmacologic treatments yet exist that can effectively prevent or reverse disease progression and only offer symptomatic relief. The purinergic P2X7 receptor and the subsequent NLRP3 inflammasome signaling pathway have well established as key players in the regulation of neuro-inflammatory responses in AD. Extracellular ATP binding to the P2X7 receptor leads to assembly of the NLRP3 inflammasome complex. Caspase-1 activation and further increase in the production of pro-inflammatory cytokines like interleukin-1 beta (IL-1β) and interleukin-18 (IL-18), speed up the injury of neurons and disease progression. As a natural alternative remedy, medicinal plants with multi-target pharmacological activities have been an object of special interest for the treatment of AD. Dalbergia sissoo Roxb. Sheesham is a common medicinal tree of the Fabaceae family that has been traditionally utilized for inflammatory, neurological and oxidative stress disorders. Plant have shown the presence of various bioactive compounds such as flavonoids and phenolic compounds, with notable antioxidant, anti-inflammatory and neuroprotective effects. The therapeutic properties of Dalbergia sissoo can be linked to its anti-oxidative properties, down-regulation of pro-inflammatory cytokines and protection of neuronal cells from inflammatory damage. Recently increases of its phytochemical ingredients may affect ATP-mediated activation of P2X7 receptor and inhibition of NLRP3 inflammasome signalling in Alzheimer's disease. The present review aims to delve into the potential mechanism of action of Dalbergia sissoo in Alzheimer's disease (AD), focusing on the interaction between the P2X7 receptor and NLRP3 inflammasome.*

Keywords: *P2X7 Receptor, NLRP3 Inflammasome, Flavonoids, Phenolic compound, Interlukin-18(IL-18), interleukin-1 beta (IL-1β).*

1. Introduction

1.1 Global burden and unmet therapeutic needs of Alzheimer's disease

Alzheimer's disease (AD) is the most prevalent neurodegenerative disease and summarizes the primary cause of dementia all over the world. It involves a gradual loss of thinking and mental skills, memory loss, abnormal behavior, and a loss of independence (Knopman et al., 2021). With the global increase in the ageing population and in life expectancy, the ratio of Alzheimer's patients has also risen significantly. Based on estimates from the global health community, the number of persons affected by AD is now in millions, and in the next few decades it is projected to increase significantly and will be a major public health problem. The disorder is found mostly in older people, and symptoms range from mild forgetfulness and confusion to total incontinence and

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death(“2026 Alzheimer’s Disease Facts and Figures,” 2026; Knopman et al., 2021; Rabinovici, 2019). Cognitive changes that occur in AD are related to learning, reasoning, language, decision-making and executive functioning. With disease progression, there is extensive loss of neurons and disruption of synapses, which results in highly debilitating and fatal consequences(Heneka et al., 2015; Soyon Hong, 2016). Aside from the deterioration of the brain the disease of Alzheimer's affects the emotional and psychological stress of care takers and family members. Alzheimer's disease places a huge cost in terms of economics and health care. Medical services, admission, rehabilitation, and care are among the most relevant costs of the provision of health care services on a global level for the long-term period(“2026 Alzheimer’s Disease Facts and Figures,” 2026; Cummings et al., 2026; Isik, 2010; Rabinovici, 2019). As the number of AD cases is rising, the burden on health care services and social support systems has grown(Isik, 2010; Rabinovici, 2019). Although there has been much research and progress in elucidating the disease process, there are few treatments that can modify the disease. Current therapy is limited to symptomatic relief, and more effective and safe therapeutic interventions are needed to stop the progression of this disease(Di Virgilio et al., 2018; Simone et al., 2014; Yiannopoulou & Papageorgiou, 2013).

1.2 Limitations of current pharmacological interventions

Today approved pharmacological treatments for AD are mainly acetylcholinesterase inhibitors (e.g. Donepezil, Rivastigmine, and Galantamine) and NMDA receptor antagonists (e.g. Memantine)(Simone et al., 2014; Yiannopoulou & Papageorgiou, 2013). Acetylcholinesterase inhibitors in turn fix cholinergic neuro-transmission by inhibiting the action of acetylcholine-esterase, an enzyme that breaks down acetylcholine in the brain, which will temporarily enhance memory and mental skills (Knopman et al., 2021). These medications may help with symptoms for a short time, but aren't good at preventing nerve cell degeneration or disease progression. The therapeutic effects in most of the cases are minimal and temporary, particularly in mid to severe Alzheimer's disease(Long & Holtzman, 2019; Rabinovici, 2019; Soyon Hong, 2016). In addition, these drugs can cause some side effects, such as nausea and vomiting, dizziness, gastrointestinal problems, headache, and cardiovascular issues, which can affect patients' adherence(Oberoi et al., 2026; Xiao et al., 2025). The plethora of failed clinical trials testing drugs aimed at treating amyloid has also reinforced the complexity and multifactorial nature of Alzheimer’s. The multiple pathological mechanisms, such as amyloid deposition, tau hyperphosphorylation, oxidative stress,

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mitochondrial dysfunction, neuroinflammation etc. make it difficult to focus on a single molecular pathway in AD, which has led to only limited success. Hence, new therapeutic alternatives that can simultaneously regulate more than one of the pathological processes associated with the evolution of a disease are an interesting objective(Azargoonjahromi, 2024; Hampel et al., 2023; Kepp et al., 2023; Morales et al., 2013; Rawat et al., 2022; Sayas & Ávila, 2021).

1.3 Neuroinflammation as a central driver of disease progression

Today, neuroinflammation is considered one of the key pathological mechanisms that underlies the onset and the progression of Alzheimer's disease. Until recently, chronic neuroinflammation was regarded as a secondary process resulting from neuronal damage, but is now recognized to actively engage in disease progression(Heneka et al., 2015; W. Zhang et al., 2023). Activated microglial cells and astrocytes produce inflammatory mediators like cytokines, chemokines, nitric oxide and reactive oxygen species continuously(Cherry et al., 2014; Monif et al., 2010). Resident immune cells within the central nervous system (CNS), called microglia, are activated in response to the presence of amyloid beta and neuronal injury. Activated microglia produce inflammatory cytokines like tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6) and interleukin-1β (IL-1β) that help to cause dysfunction of neurons and damage to synapses(Colom-Cadena et al., 2020; Lalo & Pankratov, 2023). Episodic episodes of inflammatory response also lead to oxidative stress, mitochondrial dysfunction, and increased amyloid plaque formation, further driving a neurodegenerative vicious cycle(Heneka et al., 2015; Long & Holtzman, 2019; Tanzi, 2012). Evidence mounting suggests that the abnormal inflammatory processes are a major factor in the development of cognitive changes and neuronal loss that occur in Alzheimer's disease (AD). Modulation of neuroinflammatory signalling pathways therefore has become a potential approach to slow down disease progression and maintain neuronal function(Liddelow et al., 2017; W. Zhang et al., 2023; Zhao et al., 2019).

