



Elucidating the Multi-Targeted Effects of Z-Guggulsterone in Alzheimer's Disease: Insights from Network Pharmacology and Molecular Docking

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Keywords

Alzheimer's disease, Z-Guggulsterone, Molecular docking, Network Pharmacology, Neurodegenerative disease

Abstract

Z-Guggulsterone (Z-GS) is a natural steroid that has exhibited notable neuroprotective and memory-enhancing effects. In the current bioinformatic analysis, the therapeutic effects of Z-GS against Alzheimer's disease (AD) were investigated using network pharmacology and molecular docking. Initially, the pharmacokinetic profile of Z-GS was assessed following the identification of potential target proteins from various online databases. To elucidate the cellular, molecular, and biological functional implications of the shared targets, GO enrichment and KEGG analysis were utilized to identify the relevant signaling pathways. Furthermore, the PPI network was subjected to functional and topological analyses, leading to the identification of hub targets. Finally, molecular docking was done to validate the interactions between Z-GS and the identified hub targets, providing insights into the binding affinity and interaction modes. The analysis identified ten key genes, BACE1, BCHE, CTSD, PARP2, DRD2, SRD5A1, GRM1, CYP19A1, MAPK3, and TGFBR1, that significantly contribute to the complex AD pathology. In molecular docking, among the screened targets, PARP2 and BChE emerged as the most promising with scores of -10.2 and -10.3, respectively, highlighting a high propensity for interaction. Although BACE1 also showed a significant binding affinity, scoring -8.6. While remaining targets (MAPK3, CTSD, and CREB) demonstrated weaker binding interactions, with scores of -7.9, -7.7, and -7.3. These key signalling proteins and enzymes contribute significantly to molecular cascades that drive pathological events, cognitive decline, and neurodegeneration. Hence, this integrated analysis prioritized these genes as key targets, suggesting that Z-GS exerts potential therapeutic effects by modulating these critical proteins implicated in AD pathogenesis.

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1. Introduction

Alzheimer's disease is a progressive, irreversible neurodegenerative disease and a common cause of dementia in the elderly. It is characterized by a gradual decline in cognitive function, resulting from progressive atrophy of brain tissue and the disruption of crucial synaptic connections within neural pathways [1]. Globally, more than 50 million people are experiencing AD-associated cognitive decline, with the number of new cases rapidly increasing due to longer life expectancies and an expanding elderly population [2]. AD represents a major public burden in the United States, causing over 120,000 deaths in 2019, and with an estimated 12.7 million individuals aged over 65 expected to be affected by 2050 [3]. Despite its widespread prevalence, the underlying cause for 95% of AD cases remains unclear, limiting

the prevention strategies and risk assessment [4]. The hallmark pathological features of AD are marked by excessive buildup of amyloid plaques (A β) and neurofibrillary tangles (NFT) within the brain. These pathological hallmarks contribute to synaptic dysfunction, neuronal loss, oxidative stress, the disruption of glutamatergic neurons and acetylcholine levels, particularly in the hippocampus and cortex. These affect the learning, memory, motor skills, and mood regulation in AD patients [5]. Furthermore, genetic, lifestyle, and environmental factors can also contribute to the sudden onset of AD in adults [6].

Currently, there is no cure for AD, but the existing medications (donepezil, rivastigmine, galantamine,

and memantine) provide temporary symptom relief without addressing the underlying cause. The new drugs (Lecanemab, Donanemab) aim to target amyloid pathology, one of the hallmarks of AD. Despite persistent research efforts, AD remains incurable. Existing therapies are limited to cholinergic and protein-based approaches, highlighting the urgent need for therapies that address the underlying mechanisms of the disease [7]. Herbal plants have gained attention as alternative approaches for AD due to their multitarget actions and favorable safety profiles. These plants and their phytochemicals, such as flavonoids, terpenoids, and resins, are increasingly recognized for their potential in treating neurodegenerative diseases. These compounds offer neuroprotective benefits through antioxidant, anti-inflammatory, and neurotransmitter-modulating actions and may even promote neurogenesis [8]. Fortunately, Guggul, an oleo-gum resin with a long history in Ayurvedic medicine, has been shown to address a broad spectrum of disorders. It is harvested from *Commiphora* species like *Commiphora mukul* and *Commiphora wighti* contains bioactive phytoconstituents most notably E and Z-Guggulsterone. Guggulsterone (GS), a key component of guggul resin existing as E (cis) and Z (trans) isomers, also demonstrates diverse medicinal benefits. GS has substantial evidence supporting its use in managing numerous chronic health conditions [9], [10]. Its therapeutic applications also encompass lipid metabolism, arthritis, gout, hepatic, obesity, and dermatological conditions. Z-GS has demonstrated significant neuroprotective properties in numerous diseases, such as AD, depression, and cerebral ischemia, along with modulation of diverse autoimmune disorders and inflammatory conditions, including pancreatitis [11]. Due to these promising findings, this study aims to investigate the therapeutic efficacy of Z-GS against AD through a combined approach of network pharmacology and molecular docking [12], [13], [14].

