"*In silico* Evaluation of Phytocompounds from *Withania somnifera* as Dopamine D2 Receptor Modulators for Alzheimer's Disease"

Neha singh[1] Nisha Singh[2], and Dr. Shoba Gunasekaran[3]

[1,] PG & Research Department of Biotechnology,
Women's Christian College, Affiliated to University of Madras,
Chennai 600006, Tamil Nadu (India)
[2] Central Institute of Education Technology, NCERT, New Delhi (India)
[3]Department of Biotechnology, Dwaraka Doss Goverdhan Doss Vaishnav College,
(Autonomous) Chennai - 600106 Tamil Nadu (India)

Corresponding Author- Neha Singh

Abstract-

Alzheimer's disease (AD) is a neurodegenerative disorder characterized by progressive cognitive decline, memory impairment, and behavioral disturbances. Current pharmacotherapies, despite ongoing advancements, provide only symptomatic relief and frequently entail adverse effects. The Dopamine D2 receptor (D2R), a G-protein-coupled receptor associated with cognitive, emotional, and motor functions, has been identified as a potential target for Alzheimer's disease treatment. The modulation of D2R via natural ligands presents a potential multi-target therapeutic strategy. The objective of this study was to examine the binding interactions and inhibitory potential of selected withanolides and other bioactive molecules, against the Dopamine D2 receptor utilizing molecular docking simulations. *In silico* molecular docking was performed utilizing AutoDock 4.2 to assess binding affinity, hydrogen bonding, inhibition constants (Ki), and ligand efficiency (LE) of phytoconstituents with the D2 receptor. Dihydroergotoxine and Haloperidol served as reference standards for comparison purposes. Analyses of structural interactions and binding sites were conducted to evaluate docking stability and specificity. Dihydroergotoxine demonstrated the highest binding affinity (–11.91 kcal/mol; Ki: 1.87 nM), confirming the validity of the docking protocol. Tropigline and Benzo[b]thiophene-3-carboxylic acid exhibited favorable binding energies of –7.4 and –6.8 kcal/mol, respectively, along with effective interaction profiles characterized by hydrogen bonding with key residues including THR119, SER193, and ARG132. The ligand efficiency values of –0.41 and –0.49 indicate their suitability as drugs and compatibility with the receptor. In contrast, terpenoids derived from hydrocarbons demonstrated weaker and less specific binding affinities. In conclusion, the findings indicate that Tropigline and similar natural compounds exhibit a moderate to strong affinity for the Dopamine D2 receptor, with interaction profiles that are comparable to those of standard antipsychotics. The findings underscore their potential as lead compounds for the development of innovative, plant-derived therapeutics aimed at addressing dopaminergic dysfunction in Alzheimer's disease. Additional validation via experimental pharmacology and ADME-Tox studies is necessary.

Keywords:-Alzheimer's disease; Dopamine D2 receptor; Withanolides; Molecular docking; Natural compounds; Neurodegeneration; Tropigline.

Introdution- Alzheimer's disease (AD) is the most common cause of dementia worldwide and is a progressive, irreversible neurodegenerative disorder. It primarily impacts the elderly, resulting in cognitive decline, memory impairment, behavioral disturbances, and reduced daily functioning. Selkoe *et al*. (2016) and Scheltens *et al*. (2021) have identified the pathophysiology of AD as the extracellular deposition of amyloid-beta (Aβ) plaques, intracellular neurofibrillary tangles composed of hyperphosphorylated tau protein, and widespread neuronal degeneration, particularly within the hippocampus and cortex—regions that are essential for learning and memory. The etiology of AD remains complex and multifactorial, involving genetic susceptibility (e.g., APOE ε4 allele), environmental exposure, and modifiable lifestyle risk factors such as diet, physical activity, and cardiovascular health, despite decades of scientific investigation (Lane *et al*., 2018; Livingston *et al*., 2020). The disease progresses through multiple clinical phases, commencing with subtle short-term memory loss and ultimately resulting in severe cognitive dysfunction, psychiatric symptoms (agitation, anxiety, hallucinations), and a loss of autonomy. Key Biomarkers and Molecular Mechanisms in Alzheimer's Disease Pathology - The onset and progression of AD are influenced by a number of proteins and receptors: 1. Amyloid Precursor Protein (APP) – The aberrant cleavage of Aβ peptides by β- and γ-secretases leads to the formation of plaques, which disrupts neuronal connectivity (Hardy *et al*., 1992). 2. Tau Protein – axonal transport and microtubule stability are impaired by abnormally hyperphosphorylated tau, which results in the formation of neurofibrillary tangles (Avila *et al*., 2004). 3. Glutamatergic Dysfunction (NMDA Receptors) – Excitotoxicity and subsequent neuronal mortality are the consequences of Aβ-mediated overactivation (Mattson, 2004). 4. Cholinergic Deficiencies – Synaptic transmission, memory, and learning are impaired by reduced acetylcholine levels (Francis *et al*., 1999). 5. Neuroinflammation – Neurodegeneration is exacerbated by activated microglia and elevated pro-inflammatory cytokines (Heneka *et al*., 2015).

