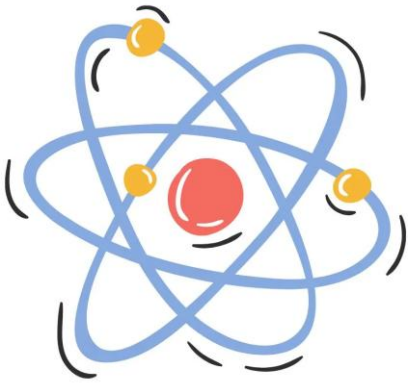

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Abstract: *Alzheimer's disease (AD) is a progressive neurodegenerative disorder marked by cognitive decline, synaptic dysfunction, and irreversible neuronal loss. Despite extensive research, currently approved pharmacological therapies offer only symptomatic relief and fail to halt disease progression. Increasing evidence identifies chronic neuroinflammation, particularly microglia-driven inflammatory signaling, as a central contributor to AD pathology. Among inflammatory regulators, the purinergic P2X7 receptor and downstream NLRP3 inflammasome axis play a pivotal role in sustaining neuroinflammatory cascades, oxidative stress, and neuronal damage. Consequently, this signaling axis has emerged as a promising therapeutic target. Herbal medicines, with their intrinsic multi-target pharmacology and favorable safety profiles, offer an alternative strategy for addressing the multifactorial nature of AD.* Cuscuta reflexa *Roxb. (Amarbel), a parasitic medicinal plant widely used in traditional systems of medicine, is rich in flavonoids, phenolic acids, glycosides, alkaloids, and lignans with documented anti-inflammatory, antioxidant, and neuroprotective properties. This review critically examines the neurotherapeutic potential of* Cuscuta reflexa *as a multi-target modulator of the P2X7–NLRP3 inflammasome axis in Alzheimer's disease. We integrate evidence from AD pathophysiology, purinergic signaling, phytochemistry, and experimental pharmacology to propose a mechanistic framework through which* Cuscuta reflexa *may attenuate chronic neuroinflammation, preserve synaptic integrity, and support neuronal survival. Finally, translational challenges, formulation strategies, and future research directions are discussed to support the development of* Cuscuta reflexa*-based interventions for neurodegenerative disorders.*

Keywords: *Alzheimer's disease, Cuscuta reflexa, P2X7 receptor, NLRP3 inflammasome, Neuroinflammation*

1. Introduction

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

The most common neurodegenerative disorder in the entire world and the major cause of dementia is the Alzheimer disease (AD) disease. It is a significant and emerging public health issue because of rising longevity of life and ageing populations (1)**.** This disease is associated with slowing down of cognition, deterioration of memory and behavioral disruptions, and loss of functional independence leading to severe disability and death (21). The socioeconomic impact of AD is enormous not only to patients but to caregivers and medical care provision due to the long-term care needs and the rising treatment expenses as well (22). Even with decades-old research efforts, there has not yet been a result of efficient disease-modifying treatment that would tackle the issue of rising incidence of AD across the globe, which creates a gaping gap between the escalating global AD problem and the efficacy of treatment intervention, which has remained unsuccessful.

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1.2 Limitations of current pharmacological interventions

The existing pharmaceutical interventions, which have been approved in the management of AD, are mainly acetylcholinesterase inhibitors and N-methyl-D-aspartate receptor antagonists (23). The drugs are only symptomatic and they do not substantially change the course of the disease and underlying neurodegenerative processes (2). These have only moderate clinical effects, temporal and are usually accompanied by side effects like gastrointestinal abnormalities, dizziness and cardiovascular side effects. In addition, most patients are not very responsive especially during moderate to advanced phases of the illness (24). The recurrent unsuccessfulness of multiple amyloid-targeting agents in late-stage clinical test has even more clearly underscored the constraints of united-target-curative approaches, as well as the suggestion to consider additional treatments that would cure the multiplexed malady that constitutes AD (pathology) (25).

1.3 Neuroinflammation as a central driver of disease progression

Neuroinflammation is currently identified as a primary pathology of the Alzheimer disease and not a byproduct of the neurological damage. Prolonged stimulation of microglia, astrocytes results in persistent production of pro-inflammatory cytokines, chemokines, and reactive oxygen species which establishes a neurotoxic microenvironment (3). The continuous stimulation of inflammatory signals enhances deposition of amyloid-B, hyperphosphorylation of tau, harm of synapses and rapid loss of neurons (26). According to growing evidence, dysregulated neuroinflammation has a pivotal role in the onset and progression of AD and as a result, inflammatory pathways are considered attractive as targets of therapeutic intervention (27).

1.4 Purinergic signaling and the role of the P2X7 receptor

The role of purinergic signaling has become one of the major regulators of neuroimmune responses in the central nervous system (28). Extracellular ATP that is released with neuronal injury or metabolic stress is a danger signal, which activates microglial receptors (4). Among them, the P2X7 receptor holds the special significance since this protein is highly expressed on the microglia and it increases the effect of inflammatory cascades. Activation of the P2X 7 receptor triggers ionic imbalance, mitochondrial dysfunction, and NLRP3 inflammasome assembly, which in turn causes caspase-1 activation and maturation of pro-inflammatory

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cytokines, including interleukin-1 80(29). Sustained neuroinflammation and neurodegeneration during Alzheimer disease has been strongly linked to the signaling of P2X7 receptors meaning it makes a good molecular target.

1.5 Rationale for multi-targeted herbal interventions

Alzheimer disease has several interrelated pathology along with amyloid aggregation, tau pathology, oxidative stress, mitochondrial dysfunction, and chronic neuroinflammation (30). Focusing on one molecule pathway has no longer been effective in stopping the progression of the disease (31). Multi-targeted treatment methods are more popular in this regard. Herbal drugs and compounds derived as a result of plants provide natural pharmacological diversity in that there are many pathways that can be simultaneously altered (5). Phytochemicals have several anti-inflammatory, antioxidant, and neuroprotective effects, enhanced tolerability, and long-term safety. These include features that render herbal interventions especially appropriate with complicated chronic neurodegenerative conditions including AD.

