INTRODUCTION

Alzheimer’s disease (AD) is the predominant form of dementia, making up at least 2/3rd of dementia cases among individuals aged 65 and older [1]. It is predicted that 40 million individuals worldwide currently experience dementia and that by the year 2050, that figure will have doubled every 20 years [2]. Neurofibrillary tangles (NFTs) and plaques containing tau are obligatory for the diagnosis of AD [3]. By impairing mitochondrial activity, these aggregation complexes cause a pathological cascade that results in the degeneration of synapses and neurons [4]. Memory and cognitive impairment are caused by the death of the hippocampus and cortical neurons in this condition [5]. Different hypotheses were intended for AD. Khachaturian was the first to put forth the calcium hypothesis, arguing that persistent intracellular calcium abnormalities are the root causes of neurodegenerative diseases such as AD [6]. A recent Swedish study revealed that older women who regularly take calcium supplements may actually raise their risk of contracting dementias such as Alzheimer’s [7]. There is more and more evidence that the disruption of neuronal calcium ion (Ca2+) homeostasis that comes with ageing may be part of what causes AD [6]. Disrupted Ca2+ could result in synaptic impairments and encourage the buildup of amyloid beta (Aβ) plaques and NFT [8].

The amyloid precursor protein (APP) significantly contributes to the pathophysiology of AD in great part due to the sequential proteolytic cleavages that result in the production of β-amyloid peptides [9]. APP is cleaved by three categories of proteases: α-, β-, and γ-secretases. β- and γ-secretase cleave at the N- and C-terminal ends of the Aβ region, respectively, releasing Aβ, whereas α-secretase cleaves within the Aβ sequence. γ-Secretase performs cleavage at multiple adjacent sites, resulting in Aβ species comprising 39–43 amino acid residues [10]. The Aβ peptide, generated from β- and γ-secretase processing of APP, has garnered significant interest as a key factor in AD [11]. Under typical physiological conditions, Aβ serves a regular function and maintains a low concentration in vivo. Nevertheless, elements such as aging, oxidative stress, and genetic mutation lead to the disturbance of Aβ homeostasis. This disruption leads to the buildup and aggregation of Aβ, giving rise to the formation...
of oligomers and fibers, and ultimately leading to the formation of plaque deposits in brains [12]. Aβ is produced in normal individuals, yet under specific conditions, it can aggregate, initiating the onset of the disease. Extensive evidence underscores that Aβ oligomers are primarily responsible for neuronal dysfunction and the progression of AD [13]. When APP levels are aberrant, A builds up, causing tau to get phosphorylated and aggregate, eventually resulting in NFTs. These NFTs are formed of hyperphosphorylated tau protein fibres that are entangled, insoluble, and concentrated in AD neurons [14].

Tau is widely recognized as a protein associated with microtubules in neurons [15]. Tau is essential for neurons, as it binds and maintains the stability of microtubules and also regulates axonal transport. These functions are controlled by phosphorylation events at specific sites [16]. Post-translational modifications such as phosphorylation, acetylation, and ubiquitination influence the role of tau. In disease conditions, regulation of the equilibrium between phosphorylation and de-phosphorylation is disrupted, resulting in increased abnormal (“hyper”) phosphorylation [17]. Tauopathies refer to neurodegenerative diseases characterized by hyperphosphorylated accumulations of the microtubule-associated protein tau [18]. Atypical phosphorylation (“hyperphosphorylation”) and aggregation of tau proteins are distinguishing features of AD [19].

According to another theory, normal brain function depends on metal homeostasis in the central nervous system (CNS) because metals work as enzyme cofactors and are important parts of both intra- and inter-neuronal communication [20]. In addition, heavy metals encourage oxidative damage that results in neuronal death in several regions of the brain with deficiencies in behaviour, memory, and cognition [21]. Ionic substances, such as aluminum, copper, zinc, and iron, have been associated with the development of extracellular beta-amyloid plaques and intracellular hyperphosphorylation of neurofibrillary tau tangles [22]. Al-induced memory and learning problems appear to be the result of a complex pathology [23]. In addition, these heavy metals cause an overactive inflammatory response, which leads to an imbalance between anti-inflammatory and pro-inflammatory cytokines. This is a key factor in the destruction of brain tissue and the development of neurodegenerative diseases [24].