1.4 Purinergic signalling and role of P2X7 receptor

Dysregulated purinergic signalling is a very important player in neuroimmune communication and inflammatory processes on the central nervous system. Purinergic receptors are expressed by cells derived from cells of the immunocompetent system, such as microglial cells, in the brain. Extracellular adenosine triphosphate (ATP) is a danger associated molecular signal that activates

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these cell types(Bedetta et al., 2025; Grygorowicz & Strużyńska, 2019; Monif et al., 2009). The P2X7 receptor has been attracting special interest amongst the purinergic receptors due to its known relevance in neuroinflammation and neurodegeneration(Díaz-Hernández et al., 2009; Monif et al., 2009). P2X7 is a ligand-gated ion channel which is highly expressed on activated microglia. In pathological conditions, extracellular ATP activates the P2X7 receptor which leads to increase in intracellular calcium and potassium efflux and activates inflammatory intracellular signalling pathways(Bedetta et al., 2025; Y. H. Chen et al., 2021; Kachappilly et al., 2026). The P2X7 receptor activation stimulates the assembly of the NLRP3 inflammasome complex leading to the activation of caspase-1 and the maturation of pro-inflammatory cytokines such as IL-1β and IL-18(Di Virgilio et al., 2017; SPERLAGH et al., 2006). Chronic activation of this inflammatory pathway causes oxidative stress, mitochondrial dysfunction, synaptic failure and ultimately neuronal death in AD(Kachappilly et al., 2026). Recent study of the P2X7 receptor–NLRP3 signalling pathway clearly reveals that this pathway is of central interest in chronic neuroinflammation and is therefore a potential target for development of new drugs for treatment of the Alzheimer disease(Beltran-Lobo, Hughes, et al., 2023; Y. H. Chen et al., 2021; Dhuna, 2019; K. Zhang et al., 2025).

1.5 Rationale for multi-target herbal interventions

Alzheimer's disease is a multifactorial disease, and the underlying pathological processes are closely linked: abnormal buildup of amyloid-β, abnormal tau levels and structure, oxidative stress, impaired mitochondrial function, abnormal excitability, and chronic neuroinflammation(Heneka et al., 2015; W. Zhang et al., 2023). Despite its successes, the molecular target approach to the development of therapeutics has had restricted clinical impact mainly as they are unable to account for the complexity of disease progression. Because of its multiple modulations of pathological pathways, herbal medicines have been receiving quite a bit of attention as alternative therapeutic agents(Y. H. Chen et al., 2021; Cherry et al., 2014; Zhao et al., 2019). Various bioactive phytochemicals, such as flavonoids, alkaloids, phenolic acids, glycosides, and terpenoids, with antioxidant, anti-inflammatory, antiapoptotic, and neuroprotective activities are present in medicinal plants(Faleye et al., 2023; Ramezani et al., 2023). The compounds may have synergic effects that make them even more effective and reduce side effects. Herbal drugs tend to be better tolerated and less harmful than synthetically based medicines when used over an extended

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period(Meng-zhen et al., 2022; Vauzour et al., 2008). Their multi-target pharmacological activities make them particularly suitable for chronic neurodegenerative disorders, such as Alzheimer's disease. Thus, the search for medicinal plants that are potential controllers of neuroinflammatory signalling pathways is an emerging area within neurotherapies(Ali Esmail Al-Snafi, 2021; Bryan et al., n.d.).

1.6 Dalbergia sissoo as a promising neurotherapeutic candidate

Dalbergia sissoo Roxb., known as Sheesham or Indian rosewood, is a medicinal plant of the Fabaceae family. It grows widely in South Asia and is used traditionally in Ayurveda and other traditional system of medicine for the treatment of inflammatory disorders, skin diseases, gastrointestinal disorders and neurological disorders(Al-Snafi, 2017a). That every part of the plant (leaves, bark, roots and heartwood) has significant medicinal value. Chemical analysis of Dalbergia sissoo revealed the presence of certain phytochemical compounds such as flavonoids, phenolic compounds, tannins, glycosides, alkaloids and saponins which are biologically active(Al-Snafi, 2017a; Hossen et al., 2023; Kasa et al., 2015). These phytochemicals display potent antioxidant, anti-inflammatory, antimicrobial and neuroprotective properties. Experimental works have shown that extract of Dalbergia sissoo has potential to decrease oxidative stress, inhibition of production of inflammatory cytokines and protection of neuronal cells from oxidative and inflammatory injury(Asif & Kumar, 2009; Brijesh et al., n.d.; Sau & Handral, 2015; Swaroop & Banerjee, 2014). The neuroprotective role of Dalbergia sissoo could be linked to the modulation of inflammatory signalling pathways such as the P2X7 receptor – NLRP3 inflammasome axis. Ultimately, Dalbergia sissoo could potentially help to reduce the chronic inflammation in the brain and impairing of the neurons that are connected to Alzheimer's disease, by doing these actions in relation to oxidative stress, cytokines and the activation of microglia. Overall, Dalbergia sissoo is a potential herbal drug to be explored more in the field of Alzheimer's disease(Al-Snafi, 2017a; Asif & Kumar, 2009; Gandhi et al., 2022; Hossen et al., 2023; Sau & Handral, 2015; Sehra & Sharma, n.d.; Swaroop & Banerjee, 2014; Vanshita & Bajpai, 2023).

2. Pathophysiology of Alzheimer's disease

Alzheimer's Disease is a complex and progressive neurodegenerative disorder which involves gradual neuronal loss, synaptic dysfunction and cognitive decrease(Knopman et al., 2021; Tanzi,

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2012). The pathogenesis of AD is linked to several molecular and cellular mechanisms which are interconnected such as accumulation of amyloid-beta, hyperphosphorylation of tau, oxidative stress, mitochondrial dysfunction, and chronic neuroinflammation(Heneka et al., 2015; Long & Holtzman, 2019; Soyon Hong, 2016). All of these pathological events may be contributing to neuronal degeneration and the progression of dementia.

2.1 Amyloid cascade hypothesis

One of the most accepted hypothesis concerning the pathogenesis of Alzheimer's disease is the amyloid cascade hypothesis. This hypothesis suggests that the amyloid precursor protein (APP) is abnormally processed leading to an increased production and accumulation of amyloid-beta (Aβ) peptides in the brain(Kepp et al., 2023; Y. Zhang et al., 2023). These peptides cluster together to create extracellular amyloid plaques, which are regarded as pathological markers of AD. Amyloid beta plaques disrupt neuronal communications and synaptic transmission, causing dysfunction of synapses and a decrease in cognitive function(Balgoon et al., 2019; Sondag et al., 2009). Soluble Aβ oligomers are especially neurotoxic and interfere with synaptic plasticity, memory formation and neuronal survival. Moreover, the deposition of amyloid beta leads to the activation of inflammatory pathways, mitochondrial dysfunction and oxidative stress, accelerating the process of neurodegeneration(Sondag et al., 2009). The accumulation of amyloid plaques is a progressive process that leads to subsequent downstream pathological events that play important roles in the development and progression of Alzheimer's disease(Azargoonjahromi, 2024; Hampel et al., 2023).