Recent advances in bioinformatics have also led to the establishment of extensive publicly available databases, offering rich datasets for drug discovery. Integrating the data from multiple databases with sophisticated bioinformatic tools allows efficient identification of the molecular targets associated with natural compounds [15], [16], [17]. Network pharmacology represents a system-level approach to drug discovery that seeks to comprehensively understand the intricate relationships between diseases and medications. Unlike traditional methods that focus on single drug-target interactions, network pharmacology uses databases, target prediction tools, PPI networks, and enrichment analysis that emphasize a broad biological context. Hence, this approach recognizes that diseases are complex and involve multiple biological pathways and molecular interactions. This study utilized network pharmacology to uncover potential protein targets of Z-GS and explore its mechanisms in AD. Additionally, molecular docking was then employed to validate the identified targets as potential

mediators of Z-GS, anti-AD effects [18], [19], [20].

2. Materials and Methods

The canonical SMILES for Z-GS “CC=C1C(=O)CC2C1(CCC3C2CCC4=CC(=O)CCC34C)C” was recovered from the PubChem (<https://pubchem.ncbi.nlm.nih.gov/>). Afterwards, structure-based pharmacological parameters, including molecular weight, drug-likeness, number of H-bond acceptors and donors, and GI absorption, were obtained through SwissADME (<http://www.swissadme.ch/>) [21]. Additionally, the blood-brain barrier (BBB) score, obtained from Molsoft (<https://molsoft.com/mprop/>), was also included as a crucial parameter in the analysis [22], [23].

The potential targets were identified using the Swiss Target Predictor (<http://www.swisstargetprediction.ch/>) and the STITCH database (<http://stitch.embl.de/>) to determine the putative targets of Z-GS. The SMILES string of Z-GS was used as input to both databases, enabling target prediction using structural similarity algorithms. Subsequently, the predicted target proteins from both sources were combined, and duplicate entries were eliminated to produce a non-redundant list of potential targets [24].

2.1. Collecting Targets Related to AD

The disease-associated genes were retrieved from the OMIM database (<https://www.omim.org/>) and the GeneCards database (<https://www.genecards.org/>) to obtain the AD-related targets. To demonstrate the common targets between Z-GS and AD, the respective target lists were imported into the Venn diagram website to get the intersection target Venn diagram (<https://bioinformatics.psb.ugent.be/w/>) [25].

2.2. Construction and Analysis of The Protein-Protein Interaction (PPI) Network

The overlapping target genes, derived from the Venn diagram, were input into the STRING database to create a PPI network. Only interactions with a confidence score of ≥ 0.4 for 'Homo sapiens' were retained for reliability. The resulting PPI data was subsequently imported into Cytoscape 3.10.2 software for network construction and further analysis.

2.3. Gene Ontology Enrichment Analysis of Core Target Genes

SR Plot was used to accomplish Gene Ontology (GO) functional annotation and Kyoto Encyclopedia of Genes and Genomes (KEGG) signaling pathway analyses. The top 20 enrichment analysis results, ranked by ascending P-values, were selected and presented as bar charts and bubble charts.

2.4. Construction of Compound-Targets-Pathways Network

A compound-target-pathway network was constructed using Cytoscape version 3.10.2 software to describe the potential anti-AD effects of Z-GS. In

the created network, nodes representing compounds, distinguished by different colours and shapes.

2.5. SynGo Gene Ontology

The SynGO online platform (<https://www.syngoportal.org/>) was utilized to investigate the functions and synaptic locations of the potential anti-AD genes. This allowed for the identification of enrichment patterns associated with AD pathology [26].

2.6. Phenotypic-genotypic Correlation Analysis

VarElect (<https://varelect.genecards.org/>) was used to identify direct and indirect gene-disease associations based on phenotypic features. By inputting the potential anti-AD gene list and the phenotypic keyword 'Alzheimer's disease', VarElect generated a table detailing gene association, average disease-causing likelihood, and scores [27], [28].

2.7. Molecular Docking

CB Dock 2 (<https://cadd.labshare.cn/cb-dock2/>) was used to evaluate the molecular binding affinity between Z-GS and AD's core targets. The three-dimensional (3D) structure of Z-GS was obtained from the PubChem database in SDF format. The crystal structure of core targets, including MAPK3, CTSD, PARP2, CREB, BACE1, and BChE, was obtained from the RCSB Protein Data Bank

targets, and disease-related pathways were (<http://www.rcsb.org/>).

