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MINI REVIEW

Countering oxysterol-driven neurodegeneration: diosgenin as a privileged steroidal scaffold for novel Alzheimer's disease therapeutics

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Abstract

Alzheimer's disease (AD) is a multifactorial neurodegenerative disorder characterized by amyloid-β accumulation, tau pathology, oxidative stress, neuroinflammation, and lipid dysregulation. The limited success of single-target therapeutics has shifted attention toward multi-target phytotherapeutics with pleiotropic neuroprotective properties. Diosgenin, a steroidal sapogenin structurally related to cholesterol-derived oxysterols, has emerged as a promising candidate owing to its antioxidant, anti-inflammatory, and neurorestorative activities. This mini-review highlights diosgenin as a structural antagonist to 7-ketocholesterol (7-KC), emphasizing its ability to modulate oxidative stress, amyloidogenesis, neuronal survival, and membrane stability. Additionally, translational strategies including semi-synthetic modification and nanocarrier-mediated brain delivery are discussed as future therapeutic avenues for AD management.

Keywords: Alzheimer's disease, diosgenin, 7-ketocholesterol, neuroprotection, steroidal sapogenins

Introduction

Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by spatiotemporally ordered neuronal loss that initiates in the entorhinal cortex (EC), the brain region exhibiting the earliest histological alterations, including neurofibrillary tangle formation and layer 2 neuronal cell death. The hippocampus, amygdala, and para-hippocampal gyrus, all crucial regions for episodic memory consolidation, are then affected by degeneration. Atrophy spreads to the frontal cortex, temporal lobe, and related limbic areas as the disease progresses, leading to increasing impairments in language, executive function, and overall cognition. The temporal sequence of cognitive decline is reflected in this regional progression: memory impairment comes before language problems, which come before executive dysfunction [1-4]. The brain's neurons are essential to all human functions, including thinking, speaking, and walking. Since the neurons in these regions of the brain are the first to be damaged, memory, language, and thinking (cognitive) problems are frequently the earliest indications of AD. An estimated 7.2 million Americans aged 65 years and older are currently living with Alzheimer's dementia, with projections reaching 13.8 million by 2060 barring the development of medical breakthroughs to prevent or cure Alzheimer's disease [5]. If medical advancements are not made to prevent or treat AD, this figure could increase to 13.8 million by 2060. In 2022, 120,122 AD deaths were listed on official death certificates. AD has been the seventh most common cause of death in the US since 2020, when COVID-19 rose to the top 10 [5]. A wide range of pathological pathways, such as neurotransmitter signaling, inflammation and immune processes, Aβ and tau biology, synaptic dysfunction, metabolism and bioenergetics, oxidative stress, proteostasis, vascular pathology, APOE/lipid pathways, the gut–brain axis, circadian regulation, epigenetic mechanisms, neuronal loss, and neurogenesis, is involved in current AD drug development. The emerging understanding that

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AD is a complex condition needing pathway-integrated therapy techniques is reflected in the development of a smaller group of candidates as multi-target medicines [6-8]. Because AD is a multifaceted illness involving intricately linked pathways that cannot be stopped by blocking a single protein, single-target Alzheimer's medications (mostly anti-amyloid or anti-tau) have mainly failed. Thirty-five percent of AD medications under development are repurposed compounds [9]. By simultaneously addressing oxidative stress, neuroinflammation, cholinergic deficiencies, and protein aggregation, multi-target phytotherapeutics offer a systemic approach. Compared to narrow monotherapies, this multi-pathway modulation more successfully restores homeostatic balance. Numerous substances originating from plants have the potential to treat AD. They function by focusing on important disease-related enzymes, such as acetylcholinesterase (AChE), butyrylcholinesterase (BuChE), β-secretase, γ-secretase, and monoamine oxidases (MAOs). Clinical trials are currently testing a number of these natural compounds in an effort to create novel medications [10, 11]. The cholesterol-derived oxysterol 7-ketocholesterol (7-KC) has become a prominent mediator of oxidative stress, neuroinflammation, and neuronal damage in AD brain tissue, and recent clinical and experimental evidence indicates that lipid peroxidation and dysregulation of cholesterol metabolism contribute to AD pathogenesis [12-15]. According to new research, membrane-associated 7-KC can increase amyloidogenic amyloid precursor protein (APP) processing, change lipid raft architecture in neurons and astrocytes, and intensify cell death pathways such ferroptosis and reduced autophagic flux. Therefore, targeting 7-KC with small compounds that lessen its membrane-associated toxicity may offer a possible treatment approach for Alzheimer's disease [16].

