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RESEARCH ARTICLE

In Silico Targeting of Ternatin C5 for the Management of Alzheimer's Disease

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Abstract: Alzheimer's disease constitutes a major neurological hurdle globally, marked by the progressive deterioration of memory and cognitive ability. The multifactorial etiology of the disease involving amyloid-beta plaque deposition and neurofibrillary tangle formation, requires therapeutic agents capable of interacting with diverse pathological markers. Ternatin C5, a specialized anthocyanin derived from the flowers of *Clitoria ternatea*, provides a potential scaffold for such multi-target intervention. Computational profiling against nine critical proteins Aβ, Tau protein, Ephexin 5, ADAM 10, BACE-1, CDK5, GSK-3β, JNK3, and P38-MAPK reveals significant binding capacities. The blind docking analysis via the CB-Dock2 platform identifies the strongest affinities for Tau protein and GSK-3β at -9.7 kcal/mol, closely followed by BACE-1 at -9.5 kcal/mol. These molecular interactions are stabilized through robust hydrogen bonding and hydrophobic contacts within key catalytic and regulatory domains, including the ATP-binding pocket of kinases and the secretase active sites. The identification of Ternatin C5 as a multi-target directed ligand supports its role in disrupting the progression of neurodegeneration by simultaneously modulating amyloidogenic processing, tau phosphorylation, and neuroinflammatory pathways. These results indicate a foundation for the neuroprotective properties of *Clitoria ternatea* and suggest a pathway for developing plant-derived therapeutics for dementia management.

Keywords: Alzheimer's disease; Ternatin C5; *Clitoria ternatea*; Multi-target directed ligands; Molecular docking.

1. Introduction

Alzheimer's disease (AD) is a chronic, progressive neurodegenerative condition and the primary cause of dementia, predominantly affecting populations over the age of 60 [1]. Current epidemiological data indicate that AD accounts for approximately 60-70% of all dementia cases globally [2]. The prevalence of the disorder is on a steep upward trajectory; in 2022, over 55 million individuals were living with the condition, a figure projected to reach 138 million by 2060 as the global population ages [2, 3]. The neurobiological landscape of AD is defined by two primary proteinopathies: the extracellular accumulation of Amyloid-beta (Aβ) plaques and the intracellular development of neurofibrillary tangles (NFTs) [4]. Amyloid plaques result from the proteolytic cleavage of the amyloid precursor protein (APP) by β-secretase (BACE-1) and γ-secretase, leading to the deposition of Aβ peptides that disrupt inter-neuronal communication and trigger oxidative stress [4, 5].

The formation of NFTs involves the hyperphosphorylation of the tau protein, a process that causes the protein to dissociate from microtubules, leading to the collapse of the neuronal cytoskeleton and subsequent transport failure [5, 6]. The clinical manifestation of AD involves a spectrum of cognitive, non-cognitive, and functional impairments that severely degrade the quality of life for patients and caregivers [7]. Early symptoms often include short-term memory loss and linguistic difficulties, which eventually progress to disorientation regarding time and place [6, 8]. Non-cognitive symptoms frequently emerge in the middle stages, including depression, aggression, apathy, and psychotic symptoms such as hallucinations or delusions [8, 9]. In advanced stages, the disease impairs basic physical functions, including swallowing, motor coordination, and bladder control, requiring a full-time palliative care [9].

Currently, there is no definitive cure for AD, and treatment focuses on symptomatic management [10]. Traditional therapies utilize acetylcholinesterase inhibitors (e.g., Donepezil) and NMDA receptor antagonists (e.g., Memantine) to delay cognitive decline [10, 11]. Recent advancements have introduced monoclonal antibodies like lecanemab, which target amyloid plaques; however, these disease-modifying agents are often associated with significant side effects and high costs [11, 12]. The complex pathogenesis of AD has led to the emergence of Multi-Target Directed Ligands (MTDLs) as a superior therapeutic intervention [12, 13]. MTDLs offer

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a more robust intervention than traditional single-target approaches by interacting with multiple pathological nodes simultaneously [13].