2.2 Hyper-phosphorylated Tau proteins and neurofibrillary tangles.

Tau is another MA protein which regulates the stability of the neuronal cytoskeletons and axonal transport. Tau normally plays a role in maintaining the integrity and regular functioning of neurons(Rawat et al., 2022; Sayas & Ávila, 2021). Hyperphosphorylation of tau protein is associated with dissociating it from microtubules and is found to be abnormal in Alzheimer's disease. Changes in the levels of hyperphosphorylated tau within neurons lead to the development of intracellular neurofibrillary tangles (NFTs) that are another pathological hallmark of AD(Rawat et al., 2022; H. Zhang et al., 2021). These tangles hinder the movement of nutrients down the axons, cause trouble in communicating between neurons, and lead to "synaptic failure. Eventually,

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an increasing number of neurofibrillary tangles are generated which causes the degeneration and death of neurons(Paolicelli et al., 2011; Shankar & Walsh, 2009). In the case of Alzheimer's disease, there is a strong correlation with the severity of the cognitive decline and the presence of tau pathology. As abnormal tau protein spreads to other areas of the brain, memory difficulties become more severe and neurological functions become impaired. As such, genesis of NFTs and tau hyperphosphorylation are a major component of neurodegeneration observed in AD(Heneka et al., 2015; Long & Holtzman, 2019).

2.3 Oxidative stress and mitochondrial dysfunction

Oxidative stress is a key pathological factor in Alzheimer's disease, and is caused by an imbalance between the generation of reactive oxygen species (ROS) and the antioxidant defence system. Due to the high metabolic rate, the inability to regenerate and their proximity to oxygen, neurons are susceptible to oxidative damage(Ali et al., 2024; Tönnies & Trushina, 2017). Over production of ROS causes damage of cell lipids, proteins and nucleic acids leading to impaired function and life of neurons(Tönnies & Trushina, 2017). Oxidative stress is also responsible for the aggregation of amyloid-beta and hyperphosphorylation of tau, thus forming a vicious circle of neuronal damage and inflammation. Mitochondrial dysfunction in the generation of ROS and in energy metabolism impairment is crucially relevant to Alzheimer's disease(Ali et al., 2024; Raheja et al., 2021). Impaired function of damaged mitochondria is characterized by decreased production of ATP, distorted calcium controls and higher levels of oxidative stress. The disease is accelerated by abnormality of the mitochondria which further increases neuronal apoptosis and reduces their functional capabilities as synapses(Armstrong et al., 2002; Sanz & Virgilio, 2000; Tewari et al., 2024). Thus, oxidative stress/mitochondrial damage has been proposed as one of the significant factors of neurodegeneration in AD.

2.4 Neuroinflammation in Alzheimer's Disease

Inflammation of the nervous system has been identified as one of the significant pathogenic processes in Alzheimer Disease (AD). The inflammatory activity of microglia and astrocytes is chronically activated after deposition of amyloid beta and injury to neurons, causing chronic inflammatory responses in the brain(Cherry et al., 2014; de Vries et al., 1997; W. Zhang et al., 2023). Microglia, which are resident immune cells in the central nervous system, are vital in

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maintaining homeostasis of the neurons. In the progression of AD, activated microglia generate the pro-inflammatory cytokines, chemokines, nitric oxide and ROS. Likewise, activated astrocytes have a role in inflammatory signalling and neuronal dysfunction(Hanisch & Kettenmann, 2007; Monif et al., 2010).

2.5 Signaling through P2X7 Purinergic receptors and NLRP3 inflammasome signalling

Purinergic signalling is an important mechanism in the regulation of inflammatory responses in the central nervous system. After the injury or stress, release of extracellular ATP serves as DAMS and activates purinergic receptors on microglial cells(Bedetta et al., 2025; Soares-Bezerra et al., 2015). P2X7 receptors are mainly expressed on activated microglia. Increased ATP in the extracellular compartment causes activation of P2X7 receptor, leading to a variety of accompanying events, including Ca influx, K efflux, and initiation of intracellular inflammatory signalling pathways(Y. H. Chen et al., 2021; Wei et al., 2025). The P2X7R activation stimulates the assembly of NLRP3 inflammasome complex, composed of NLRP3 protein, ASC adaptor protein and pro-caspase-1. This complex formation induces the maturation and release of pro-inflammatory cytokines, e.g. interleukin-18 (IL-18) and interleukin-1β (IL-1β) through maturation of caspase-1(Francistiová et al., 2020; Huang et al., 2024; Wei et al., 2025). The P2X7 receptor-NLRP3 inflammasome axis is chronically activated, leading to oxidative stress, mitochondrial dysfunction, chronic neuroinflammation and neuronal degeneration in Alzheimer's disease. Hence, modulation of this signalling cascade has become a therapeutic target for preventing neuroinflammation-mediated damage and to halt the progression of AD(L. H. Jiang & Roger, 2020; Martin et al., 2019; Territo & Zarrinmayeh, 2021).

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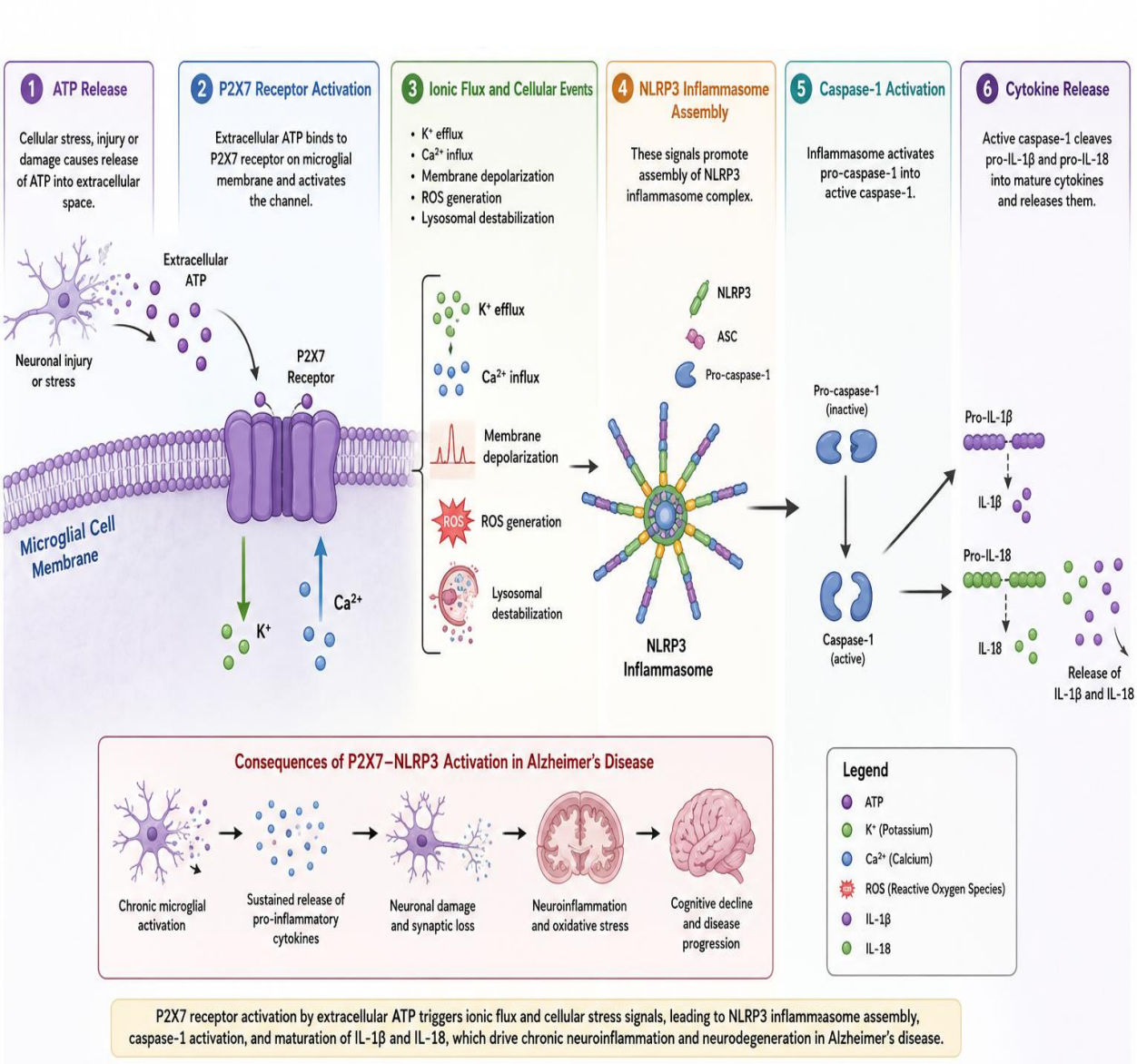