3. Results and Discussion

The structural information of Z-GS was obtained from PubChem, and relevant information was retrieved from Swiss ADME and Molsoft, indicating high GI absorption, good BBB permeability, a Drug likeness score of 0.72, and a Bioavailability Score of 0.55, thereby affirming good oral absorption. This finding aligns with previously published research on the bioavailability of Z-GS.

3.1. Analysis of Targets of Z-Guggulsterone and AD

A total of 100 protein targets were identified as potentially affected by Z-GS, which was collected from Swiss target prediction and STITCH, after removing duplicate targets (Table S1). Databases such as OMIM and GeneCards were used to identify potential targets relevant to AD. The set of genes called "genes of AD", containing 14285 genes, was finalized by integrating the obtained genes and removing superfluous data. A Venn diagram analysis revealed 92 shared targets between Z-GS and the AD gene dataset (Figure 1a). These 92 proteins were prioritized as potential therapeutic targets of AD against 14285 disease-related targets (Table S2).

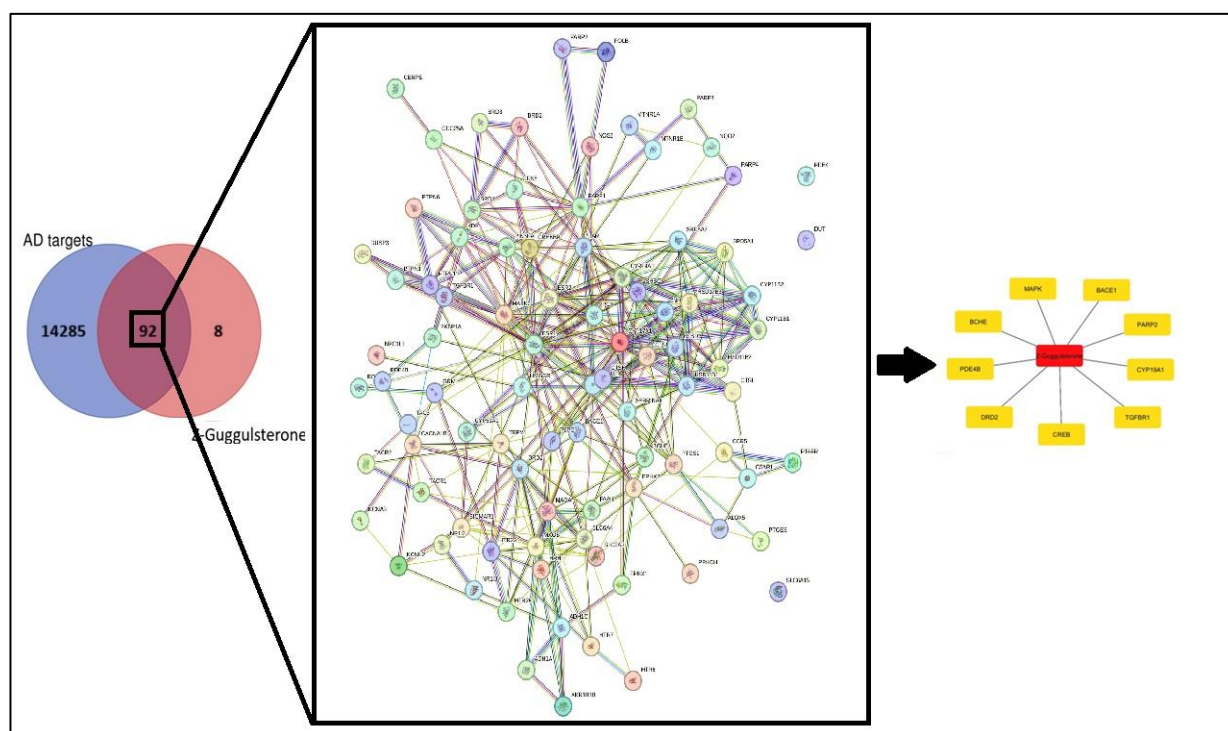


Figure 1: (a) Common overlapping 92 targets of Z-Guggulsterone and AD, (b) Protein-protein interaction network overlapped targets obtained from the STRING database, consisting of 91 nodes and 352 edges with an average node degree value of 7.74, and (c) The top 10 Hub genes (identified within the Z-Guggulsterone target network that were obtained from CytoHubba's MCC algorithm).