Clitoria ternatea, commonly known as Butterfly Pea or Aparajitha, is a traditional herb highly regarded in Ayurvedic medicine for its memory-enhancing and cognitive properties [19]. The plant contains a diverse array of secondary metabolites, including flavonoids, triterpenoids, and unique acylated anthocyanins known as ternatins [20, 21]. Ternatin C5, a structurally significant anthocyanin, has been hypothesized to contribute to the plant's anti-inflammatory and neuroprotective effects [21]. This investigation provides a detailed molecular analysis of Ternatin C5's ability to act as a multi-modal agent in AD.

2. Methodology

2.1. Ligand Retrieval and Preparation

The structural configuration of Ternatin C5 (Delphinidin 3-O-(6"-O-malonyl)-β-glucoside-3',5"- di-O- β-glucoside) was retrieved from the PubChem database. Molecular identification was confirmed using the Canonical SMILES and ChEBI identifiers. The ligand was prepared by optimizing its three-dimensional geometry to ensure the most stable conformation for docking simulations [22].

2.2. Target Protein Selection and Refinement

A total of nine protein targets central to the AD pathological network were selected for the docking study. These targets were retrieved from the RCSB Protein Data Bank (PDB) using specific accession codes.

Table 1. List of target Proteins and their PDB ID's retrieved from PDB database

S.No	Target Protein	PDB ID	S.No	Target Protein	PDB ID	S.No	Target Protein	PDB ID
1	Aβ	1LTY	4	ADAm 10	6BE6	7	GSK-3β	1UV5
2	Tau Protein	IJIB	5	BACE 1	6EJ3	8	JNK3/SAPKβ	7S1N
3	Ephexin 5	-	6	CDK5	4AU8	9	P38 MAPK	5ML5

The target panel includes:

1. Aβ (1LTY): Major component of amyloid plaques.
2. Tau Protein (1J1B): Involved in microtubule stabilization.
3. Ephexin 5: A RhoGEF involved in synapse loss.
4. ADAM 10 (6BE6): The α-secretase involved in non-amyloidogenic processing.
5. BACE-1 (6EJ3): The β-secretase initiating amyloid production.
6. CDK5 (4AU8): A kinase driving tau hyperphosphorylation.
7. GSK-3β (1UV5): A primary kinase implicated in neurofibrillary tangle formation.
8. JNK3 (7S1N): A stress-activated kinase involved in apoptosis.
9. P38-MAPK (5ML5): A mediator of neuroinflammation.

2.3. Computational Docking using CB-Dock2

The molecular docking simulations were performed using CB-Dock2 (Cavity-detection guided Blind Docking). This tool utilizes a curvature-based algorithm to identify potential binding cavities on the protein surface, followed by blind docking to determine the most favorable ligand orientation [22, 23].

2.3.1. Simulation and Scoring

The platform automatically calculates the center, size, and location of potential binding pockets. The docking scores, represented as binding free energy (ΔG) in kcal/mol, were used to rank the affinity of Ternatin C5 for each receptor [24, 25].

2.3.2. Molecular Interaction

The top-ranked docking poses were analyzed for molecular interactions, focusing on hydrogen bonding, hydrophobic contacts, and pi-interactions with key active site residues.

3. Results and Discussion

3.1. Multi-Target Binding Affinity Analysis

The molecular docking simulations revealed that Ternatin C5 possesses a versatile structural framework capable of high-affinity interactions across a broad spectrum of Alzheimer's disease (AD) targets. The binding energies (shown in Table 2) ranged from -7.7 kcal/mol to -9.7 kcal/mol, indicating a favorable thermodynamic profile for spontaneous binding.