It is generally known that activation of the microglia is a significant inducer of neuroinflammation including, in particular, AD and Parkinson’s diseases [25]. Therefore, inhibiting microglial activation is a primary objective in the quest to improve the survival of neuronal cells [26]. These aggregation complexes interfere with the operation of the mitochondria, which sets off a pathological chain reaction that ultimately results in the death of synapses and neurons [27].

Oxidative stress in the brain is increasingly recognized as a possible role in the aging process and in age-related neurodegenerative diseases [28]. There is a significant lack of cholinergic activity in both the cortical and hippocampus regions of patients with AD, as indicated by numerous pieces of data [29]. AD is characterized by a fundamental process that is responsible for the clinical manifestations of the disease [30]. This process involves the degeneration and death of neurons [31].

There are a significant number of studies that describe the preventive benefits of different polyphenols against AD [32]. In addition, certain polyphenolic substances have been noted to exhibit a capacity to impede amyloid fibrillation [33]. This review article provides a condensed overview of the recent research that has been conducted on the link between Chrysin and AD, as well as its possible role as a revolutionary molecule in many clinical applications [34].

Chrysin is an inherently occurring hydroxylated flavonoid that can be found in bee propolis, honey, and a variety of plants, including mushrooms, passion flowers, carrots, Passiflora caerulea, Pelargonium crispum, carrots, Passiflora incarnata, and Oroxylum indicum [35]. The chemical formula of chrysin is C_{16}H_{10}O_{4} and its other name is 5,7-dihydroxy-2-phenyl-4H-1-benzopyran-4-one [36]. The significance of oxygenation at the C-3 position is a trait that is unique to flavones and can be seen to be present in chrysin. This feature distinguishes flavones from other types of molecules [37]. In contrast to the majority of flavonoids, which have either one (often at C-4’) or two hydroxy (C3’, C4'-di, ortho hydroxy) functional groups in ring-B, these flavonoids only have one hydroxy group (Fig. 1) [38]. The number of hydroxyl groups and where they are located, in addition to the configuration of the polyphenolic rings, may all have an influence on the inhibitory action of the compound [39]. Chrysin, originally discovered in 1949 by Gösta Linstedt at the KTH Royal Institute of Technology in Stockholm, was initially derived from the wood of pine trees [40].

In its chemical composition, chrysin has two benzene rings (A and B) and a pyran-like heterocyclic ring that contains oxygen (Fig. 1). Because of the conjugation, the double bond between C2 and C3 and ring B in the chemical structure of chrysin is going to be coplanar with the rings A and C. Each of these three rings has undergone structural alterations that primarily influence unique biological outcomes [41].

Chrysin possesses a diversity of pharmacological effects, including anticancer, antiapoptotic, antioxidant, neuroprotective, anti-inflammatory, antimelotypic, and antihypertensive [42]. Figure 1 presents a visual representation of the numerous pharmacological activities that have been described [40]. Due to the fact that it can treat a wide variety of conditions through a variety of different pathways, chrysin has garnered a lot of interest recently for the benefits it provides [43]. Chrysin provides prominent neuroprotective properties and decreases neuroinflammation [44]. Chrysin exhibits the ability to overwhelm cognitive impairment and possesses efficacious encephalo-protective properties [45].

**CHRYSIN IN AD**

The pathophysiology of AD primarily involves two key elements: the accumulation of A and the hyperphosphorylation of tau protein [46]. There is a connection between oxidative stress, the activation of microglia, neuroinflammation, and AD [47].