3.2. Construction and Analysis of The Protein-Protein Interaction (PPI) Network of Z-Guggulsterone

PPIs are crucial for understanding disease-related protein functions and cellular pathways. Given their

involvement in diseases like cancer and AD, PPIs represent a promising strategy for drug and protein design. Hence, to identify the potential interconnectivity and functional relationships among these targets, the selected 92 targets were input into

the STRING database to construct a PPI network edges, with an average node degree value of 7.74 (Table S3). Here, nodes represent target proteins, edges represent interactions between them, and the degree value indicates the strength of these interactions. The PPI network was further analysed and visualised using Cytoscape 3.10.2 (Table S4), revealing a network of nodes and edges. CytoHubba's MCC algorithm was then used to extract the top 10 nodes or hub genes (Figure 1c) with the shortest paths to identify core targets. The analysis identified ten key genes (BACE1, BCHE, CTSD, PARP2, DRD2, SRD5A1, GRM1, CYP19A1, MAPK3, and TGFBR1) with high connectivity and centrality within the PPI network, implying their substantial regulatory influence in AD pathogenesis. BACE1 is central, initiating the formation of A β plaques, a hallmark of AD. BChE further reduces acetylcholine, a neurotransmitter vital for memory, particularly in later AD stages. CTSD dysfunction contributes to impaired protein clearance, a key feature of the disease. Dysregulation of DRD2 (Dopamine Receptor D2) can impact cognitive and behavioral symptoms. The MAPK pathway, especially p38 MAPK, is frequently activated, driving neuroinflammation and tau pathology. Lastly, elevated MAO activity in AD increases oxidative stress, promoting A β deposition and tangle formation. Together, these molecular players highlight the intricate mechanisms driving AD progression. This comprehensive approach provides a robust framework for understanding Z-GS's potential therapeutic mechanisms in AD by elucidating its interactions with these critical

(Figure 1b). The analysis comprises 91 nodes and 352 molecular targets.

3.3. GO and KEGG Enrichment Analysis

SR Plot was used to perform GO and KEGG enrichment analysis on the 92 potential Z-GS targets for AD treatment. GO analysis (Fig. 2) revealed substantial enrichment in biological processes (BP) such as plasma membrane organisation, GPCR signaling, MAPK cascades, and steroid/hormone metabolic processes (Table S5). Cellular components (CC) enriched included endolysosomes, membrane rafts/microdomains, nuclear envelope lumen, and synaptic membrane components (Table S6). Molecular functions (MF) showed enrichment in phospholipase C activity, steroid/nuclear receptor binding/activity, steroid dehydrogenase activity, and GPCR serotonin activity (Table S7). These results indicate that Z-GS may modulate AD through diverse cellular and molecular mechanisms. Subsequently, KEGG pathway analysis (Fig. 3) identified enriched pathways, including calcium signaling, cAMP signaling, steroid biosynthesis, apoptosis, autophagy, and inflammatory pathways (FOXO, HIF-1 α , NF κ B, VEGF, IL-17, PI3K/AKT). Notably, pathways directly related to AD, calcium signaling, serotonergic/dopaminergic neurotransmission, and endocrine signaling were also enriched (Table S8). Collectively, the GO and KEGG analyses suggest that Z-GS may alleviate AD by influencing neurotransmitter signaling, metabolism, and synaptic regulation.

