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Mechanistic insight unrevealing the potential of Diadzein in ameliorating the Alzheimer's disease

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ABSTRACT
Alzheimer's disease (AD), a progressive neurodegenerative disorder, is characterized by the accumulation of Aβ plaques, tau protein tangles, oxidative stress, and chronic neuroinflammation. Natural compounds, such as daidzein, a phytoestrogen found predominantly in soy products, may have therapeutic potential in mitigating the symptoms and progression of AD. Emerging research has suggested that daidzein exhibits a range of neuroprotective properties, including antioxidant, anti-inflammatory, and estrogenic effects, which are believed to be beneficial in Alzheimer's pathology. The phytoestrogen exhibits estrogenic activity, as declining estrogen levels have been linked to the increased risk of developing AD, especially in postmenopausal women. By binding to estrogen receptors, daidzein can modulate neuroinflammation and promote synaptic plasticity, which may protect against cognitive decline. Additionally, daidzein has been shown to inhibit Aβ aggregation, reduce oxidative damage to neurons, and improve mitochondrial function, all contributing to the neuroprotection observed in experimental models. According to study findings, daidzein provides neuroprotection by preventing oxidative stress, inflammation, and apoptosis, which are major causes of neuronal damage and degeneration. Moreover, studies revealed that daidzein inhibited oxidative stress by increasing SOD, CAT, and GSH levels and also it significantly decreased the p-eIF-2α levels and general protein synthesis. Additionally, it also ameliorated the increased AChE and MDA levels. In addition to this, it also reduced the ERK, JNK, Akt, NF-κB and GSK-3β levels. The abstract reviews the multifaceted role of daidzein in AD, highlighting its potential as a neuroprotective agent. Further clinical investigations are needed to fully elucidate its efficacy and potential as a complementary treatment in AD therapy.

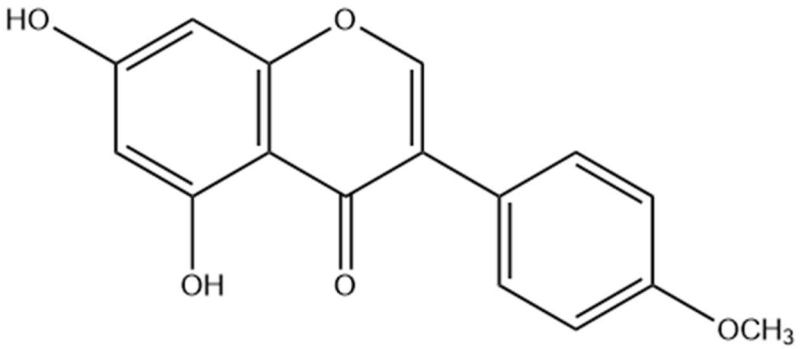
Keywords: *Daidzein, Alzheimer's disease, Neuroprotection, Aβ, NF-κB, GSK-3β, AChE.*

INTRODUCTION

Neurodegenerative disorders involve progressive dysfunction and loss of synapses and neurons and brain atrophy, slowly declining memories and cognitive skills, throughout a long process [1]. The most common neurodegenerative diseases are Alzheimer's disease (AD) and Parkinson's disease (PD). Depending on where in the brain the neurons disappear, numerous diseases can be identified by their distinctive symptoms [2]. The rise in the older population in recent years has contributed to the rise in the prevalence of certain age-dependent illnesses [3]. The neurological disorder known as dementia is defined as a gradual loss of ability to do instrumental and/or fundamental activities of daily life in two or more cognitive domains, such as memory, language, executive and visuospatial function,