**Chrysin inhibit the aggregation of amyloid**

The amyloid hypothesis is one of the established hypotheses for AD [48]. It proposes that the buildup of Aβ peptide is the key factor that leads to the incidence of AD [49].
The formation of $A\beta$ requires the proteolysis of the APP, which results in the evolution of 39–43 amino acids in the $A\beta$ [50]. The $\beta$-secretase and $\gamma$-secretase enzymes work in tandem to carry out this particular proteolysis in a step-by-step fashion [51]. The protein is cleaved by each secretase at a distinct cleavage site, which results in the creation of a variety of different APP fragments [52]. One of these fragments is the solvable A isoform, which is the more neurotoxic form [53]. In contrast, the insoluble form encourages the generation of reactive oxygen species (ROS) [54]. Therefore, mutations in $\gamma$-secretase and $\beta$-secretase that hoist up their APP expression and increase their enzymatic activity might be plausible reasons for the buildup of $A\beta$ [55]. The search for anti-amyloid medicines has emerged as a prominent method in AD-related research [56]. This is due to the fact that amylin is believed to be the originator of events that promote neurotoxicity and the clinical signs of AD [57]. Various flavonoids are strongly associated with this hypothesis [58]. Quercetin is one of the flavonoids that has previously been recognized as preventing the aggregation of amylin and disaggregating its fibers [59].

According to the findings of an in-silico and in-vitro study, chrysin has the ability to avert the aggregation of human amylin [60]. Chrysin is able to inhibit the emergence of amyloid aggregates, as demonstrated by the findings of the thioflavin T binding turbidimetry assay [61]. Compatible with thio-flavin T binding, chrysin was reported to prevent the production of amyloid aggregates [62]. In addition, the evaluation of Chrysin’s molecular interactions with amylin indicated that the protein has a substantial binding affinity for amylin [63]. Chrysin’s molecular docking and in vitro results suggest that it may have potential therapeutic applications, one of which is the prevention of amylin aggregation [59]. Chrysin-loaded chitosan nanoparticles were shown to have properties that prevented the aggregation of ROS and $A\beta_{42}$ proteins in a different body of study [64]. In addition, the activity of the enzymes butyryl cholinesterase (BChE) and acetyl cholinesterase (AChE) is inhibited to a significant degree by compounds having heterocyclic motifs, such as tacrine, donepezil, rivastigmine, and galantamine, which serve in the capacity of potent inhibitors of both enzymes [65]. In addition to this, the results of investigations on the kinetics and docking of chrysin generated conclusions that were consistent with these findings [66]. According to research that was achieved in 2019 by Taslimi et al. [67] chrysin has the ability to inhibit acetylcholinesterase and BChE, which results in anti-cholinergic action. This activity was tested on rats that had numerous organs damaged as a result of cyclophosphamide [68]. Chrysin, carvacrol, zingerone, hesperidin, and naringin are natural phenols known for their remarkable suppression effects against human carbonic anhydrase catalysts I and II, as well as $\alpha$-glucosidase, AChE, and BChE enzymes [69]. These phenols also block the activity of naringin, which has been demonstrated to have anti-cancer properties [70]. The combination of chrysin and luteolin was found to have a protective effect against the development of advanced glycation end products and the aggregation of albumin protein that was generated by glyoxal in in-vitro and molecular docking investigations. These results were obtained by combining the two compounds [71].

**Chrysin inhibits the calcium influx-induced $\beta$ amyloid aggregation and apoptosis**

Multiple studies have identified calcium influx and the development of ROS as potential mechanisms responsible for $A\beta$-induced neurotoxicity [72]. Studies propose that the main occurrence subsequent to $A\beta$ treatment of cultured neurons and neuroblastoma involves calcium influx, most likely facilitated by the L voltage-sensitive calcium channel [73]. This is due to the fact that blocking this channel and/or calcium chelation averts all other consequences [74].