1.6 *Cuscuta reflexa* as a promising neurotherapeutic candidate

Cuscuta reflexa Roxb., often referred to as Amarbel is a medicinal plant that is the presence of that is extensive in the system of traditional medicine. Phytochemical studies have shown the existence of flavonoids, phenolic acid, glycoside, alkaloids, and lignans with known anti-inflammatory and antioxidant effects (32). The results of experimental researches indicate that Cuscuta reflexa has neuroprotective activity due to the regulation of oxidative stress, inflammatory mediators, and neuronal signaling pathways (33). Considering its excellent phytochemical character and biological effects, Cuscuta reflexa is an excellent multi-target herbal contender in the control of neuroinflammatory processes, specifically the P2X7 receptorNLRP3 inflammasome, in Alzheimer disease.

2. Pathophysiology of Alzheimer's Disease

Alzheimer disease (AD) is a multifactorial and complicated neurodegenerative disease that is progressive in nature and is characterized by the loss of neurons, abatement of synapses and cognitive deterioration(6)**.** Its pathogenesis is the combination of multiple molecular and cellular responses, which are the abnormal aggregation of proteins, oxidative stress,

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mitochondrial dysfunction, and chronic neuroinflammation (34). These mechanisms are highly interrelated and jointly promote the development of diseases and their course.

2.1 Amyloid cascade hypothesis

Amyloid cascade hypothesis is one of the oldest and most popular models of pathogenesis of AD (35). It hypothesizes that an excessive production and accumulation of amyloid-2 peptides in the brain result because of abnormal processing of amyloid precursor protein (36). These peptides are clustered in extracellular amyloid plaques, ultimately breaking the relationship of synapses and deteriorating the work of neurons **(**7). Soluble amyloid- B oligomers have been suggested to be neuro-toxic with respect to obstructing synaptic plasticity and memory formation (37). Downstream events that are initiated by deposition of amyloid substrate also include oxidative stress, tau pathology, and cellular neuroinflammatory responses and, consequently, are initiating factors in the disease cascade (38).

2.2 Tau hyperphosphorylation and neurofibrillary tangles

Tau is the microtubule-related protein that is vital in ensuring neuronal cytoskeleton and axonal transportation (39). Adequate hyperphosphorylation of the tau occurs in AD, leading it to dissociate with microtain tubules and form intracellular neurofibrillary tangle (40). These tangles cause the impairment of axonal transport, loss of synaptic integrity, and eventually issue with the neuronal death (41)**.** Cognitive decline and disease severity is similar to the regional locationand load of tau pathology and tau dysfunction is postulated to be a central determinant of neurodegeneration in AD (42).

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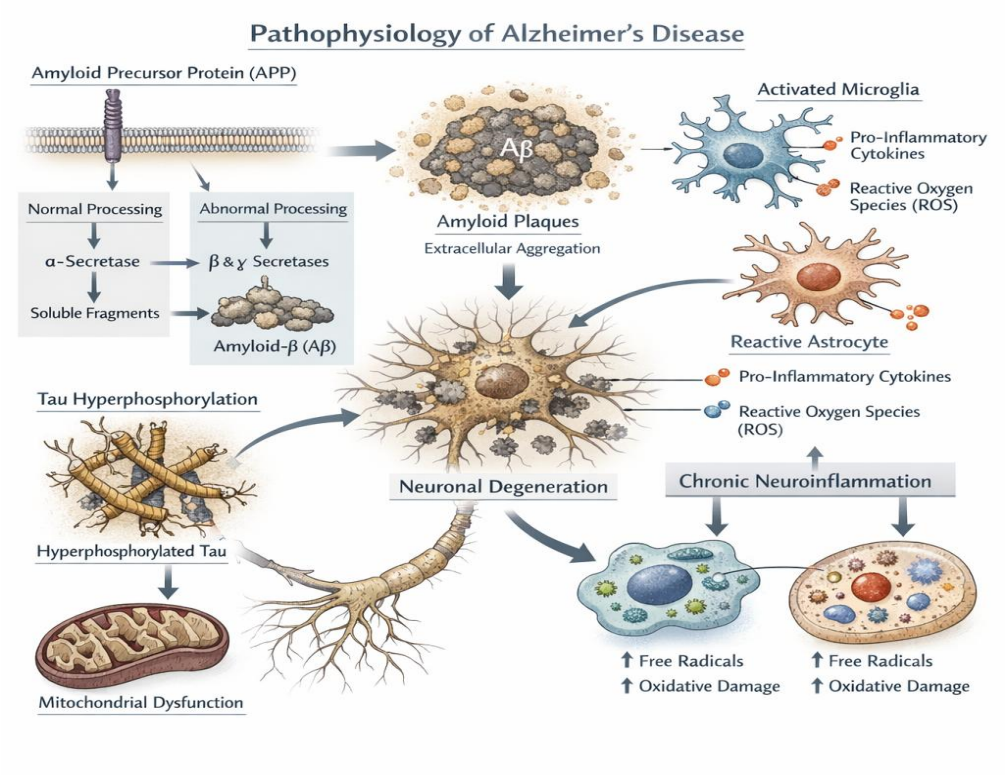

Figure 1. Pathophysiology of Alzheimer's Disease

Source:-(26) **Inflammatory process in Alzheimer's disease. Journal:** ***Frontiers in Integrative Neuroscience. https://www.frontiersin.org/articles/10.3389/fnint.2013.00059/full***

2.3 Oxidative stress and mitochondrial dysfunction

Another characteristic feature of the Alzheimer disease is oxidative stress, which is the result of the violation of the ratio of the quantity of reactive oxygen species generated and antioxidant defense systems maintained (43). Oxidative damage of neurons is especially susceptible because of the high metabolic rate and the inability of cells to regenerate (44). mitochondrial dysfunction Mitochondrial dysfunction is an important factor in oxidative stress and may induce energy metabolism deficiency and promote the production of reactive oxygen species (45). Further mechanisms of degradation of neurons and hastens the onset of the disease include oxidative damage of lipids, proteins, and nucleic acids **(**8**).** The accumulation of Amyloid- 2 and tau have been demonstrated to damage mitochondrial activity forming vicious cycle of energy deficiency and oxidative damage.

2.4 Neuroinflammatory mechanisms in Alzheimer's disease

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Chronic neuroinflammatory is now considered one of the key AD pathology. The chronic stimulation of microglia and astrocytes leads to the sustained release of the pro-inflammatory cytokines, chemokines, and reactive oxygen species (9). Although acute responses to inflammation can have a protective effect in the early phases, chronic neuroinflammation can be harmful, which facilitates synaptic loss, neuronal damage, and increases amyloid and tau pathology (46). Genetic and experimental literature is converging toward the opinion lately that dysregulated innate immune responses actively participate in the development of diseases and not passively react to the underlying pathology.