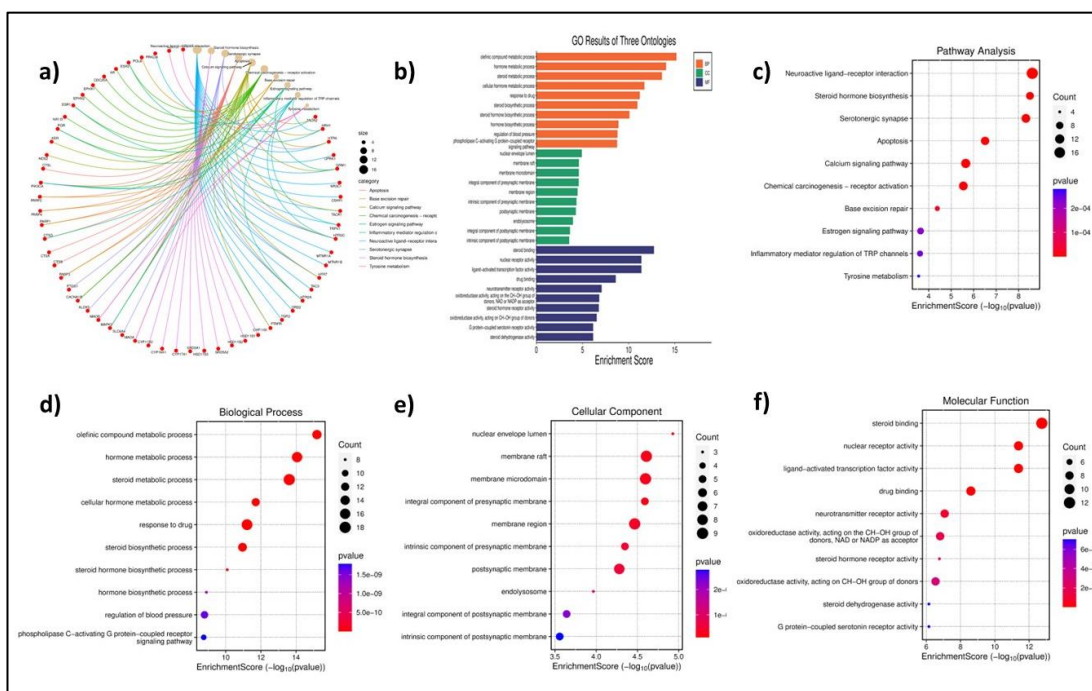


Figure 2: GO enrichment analysis of target genes. (a) Network of enriched GO terms. (b) Bar plot showing the top enriched GO terms across three ontologies. (c) Bubble plot depicting enriched pathways. (d-f) Bubble plot highlighting enriched GO terms in the BP, CC, and MF ontology, respectively.

3.4. Z-Guggulsterone Targets-Pathways Network

Using the Cytoscape 3.10.2 software, a network of compound-targets-pathways was built to describe the

treatment mechanisms of Z-GS potential anti-AD effects, as shown in Figure 4.

3.5. The SynGO Analysis

over time, known as synaptic plasticity, plays a connections. Additionally, oxidative stress and inflammation, which are also associated with AD, can further damage synapses and impair plasticity that has been linked to several cognitive deficits, including memory loss, difficulty with language, and impaired executive function.

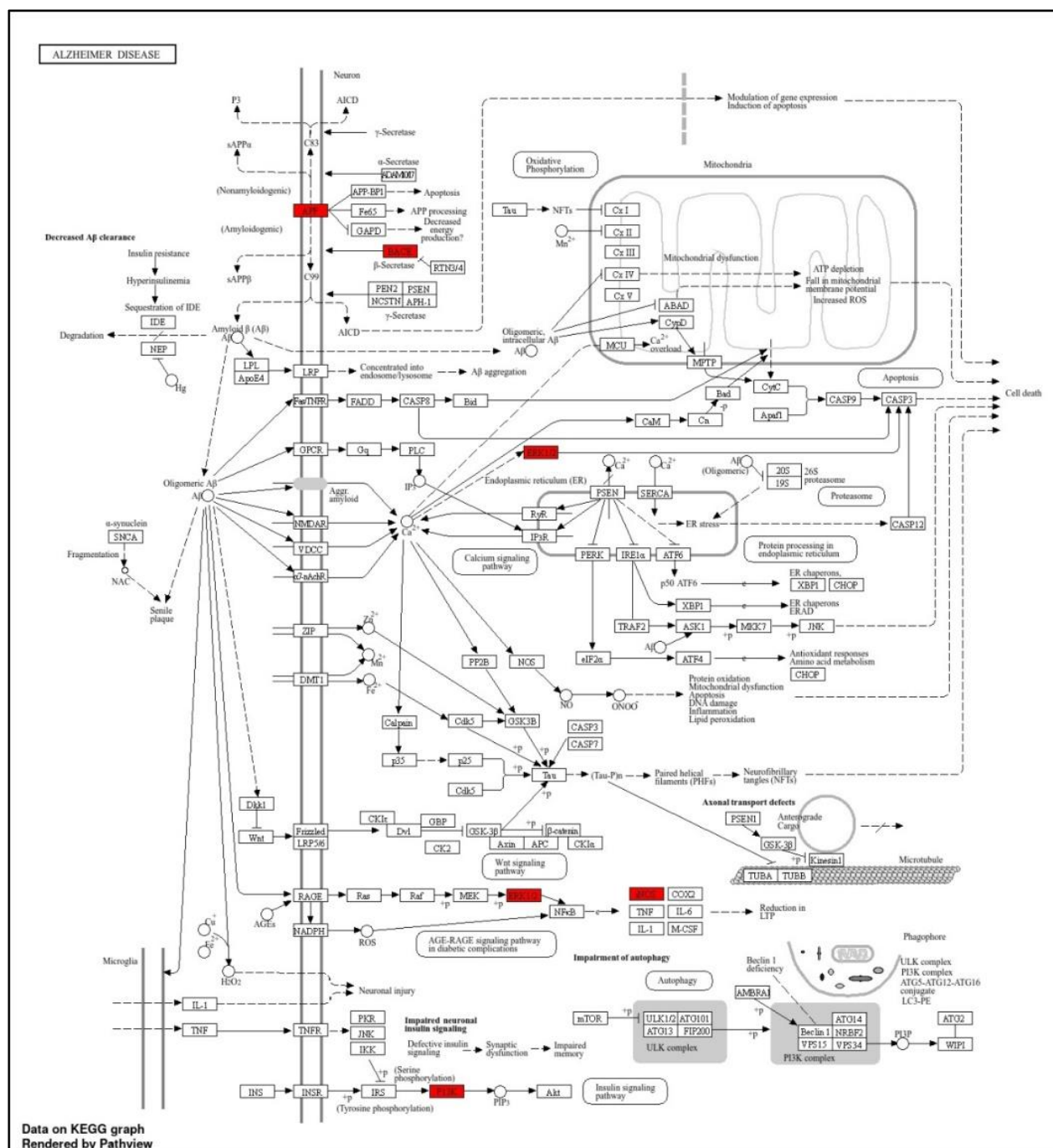


Figure 3: KEGG Pathway of AD and potential targets of Z-Guggulsterone.