Table 2. Results of Molecular Docking and Interactions of Ternatin C5 with selected target proteins

Target protein	Ligand	Binding Score (kcal/mol)	Interacting Amino acid residues
Amyloid beta	Ternatin C5	-7.7	ASN:384, ASP:383, GLN:46, ASN:322, SER:323, ARG:316, ASP:324, ARG:381, PRO:350
Tau protein	Ternatin C5	-9.7	ARG:641, CYS:699, GLN:685, LYS:683, SER:566, ASP:264,
Ephexin 5	Ternatin C5	-8.5	GLU:363, GLY:367, ARG:417, ASN:569, SER:421, TYR:356
ADAM	Ternatin C5	-9.0	SER:347, LYS:348, SER:340, SER:339, LYS:447, ARG:420, ARG:636, GLU:403, ASN:633
BACE-1	Ternatin C5	-9.5	THR:329, ARG:235, LYS:107, TYR:71, GLY:230, ILE:118, TRP:76, ARG:128, TYR:198, LYS:224, THR:72, THR:231
CDK5	Ternatin C5	-7.7	ASN:265, GLN:226, CYS:269, GLY:220, LYS:268, ASP:261
GSK-3β	Ternatin C5	-9.7	LYS:183, SER:66, ASP:181, ILE:217, ASP:200, TYR:216, GLN:185, THR:138, ASN:64
JNK3/SAPKβ	Ternatin C5	-8.7	ASN:194, ARG:107, LYS:191, ARG:227, MET:219, ARG:230, TYR:268, SER:217, ARG:188, GLN:102, GLN:75
P38-MAPK	Ternatin C5	-9.2	ASN:155, ASP:168, ARG:67, SER:56, GLU:71, LEU:55, THR:68, TYR:35, LYS:53, VAL:38, PHE:169, ASP:150, HIS:148

ADAM:A Disintegrin and Metalloproteinase; BACE-1:Beta-Site Amyloid Precursor Protein Cleaving Enzyme-1; CDK5:Cyclin Dependent Kinase 5; GSK-3β:Glycogen Synthase Kinase-3β; JNK3:c-Jun N-terminal Kinase; SAPKβ:Stress Activated Protein Kinase-β; P38-MAPK:P38 Mitogen Activated Protein Kinase.

3.1.1. Primary High-Affinity Targets

The most significant binding affinities were observed for Tau protein and Glycogen Synthase Kinase-3β (GSK-3β), both achieving a docking score of -9.7 kcal/mol (shown in Figure 1 and Figure 2). These scores represent a high level of ligand-receptor stability. In the Tau protein complex (Figure 2b), Ternatin C5 established a robust network of hydrogen bonds with residues ARG641, CYS699, GLN685, and LYS683. Such interactions within the microtubule-binding repeat domains may interfere with the aggregation kinetics of tau, potentially preventing the formation of toxic oligomers.

For GSK-3β (Figure 2a), the binding was primarily localized within the ATP-binding pocket, involving residues LYS183, ASP181, and TYR216. Since GSK-3β is a master regulator of tau phosphorylation, the high affinity suggests that Ternatin C5 could serve as an effective kinase inhibitor, thereby addressing one of the most critical upstream events in the tauopathy cascade [26].