Figure 2. P2X7 Receptor–NLRP3 Inflammasome Activation

The figure demonstrates ATP-mediated activation of the P2X7 receptor on microglial cells, leading to potassium efflux, ROS generation, NLRP3 inflammasome assembly, caspase-1 activation, and release of inflammatory cytokines including IL-1β and IL-18, which contribute to chronic neuroinflammation and neuronal injury in Alzheimer's disease.

3. P2X7 receptor as a therapeutic target in AD.

The purinergic P2X7 receptor (P2X7R) has become a key molecular target in Alzheimer's disease, because of its key role in neuroinflammatory signalling and in neuronal degeneration. There is

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growing evidence that dysregulated activation of the P2X7 receptor is found in chronic inflammation, oxidative stress, dysfunction of synapses, and progressive loss of neurons as seen in Alzheimer's disease(P. Jiang et al., 2025; Ryu & McLarnon, 2008). Modulation of P2X7 receptor signalling therefore has become a focus of interest for the potential treatment of AD, as neuroinflammation is now known to play a significant role in the pathology of the disease(Beltran-Lobo, Reid, et al., 2023; Grygorowicz & Strużyńska, 2019).

3.1 Expression and function of P2X7R in CNS

P2X7 receptor is a ligand-gated ion channel of the P2X family, which is mainly activated by extracellular adenosine triphosphate (ATP). P2X7 receptors are abundantly expressed on microglial cells within the central nervous system (CNS), with lower levels of expression also seen on astrocytes and oligodendrocytes and in some neuronal sub-populations(Faria et al., 2012; Hardebo et al., 1987; Katkar, 2026). In normal physiological states, P2X7R expression is relatively low, and it plays a supporting role in maintaining immune surveillance, neurotransmitter release and cellular homeostasis. When the receptor is activated physiologically, it plays a role in regulating immune responses and neuronal communication in the brain(Godoy et al., 2019; Grygorowicz & Strużyńska, 2019; Kachappilly et al., 2026). In pathological situation, however, such as oxidative stress, trauma, amyloid-β accumulation or neurodegeneration, the concentration of ATP in the outside increases considerably, causing the longer activation of the P2X7 receptor(Y. H. Chen et al., 2021). The continued activity of P2X7R results in the influx of calcium, the efflux of potassium, the depolarization of the membrane and the activation of inflammatory signalling pathways. Receptor over-activation also facilitates mitochondrial dysfunction, production of reactive oxygen species and the assembly of inflammasomes, which allows for neuronal damage and neurodegeneration. Hence, P2X7R is emerging as a critical link connecting neuronal damage with inflammatory reactions in AD(Y. H. Chen et al., 2021; Francistiová et al., 2020; Sperlágh et al., 2002).

3.2The microglial activation and release of cytokines P2X7R.

The resident CNS immune cells called microglia are essential for maintaining neuronal homeostasis. In the context of Alzheimer 's disease, amyloid beta deposition and neuronal injury activates the microglial cell leading to increased expression and activation of the P2X7

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receptor(Grygorowicz & Strużyńska, 2019; Monif et al., 2009). If P2X7R is activated, then microglial transformation occurs by adopting pro-inflammatory phenotype which releases excessive inflammatory mediators(Bedetta et al., 2025; K. Zhang et al., 2025). NLRP3 inflammasome complex activation is stimulated by ATP mediated stimulation of P2X7R and results in caspase-1 activation and maturation of pro-inflammatory cytokines, including interleukin-1β (IL-1β) and interleukin-18 (IL-18). Moreover, activated microglia can produce tumor necrosis factor-alpha (TNF-α), nitric oxide and reactive oxygen species, which can further exacerbate neuroinflammation and neuronal damage(Islam et al., 2022; L. H. Jiang & Roger, 2020; Shieh et al., 2014). Chronic inflammatory signalling stimulated by the activation of P2X7R leads to dysfunction at the synapse, oxidative stress, mitochondrial impairment and apoptosis of neurons. A neurotoxic environment is brought about through the chronic production of IL-1β and TNF-α which accelerates cognitive decline and progression of Alzheimer's disease. Thus, the inhibition of P2X7R regarding microglial activation could be a possible therapeutic target for modulating neuro-inflammatory damage in AD(Bockstiegel et al., 2023; Lin et al., 2026).

3.3 Experimental Evidence in the Field of AD Models Targeting P2X7R

Targeting the P2X7 receptor in Alzheimer’s disease is therapeutically important as seen from several experimental studies in cellular and animal models(Kachappilly et al., 2026). The P2X7R has been implicated directly in the disease pathogenesis with increased expression reported in microglial cells located near the amyloid plaques in the AD brain(Maschio et al., 2024; Ni et al., 2013). The pharmacological blockade of P2X7R or genetic deletion of this receptor has demonstrated to prevent neuroinflammation, microglial activation, and pro-inflammatory cytokines production in animal studie(Di Lauro et al., 2022; Ryu & McLarnon, 2008)s. Excessive activation of P2X7R signalling has been correlated with increases in amyloid-beta (Aβ) deposition, impairment of synapses plasticity and decreases in cognitive performance in transgenic mouse models of Alzheimer's disease (AD). It has also been shown that blockade of the P2X7 receptor reduces oxidative stress, mitochondrial dysfunction and protects the survival of neurons in experimental models(Di Lauro et al., 2022; Ryu & McLarnon, 2008). The results are consistent with the hypothesis that modulation of P2X7R-mediated signaling pathways may delay the progression of disease and be neuroprotective in Alzheimer's disease. Synthetic P2X7 receptor antagonists and limitations

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3.4 Synthetic P2X7 receptor antagonists and limitations

There are a number of synthetic P2X7 receptor antagonists developed and studied for anti-inflammatory and neuroprotective properties. Brilliant blue G, A-740003 and other selective antagonists have shown encouraging activity in pre-clinical models that have been associated with reduced inflammasome activation, cytokine release and neuronal damage(X. Chen et al., 2014; Honore et al., 2006). However, although some very promising preclinical data have emerged, clinical translation of synthetic P2X7 antagonists has proven problematic. Poor blood–brain barrier (BBB) penetration is one major disadvantage that impedes sufficient drug delivery to the central nervous system (CNS)(de Koning et al., 2025; de Vries et al., 1997; Lee & Funk, 2023). However, many synthetic antagonists are poorly bioavailable, have short half-lives and lack selectivity. Adverse effects of long-term use of synthetics can also include hepatotoxicity, immunosuppression and off-target toxicity. Because several pathological processes are thought to underpin the pathology of Alzheimer's disease, an intervention approach that focuses on the P2X7 receptor alone may not yield the desired therapeutic effect(Y. H. Chen et al., 2021; McLarnon et al., 2006; Parvathenani et al., 2003). These restrictions have motivated scientists to find multi-target and safer therapeutic interventions. Natural, multi-target P2X7 modulators with increased safety are needed.