PTPN1, SIGMAR1, NR3C1, GRM1, TACR1, and TRPV1 with synaptic properties localized to the synaptic membrane. Twelve genes were found in the presynapse, specifically within the presynaptic cytosol, cytoskeleton, intermediate filament cytoskeleton, and actin cytoskeleton. Fifteen genes were located in the postsynaptic membrane, including those localized to the postsynaptic cytosol, cytoskeleton, Golgi apparatus, ribosomes, endoplasmic reticulum, synapse, ion channels, and

GPCRs (Table S9). Proteins BACE1, BCHE, DRD2, development and neuronal migration. Dysfunction of CASP3 and APP proteins could disrupt synaptic transmission, suggesting the potential influence of

and MAPK3 were shown to facilitate synapse these proteins in the development of neuronal disorders.

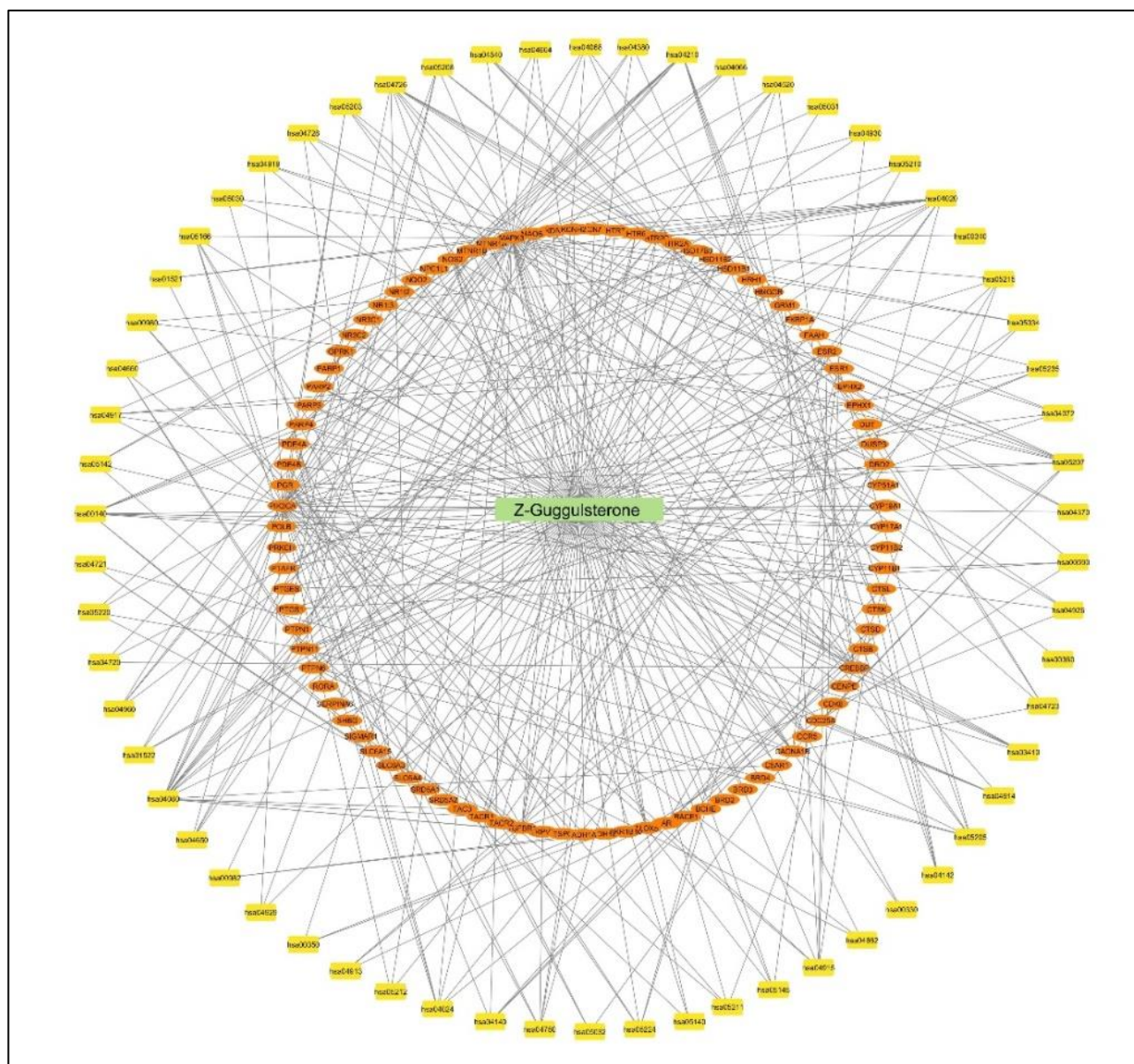


Figure 4: Compound-targets-pathways network of Z-Guggulsterone. The central green node denotes Z-Guggulsterone, while the surrounding orange nodes represent the predicted protein targets identified. The outer yellow nodes correspond to the major signaling pathways enriched from these targets.

3.6. VarElect Analysis of the Key Genes

Ninety-two overlapping genes were analysed using the VarElect database to comprehensively assess their potential influence on the relationship between genotype and phenotype, and the findings of this analysis were detailed in Table S10. In VarElect, it was found that numerous genes, including BACE1, BChE, SIGMAR1, CSTD, DRD2, MAO, and MAPK3, are involved in AD, with a greater likelihood of contributing to the disease. Beta-secretase 1 (BACE1) and butyrylcholinesterase (BChE) emerged as the top-ranked potential targets, exhibiting an approximate 78% probability of contributing to the disease. This enzyme initiates the first critical step in the production of A β peptides, a key component of the plaques found in AD. BACE1 is indeed crucial in