2.5 Purinergic P2X7 receptor and NLRP3 inflammasome signalling

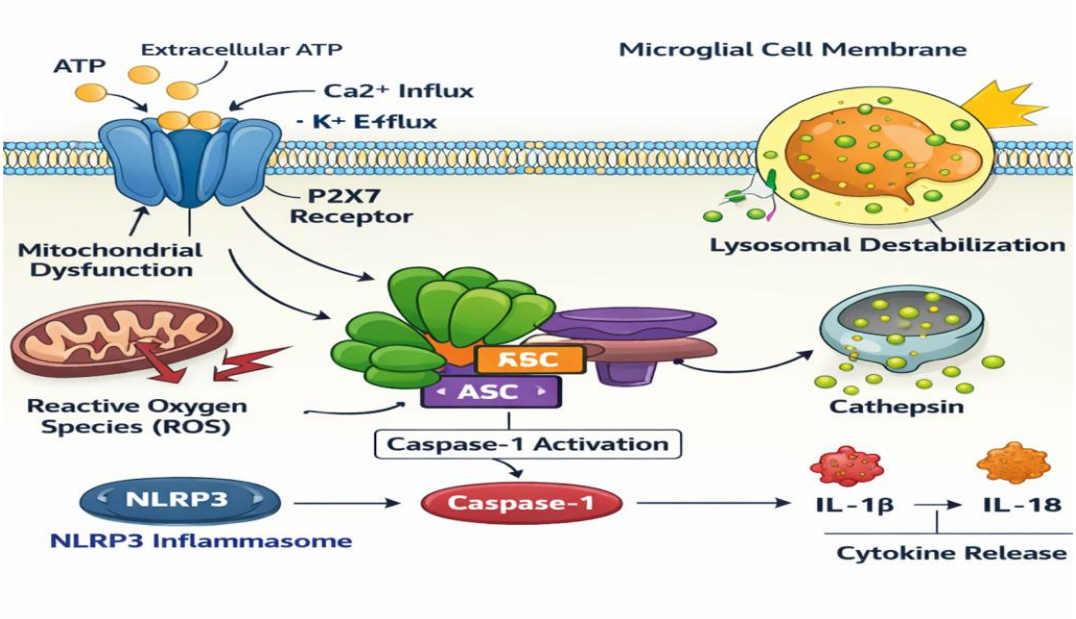

Figure 2. P2X7 Receptor–NLRP3 Inflammasome Activation

Source:-(29) **P2X7 as a common therapeutic target in brain diseases Journal:** ***Frontiers in Molecular Neuroscience***

https://www.frontiersin.org/articles/10.3389/fnmol.2021.662585/full

Purinergic signaling has a fundamental role in the neuromuscular interaction control in the AD brain 47. Extracellular adenosine triphosphate is secreted during neuronal stress or injury, which is treated as a danger signal which activates microglial purinergic receptors (48). The most significant ones include the P2X7 receptor, which is associated with the enhancement of inflammatory reactions. The resulting action of the P2X7 receptor stimulation results in ionic flux, mitochondrial harm, and inflammasome complex of NLRP3, which contributes to

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caspase-1 activation and maturation of pro-inflammatory cytokines, including interleukin-12ness-illa-1 and interleukin-18 49. Continuous stimulation of the P2X7 - NLRP3 signaling axis is implicated in persistent neuroinflammation, synaptic dysfunction and neuronal loss, which underscores the utility of this pathway as a therapeutic target in Alzheimer disease (29).

3. P2X7 Receptor as a Therapeutic Target in Alzheimer's Disease

Purinergic P2X7 receptor has become a key mediator of neuroinflammatory signaling in Alzheimer's disease and it is becoming a therapeutic target worth drug development (50). Compared to the other purinergic receptors, P2X7R is selectively activated in the pathological conditions of high extracellular concentrations of ATP and is therefore especially important in chronic neurodegenerative diseases.

3.1 Expression and function of P2X7R in the central nervous system

P2X7 receptor is a ligand-gated ion channel selectively and highly expressed on microglia and it is lowerly expressed in astrocytes, in oligodendrocytes and some of the neuronal groups (51). In physiological conditions, P2X7R is minimally active but in a case of neuronal stress, injury, or inflammation, higher extracellular ATP levels are robust activators of the receptor. Activation of P2X7R causes high-speed influx of cation and release of potassium, which triggers subsequent downstream signaling pathways, which govern immune responses, cell survivability and cytokine secretion. Prolonged P2X7R activation in the central nervous system is linked to inflammatory enhancement and cellular homo-cysteine imbalance (52).

3.2 P2X7R-mediated microglial activation and cytokine release

Microglial cells are important in the innate immune surveillance in the brain. The P2X7R activation of microglia provokes a change in their phenotype towards a pro-inflammatory one with enhanced cytokine secretion including interleukin-18, interleukin-1 and tumor necrosis factor-A. P2X7R signaling stimulates assembling of NLRP3 inflammasome, caspase-1 stimulation and consequential maturation of pro-inflammatory cytokines. The chronic stimulation of this pathway leads to continued neuroinflammation, synaptic dysfunction, and neuronal damage, which are some of the features of the biology of the Alzheimer disease.

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3.3 Preclinical and experimental evidence targeting P2X7R in AD models

P2X7R has been strongly implicated in the progression of the Alzheimer disease through the use of cellular and animal models of the disease through experimental studies. P2X7R genetic deletion and P2X7R pharmacological inhibition have been demonstrated to suppress microglial-activation, release of inflammatory cytokines, and decrease neuronal-damage. Few researchers have linked transgenic AD models responding to the blockade of P2X7R with reduced amyloid burden, elevated synaptic plasticity, and reduced cognitive perception levels. The overall results are favorable to the therapeutic value of the targeting of P2X7R-mediated neuroinflammation in Alzheimer disease(11).

3.4 Synthetic P2X7 receptor antagonists and their limitations

A number of synthetic P2X7 receptor antagonists have been made and their anti-inflammatory and neuroprotective qualities have been tested in preclinical trials. Although their results were promising in the course of the experiments, their application in clinical practice has been minimal. Critical areas are the lack of drug penetration through the blood-brain barrier, short half-life, off-target effect, and dose-limiting toxicity. Also, inhibition of one of the inflammatory targets selectively might not be sufficient to handle the complication and the multifactorial aspect of Alzheimer disease (12). The effects of these limitations on clinical success of synthetic P2X7R antagonists have added to its search which seeks alternative therapeutic modalities.