Diosgenin as a structural counterpart to 7-ketocholesterol

Diosgenin was chosen because of its structural similarity to oxysterols generated from cholesterol, which share the same tetracyclic steroidal backbone but have essentially different biological characteristics. Diosgenin exhibits strong antioxidant, anti-inflammatory, neurogenic, and membrane-stabilizing properties in contrast to 7-KC, a significant non-enzymatic oxidation product of cholesterol that aggravates neurotoxicity through mitochondrial dysfunction, lipid peroxidation, reactive oxygen species (ROS) generation, ferroptosis, and neuroinflammation via TLR4 activation [16]. While avoiding the cytotoxic membrane permeability changes and oxidative stress induction typical of 7-KC, its steroidal sapogenin architecture permits biophysical interactions with lipid-rich neuronal membranes, as demonstrated by X-ray diffraction and differential scanning calorimetry studies demonstrating concentration-dependent modulation of phospholipid bilayer structural perturbation and phase transition cooperativity. Additionally, diosgenin has been shown to have strong neuroprotective effects in experimental models of Alzheimer's disease. Diosgenin is an appealing phytochemical scaffold for the simultaneous targeting of several pathogenic pathways in AD because of these complex processes, which include antioxidant, anti-inflammatory, anti-apoptotic, and neuro-regenerative qualities. Additionally, diosgenin has been shown to have strong neuroprotective effects in experimental models of Alzheimer's disease. Diosgenin is an appealing phytochemical scaffold for the simultaneous targeting of several pathogenic pathways in AD because of these complex processes, which include antioxidant, anti-inflammatory, anti-apoptotic, and neuro-regenerative qualities [17-20]. Steroidal compounds have long been at the forefront of drug discovery because of their rigid frameworks, membrane permeability, and receptor-binding versatility. Among them, diosgenin, a naturally occurring steroidal sapogenin [21, 22], has consistently attracted attention for its bioactivity across cancer, metabolic, and inflammatory diseases. In contrast, 7-KC, a pro-oxidant oxysterol, contributes to atherosclerosis, AD, and retinal degeneration by driving oxidative stress, mitochondrial dysfunction, and cell death [23, 24]. This review highlights diosgenin's unique potential as a structural antagonist to 7-KC, positioning it as a scaffold for therapeutic innovation in phytotherapy-driven drug design. Diosgenin ($C_{27}H_{42}O_3$; molecular weight 414.62 g/moL) is a rigid, highly lipophilic steroidal sapogenin characterized by a high fraction of sp^3-hybridized carbon (0.93), zero rotatable bonds, low polarity. It has a topological polar surface area (TPSA) 38.69 Å2, and limited hydrogen-bonding capacity. Collectively, these physicochemical features favor membrane association and support its use as a structurally constrained scaffold in steroid-based drug design. Medicinal chemists recognize that subtle structural variations in steroidal frameworks can profoundly influence biological outcomes. Nobel laureate James Black famously remarked that "beginning with an old drug is the most fruitful basis for the discovery of a new drug," a principle equally applicable to natural product scaffolds. Diosgenin exemplifies this philosophy: while sharing the cyclopentanoperhydrophenanthrene nucleus with oxysterols, it diverges in key substituents that confer redox stability and non-toxic pharmacodynamics [25]. A comparison underscores these contrasts. Diosgenin is a spirostane steroidal sapogenin, distinguished by a rigid spiroketal substituent at C17, whereas 7-KC is a cholestane oxysterol with a ketone at C7. Both share a conserved 3β-hydroxy group and Δ^5 unsaturation, but their functional divergence is profound: diosgenin acts as an antioxidant and non-toxic sterol, while 7-KC is pro-oxidant and pro-apoptotic. This structural antagonism provides a rationale for considering diosgenin as a counter-molecule to pathological oxysterols [26, 27]. Several drug-like features of diosgenin reinforce this notion. The spiroketal moiety stabilizes the D-ring and resists oxidative degradation, reducing susceptibility to enzymatic oxidation. Unlike 7-KC, which bears an electrophilic center capable of initiating harmful thiol reactions, diosgenin is chemically inert in this respect, thereby offering a safer scaffold for drug de-