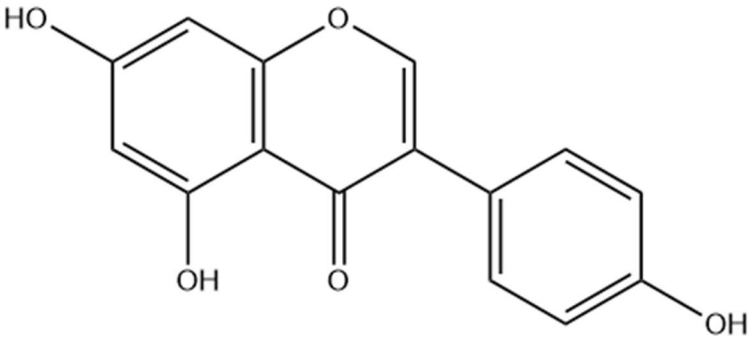
personality, and behavior. Approximately 80% of dementia diagnoses are due to AD which is by far the most frequent cause of dementia [4]. AD is an illness that typically lasts 8-10 years in clinical stages, with prodromal and preclinical phases lasting 20 years. The illness has an incidence of 1-3 percent and an estimated prevalence of 10-30 percent in people over 65 [5]. The upstream brain accumulation of amyloid-beta (Aβ) species and plaques, which occurs up to 20-30 years before the spread of tau, neuronal loss, and eventually clinical manifestations, is a descriptive hypothetical model of AD pathophysiology supported by translational studies conducted over the past 25 years, including experimental animal and human neuropathological, genetic, and in vivo biomarker-based evidence [6]. Compared to 4% of individuals with typical symptoms, 53% of patients with atypical presentations in a neuropathologically verified cohort with young-onset AD were misdiagnosed [7]. It was estimated that by 2050 the number of ill patients will increase to approximately 152 million, with the highest increase expected in developing countries [8]. According to histopathology, the two main characteristics of AD are (i) neurofibrillary tangles (NFTs), which are made up of hyperphosphorylated tau protein linked to microtubules, and (ii) significant brain shrinkage caused by amyloid plaques constituted of Aβ deposits [9]. Evidence indicates that APP, a transmembrane protein, extensively expressed in brain neurons, initiates the synthesis of Aβ [10, 11]. Research has shown that the neurotoxicity of Aβ oligomers and the interactions between acetylcholinesterase (AChE) and Aβ peptide are linked to cholinergic synaptic loss and the development of amyloid fibrils [12]. Inhibiting AChE to raise cholinergic levels is thought to be one of the treatment approaches that improves neuronal cell and cognitive function. AChEIs work by preventing the synaptic breakdown of acetylcholine, which causes ACh to continuously build up and cholinergic receptors to become active [13]. Furthermore, the interaction of reactive oxygen species (ROS) with glycoproteins causes AD. The byproducts, advanced glycoxidation end products (AGEs), are extremely harmful to nerve cells and could produce inflammatory mediators like TNF-α and IL-1, which would cause neuroinflammation in an AD brain [14]. Moreover, memory consolidation, neurogenesis, synaptic plasticity, long-term potentiation, and inflammation have all been connected to Glycogen Synthase Kinase-3 beta (GSK-3β) activity. Additionally, dysregulation of this GSK-3β has been observed to affect both Aβ and tau metabolism and toxicity in vitro and in vivo AD models [15]. Furthermore, the NF-κB signaling cascade also causes the brain to release several pro-inflammatory chemicals, including cytokines and chemokines, which contribute to AD patients' symptoms [16]. A naturally occurring phytoestrogen that belongs to the class of nonsteroidal estrogens, daidzein [7-hydroxy-3-(4-hydroxyphenyl)-4H-1-benzopyran-4-one] has a variety of pharmacological properties, including antihemolytic, antioxidant, and anti-inflammatory properties [17]. Recent studies have indicated that daidzein may also enhance the clearance of Aβ by promoting autophagy and boosting the activity of microglial cells, thereby reducing the burden of toxic protein aggregates [18]. Various lines of evidence indicate that daidzein significantly attenuated the dephosphorylation and activation of GSK-3β and also attenuated the tau hyperphosphorylation. In addition to this, western blot analysis revealed that it reduced the increased ERK, JNK, Akt, NF-κB, and GSK-3β levels (Table no. 1). Therefore, by synthesizing the published reports on the neuroprotective capabilities of daidzein, this review aims to elucidate their mechanistic potential in neuroprotection.