3.5 Need for safer, natural, multi-target P2X7 modulators

Herbal medicines possess multi-target pharmacological properties and are generally associated with improved safety and tolerability during long-term administration(Prakash Dahiya et al., 2025a). Many plant-derived compounds including flavonoids, phenolic acids, alkaloids, and tannins, exhibit anti-inflammatory, antioxidant, and neuroprotective effects. These phytochemicals can simultaneously regulate multiple pathological pathways involved in Alzheimer’s disease, including oxidative stress, mitochondrial dysfunction, cytokine production, and inflammasome activation. Herbal interventions also provide synergistic effects through interactions among multiple bioactive compounds, thereby enhancing therapeutic efficacy(Bidula et al., 2025; Fischer et al., 2014; Liang et al., 2025).

Compared to synthetic antagonists, natural P2X7 modulators may demonstrate better long-term safety profiles and reduced toxicity. Therefore, identification and development of herbal

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compounds capable of regulating P2X7 receptor–NLRP3 inflammasome signalling may provide promising therapeutic strategies for Alzheimer's disease management(Bidula et al., 2025; Riya A Nalawade et al., 2025).

Table 1. Comparison of Synthetic versus Herbal P2X7 Receptor Modulators

Compound / Extract	Type	Mechanism of Action	Therapeutic Effects	Limitations
A-740003	Synthetic antagonist	Competitive inhibition of P2X7R	Reduces IL-1β release and neuroinflammation	Poor BBB penetration
Brilliant Blue G	Synthetic dye	Blocks ATP binding to P2X7R	Suppresses microglial activation	Low selectivity and bioavailability
Curcumin	Natural phytochemical	Inhibits P2X7–NLRP3 signalling	Antioxidant and anti-inflammatory effects	Poor solubility
Resveratrol	Natural polyphenol	Downregulates P2X7R expression	Reduces oxidative stress and cytokine release	Low oral bioavailability
Dalbergia sissoo extract	Herbal extract	Multi-target modulation of inflammatory pathways	Antioxidant, anti-inflammatory, neuroprotective effects	Limited direct clinical evidence

4. Pharmacological and Phytochemical Profile of *Dalbergia sissoo*

4.1 Botanical description and ethnomedicinal significance

Dalbergia sissoo Roxb., commonly known as Sheesham or Indian rosewood, is a deciduous medicinal tree belonging to the family Fabaceae. It is widely recognized for its therapeutic importance and has been extensively used in traditional systems of medicine including Ayurveda, Unani, and folk medicine. The plant is valued not only for its durable timber but also for its

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medicinal properties associated with different plant parts such as leaves, bark, roots, flowers, and seeds(Al-Snafi, 2017b; Hossen et al., 2023; Prakash Dahiya et al., 2025a).

Taxonomy

Taxonomic Rank	**Classification**
Kingdom	Plantae
Division	Magnoliophyta
Class	Magnoliopsida
Order	Fabales
Family	Fabaceae
Genus	*Dalbergia*
Species	*Dalbergia sissoo* Roxb.

Dalbergia sissoo is native to the Indian subcontinent and is widely distributed throughout India, Pakistan, Nepal, Bangladesh, and Afghanistan. It commonly grows in subtropical and tropical regions, particularly near riverbanks and alluvial soils. Due to its medicinal and economic importance, the plant is also cultivated in several Asian and African countries(Hossen et al., 2023; Prakash Dahiya et al., 2025a).

Traditionally, *Dalbergia sissoo* has been used for the treatment of various inflammatory, infectious, gastrointestinal, and neurological disorders. Different plant extracts are utilized for management of fever, skin diseases, wounds, ulcers, diarrhea, rheumatism, and pain. In traditional medicine, the plant is also considered useful in strengthening the nervous system and improving general health(Al-Snafi, 2017a; Brijesh et al., n.d.; Hossen et al., 2023).

4.2 Traditional uses related to neurological and inflammatory disorders

In traditional medicinal systems, *Dalbergia sissoo* has been regarded as a valuable therapeutic agent for neurological and inflammatory disorders(Sehra & Sharma, n.d.; Swaroop & Banerjee, 2014). The leaves and bark extracts are believed to possess brain-stimulating and nervine tonic

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properties that may help improve mental performance and reduce weakness associated with neurological dysfunction(Qin et al., 2024; Vanshita & Bajpai, 2023).

Traditional healers have used *Dalbergia sissoo* preparations as a brain tonic for improving memory, concentration, and mental alertness. The plant has also been used in conditions associated with fatigue, stress, and age-related cognitive decline(Article et al., 2016; Raheja et al., 2021). These medicinal claims suggest possible neuroprotective and cognitive-enhancing effects of the plant(Al-Snafi, 2017b; Gandhi et al., 2022; Prakash Dahiya et al., 2025a).

Anti-inflammatory applications

Extracts of *Dalbergia sissoo* have long been used for treating inflammatory conditions such as arthritis, joint pain, swelling, and inflammatory skin disorders. The anti-inflammatory activity of the plant is mainly attributed to its flavonoids, tannins, and phenolic compounds, which help suppress inflammatory mediators and oxidative stress(Asif & Kumar, 2009; Sagar & Upadhyaya, 2010).

The traditional use of *Dalbergia sissoo* in inflammatory disorders provides scientific rationale for investigating its therapeutic role in neuroinflammation-associated diseases such as Alzheimer's disease(Al-Snafi, 2017a; Brijesh et al., n.d.; Gandhi et al., 2022; Hossen et al., 2023).

4.3 Phytochemical constituents of *Dalbergia sissoo*

Phytochemical investigations have revealed that *Dalbergia sissoo* contains a wide range of bioactive compounds responsible for its pharmacological activities(Brijesh et al., n.d.; Hossen et al., 2023; Sehra & Sharma, n.d.; Vanshita & Bajpai, 2023). Major phytochemical groups identified in the plant include flavonoids, phenolic compounds, glycosides, tannins, alkaloids, saponins, and terpenoids(Farag et al., 2001; Prakash Dahiya et al., 2025a). These compounds exhibit antioxidant, anti-inflammatory, antimicrobial, and neuroprotective activities(Brijesh et al., n.d.; Hossen et al., 2023; Sehra & Sharma, n.d.; Vanshita & Bajpai, 2023).

4.3.1 Flavonoids

Flavonoids are among the major phytochemical constituents present in *Dalbergia sissoo*. These compounds possess strong antioxidant and anti-inflammatory properties that contribute significantly to neuroprotection(Meng-zhen et al., 2022; Spencer, 2009).