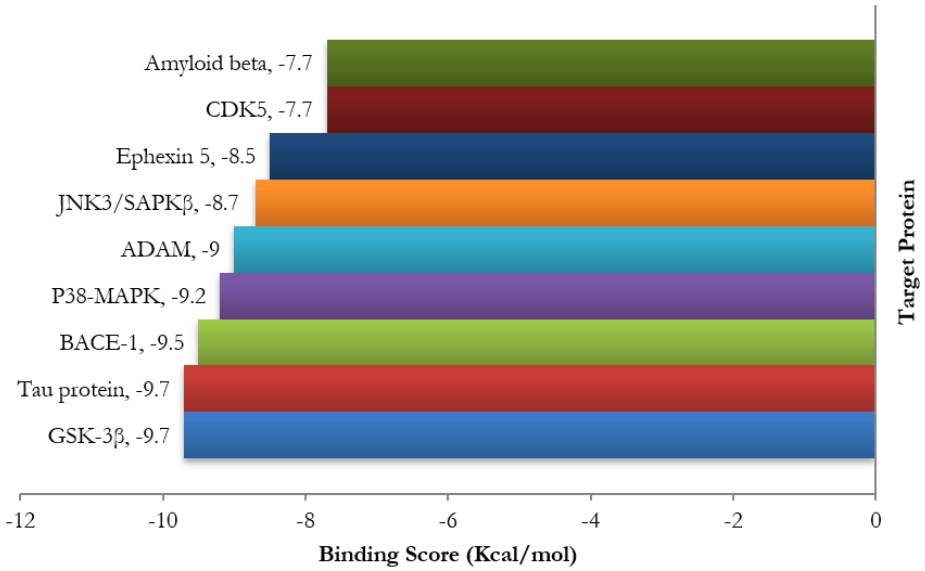

Figure 1. Binding Affinity of Ternatin C5 with AD related Target Proteins

3.2. Modulation of Amyloidogenic and Non-Amyloidogenic Processing

3.2.1. BACE-1 Inhibition and Amyloid Reduction

Ternatin C5 showed a substantial affinity for BACE-1 (-9.5 kcal/mol), the enzyme responsible for the initial cleavage of APP in the amyloidogenic pathway. The interaction analysis revealed that the ligand forms stable hydrogen bonds and pi-interactions with TYR71, TRP76, and ARG128 (Figure 2c). These residues are often involved in the stabilization of the BACE-1 flap or the catalytic dyad, suggesting that Ternatin C5 might block substrate access to the active site, effectively reducing the production of Aβ42 peptides.

3.2.2. Regulatory Potential for ADAM 10

The interaction with ADAM 10 yielded a binding score of -9.0 kcal/mol, involving residues SER347, LYS447, and ARG636 (Figure 2e). As ADAM 10 facilitates the neuroprotective α-secretase pathway, the interaction of Ternatin C5 with this target suggests a potential regulatory role. Modulating ADAM 10 to favor non-amyloidogenic processing is a highly sought-after attribute in multi-target drug discovery.

3.3. Mitigation of Neuroinflammation and Synaptic Loss

3.3.1. MAPK Pathway Intervention (P38 and JNK3)

Chronic neuroinflammation in AD is largely driven by the P38-MAPK and JNK3 signaling pathways. Ternatin C5 exhibited strong binding to P38-MAPK (-9.2 kcal/mol) through interactions with SER56, ASP168, and ARG67 (Figure 2d). Similarly, JNK3 binding (-8.7 kcal/mol) involved critical residues like ARG107 and TYR268 (Figure 2f). Ternatin C5 may suppress the release of pro-inflammatory cytokines and protect neurons from apoptosis induced by oxidative stress by potentially inhibiting these stress-activated kinases [27].

3.3.2. Ephexin 5 and Synaptic Maintenance

The docking score for Ephexin 5 was -8.5 kcal/mol, with interactions observed at ARG417 and TYR356 (Figure 2g). Ephexin 5 is known to promote synapse loss in the presence of Aβ; therefore, the ability of Ternatin C5 to bind this RhoGEF might contribute to the preservation of dendritic spines and excitatory synapse density, directly supporting cognitive health.

3.4. Auxiliary Mechanisms: Aβ Fibrils and CDK5

Moderate binding affinities were noted for Aβ fibrils (Figure 2h) and CDK5, both at -7.7 kcal/mol. The interaction with Aβ residues ASN384 and ASP383 suggests that Ternatin C5 may associate with the core of amyloid aggregates, possibly hindering further fibril

elongation. The interaction with CDK5, involving ASN265 and LYS268 (Figure 2i), provides a secondary mechanism to control tau hyperphosphorylation, reinforcing the compound's status as a comprehensive multi-target ligand [28]