General chemistry of Isoflavones



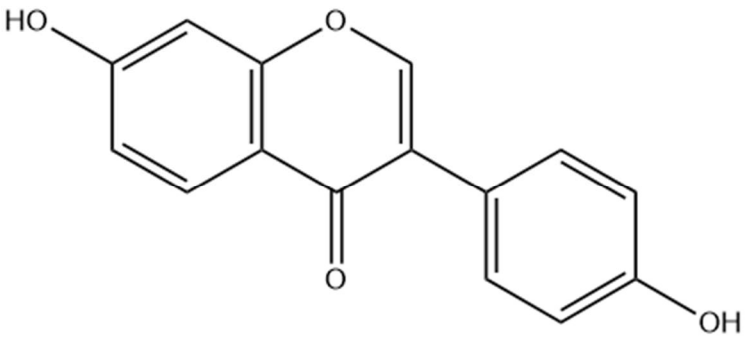
Biochanin A

Fig. no 1 Structure of Biochanin A



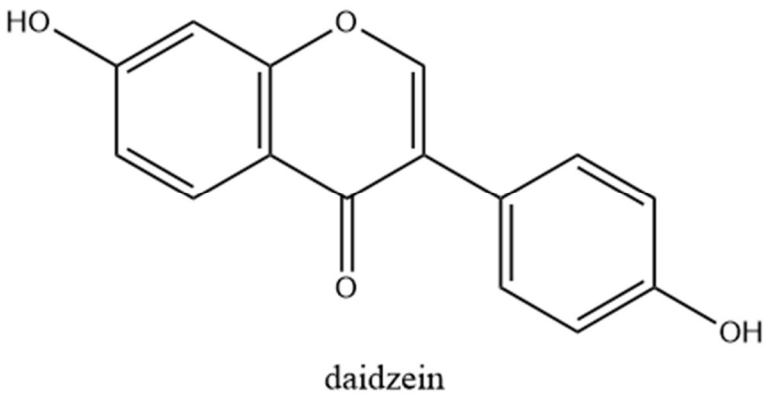
Genistein

Fig. no. 2 Structure of Genistein



Formononetin

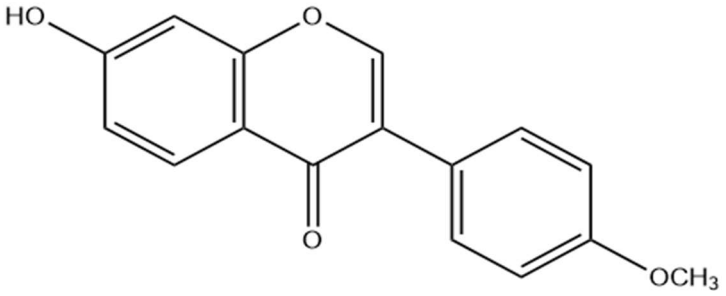
Fig. no. 3 Structure of Formononetin



daidzein

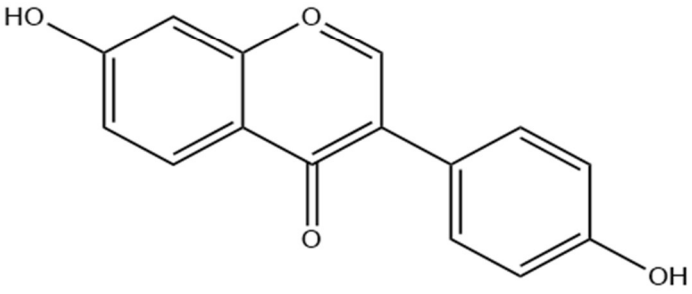
Fig. no. 4 Structure of Diadzein

General preparation of Diadzein



Formononetin

Demethylation



Diadzein

Fig.no. 5 Chemical Synthesis of diadzein from Formononetin

Mechanism of diadzein

Inhibition of oxidative stress by diadzein to potentiate Anti-Alzheimer's effect

Decreased SOD, CAT, and GSH an increase in oxidative stress. Oxidative stress plays a crucial role in AD [19]. Increased oxidative stress diminished the mitochondrial activity which posseses AD. To date numerous in-vivo and in-vitro studies were done that may results in neuroprotection effect of