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Quercetin: Quercetin is a well-known flavonoid identified in *Dalbergia sissoo*. It exhibits potent free radical scavenging activity and helps reduce oxidative stress-induced neuronal damage. Quercetin has also been reported to inhibit inflammatory cytokine production and suppress activation of inflammatory signalling pathways, including the NLRP3 inflammasome pathway(Ma et al., 2020; Minocha et al., 2022).

Kaempferol: Kaempferol is another important flavonoid present in *Dalbergia sissoo*. It demonstrates antioxidant, anti-inflammatory, and neuroprotective properties. Kaempferol helps protect neuronal cells from oxidative injury and may regulate microglial activation associated with neuroinflammation(Faleye et al., 2023; Hole & Williams, 2020; Khanna et al., 2025).

4.3.2 Phenolic compounds

Phenolic compounds present in *Dalbergia sissoo* contribute significantly to its antioxidant and anti-inflammatory effects(Al-Snafi, 2017).

Gallic acid: Gallic acid is an important phenolic compound known for its strong antioxidant activity. It protects neuronal tissues against oxidative stress by neutralizing reactive oxygen species and inhibiting lipid peroxidation(Deepali et al., 2025; Hossen et al., 2023).

Polyphenols

Polyphenolic compounds present in *Dalbergia sissoo* exhibit significant neuroprotective effects through modulation of inflammatory responses and oxidative stress pathways. These compounds may help maintain mitochondrial integrity and improve neuronal survival(Hossen et al., 2023).

4.3.3 Glycosides, tannins, and alkaloids

Dalbergia sissoo also contains glycosides, tannins, alkaloids, and other secondary metabolites that contribute to its therapeutic effects(Brijesh et al., n.d.; Farag et al., 2001; Vanshita & Bajpai, 2023). Glycosides possess anti-inflammatory and membrane-stabilising activities, while tannins exhibit antioxidant and antimicrobial properties. Alkaloids present in the plant may influence neurotransmitter activity and central nervous system function. Collectively, these bioactive compounds contribute to the multi-target pharmacological profile of *Dalbergia sissoo*(Al-Snafi, 2017; Farag et al., 2001; Vauzour et al., 2008; Yu et al., 2016).

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Table 2. Phytochemicals Isolated from *Dalbergia sissoo* and Their Biological Activities

Category	Compound Name	Chemical Class	Reported Biological Activity
Flavonoid	Kaempferol	Flavonol	ROS scavenging, anti-inflammatory activity
Phenolic compound	Gallic acid	Polyphenol	Antioxidant and free radical scavenging
Tannin	Tannic acid	Polyphenolic tannin	Anti-inflammatory and antimicrobial activity
Glycoside	Sissooside	Glycoside	Membrane stabilization and anti-inflammatory effects
Alkaloid	Various alkaloids	Nitrogen-containing compounds	CNS modulation and neuroprotection

4.4 Pharmacological activities relevant to neuroprotection

The pharmacological activities of *Dalbergia sissoo* are closely associated with mechanisms involved in neurodegeneration and Alzheimer's disease pathology. The plant demonstrates anti-inflammatory, antioxidant, and neuroprotective properties that may help reduce neuronal damage and cognitive impairment(Asif & Kumar, 2009; Prakash Dahiya et al., 2025a; Sau & Handral, 2015; Vanshita & Bajpai, 2023).

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4.4.1 Anti-inflammatory activity

Dalbergia sissoo exhibits significant anti-inflammatory activity through suppression of inflammatory mediators and cytokines. Experimental studies have demonstrated reduction in pro-inflammatory cytokines such as IL-1β, TNF-α, and IL-6 following administration of plant extracts(Asif & Kumar, 2009; Sagar & Upadhyaya, 2010; Yu et al., 2016). The anti-inflammatory effects are mainly attributed to inhibition of inflammatory signalling pathways and suppression of microglial activation by reducing chronic inflammatory responses. *Dalbergia sissoo* may help prevent neuronal injury associated with Alzheimer's disease(Asif & Kumar, 2009; Boongird et al., 2025; Prakash Dahiya et al., 2025).

4.4.2 Antioxidant activity

The antioxidant activity of *Dalbergia sissoo* is primarily mediated by flavonoids and polyphenolic compounds that neutralize reactive oxygen species (ROS) and reduce oxidative stress.Plant extracts have been shown to enhance endogenous antioxidant defense systems including superoxide dismutase, catalase, and glutathione peroxidase. Reduction of oxidative stress helps preserve mitochondrial function and neuronal membrane integrity(Deepali et al., 2025; Jain et al., 2025).

4.4.3 Neuroprotective and cognitive-enhancing effects

Experimental studies suggest that *Dalbergia sissoo* possesses neuroprotective and cognitive-enhancing properties. Plant extracts have demonstrated beneficial effects on learning ability, memory retention, and neuronal survival in animal models(Swaroop & Banerjee, 2014). Neuroprotective activity may result from combined antioxidant and anti-inflammatory mechanisms, along with regulation of neuronal signalling pathways. By suppressing oxidative stress and inflammatory damage, *Dalbergia sissoo* may help preserve synaptic function and reduce progression of neurodegeneration associated with Alzheimer's disease(Al-Snafi, 2017a; Swaroop & Banerjee, 2014).

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5. Proposed Mechanistic Interplay Between *Dalbergia sissoo* and the P2X7–NLRP3 Axis

Neuroinflammation in Alzheimer's disease is mediated through complex molecular pathways involving immune activation, oxidative stress, and inflammatory signalling. Among these mechanisms, the ATP-mediated P2X7 receptor–NLRP3 inflammasome pathway plays a central role in amplifying chronic neuroinflammatory responses and neuronal degeneration(Y. H. Chen et al., 2021; Fan et al., 2020; Heneka et al., 2015). The phytochemical constituents of *Dalbergia sissoo* possess significant antioxidant and anti-inflammatory properties that may interfere with multiple stages of this signalling cascade(Hossen et al., 2023; Prakash Dahiya et al., 2025; Sau & Handral, 2015). Therefore, *Dalbergia sissoo* may function as a multi-target neuroprotective agent capable of modulating neuroinflammation and neuronal injury associated with Alzheimer's disease(Swaroop & Banerjee, 2014).

5.1 ATP-induced P2X7 receptor activation and downstream signalling

Extracellular adenosine triphosphate (ATP) acts as an important danger-associated molecular signal released from damaged or stressed neurons during neurodegeneration. Elevated extracellular ATP concentrations activate the P2X7 receptor present predominantly on microglial cells in the central nervous system(L.-H. Jiang et al., 2021; Muñoz et al., 2021; Tewari et al., 2024).

Activation of the P2X7 receptor causes rapid ionic imbalance characterized by calcium influx and potassium efflux across the cell membrane(Karmakar et al., 2016). This ionic disturbance leads to membrane depolarization and initiation of downstream inflammatory signalling pathways. Sustained activation of P2X7R also promotes mitochondrial dysfunction and excessive generation of reactive oxygen species (ROS)(D'amico et al., 2021; Lenertz et al., 2009).

ROS generation contributes significantly to oxidative stress, cellular injury, and activation of inflammasome signalling pathways. In addition, prolonged P2X7 receptor stimulation enhances microglial activation and release of inflammatory mediators, thereby intensifying neuronal damage and synaptic dysfunction in Alzheimer's disease(Aktary et al., 2025; D'amico et al., 2021; Lenertz et al., 2009).