The accumulation of especially (Ca$^{2+}$), metal ions can accelerate the production of amyloid plaques and NFT [75]. However, there has been no comprehensive investigation into the processes by which Ca$^{2+}$ affects the evolution of AD [76]. In light of this fact, the current article provides a synopsis of the methods by which Ca$^{2+}$ is transported into and out of cells and organelles, such as the cell, mitochondrial, endoplasmic reticulum, and lysosomal membranes, to influence the equilibrium of intracellular Ca$^{2+}$ levels [77]. In addition, Ca$^{2+}$ dyshomeostasis plays a significant part in the regulation of the pathogenesis of AD by having an effect on the formation and aggregation of peptides as well as the phosphorylation of tau protein [78]. This is in addition to the fact that a disruption in the metabolic balance of Ca$^{2+}$ can have an effect on the cognitive abilities and memories of people who have AD [79]. Chrysin was able to reduce both the passive cutaneal anaphylaxis and the systemic pseudo-allergy that was observed in an in vivo animal model. The chrysin inhibited Laboratory of Allergic Diseases 2 cell degranulation, Ca$^{2+}$ inflow, and adenosine 5’-triphosphate content in a dose-dependent manner, which led to substantial suppression of these processes depicted in Figure 2. Chrysin was able to decrease pseudo-allergic reactions by inhibiting the PLC/IP3/Ca$^{2+}$ route as well as the ERK/STAT3 serine 727 pathway, all of which are downstream of MrgX2 [80]. Furthermore, these substances inhibited apoptosis by reducing mitochondrial dysfunction,

![Chemical structure and pharmacological activities of chrysin.](image-url)
including mitigating the mislaying of membrane potential, suppressing Ca2+ accumulation, and regulating the ratio of Bax/Bcl-2 [81]. Moreover, chrysin hindered the expression of cyclooxygenase 2 (COX-2) and inducible nitric oxide synthase (iNOS), leading to the suppression of inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), nitric oxide (NO), and prostaglandin E2 (PGE2) [82]. Significantly, all the compounds demonstrated anti-inflammatory effects by inhibiting the nuclear factor-kappa beta (NF-κB)/mitogen-activated protein kinase (MAPK) pathway [83]. Excessive activation of calcium-calmodulin-dependent protein kinase 2 or AMP-activated protein kinase alone is adequate to trigger the loss of dendritic spines. Conversely, chrysin hinders the activity of these factors and safeguards hippocampal neurons from the synaptotoxic impact of Aβ42 oligomers [84].

**Chrysin suppress microglial activation**

Under typical circumstances in the brain, microglia are responsible for regulating homeostasis and providing a line of shielding against damage [85]. Activated microglia exhibit a diversity of individual traits, including pro-inflammatory (M1-like) and anti-inflammatory (M2-like) phenotypes [86]. Depending on the individual traits activated, microglia can produce cytotoxic or neuroprotective effects [87]. However, overactive microglia can cause the production of proinflammatory and cytotoxic substances, which can lead to the evolution of progressive neurological disorders such as AD, ischemia, and Parkinson’s diseases (PD) [88]. Hence, inhibiting the animating or microglia may play a significant role in preserving the well-being of neuronal cells [89]. Reactive glial cells may lead to variations in the typical functioning of the CNS [90]. In spite of the fact that glial activation is initially advantageous, glial reactivity that is excessive and persists for an extended time might result in an inflammatory response that has detrimental consequences on neuronal cells (Fig. 3) [91]. Reactive glial cells are responsible for the production of a number of neurotoxic compounds, but they are also responsible for the production of agents that have the potential to be neurotoxic [92]. It has been hypothesized that the neurotoxic effect of reactive glia is mediated by NO, pro-inflammatory cytokines, and ROS [93]. Chrysin ability to inhibit the expression of cytosine-cytosine-adenosine-adenosine-thymidine/magnifying the binding protein δ in microglial cells leads to beneficial outcomes, including anti-inflammatory and neuroprotective effects [41]. In addition, chrysin increased the level of interleukin-4 while inhibiting the secretion of interferon, tumor necrosis factor, interleukin-1, interleukin-2, interleukin-6, and interleukin-12 by splenic mononuclear cells [94]. These substances have the capability to decrease the expression of pro-inflammatory cytokines (IL-6, TNF-α, and IL-1β) and neurotoxic mediators (NO, PGE2, iNOS, and COX-2), thereby reducing inflammatory markers and protecting against neural damage [95]. Experimental data demonstrates that these substances exert anti-inflammatory effects by regulating pertinent signaling pathways NF-κB, Janus kinase/Signal transducers and activators of transcription, MAPKs, phosphatidylinositol 3-kinase/Akt (protein kinase B), and nuclear factor erythroid 2-related factor 2/heme oxygenase 1) [96].