the processing of APP because it cleaves APP at a specific site, generating a smaller fragment called C99. This C99 fragment is subsequently cleaved by another enzyme, gamma-secretase (γ -Secretase), ultimately leading to A β peptides generation. Conversely, BChE hydrolyzes acetylcholine, a neurotransmitter crucial for cognitive function and the clearance of A β . In the AD brain, elevation of BChE activity contributes to neuroinflammation and oxidative stress, leading to neuronal damage [41]. The D2 receptor (DRD2) is essential for cognitive processes, and its reduced availability in brain regions in AD reflects disrupted dopamine signalling. This reduction may contribute to cognitive decline by impairing synaptic plasticity and potentially exacerbating neuroinflammation. Moreover, p38

MAPK plays a significant role in AD pathogenesis, abnormal tau protein phosphorylation, and potentially influencing A β production, highlighting

contributing to neuroinflammation, modulating its potential as a therapeutic target to slow disease.

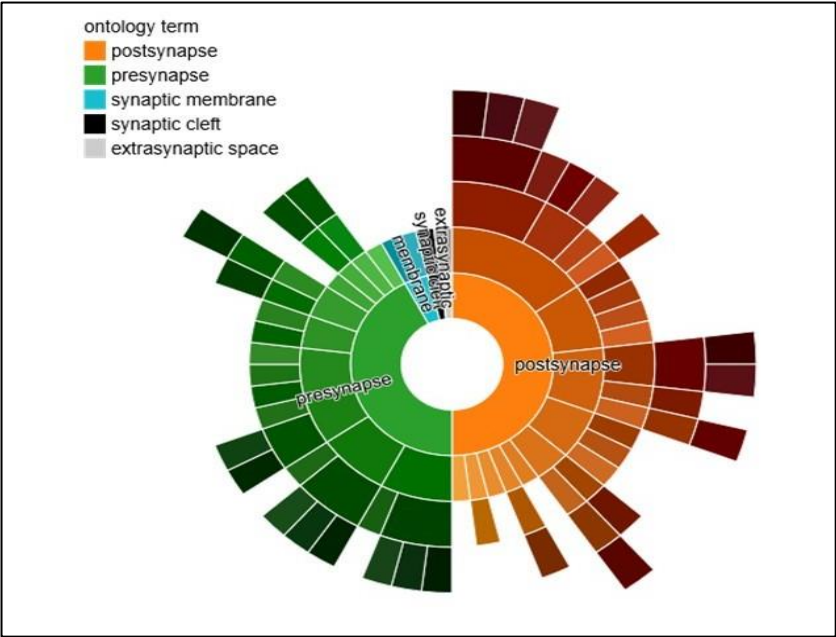


Fig. 5. SynGO analysis identifying specific synaptic genes and functional categories that are modulated by Z-Guggulsterone in AD.

3.7. Molecular Docking

Molecular docking studies were accomplished using CB Dock 2 to assess the binding affinity of Z-GS to six key proteins: BACE1 (6EQM), BCHE (6SAM), CTSD (4OD9), MAPK3 (4O2Z), CREB (5CGP), and PARP-2 (4TVJ) involved in AD. Molecular docking analysis revealed that Z-GS demonstrates a binding affinity for all six target proteins, as evidenced by negative Vina scores, suggesting potential interactions (Figure

6). Notably, the compound exhibited the strongest binding affinities towards PARP2 and BChE, with scores of -10.2 and -10.3, respectively, highlighting a high propensity for interaction. BACE1 also displayed a significant binding affinity, scoring -8.6. While MAPK3, CTSD, and CREB also showed binding interactions, with scores of -7.9, -7.7, and -7.3, respectively, these affinities were comparatively weaker than those observed for PARP2 and BChE.