rivatization. Furthermore, the preserved 3β-hydroxy group facilitates interactions with sterol-sensing proteins and nuclear receptors such as Liver X Receptor (LXR) and Farnesoid X Receptor (FXR), enabling functional mimicry of oxysterols without incurring cytotoxic liabilities. Its lipophilicity (log*P* ~4.9) supports membrane integration and oral bioavailability, further enhancing its translational potential [28]. It has long been known in medicinal chemistry that minute structural alterations in steroidal scaffolds can result in significant variations in biological activity. In this context, diosgenin provides an instructive contrast to 7-KC: both retain a steroidal nucleus with a 3β-hydroxyl group and Δ^5 unsaturation, yet they differ markedly in their physicochemical and biological effects, with diosgenin generally associated with cholesterol-lowering and membrane-modulatory properties, whereas 7-KC is widely regarded as a pro-oxidant, membrane-damaging oxysterol [29-32]. Diosgenin is a prime example of this idea: although it and 7-KC share a conserved 3β-hydroxy group and Δ^5 unsaturation, their functional profiles are entirely different. 7-KC contains a C7 oxo group that alters the electronic and physicochemical properties of the sterol nucleus, contributing to membrane perturbation and pro-oxidant toxicity. In contrast, diosgenin is a spiroketal steroidal sapogenin with a rigid architecture that is comparatively resistant to oxidative modification. This structural divergence may underlie diosgenin's ability to modulate sterol-rich membranes as a redox-stable scaffold without reproducing the cytotoxic liabilities associated with 7-KC. The term "structural antagonist" here does not refer to classical receptor antagonism. Rather, it explains how diosgenin functions as a membrane-compatible sterol analogue that inhibits downstream oxidative/inflammatory signaling from 7-KC, competitively affects lipid microdomain architecture, and lessens oxysterol-induced membrane damage. In this context, "antagonism" does not refer to direct receptor blocking but rather to physicochemical and functional interference. Figure 1 depicts the structural and functional comparison of diosgenin and 7-ketocholesterol (7-KC).

Polypharmacological mechanisms in neuroprotection

Diosgenin has a multi-target neuroprotective profile that could be related to AD. Its lipophilicity and sterol-like structure may enable interactions with membrane environments, thereby preventing oxysterol-induced breakdown of lipid rafts. In addition, diosgenin has been shown to reduce oxidative stress, inflammation, and amyloid-associated damage in experimental animals by modulating metabolic nuclear receptor signaling and activating cytoprotective pathways such as autophagy and Nrf2-linked antioxidant responses [17, 33, 34]. Additionally, new research indicates that diosgenin's antioxidant action, improvement of Nrf2 signaling, maintenance of mitochondrial function, and decrease of lipid peroxidation may