**Chrysin inhibits heavy metal-induced AD**

Metals, such as lead, zinc, aluminum, copper, and others, are believed to be associated with various neurological conditions, with many of these conditions linked with an elevation in ROS production [97]. Including this, there is mounting evidence to suggest that the metal might amplify oxidative and inflammatory reactions, which can result in harm to the issue [98]. Chrysin helps to remediate learning and memory deficiencies caused by aluminum, and also helps to untangle some of the relevant underlying mechanisms [99]. In addition, lead is a toxic heavy metal and its exposure causes cognitive decline, imbalance of pro- and anti-inflammatory cytokines, and suppression of the hippocampal long-term potentiation (LTP) induction [100]. In addition, after exposure to lead, its concentration increases in both vital fluid and brain cells, leading to the apoptosis of neurons [101]. In an investigation involving lead-exposed rats, the administration of chrysin improved cognitive function, mitigated hippocampal LTP impairment, regulated inflammatory responses, lowered lead levels, and prevented neuronal cell death [102]. According to the findings, chrysin ameliorates the cognitive deficit, perhaps by reducing the malfunctioning of hippocampal synapses, modulating the inflammatory response, lowering lead concentrations, and preventing neuronal death (Fig. 4) [103].

**Chrysin inhibits oxidative stress in AD**

A contrast in the redox state can cause oxidative stress in the brain [104]. This can be caused by the production of an excessive amount of ROS or by a failure in the antioxidant system [105]. Oxidative stress is a process that becomes more prevalent in an aging brain [106]. Patients with AD have brains with a significant amount of oxidative damage, which is related to an abnormal accumulation of Aβ and the deposition of NFT [107]. After administering Aβ25–35, considerable oxidative stress was observed, evident by a significant rise in the levels of thiobarbituric acid reactive substance, acetylcholinesterase, and a decrease in the activities of glutathione peroxidase, glutathione reductase, reduced glutathione, superoxide dismutase, catalase, and Vitamin C [108]. Chrysin administration at doses of 25 and 50 mg/kg body weight
effectively hindered the activation of two essential signaling molecules associated with neuroinflammation: (c-Jun N-terminal kinase) JNK and NF-kB [121].

Formulations of chrysin in the management of AD

Natural substances have been shown to be effective against neurodegenerative disease through different molecular pathways, such as the prevention of the evolution of ROS, the elimination of the deteriorated biomolecules before their buildup has an effect on cell metabolism, and the improvement of disease circumstances [122,123]. However, the distribution of natural compounds into the CNS is limited by the presence of the blood–brain barrier as well as the antagonistic pharmacokinetic features of natural compounds [124]. To reduce the severity of this issue and improve the transport of a drug into the brain at a therapeutically appropriate dose, it is necessary to come up with an innovative and applicable method [125]. According to the findings of numerous research, nanoformulations and microneedles incorporating natural ingredients, such as ferulic acid, quercetin, chrysin, piperine, curcumin, resveratrol, huperzine, berberine, baicalein, and hesperetin, have demonstrated significant potential in enhancing neurodegenerative conditions [126].

A comparison was conducted between the effect of treatment using lipid-core nanocapsules loaded with chrysin and without chrysin. Chrysin was observed to increase the levels of Glutathione reductase (GR), Glutathione peroxidase (GPx), Glutathione S-transferase (GST), and Catalase (CAT), while simultaneously reducing net positive suction head and ROS [127]. Both the hippocampus and the prefrontal cortex were shown to have increased levels of IL-10, which decreases the levels of proinflammatory mediators such as TNF-α and IL-1β [128]. The binding of pharmaceuticals is made possible by magnetic nanoparticles through entrapping the medications on the particles, covalent attachment, or adsorption [129]. In this investigation, we used chrysin-loaded magnetic PEGylated silica nanospheres (MChRPNPs) that were broadly defined and had the potential for enhanced protective features against the reversed memory deficits observed in rats induced with Aβ₂₅₋₃₅ [109]. Memory loss caused by exposure to Aβ₂₅₋₃₅ was reversed in rats by giving them chrysin at doses of 25 and 50 mg/kg of body weight [110]. Chrysin treatment has the potential to reduce oxidative damage, as shown in attenuating levels of thiobarbituric acid reactive substance and acetylcholinesterase, as well as a repair in the activity of antioxidant enzymes [41].