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

Since the Alzheimer disease is chronic and requires a long period of treatment, safety and tolerability become the crucial points. There is a potential alternative in natural products and plant-derived compounds since they exhibit multi-target pharmacology and in most cases, have a good safety margin. Most phytochemicals have the capacity to indirectly activate P2X7R signaling and at the same time able to suppress oxidative stress, mitochondrial dysfunction and other mechanisms of inflammation. Multi-target modulation can be particularly beneficial in the case of Alzheimer which is a disease with multiple pathophysiological processes that interact. Such reasoning justifies an investigation into modes of herbal modulators such as Cuscuta reflexa as safer and possibly more effective approaches to the control of P2X7 receptor based neuroinflammation.

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Table 2. Comparison of synthetic versus herbal P2X7 receptor modulators

Compound / Extract	Type	Mechanism of Action	Efficacy (Preclinical/Clinical)	Toxicity / Limitations	Reference
A-740003	Synthetic	Competitive P2X7 receptor antagonist	Reduced IL-1β release and neuroinflammation in AD models (Dempsey et al., 2016)	Short half-life, limited CNS penetration	C. Dempsey, A.R. Araiz, K. Bryson, O. Finucane, C. Larkin, E. Mills, A. Robertson, M. Cooper, L. O'Neill, M. Lynch, Inhibiting the NLRP3 Inflammasome with MCC950 Promotes Non-Phlogistic Clearance of Amyloid-β and Cognitive Function in APP/PS1 Mice, *Brain, Behavior, and Immunity*, 61, (2017) 306–316. DOI: 10.1016/j.bbi.2016.12.014.
Brilliant Blue G	Synthetic dye	Blocks ATP binding to P2X7 receptor	Suppresses microglial activation (Wada et al., 2000)	Poor selectivity, low bioavailability	R. Wada, C.J. Tifft, R.L. Proia, Microglial Activation Precedes Acute Neurodegeneration in Sandhoff Disease and is Suppressed by Bone Marrow Transplantation, *Proceedings of the National Academy of Sciences*, 97(20), (2000) 10954–10959. DOI:

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					10.1073/pnas.97.20.10954
Curcumin	Natural	Inhibits P2X7–NLRP3 signaling pathway	Cognitive improvement in AD animal models (Arosio et al., 2022)	Poor solubility and stability	B. Arosio, F.R. Guerini, I. Aprahamian, *Behavioral and Cognitive Impairments Across the Life Span*, Frontiers Media SA, (2022).
Resveratrol	Natural	Downregulates P2X7 receptor expression	Reduced cytokine release and oxidative stress(Viarengo et al., 2000)	Low oral bioavailability	A. Viarengo, B. Burlando, N. Ceratto, I. Panfoli, Antioxidant Role of Metallothioneins: A Comparative Overview, *Cellular and Molecular Biology*, 46(2), (2000) 407–417.
***Cuscuta reflexa* extract**	Natural	Flavonoid-mediated inhibition of ATP-induced P2X7 activation	Proposed multi-target neuroprotection (Fontaine et al., 2002)	Limited direct in vivo AD evidence	V. Fontaine, S. Mohand-Said, N. Hanoteau, C. Fuchs, K. Pfizenmaier, U. Eisel, Neurodegenerative and Neuroprotective Effects of Tumor Necrosis Factor (TNF) in Retinal Ischemia: Opposite Roles of TNF Receptor 1 and TNF Receptor 2, *Journal of Neuroscience*, 22(7), (2002) RC216. DOI: 10.1523/jneurosci.22-07-j0001.2002.

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4. Pharmacological and Phytochemical Profile of *Cuscuta reflexa*

4.1 Botanical description and ethnomedicinal significance

Cuscuta reflexa Roxb., also referred to as Amarbel or dodder, is a perennial parasite plant that grows in the family of Convolvulaceae. It has no real leaves and roots and lives at the expense of having haustorial contacts with its host plants, where it receives water and nutrition. The plant is very common in South Asia such as India, Nepal and Sri Lanka. Cuscuta reflexa has been considered to have therapeutic effects and is referred to as a nerve tonic and rejuvenating agent in the traditional types of medicine like the Ayurveda and Unani. The long-term ethnomedical use of it has piqued a scientific interest in the idea of its pharmacological uses, especially in disorders closely related to inflammation and neurodegeneration.

4.2 Traditional uses related to neurological and inflammatory disorders

Long usage Cuscuta reflexa has been considered as having all manner of applications, such as liver disorders, skin diseases, fever, and inflammatory conditions. On the neurological health front, it has been used as a tonic in the brain to enhance memory, anxiety and dealing with nervous disorders (14). Its use has also been reported in folk medicine practices which are linked to weakness, fatigue and mental impairment. These classical assertions pose the possibility of it to regulate the functioning of the central nervous system and associated inflammatory events, hence the logicality of it being subjected to research in the neurodegenerative disease arena including Alzheimer disease.

4.3 Phytochemical constituents of *Cuscuta reflexa*

Phytochemical examination of Cuscuta reflexa has identified a wide range of bioactive compounds that make C. reflexa to have a wide pharmacological range. These compounds contribute mostly to its antioxidant effects, anti-inflammatory effects and neuroprotective effects.

4.3.1 Flavonoids

Flavonoids are some of the major group of phytochemicals that have been found in cuscuta reflexa. Some of the compounds include quercetin and kaempferol that have been reported in

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different extracts of the plant. It is a well-established fact that these flavonoids have the property to scavenge reactive oxygen species and subdue the pro inflammatory signaling pathways as well as take care of neuronal cells against oxidative damages. Their ability to suppress inflammatory mediators gives them a possibility of controlling neuroinflammatory processes that are pertinent to Alzheimer disease (15)**.**

4.3.2 Phenolic acids

Gallic acid and other polyphenolic acids such as phenolic acids are found in methanolic and ethanol extracts of Cuscuta reflexa. These are potent antioxidants, which minimize the effects of free radicals and lipid peroxidation. Phenolic acids regulate inflammatory signaling as well as have the ability to preserve the functionality of mitochondria, which also helps in cell survival during pathological scenarios (16)**.**

4.3.3 Glycosides, alkaloids, and lignans

Besides flavonoids and phenolic acids, Cuscuta reflexa also has steroidal glycosides, alkaloids like cuscutine and lignans like arctigenin. The membrane-stabilizing effect and the anti-inflammatory effect have been linked to steroidal glycosides whereas the effect of alkaloids on central nervous system activity has been reported. Lignans are antioxidants and neuroprotectants, and have been found to participate in the regulation of inflammatory pathways, and apoptotic pathways. These different compounds justify the multi-target therapeutic attribute of Cuscuta reflexa.