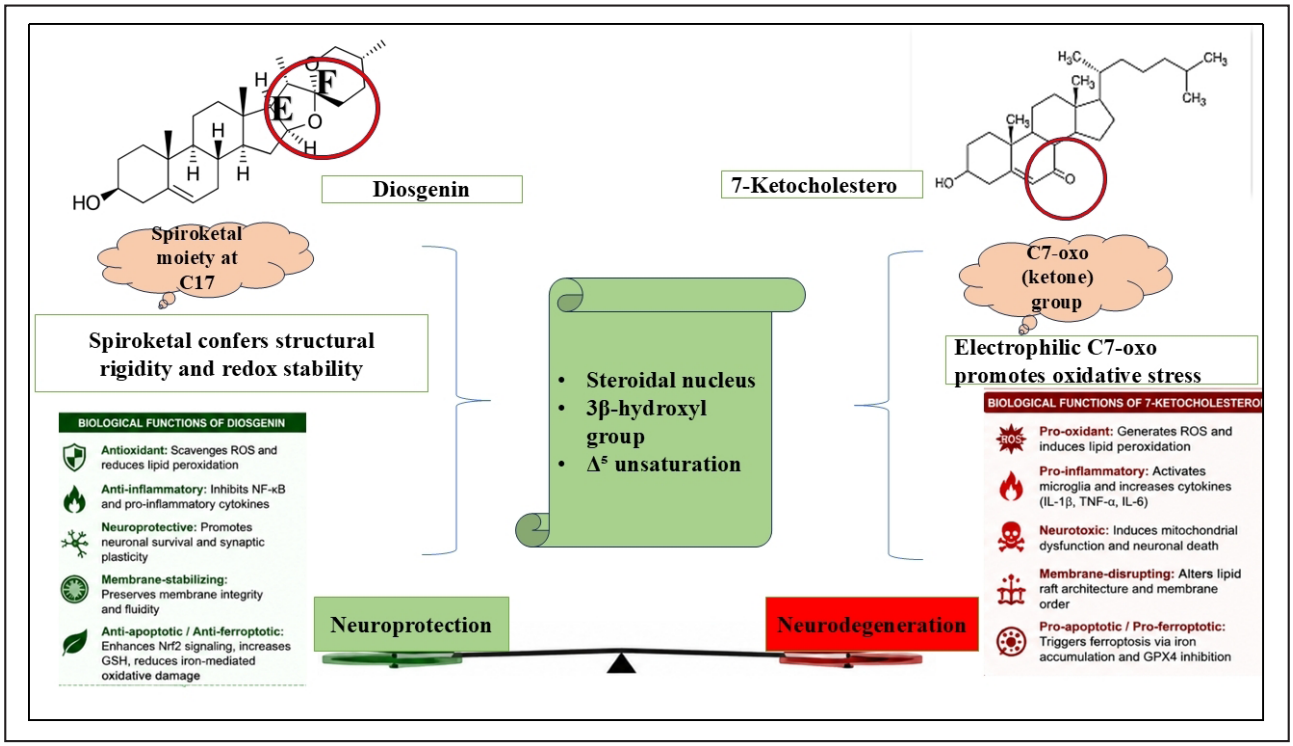

Figure 1. Structural and functional comparison of diosgenin and 7-ketocholesterol (7-KC). Both molecules share a common steroidal nucleus containing a 3β-hydroxyl group and Δ^5 unsaturation. However, diosgenin contains a characteristic spiroketal moiety at C17 that confers structural rigidity, redox stability, and neuroprotective properties, whereas 7-ketocholesterol possesses an electrophilic C7-oxo (ketone) group associated with oxidative stress, inflammation, ferroptosis, and neuronal injury. These structural differences underpin their opposing biological effects, with diosgenin exhibiting antioxidant, anti-inflammatory, membrane-stabilizing, and neuroprotective activities, while 7-ketocholesterol promotes neurodegenerative processes. The balance between these contrasting mechanisms highlights diosgenin as a potential structural and functional antagonist of 7-ketocholesterol-induced neurotoxicity in Alzheimer's disease.

reduce ferroptosis-associated pathways. These findings may further support diosgenin's protective benefits against oxysterol-induced neurotoxicity, as 7-KC has been linked to ferroptotic neuronal death. In rat models with $A\beta_{1-42}$, diosgenin dramatically enhances cognition, restoring spatial learning and memory in radial arm maze and passive avoidance tests. It protects hippocampal neurons, lessens oxidative stress and neuroinflammation, and lowers the burden of Aβ plaque. Mechanistically, diosgenin promotes neurogenesis and synaptic repair by stimulating NGF, activating PI3K/Akt signaling, inhibiting GSK3β, and upregulating brain-derived neurotrophic factor (BDNF) and cAMP response element-binding protein (CREB) phosphorylation. Diosgenin reduces acetylcholinesterase activity and rescues memory impairments in scopolamine and Aβ neurotoxicity models. These results show the multitarget neuroprotective effects of diosgenin against AD pathogenesis [35-37].

The semi-synthetic roadmap for blood–brain barrier (BBB) penetration

From a drug discovery perspective, structural-activity relationship and formulation techniques may be utilized to alleviate diosgenin's inherent bioavailability constraints and enhance its translational potential for Alzheimer's disease. A viable method to enhance aqueous solubility and adjust pharmacokinetic characteristics at the scaffold level is C3 derivatization with amino-containing groups or conjugates based on amino acids. While lipid-based nanocarriers or polymeric nanoparticles can further increase brain delivery and overall central nervous system (CNS) exposure, semi-synthetic modification of the steroidal core may be utilized to improve metabolic stability [35, 38-40]. The therapeutic implications are significant. By structurally resembling oxysterols while functionally avoiding their liabilities, diosgenin derivatives could competitively inhibit 7-KC binding at membrane microdomains or receptor sites, reducing its accumulation in vulnerable tissues. This strategy may hold value in conditions such as vascular dysfunction, age-related macular degeneration, and neurodegenerative disorders where oxysterol toxicity is implicated. From a drug discovery standpoint, diosgenin's scaffold offers opportunities for semi-synthetic modification, allowing medicinal chemists to generate redox-stable analogues tailored toward selective receptor modulation, improved pharmacokinetics, or targeted delivery.

Conclusions

Diosgenin represents a promising multi-target neuroprotective scaffold for AD owing to its structural compatibility with sterol-rich neuronal membranes and its ability to counteract oxidative stress, neuroinflammation, amyloid toxicity, and synaptic dysfunction. Unlike the pro-oxidant oxysterol 7-ketocholesterol, diosgenin exhibits redox-stable and neurorestorative properties that may attenuate multiple pathological hallmarks of AD. Future investigations focusing on BBB-targeted formulations, semi-synthetic optimization, and clinical translation may establish diosgenin as a novel phytotherapeutic candidate for AD intervention.

Declarations

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