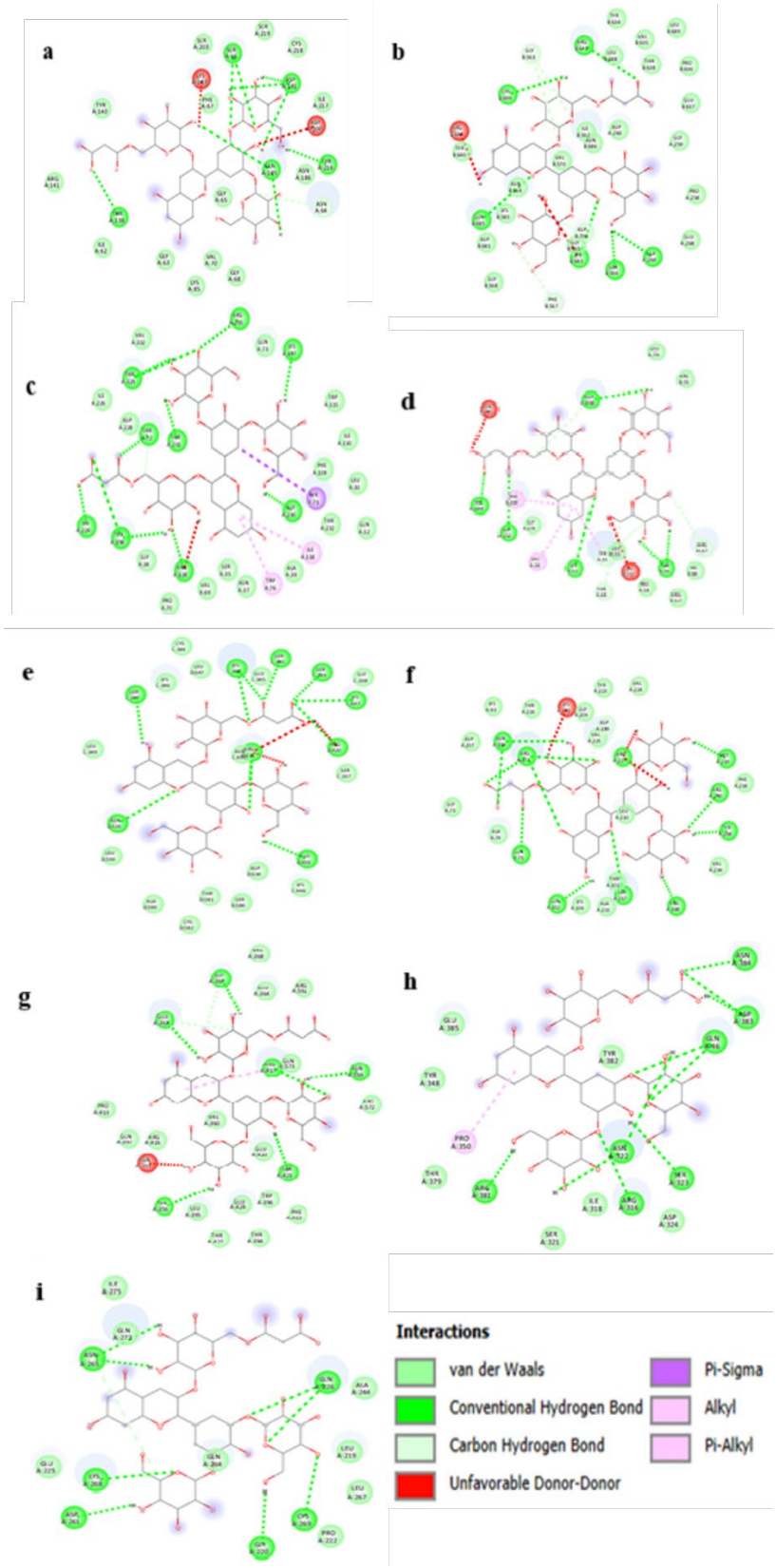

Figure 2. Molecular docking showing 2D interactions of Ternatin C5 with a) GSK-3β; b) Tau protein c) BACE-1; d) P38-MAPK; e) ADAM-10 f) JNK-3; g) Ephexin-5; h) Amyloid-β; i) CDK-5

4. Conclusion

The work presented here confirms that Ternatin C5, a bioactive anthocyanin from *Clitoria ternatea*, functions as a potent multi-target directed ligand (MTDL) for Alzheimer's disease. The high binding affinities for GSK-3β, Tau, BACE-1, and P38-MAPK suggest that the compound can simultaneously address the multiple facets of AD pathology, including amyloidogenic processing, tau hyperphosphorylation, and neuroinflammation. These interactions are stabilized by a consistent pattern of hydrogen bonding and hydrophobic contacts within biologically significant domains. While these results provide a strong theoretical basis for the neuroprotective efficacy of Ternatin C5, further *in vitro* and *in vivo* studies are essential to validate its functional activity and evaluate its pharmacokinetic profile. The results show Ternatin C5 as a promising natural lead for the development of multi-modal interventions in neurodegenerative disorders.

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