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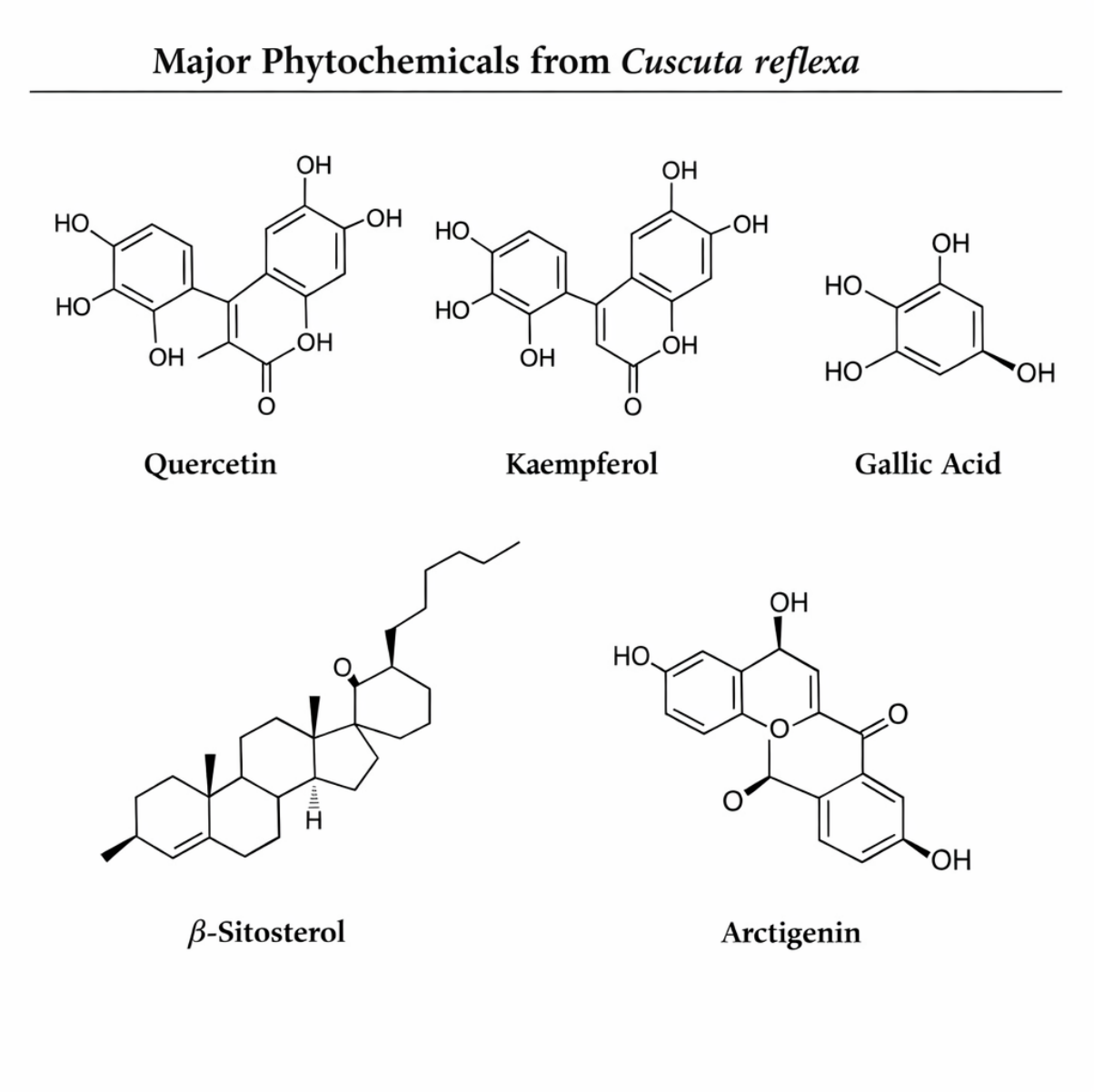

Figure 3. Chemical Structures of Major Phytochemicals

Sources – (23) Review of pharmacotherapeutic targets in Alzheimer's disease and its management using traditional medicinal plants. https://doi.org/10.2147/DNND.S452009

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Table 1. Phytochemicals isolated from *Cuscuta reflexa* and their reported biological activities

Category	Compound Name	Chemical Class	Major Source (Plant Part)	Reported Biological Activity	Reference
Flavonoid	Quercetin	Flavonol	Whole plant	Antioxidant, anti-inflammatory, inhibition of NLRP3 signaling	R. Weiskirchen, D. Sorrentino, W.R. Stremmel, *Inflammation and Fibrosis in the Gastrointestinal Tract and Liver: Mechanisms and Targets*, Frontiers Media SA, (2023)
Flavonoid	Kaempferol	Flavonol	Stem extract	Neuroprotective, anti-inflammatory, ROS scavenging	O. Vicente, M. Boscaiu, Flavonoids: Antioxidant Compounds for Plant Defence and for a Healthy Human Diet, *Notulae Botanicae Horti Agrobotanici Cluj-Napoca*, 46(1), (2017) 14–21. DOI: 10.15835/nbha46110992.
Steroidal glycoside	β-Sitosterol	Phytosterol	Aerial parts	Anti-inflammatory, membrane stabilizing (Anderson et al., 1996)	R. Anderson, C. Feldman, A. Theron, G. Ramafi, P. Cole, R. Wilson, Anti-Inflammatory, Membrane-Stabilizing Interactions of Salmeterol with Human Neutrophils *In Vitro*, *British Journal of Pharmacology*, 117(7), (1996) 1387–1394. DOI:

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					10.1111/j.1476-5381.1996.tb15297.x
Phenolic acid	Gallic acid	Polyphenol	Methanolic extract	Antioxidant, free radical scavenging (Amarowicz et al., 2003)	R. Amarowicz, R. Pegg, P. Rahimi-Moghaddam, B. Barl, J. Weil, Free-Radical Scavenging Capacity and Antioxidant Activity of Selected Plant Species from the Canadian Prairies, *Food Chemistry*, 84(4), (2003) 551–562. DOI: 10.1016/s0308-8146(03)00278-4.
Alkaloid	Cuscutine	Alkaloid	Whole plant	CNS modulation, sedative activity	P.S. Siqueira-Lima, F.R. Passos, A.M. Lucchese, I.R. Menezes, H.D. Coutinho, A.A. Lima, G. Zengin, J.S. Quintans, L.J. Quintans-Júnior, Central Nervous System and Analgesic Profiles of *Lippia* Genus, *Revista Brasileira de Farmacognosia*, 29(1), (2018) 125–135. DOI: 10.1016/j.bjp.2018.11.006.
Lignan	Arctigenin	Lignan	Ethanolic extract	Neuroprotective, anti-oxidative (Asanuma et al., 2001)	M. Asanuma, S. Nishibayashi-Asanuma, I. Miyazaki, M. Kohno, N. Ogawa, Neuroprotective Effects of Non-Steroidal Anti-Inflammatory Drugs by Direct Scavenging of Nitric Oxide Radicals, *Journal of Neurochemistry*, 76(6), (2001) 1895–1904. DOI:

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					10.1046/j.1471-4159.2001.00205.x.

4.4 Pharmacological activities relevant to neuroprotection

The pharmacological characteristics of Cuscuta reflexa match with major pathology processes that occur in the case of Alzheimer disease, especially inflammation in the brain, oxidative stress, and dysfunction of neurons.

Table 3. Summary of in vivo studies evaluating *Cuscuta reflexa* or related herbal models

Animal Model	Inducing Agent / Condition	Dose and Duration	Observed Effects	Mechanism / Biomarkers Studied	Reference
Wistar rats	LPS-induced neuroinflammation	200 mg/kg, oral, 21 days	Decreased TNF-α and IL-1β, increased SOD	Anti-inflammatory and antioxidant effects (Yu et al., 2017)	G. Yu, H. Kubota, M. Okita, T. Maeda, Anti-Inflammatory and Antioxidant Effects of Melatonin on LPS-Stimulated Bovine Mammary Epithelial Cells, *PLoS ONE*, 12(5), (2017) e0178525. DOI: 10.1371/journal.pone.0178525.
Swiss albino mice	Scopolamine-induced memory impairment	100 mg/kg, oral	Improved learning and memory	Acetylcholinesterase inhibition (Fulton & Key, 2001)	M.H. Fulton, P.B. Key, Acetylcholinesterase Inhibition in Estuarine Fish and Invertebrates as an Indicator of Organophosphorus Insecticide Exposure and

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					Effects, *Environmental Toxicology and Chemistry*, 20(1), (2001) 37–45. DOI: 10.1002/etc.5620200104 .
Diabetic rats	Streptozotocin-induced neuropathy	250 mg/kg, oral, 28 days	Reduced oxidative stress	Activation of antioxidant defense pathways (Ulhassan et al., 2025)	Z. Ulhassan, Y. Hamid, W. Zhou, *Role of Antioxidants in Abiotic Stress Management*, Academic Press, (2025).
AD rat model	Amyloid-β injection	200 mg/kg, oral, 30 days	Reduced amyloid burden and cognitive improvement	Proposed P2X7–NLRP3 modulation (Rocha et al., 2021)	F.A.C. Rocha, J.E. Fonseca, A. Mobasheri, O. Gualillo, H.E. Henrotin, R. Largo, G. Herrero-Beaumont, *Inflammation and Biomarkers in Osteoarthritis*, Frontiers Media SA, (2021).

4.4.1 Anti-inflammatory activity

It has been shown in experimental studies that Cuscuta reflexa extracts can be utilized to diminish by a large margin the concentration of pro-inflammatory cytokines including tumor necrosis factor-alpha and interleukin-1 beta. The plant has been depicted to make suppression of inflammatory signaling pathways and inhibition of microglial activation, implying that of chronic neuroinflammation. So these anti-inflammatory effects are more applicable in the example of P2X7 receptor mediated inflammatory cascades.

4.4.2 Antioxidant activity

Cuscuta reflexa manifests itself with a strong antioxidant activity by boosting endogenous antioxidant activities and direct radical scavenging of the reactive oxygen species. The plant

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aids in the maintenance of mitochondrial integrity and neuronal functionality by inhibiting the oxidative stress and lipid peroxidation (17)**.** This antioxidant activity is very important in overcoming the oxidative destruction related to amyloid toxicity and mitochondrial dysfunction in Alzheimer disease.

4.4.3 Neuroprotective and cognitive-enhancing effects

Cuscuta reflexa is found to produce neuroprotective action in experimental animal models of arduation of cognitive functions and neurotoxicity. Plant extract treatment has also been linked to enhanced memory, and less neuronal damage and neurotransmitter systems. The mechanisms by which these effects take place are probably intertwined with anti-inflammatory, antioxidant, and signaling-regulatory effects. All these pharmacological characteristics make Cuscuta reflexa a promising multi-target neuroprotective agent that may have an important application in the field of Alzheimer disease.

5. Mechanistic Interplay Between *Cuscuta reflexa* and the P2X7–NLRP3 Axis

In Alzheimer disease neuroinflammation is caused by tight, complex neuromolecular signaling pathways mediating cellular stress to innate immune responses. The ATP -P2X7 receptor - NLRP3 inflammasome axis is one of them that centrally involves the escalation of the inflammatory response and facilitates the progression of neurodegeneration. The phytochemical composition of Cuscuta reflexa can imply the possibility of Cuscuta reflexa to regulate several nodes of this pathway, which can have a neuroprotective effect.

5.1 ATP-induced P2X7 receptor activation and downstream signaling

Damaged or stressed cells release extracellular adenosine triphosphate in high levels and this reflects evidence of danger-associated molecular signal in the brain. Higher ATP levels activate the P2X7 receptor which is a ligand-gated ion channel mostly found on microglial cells. Activation of P2X7R causes rapid potassium efflux and calcium influx, which cause membrane depolarization and generation of downstream respective inflammatory signalling pathways. P2X7R is also sustained and promotes the creation of reactive oxygen species, inflation of mitochondrial dysfunction, and the recruitment of adaptor proteins that are needed to assemble

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the inflammasome. Chronic ATP-mediated P2X7R stimulation is involved in persistent microglial stimulation and spreading neuroinflammatory damage in Alzheimer disease.