daidzein especially in AD [20, 21]. By using streptozotocin-induced AD rat model author documented that daidzein increased the reduced memory in rats. Moreover, it also significantly increased the reduced locomotor activity. Furthermore, it also significantly increased the reduced SOD, CAT, and GSH in the brain. It also reduced the increased MDA level. Histopathological analysis revealed that it reversed the increased neuronal loss in the cerebral and hippocampus part of brain [20]. In homocysteine-mediated neuronal degeneration in SH-SY5Y cell model, author documented that daidzein significantly reduced the increased cytotoxicity. DAPI staining revealed that it ameliorates the increased apoptosis. Moreover, it also attenuated the induction of UPR in SH-SY5Y cells. Furthermore, it significantly decreased the p-eIF-2α levels and general protein synthesis. Moreover, it also significantly increased the intracellular SAH levels. It also posseses a consequent reduction in the SAM/SAH ratio in cells. Furthermore, it significantly attenuated the tau hyperphosphorylation. It also significantly increased the activity of PP2Ac. Moreover, it also significantly attenuated the dephosphorylation and activation of GSK-3β as shown in fig no. 6 [21].

Activity of diadzein on acetylcohlinesterase enzyme level leading to anti-Alzheimer's effect

AChE is an enzyme which dissociate the acetylcholine in acetyl and choline. Increased AChE results in increased dissociation of acetylcohline that reduced the concentration of acetylcholine in our body which posseses AD [22]. AChE plays a pivotal role in AD [23]. AChE is an enzyme responsible for breaking down acetylcholine, a neurotransmitter crucial for memory and cognitive function [24]. In AD, there is a marked deficiency of acetylcholine in the brain, which contributes to the cognitive decline observed in patients [25]. Moreover, occurrence of AD increased due to increased MDA level in the body. By using scopolamine induced amnesia author demonstrated that daidzein attenuated the scopolamine induced memory loss and also activated the ChAT activation [26]. Moreover, it also ameliorates the increased AChE and MDA levels in the hippocampus part of brain [27]. These various in-vivo and in-vitro models are presented in Table no 1.

Table no. 1: Various In-vitro and In-vivo model those represent the dephricizing activity in Alzheimer's disease

SR. No.	Model	Effect	Reference
1.	Streptozocin-induced Alzheimer's rat model	Increased the reduced locomotor activity. Increased the reduced memory. Increased the level of SOD, CAT, GSH. Reduced the increased MDA level.	20
2.	Homocysteine mediated neuronal degeneration SH-SY5Y cell model	Significantly reduced the increased cytotoxicity. Reduced the increased Apoptosis. Decrease the level of eIF-2α levels. Reduced the increased GSK-3β.	21
3.	Scopolamine induced amnesia	Attenuated the activity of ChAT activation. Ameliorated the increased AChE and MDA levels.	27
4.	Lipopolysaccharide stimulated BV2 microglial cell model	Significantly ameliorated the increased NO concentration. Reduced the increased COX-2 level and IL-6 production.	28

Activity of diadzein on Inflammatory cytokines to potentiate Anti-Alzheimer's effect

Mitogen activated protein kinase (MAPK) is a pathway that results in the activation of ERK, JNK pathway that further results in nuclear translocation of NF-κB. The nuclear translocation of NF-κB may potentiate the release of pro-inflammatory cytokines and COX-2 which results in neuroinflammation and also AD. Mainly this MAPK is activated due to increased oxidative stress or nitric oxide [29, 30]. By using LPS induced astrocyte cell model author documented that daidzein increased the reduced proliferation and cell viability. Moreover, it also reduced the increased Aβ and NO. Furthermore, it also ameliorated the increased effect of IL-6, TNF-α, ER-β, IL-1 mRNA levels [31]. By using H19-7 neuronal cell line model author documented that daidzein increased the reduced cell viability. Moreover, it also increased the reduced cell proliferation in the hippocampus part. Furthermore, it also significantly increased the BDNF mRNA level [32]. By using scopolamine induced amnesia mice model author documented that daidzein significantly increased spontaneous alteration. Furthermore, it also significantly reduced the step-through latency time and also restored the memory dysfunction induced by scopolamine. Western blot analysis revealed that it significantly enhanced the expression of BDNF, p-ERK, p-CREB [27]. GSK-3β plays a crucial role in the pathogenesis of AD [33]. This kinase is involved in several key processes that contribute to the development and progression of AD, including the hyperphosphorylation of tau protein, the formation of NFTs, and the production and accumulation of Aβ peptides [34]. Increased oxidative stress increased the production of Aβ in the brain that further also activate the pro-inflammatory cytokines and ROS that posseses neurodegeneration. Western Blot analysis revealed that it reduced the increased ERK, JNK, Akt, NF-κB and GSK-3β levels [28]. By using lipopolysaccharide stimulated BV2 microglial cells author demonstrated that MTT assay revealed that daidzein significantly ameliorated the increased NO concentration. Furthermore, it also reduced the increased iNOS, COX-2 levels and IL-6 production in a dose dependent manner. Moreover, it also reduced the increased ROS in LPS stimulated cells [35].