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5.2 Role of NLRP3 inflammasome in neurodegeneration

The NLRP3 inflammasome is a multiprotein inflammatory complex involved in regulation of innate immune responses and neuroinflammation. Activation of the NLRP3 inflammasome occurs in response to ATP-mediated P2X7 receptor stimulation, mitochondrial dysfunction, oxidative stress, and amyloid-beta accumulation(D'amico et al., 2021; Karmakar et al., 2016; Y. Zhang et al., 2020). The inflammasome complex consists of NLRP3 protein, ASC adaptor protein, and pro-caspase-1. Assembly of this complex results in activation of caspase-1, an important inflammatory enzyme responsible for processing immature cytokines into their active forms(Bockstiegel et al., 2023; Heneka et al., 2013).

Activated caspase-1 promotes maturation and release of pro-inflammatory cytokines such as interleukin-1β (IL-1β) and interleukin-18 (IL-18). These cytokines contribute to chronic neuroinflammation, synaptic dysfunction, neuronal apoptosis, and progression of neurodegeneration in Alzheimer's disease(Bai & Zhang, 2021; Mariathasan et al., 2004; McManus & Latz, 2024). Persistent activation of the NLRP3 inflammasome establishes a vicious inflammatory cycle that further enhances oxidative stress, amyloid-beta toxicity, and neuronal injury. Consequently, inhibition of NLRP3 inflammasome activation has emerged as an important therapeutic strategy for controlling neuroinflammatory damage in AD(Bai & Zhang, 2021; Li & Gong, 2025).

5.3 Evidence supporting phytochemical modulation of P2X7R and NLRP3

Bioactive compounds present in *Dalbergia sissoo*, particularly flavonoids and phenolic compounds, exhibit strong antioxidant and anti-inflammatory activities that may interfere with ATP-mediated inflammatory signalling(Deepali et al., 2025; Hossen et al., 2023). Flavonoids such as quercetin and kaempferol have been reported to inhibit microglial activation, suppress inflammatory cytokine production, and reduce oxidative stress(Minocha et al., 2022; Spencer, 2009). These compounds may inhibit ATP-induced P2X7 receptor activation and prevent ionic imbalance associated with inflammasome assembly.

In addition, phytochemicals present in *Dalbergia sissoo* may suppress reactive oxygen species generation and mitochondrial dysfunction, thereby reducing activation of the NLRP3 inflammasome complex due to Their anti-inflammatory mechanisms include inhibition of

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inflammatory transcription factors, reduction of cytokine release, and suppression of microglial-mediated neuronal toxicity(Hossen et al., 2023; Vanshita & Bajpai, 2023). Although direct experimental evidence involving *Dalbergia sissoo* and P2X7–NLRP3 signalling in Alzheimer's disease remains limited, the known pharmacological activities of its phytochemicals strongly support its potential neuroprotective role.

5.4 Comparative mechanisms with other natural P2X7/NLRP3 inhibitors

Several natural compounds have demonstrated the ability to regulate P2X7 receptor signalling and inhibit NLRP3 inflammasome activation in neurodegenerative disorders(Bidula et al., 2025).

Curcumin: Curcumin, a polyphenolic compound derived from *Curcuma longa*, exhibits potent antioxidant and anti-inflammatory activities(Faria et al., 2012; Nuka et al., 2018). Experimental studies have shown that curcumin suppresses activation of the P2X7 receptor and inhibits assembly of the NLRP3 inflammasome complex. Curcumin also reduces production of inflammatory cytokines, oxidative stress, and neuronal apoptosis, thereby improving cognitive function in Alzheimer's disease models(Faria et al., 2012; Fischer et al., 2014; Liang et al., 2025).

Resveratrol: Resveratrol, a natural polyphenol present in grapes and berries, has also demonstrated neuroprotective effects through modulation of inflammatory signalling pathways. Resveratrol suppresses P2X7 receptor expression, inhibits inflammasome activation, and reduces release of IL-1β and TNF-α. In addition, it protects neurons against oxidative stress and mitochondrial dysfunction(Bissacotti et al., 2025; Chiang et al., 2025; Feng & Zhang, 2019).

Similar to curcumin and resveratrol, phytochemicals present in *Dalbergia sissoo* may exert neuroprotective effects through simultaneous regulation of oxidative stress, inflammatory signalling, and inflammasome activation(Bissacotti et al., 2025; Chiang et al., 2025; Faria et al., 2012; Feng & Zhang, 2019; Fischer et al., 2014). The multi-component phytochemical profile of *Dalbergia sissoo* may provide synergistic therapeutic benefits compared to single-compound interventions.

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6. Integrative Perspective and Future Research Directions

The current increased knowledge of the importance of neuroinflammation in Alzheimer's disease has led to the desire to find new therapeutic compounds that can target several different pathways in the pathology simultaneously(Förstl & Kurz, 1999). The results have demonstrated the high antioxidant, anti-inflammatory, and neuroprotective properties of Dalbergia sissoo, which could have potential therapeutic applications in neurodegenerative diseases(Gandhi et al., 2022). While, there is initial pharmacological evidence to suggest that it may have medicinal value, there is still much work to do before it can be clinically significant in the management of Alzheimer's disease.

6.1 Gaps in current evidence and need for experimental validation

Further studies should be done to validate the molecular mechanism of neuroprotection of D. sissoo especially modulation of P2X7 receptor-NLRP3 inflammasome signalling pathway(Aktary et al., 2025; Grygorowicz & Strużyńska, 2019; Herdiana, 2025). Moreover, advanced formulation strategies and translational studies are needed to enhance therapeutic-efficacy and clinical-applicability. To date, there is a lack of evidence to fill in the missing pieces and further experimental validations are still needed(Aktary et al., 2025; D. Chen & Sun, 2025). The antioxidant and anti-inflammatory features of Dalbergia sissoo have been highlighted; however direct experimental studies to assess its therapeutic efficacy in Alzheimer's disease are few(Simone et al., 2014; Stanciu, 2025). The studies currently available focus mainly on the general pharmacological activities including anti-inflammatory, antimicrobial, hepatoprotective and antioxidant activity; with little or no attention on specific neurodegenerative activities(Prakash Dahiya et al., 2025). Well-designed in vivo and in vitro study is missing on direct interaction of the phytochemical constituents of Dalbergia sissoo with the P2X7 receptor–NLRP3 inflammasome pathway in the models of Alzheimer's disease and Physiologic validation by transgenic animal models of AD, neuronal cell culture, and mechanistic studies based on biomarkers is needed to validate its proposed neuroprotective effects. Further research should confirm the evaluation of parameters like inflammatory cytokines, oxidative stress markers, amyloid beta burden, synaptic integrity, mitochondrial function and cognitive performance after dalbergia sissoo extracts or isolated phytochemicals(Aktary et al., 2025; Ayodele et al., 2021; D. Chen & Sun, 2025; Simone et al., 2014; Yiannopoulou & Papageorgiou, 2013). These studies will

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give better scientific data to support the use of it for therapeutic purposes in neurodegenerative disease.