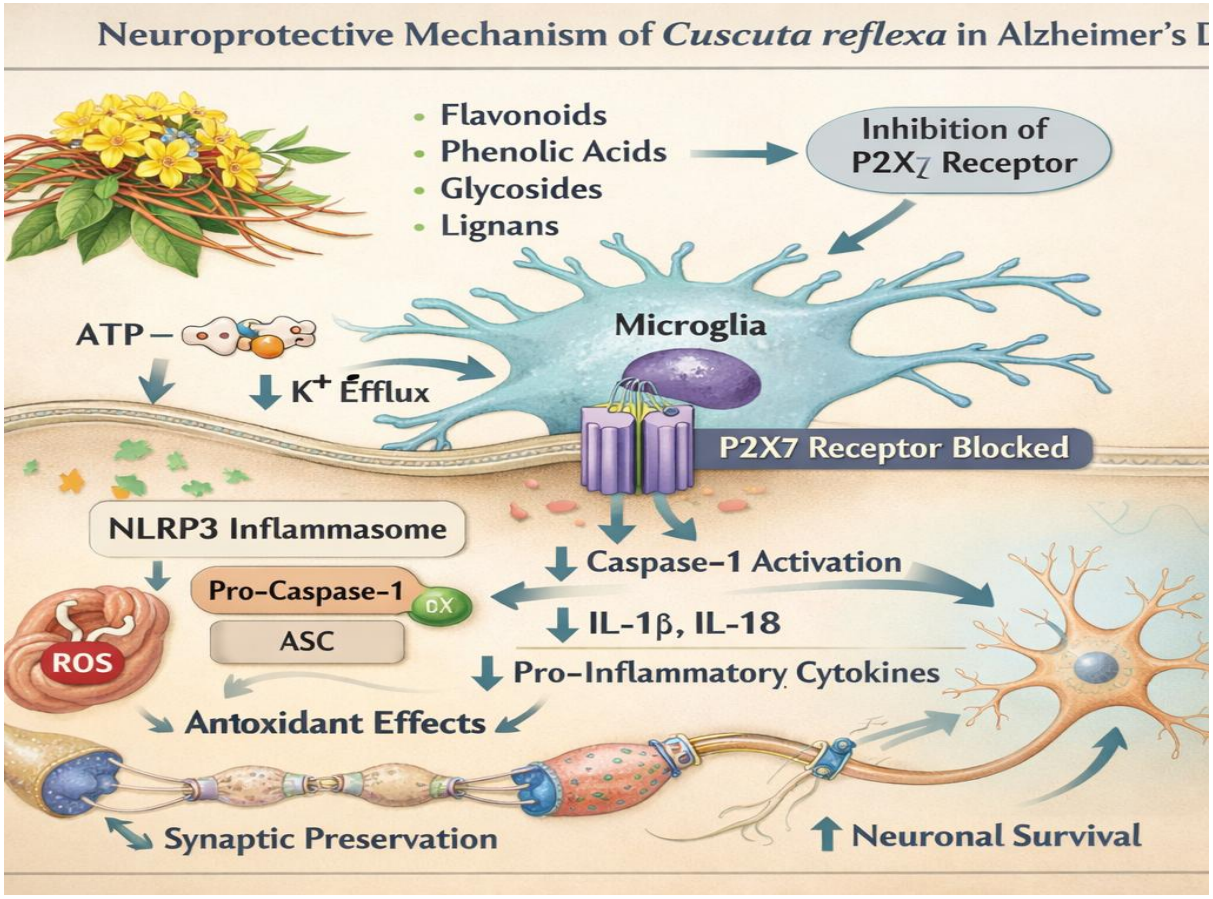

Figure 4. Hypothetical Neuroprotective Mechanism of Cuscuta reflexa

Review of pharmacotherapeutic targets in Alzheimer's disease and its management using traditional medicinal plants. Journal: *Degenerative Neurological and Neuromuscular Disease.* ***https://doi.org/10.2147/DNND.S452009***

5.2 Role of NLRP3 inflammasome in neurodegeneration

NLRP3 inflammasome is a cytosolic multiprotein complex, which is an important controller of innate immune response (18)**.** When activated, it mixes with the adaptor protein ASC and pro-caspase-1, triggering caspase-1 activation and consequently making pro-inflammatory cytokines like interleukin-1 8 interleukin-18 mature. The activation of NLRP3 inflammasome in the brain of patients with Alzheimer disease strongly correlates with the accumulation of amyloid- B, Tau pathology, oxidative stress, and defective synapses. Continuous stimulation of this inflammasome supports a vicious cycle of inflammatory response, which enhances

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neuronal loss and cognitive impairments, which emphasizes its importance in neurodegeneration.

5.3 Evidence supporting phytochemical modulation of P2X7R and NLRP3

Accumulating experimental data shows that a variety of plant-based phytochemicals have the ability to control the activity of P2X7 receptor and inhibit the NLRP3 inflammasome activation. Phenolic and flavonoid compounds have been indicated to suppress ATP-mediated activations of P2X7R, prevent potassium extravasation, and suppress downstream mediated inflammatory. Pharmacologic blockage of mitochondrial production of reactive oxygen species, as well as lysosome labilization, to prevent NLRP3 inflammasome assembly are also inhibited by these compounds. Though the actual experimental evidence in Cuscuta reflexa in AD models is scarce, its phytochemicals are structurally and functionally similar to the established natural inhibitors of the P2X79NLRP3 system, which enables the argument to a plausible place of action.

5.4 Comparative mechanisms with other natural P2X7/NLRP3 inhibitors

Natural products like curcumin, resveratrol, and other polyphenols have proven effective in the inhibition of the expression of P2X7 receptors, deactivation of inflammasomes and inhibition of the production of pro-inflammatory cytokines in neurodegenerative models. The agents are reported to function in more than one way; among them being antioxidant effect, control of intracellular calcium signaling and control of transcription factors that regulate inflammatory gene expression. Comparatively, Cuscuta reflexa has a complicated phytochemical architecture which can affect the same activities at synergistic levels of oxidative stress, membrane stability, and inflammatory cascading. The multi-target activity could have more benefits compared to single-molecule inhibitors since it could target several pathological processes at once.