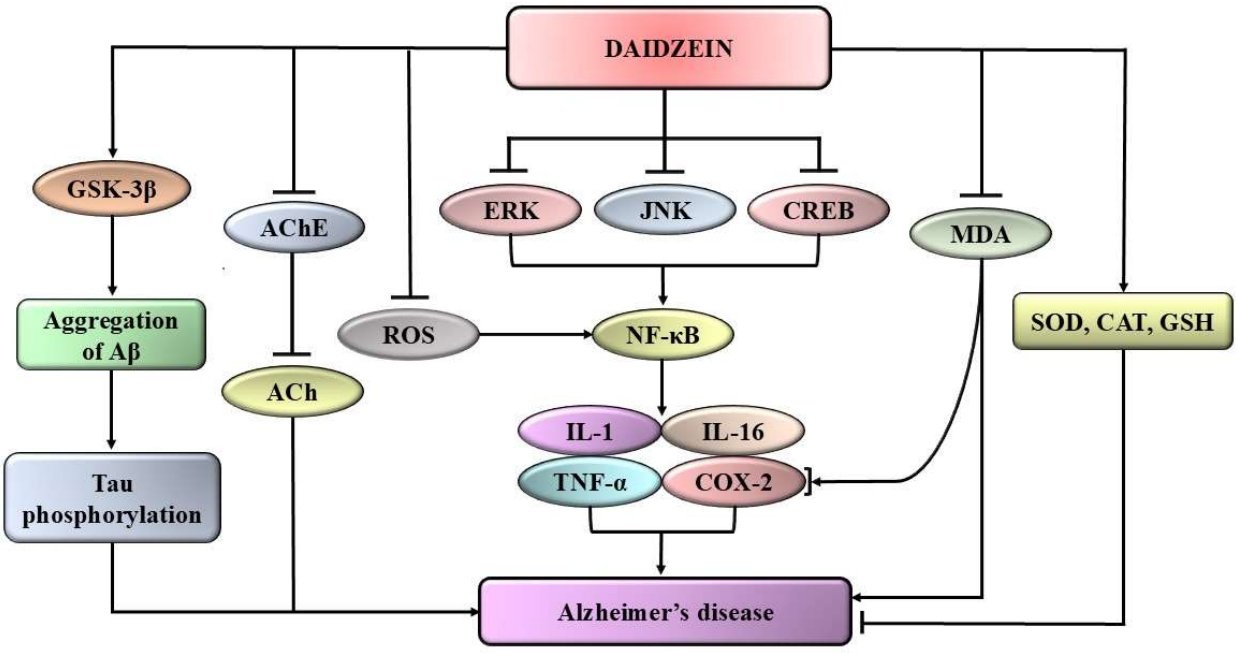


Fig. no. 6 Mechanistic interplay of daidzein in dephricizing the alzheimer's disease

CONCLUSION

Daidzein, a naturally occurring phytoestrogen, exerts antioxidant, anti-inflammatory, and estrogenic effects making it a potential therapeutic candidate for mitigating neuronal damage and cognitive decline. It has been prepared after the demethylation of formononetin. It has demonstrated efficacy in reducing Aβ aggregation, combating oxidative stress, and promoting synaptic plasticity, all of which are critical for maintaining neuronal health. It appears to attenuate the dephosphorylation and activation of GSK-3β and also attenuated the tau hyperphosphorylation. Moreover, it reduced the iNOS, COX-2 levels, and IL-6 production. In addition to this, it also reduced the ERK, JNK, Akt, NF-κB, and GSK-3β levels. In summary, several conclusive evidence underscores the neuroprotective potential of daidzein, highlighting its mechanism of action. These findings suggest that daidzein's multifaceted mechanisms offer a compelling avenue for developing novel neuroprotective strategies, particularly for individuals at risk of or suffering from neurodegenerative disorders.

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