6.2 Challenges in translation

While the pharmacological potential of Dalbergia sissoo has shown some promise, different challenges have to be surmounted before its clinical application can be realised(Deepali et al., 2025). These limitations are associated with low bioavailability, variation in phytochemical composition and non-standardization of the therapeutic formulations(D. Chen & Sun, 2025; Hossen et al., 2023).

6.2.1 Bioavailability and pharmacokinetics

A drawback of phytochemicals derived from plants is their inability to be well absorbed in the human stomach and intestine(Al-Snafi, 2017b; Sehra & Sharma, n.d.). The flavonoids and phenolic compounds which are available in Dalbergia sissoo have low water solubility, poor absorption, rapid metabolism, and low systemic circulation(Deepali et al., 2025; Spencer, 2009; Vauzour et al., 2008). The utility of these drugs for therapeutic use may be limited by these pharmacokinetic properties, and the drugs may not be delivered adequately to the brain. Furthermore, the crossing of the blood-brain barrier (BBB) is a great problem in the treatment of neurodegenerative diseases. The failure to reach adequate levels in the central nervous system could mean that bioactive compounds do not adequately enter the CNS to regulate the neuro-inflammatory pathways(de Koning et al., 2025; de Vries et al., 1997). It is therefore necessary to conduct comprehensive studies over the absorption, distribution, metabolism, excretion and BBB permeability of the phytochemicals from Dalbergia sissoo(de Koning et al., 2025; Raheja et al., 2021). Optimization of drug delivery systems and dosing strategies will also be crucial to enhance the therapeutic outcomes.

6.2.2 Standardization and quality control

Standardization of herbal medicines represents another major challenge in translational research. The phytochemical composition of *Dalbergia sissoo* may vary depending on geographical origin, environmental conditions, harvesting methods, and extraction procedures(Gandhi et al., 2022).

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Variability in phytochemical content can lead to inconsistencies in therapeutic efficacy and reproducibility of experimental results(Gandhi et al., 2022). Therefore, maintaining batch-to-batch consistency is essential for development of reliable and clinically acceptable herbal formulations(Gandhi et al., 2022; Sau & Handral, 2015).

Advanced phytochemical profiling techniques such as high-performance liquid chromatography (HPLC), mass spectrometry, and spectroscopic analysis should be employed for identification and quantification of major bioactive compounds. Standardization based on specific phytochemical markers would help ensure quality control, safety, and therapeutic consistency of *Dalbergia sissoo*-based formulations(Article et al., 2016; Brijesh et al., n.d.; Gandhi et al., 2022; Swaroop & Banerjee, 2014).

6.3 Advanced strategies for enhanced efficacy

To overcome translational limitations and improve therapeutic efficacy, advanced pharmaceutical and nanotechnological approaches should be explored for delivery of *Dalbergia sissoo* phytochemicals.

6.3.1 Nanoformulations and targeted delivery

Herbal compounds can be improved in their bioavailability and brain-targeting efficiency with use of nanotechnology-based drug delivery system (NDDDS)(Herdiana, 2025; Kaczmarek-Hajek et al., 2018). Phytochemicals of D. sissoo could be improved with the advantage of solubility, stability, and controlled release by encapsulation in the form of nanoparticles, liposomes, nano emulsions, or polymeric carriers(Vanshita & Bajpai, 2023). Nanoparticles are potential nanocarriers to overcome the blood-brain barrier and target the neuronal tissues with bioactive compounds. Likewise, liposomal formulations might help resist degradation of phytochemicals and prolong their time in systemic circulation(Article et al., 2016; Herdiana, 2025; Vanshita & Bajpai, 2023). Finally, specific delivery systems could minimize unwanted activity and enhance therapeutic efficacy by specifically regulating inflammatory signalling pathways associated with Alzheimer's disease(Herdiana, 2025). Thus, adapting such nanoformulation strategies could perhaps be a great deal in delivering clinical application of Dalbergia sissoo; which could be very interesting in neurodegenerative disorders.

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6.3.2 Synergistic phytochemical combinations

Synergistical effect between many of the active ingredients present in the seed might exert a reinforcing effect, thus increasing the therapeutic efficacy of Dalbergia sissoo(Al-Snafi, 2017b). The combined actions of flavonoids, phenolic compounds, tannins, and alkaloids found in the plant could play a role in managing oxidative stress, inflammatory pathways, mitochondrial dysfunction, and apoptosis of neurons(Brijesh et al., n.d.; Farag et al., 2001; Hossen et al., 2023; Sehra & Sharma, n.d.). Phytochemical synergism has the potential to enhance inhibition of inflammatory cytokines, decrease oxidative stress and increase neuronal survival(Hossen et al., 2023). Using a network pharmacology and systems biology perspective might help guide the identification of potential synergistic interactions between phytochemicals in order to better understand the multi-target therapeutic mechanisms(Sehra & Sharma, n.d.). This may help in formulating effective herbal medicine for managing Alzheimer's Disease.

6.4 prospects for clinical studies and clinical relevance.

The increasing setting of neuroinflammation as a therapeutic effects goal in Alzheimer's disease supplies powerful motivation for considering the interventions utilizing Dalbergia sissoo in a scientific atmosphere(Angioni et al., 2024; Förstl & Kurz, 1999). It is currently based on preliminary experimental findings of its antioxidant, anti-inflammatory and neuroprotective properties, indicating substantial translational potential. Future research should be aimed at investigating the safety, tolerability, pharmacokinetics and therapeutic efficacy of a standardized formulation of Natural Plants in mild cognitive impairment and Alzheimer's disease patients(Colom-Cadena et al., 2020; Territo & Zarrinmayeh, 2021; J. Zhang et al., 2024). With a focus on inflammatory mediators, oxidative stress parameters, amyloid-beta burden, and cognitive performance, biomarker-based studies may offer insightful information regarding the status of treatments(Aktary et al., 2025; Colom-Cadena et al., 2020). The use of more controlled systems of drug delivery and well-defined phytochemical formulations could prove useful in the course of clinical trials and help the researchers who are trying to convert the usefulness of *Dalbergia sissoo* into a therapeutic use as an adjuvant or complementary treatment in neurodegenerative conditions(Brijesh et al., n.d.; Gandhi et al., 2022; Prakash Dahiya et al., 2025a). This merging of ancient traditional healing practices and contemporary neuroscience research could thus aid in the formulation of more effective and safe therapeutic approaches to Alzheimer's disease.

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7. Conclusion

Dalbergia sissoo is a highly promising, multi-target herbal therapy for Alzheimer's disease, rich in bioactive phytochemicals that provide robust antioxidant, anti-inflammatory, and neuroprotective defenses. A core mechanism of its efficacy is the modulation of the ATP-mediated P2X7–NLRP3 inflammasome axis. By suppressing this pathway, D. sissoo constituents prevent caspase-1 activation and the release of toxic pro-inflammatory cytokines like IL-1β and IL-18, thereby halting microglial hyperactivation and protecting neurons.

This multi-target botanical approach offers reduced toxicity and improved long-term safety compared to single-target synthetic antagonists. Although comprehensive clinical trials, standardized formulations, and innovative drug delivery methods are still required to fully validate its clinical efficacy, D. sissoo demonstrates extraordinary translational potential, successfully uniting traditional herbal medicine with modern neurotherapeutics.

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