5.5 Hypothesized multi-target mechanism of *Cuscuta reflexa* in Alzheimer's disease

It is postulated that Cuscuta reflexa has a neuroprotective effect in coordinating P2X7 NLRP3 axis modulation considering the presence of several phytochemicals and reported pharmacological actions. Phenolic compounds and flavanoids in the plant could inhibit the ATP process of P2X7 receptor activation, and inhibited potassium release and inflammatory

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response along the downstream. Simultaneously, inhibition of oxidative activity at the same time with mitochondrial dysfunction additionally restrains NLRP3 activation and release of pro-inflammatory cytokines. By all of these mechanisms, Cuscuta reflexa has the potential to reduce chronic neuroinflammation, maintain synaptic health and eventually enhance neuronal survival and cognitive processes in Alzheimer disease.

6. Integrative Perspective and Future Research Directions

6.1 Gaps in current evidence and need for experimental validation

Even though growing bodies of evidence suggest the anti-inflammatory and neuroprotective actions of Cuscuta reflexa, the direct experimental validation to explain the role of Cuscuta reflexa in regulating the P2X7 receptor-NLRP3 axis of inflammations remains absent in Alzheimer disease. The data that are readily available are based on in vitro tests or animal models of the effects of general anti-inflammatory or antioxidant effects as opposed to disease xenebiotics. Properly designed preclinical trials based on approved bone target and disease models of the Alzheimer disease are required to verify the target dynamics, dose response patterns and molecular selectivity (19). Also, the presence of molecular researches that examine the level of P2X7 receptor sorrow, indicators of inflammasome activation, and outcomes profiles of downstream cytokine schemata are imperative to support the suggested therapeutic control.

6.2 Challenges in translation

Although the preclinical evidence of Cuscuta reflexa application indicates promising results, a number of issues need to be resolved to allow translation of Cuscuta reflexa-based interventions into clinical practice.

6.2.1 Bioavailability and pharmacokinetics

Most of the phytochemicals within Cuscuta reflexa such as flavonoids and phenolic compounds have low bioavailability orally because they have low solubility, are readily metabolized, and have less systemic bioavailability. Such pharmacokinetic limitations may limit the effective levels of the brain and or decrease the efficacy of therapy. To optimize the dosing strategies,

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extensive pharmacokinetic research to establish the absorption, distribution, metabolism, and elimination data and blood-brain barrier permeability are required *(*20**).**

6.2.2 Standardization and quality control

Plant source variability, conditions at harvest, and modes of extraction, phytochemical compositions are all significant problems with regard to reproducibility and clinical translation. To achieve consistency and predictable therapeutic effects on a batch-to-batch basis, standardization of Cuscuta reflexa extracts should be done on the basis of specified bioactive markers. There should be strong quality control procedures such as phytochemical fingerprinting and quantitative analysis to help in approval of regulatory and clinical use.

6.3 Advanced strategies for enhanced efficacy

To overcome translational barriers and enhance therapeutic potential, advanced formulation and combinatorial strategies should be explored.

6.3.1 Nanoformulations and targeted delivery

Research as Nanotechnology: The way forward to enhance bioavailability and brain targeting of plant-derived products is via nanotechnology based-delivery systems. Cuscuta Reflexa phytochemicals encapsulated within nanoparticles, liposomes or polymeric carriers could be useful in increasing stability, prolonging circulation and penetration of the blood-brain barrier. The efficacy of therapies could be enhanced with further control of off-target effects by the use of targeted delivery methods.

6.3.2 Synergistic phytochemical combinations

Cuscuta reflexa has a multi-component nature that offers the possibilities of synergistic reactions between its phytochemicals. The synergistic promotion of effects of flavonoids, phenolic acids, and other bioactive components may lead to better regulation of neuroinflammatory and oxidative stress events than their individual components. Network pharmacology and experimental validation of systematic evaluation of synergistic

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combinations would be useful in optimization of therapeutic formulations in Alzheimer disease.

6.4 Prospects for clinical studies and translational relevance

The increased awareness of neuroinflammation as a treatment goal in the context of Alzheimer's disease offers a good justification to consider the Cuscuta reflexa-based interventions to be translated into clinical studies. Premilininu clinical trials in which safety and tolerability, along with biomaker-based outcomes undergo testing, will be worthwhile in determining the translational viability. Possible ways to develop Cuscuta reflexa as a complementary or adjunctive therapy using phytochemical standardization, sophisticated delivery platform, and mechanistic biomarkers could bring about this. All of these measures can positively contribute to the small steps taken in the bridge between traditional herbal medicine and modern neurotherapeutics as the next step in translational efforts in the treatment of Alzheimer disease.

7. Conclusion

7.1 Summary of neurotherapeutic potential

The medical challenge has not been addressed significantly since Alzheimer disease has a complex and multifactorial pathophysiology. There is growing evidence pointed to neuroinflammation as a fundamental pathophysiological process in the context of the formation of the pathology of amyloid and tau, oxidative stress, and mitochondrial dysfunction. That is why, Cuscuta reflexa may become an encouraging choice as a neurotherapeutic application because of its rich phytochemical content and diverse pharmacological signature. The anti-inflammatory, antioxidant, and neuroprotective activities of the plant correspond well with the main pathological mechanisms involved in the development of Alzheimer disease.

7.2 Translational significance of P2X7–NLRP3 modulation

Inflammasome P2X7 receptor -NLRP3 is a strategically relevant target lens through which chronic neuroinflammation of the Alzheimer disease can be managed. Continuous stimulation of this pathway increases the inflammatory reactions mediated by microglia and increases the rate at which neurons get damaged. P2X77NLRP3 signaling is a promising modulation and has

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the capability to inhibit pro-inflammatory cytokine secretion, oxidative stress response, and synaptic dysfunction. This multi-level regulation of this pathway by the ability of plant-derived phytochemicals makes their use a biologically realistic and therapeutically relevant tool that can be used in addition to successfully used pharmacological methods.

7.3 Positioning *Cuscuta reflexa* as a multi-target herbal intervention for Alzheimer's disease

Cuscuta reflexa, with its ethnomedical applicability and phytochemical variety, and the new understanding of mechanisms, could be placed as a multi-target herb intervention useful in the control of Alzheimer disease. It compensates the flaws of individual-target therapies by concomitantly interfering with neuroinflammatory signaling, oxidative stress and neuronal survival pathways. Although, the Cuscuta reflexa needs to be further supported with experimental and clinical work, it is a promising alternative of the traditional medicine with the modern neurotherapeutics that will bring new insights to the creation of the safer and more effective treatment of the Alzheimer disease.

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