Chrysin inhibits inflammation in AD

It has been demonstrated that Aβ itself can operate as a pro-inflammatory agent, which leads to the activation of the inflammatory machinery [111]. Inflammation is a physiological response that has two main objectives. One is to shield the body from potentially deleterious stimuli, and the second is to initiate the healing process to bring the tissue back to its normal state of homeostasis [112]. The expression of pro-inflammatory cytokines including IL-1β, IL-6, and TNF-α can be elicited by activated microglia, which can then have an effect on the surrounding neurons and have the potential to play a potentially negative function [113]. Recent investigation has shown that activation of pro-inflammatory cytokines has many roles in both neurodegeneration and neuroprotection processes [114]. In addition, research on the origins of AD has shown that microglia is the initiator of the Aβ protein [115]. This protein is pro-inflammatory and is responsible for the activation of a number of other inflammatory components [116]. The application of chrysin resulted in a decrease in the expression levels of TNF-α, TBARS, caspase-3, and caspase-8. Chrysin considerably reduced inflammation by bringing down the expression of NF-kB/p65/IKK-β and the level of TNF-α [117]. In addition, chrysin had a strong inhibitory effect on apoptosis, by stimulation of Bcl-2 expression and the downregulation of caspase-3 expressions and Bax [118]. Inclusion, chrysin was able to reduce nitro-oxidative stress by restoring normal levels of 8-OHdG, NO, TBARS, CAT, and GSH, as well as manganese superoxide dismutase, NADPH oxidase 4, endothelial nitric oxide synthase), and nucleotides expression [119]. Chrysin also had a powerful inhibitory effect on the expressions of inducible COX-2 and NO synthase (iNOS) [120]. In addition, chrysin
oxidative stress generated by amyloid [130]. In rat hippocampus cell cultures, the interactions of MChRPNPs with Aβ were observed [131]. An anti-Alzheimer’s effect was observed in the rat hippocampus region when chrysin-loaded solid lipid nanoparticles were tested against Aβ25-35 caused oxidative stress [110]. It was discovered that the chrysin formulation was entirely effective in treating AD [110]. The formulation of chrysin (0.5 mg/kg) using nose-to-brain administration of transfersomal and composite vesicles showed a protective effect against doxorubicin-induced cognitive impairment in rats. It achieved this by reducing oxidative stress and inhibiting the TLR4/NF-kB/NLRP3 pathways [132]. The similar research was conducted by another researchers too [133,134].

**Examples of formulation of chrysin**

In comparison to chrysin suspension, it was discovered that chrysin-loaded nano-emulsion formulation significantly improved drug delivery to the hippocampus of rats [135]. The diabetic rats treated with chrysin-loaded nano-vesicles showed the greatest therapeutic benefit. To combat diabetes, putting chrysin onto nanovesicles has the potential to be investigated [136]. In MCF-7 human breast cancer cells, selenium-containing chrysin and quercetin successfully inhibited clonal development and hampered TrxR activity, which resulted in apoptotic cell death [137].

**CONCLUSION AND FUTURE PERSPECTIVES**

Chrysins has established itself as a useful polyphenol and is currently the subject of a significant amount of research. Chrysins is capable of a diverse range of biological activities, some of which include the protection against oxidative stress, inflammation, and neurodegeneration. Chrysin also possesses a wide spectrum of biological activity. The current review showed that chrysin has neuroprotective advantages in AD by lowering the aggregation of amyloid, activation of calcium, the association of heavy metals, and neuroinflammation. In spite of the numerous pre-clinical studies that have highlighted the conceivable function of chrysin in different neurological disorders, there is still a paucity of clinical data. This is mostly due to the fact that chrysin has a low bioavailability and metabolically unstable. Because of the importance of the blood–brain barrier in the progression of AD, we also placed an emphasis on the development of novel methods of administration and nanotechnology-based drug delivery systems.

**AUTHOR CONTRIBUTIONS**

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of the work. All the authors are eligible to be an author as per the International Committee of Medical Journal Editors (ICMJE) requirements/guidelines.

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