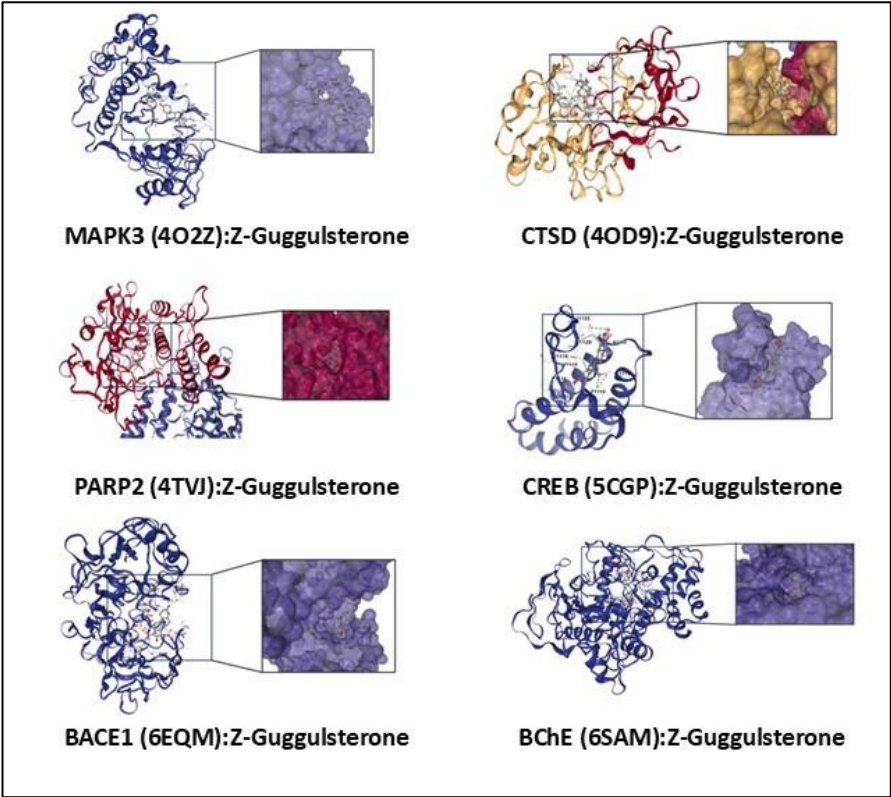


Figure 6: 3D conformations illustrating the binding of the Z-Guggulsterone with each target protein.

Conclusion

AD, characterized by aggregation of protein plaques and tangles in the brain, remains a formidable challenge, with its precise cause still elusive. Current pharmacological interventions primarily offer symptomatic relief and have a limited impact on disease progression. This critical gap highlights the need for plant-derived phytochemicals, which are being explored for their potential to target multiple aspects of AD pathology, from reducing inflammation and oxidative stress to improving neurotransmitter function, offering a promising avenue for future therapies. *Commiphora species* are known to produce a unique class of plant steroids, among which Z-GS, a bioactive steroidal constituent of guggul resin, has recently attracted significant scientific attention. Emerging evidence also suggests that Z-GS holds promise as an AD treatment, due to its beneficial effects in various diseases. The analysis in the present study identified genes such as BACE1, BCHE, CTSD, PARP2, DRD2, SRD5A1, GRM1, CYP19A1, MAPK3, and TGFBR1, which plays role in AD pathology. Further molecular docking also affirms the binding affinity of Z-GS with target proteins, providing the basis for its potential to modulate key pathways in AD. Hence, this research suggests that Z-GS reduces inflammation and oxidative stress, preventing A β aggregation and boosting neuronal survival, thereby acting as a promising therapeutic option for AD, although

further research is needed to understand its neuroprotective mechanisms fully.

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None

Author Contributions

PC: Conceptualization, Investigation, Methodology, Formal analysis, Data curation, Software, Visualization, Writing – original draft, Writing – review & editing; **KW:** Writing – review & editing, Formal analysis, Data curation; **GS:** Conceptualization, Methodology, Formal analysis, Supervision.

Conflict of Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Declaration

The authors declare that no generative artificial intelligence (AI) was utilized for the generation, collection, or analysis of the scientific data presented in this manuscript. AI tools were employed solely for the purpose of refinement and paraphrasing to enhance the grammatical accuracy and overall readability of the text. The authors maintain full responsibility for the intellectual content, scientific integrity, and final version of the manuscript.

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