Present Therapeutic Landscape and Its Constraints - While AD has no cure, there are numerous therapeutic classes that are designed to mitigate symptoms or delay its progression: - Acetylcholine availability is increased by cholinesterase inhibitors (donepezil, rivastigmine, galantamine) by inhibiting its degradation (Birks, 2006). NMDA receptor antagonists (memantine) reduce glutamate-mediated excitotoxicity (Lipton, 2004). Anti-amyloid monoclonal antibodies, such as aducanumab, are intended to decrease the burden of Aβ plaques (Sevigny *et al*., 2016). Anti-tau therapies are currently being developed to prevent hyperphosphorylation and tau aggregation (Wang *et al*., 2016). Nevertheless, these agents are restricted by their modest efficacy and adverse effects, which include gastrointestinal disturbances, dizziness, bradycardia, and, in the case of monoclonal antibodies, serious immunologic reactions such as amyloid-related imaging abnormalities (ARIA) (Sevigny *et al*., 2016; Heneka *et al*., 2015).

The Emerging Role of the Dopamine D2 Receptor in Alzheimer's Disease--- G-protein-coupled receptors (GPCRs) are essential for central dopaminergic signaling, including the

dopamine D2 receptor (D2R). D2R, which is primarily expressed in the striatum, substantia nigra, and prefrontal cortex, is responsible for the regulation of motor activity, cognition, emotion, and reward (Missale *et al*., 1998). Seven transmembrane domains are present in the receptor, which transmits signals through Gi/o proteins, resulting in the inhibition of adenylate cyclase and a decrease in cyclic AMP levels. Alternative splicing generates two isoforms, D2S (short) and D2L (long), which serve distinct physiological functions (Glickstein *et al*., 2004).
The following are key D2R-mediated functions: 1. Motor regulation through basal ganglia circuits (Surmeier *et al*., 2007).
2. Addiction and reward processing through the mesolimbic pathway (Volkow *et al*., 2009).
3. Endocrine modulation, with a particular emphasis on the secretion of prolactin (Ben-Jonathan *et al*., 2001).
4. Executive function and cognitive control, particularly in the prefrontal cortex (Frank *et al*., 2006).

Alzheimer's Disease and D2 Receptor Dysfunction: Recent research suggests that the neuropsychiatric and cognitive impairments observed in AD are substantially influenced by D2R dysregulation. In Alzheimer's disease patients, impaired memory, attention, and emotional regulation are associated with altered dopaminergic signaling in the limbic system and cortex (Cordella *et al*., 2022). Additionally, dopaminergic hypoactivity has been associated with elevated susceptibility to Aβ and tau pathology, reduced neuronal plasticity, and synaptic dysfunction. D2R agonists may alleviate cognitive and behavioral symptoms of AD by modulating synaptic transmission and enhancing dopaminergic tone, according to preclinical studies (Emamzadeh *et al*., 2018). Furthermore, the activation of D2Rs may interact with neurotrophic and inflammatory pathways, resulting in neuroprotective effects. Justification for In-Silico Studies with Withanolides- The interest in the exploration of natural compounds, particularly phytochemicals with multi-target potential and fewer adverse effects, is on the rise due to the systemic side effects and limitations of current synthetic pharmaceuticals. Withanolides, bioactive constituents derived from Withania somnifera (Ashwagandha), have exhibited neuroprotective, anti-inflammatory, and antioxidant properties in a variety of neurodegenerative models. Their potential to regulate a variety of pathways, such as oxidative stress, inflammation, and amyloidogenesis, renders them as promising candidates for AD therapeutics (Kuboyama *et al*., 2005; Jayaprakasam *et al*., 2010).

Materials and Methods- The chemical structures of selected ligands were drawn using ChemSketch (ACD/ChemSketch). The generated structures were saved in MOL format and subsequently converted to PDB format using Open Babel, a molecular format conversion software. The three-dimensional crystallographic structures of the target proteins were retrieved from the RCSB Protein Data Bank (PDB) (https://www.rcsb.org). The specific PDB IDs used for this study were: Dopamine D2 receptor (PDB ID: T67162). Prior to docking, all protein structures were prepared by removing water molecules, heteroatoms, and co-crystallized ligands to ensure accurate binding interaction analysis. Molecular docking simulations were conducted using AutoDock version 4.2. Polar hydrogens were added, and Gasteiger and Kollman charges were assigned to the protein and ligand structures. All torsional rotatable bonds in ligands were defined, and the resulting files were saved in PDBQT format.

Docking was performed by preparing grid boxes covering the active sites of each target protein. The Lamarckian Genetic Algorithm was used to perform flexible docking runs, and

the most stable binding conformations were selected based on binding energy scores. All docked complexes were visualized and analyzed using Discovery Studio Visualizer (BIOVIA). Molecular interactions such as hydrogen bonding, hydrophobic contacts, van der Waals forces, and any steric clashes were thoroughly evaluated. This workflow was consistently applied across all selected phytochemical ligands and standard anti-Alzheimer's drugs used as controls in the study.

Results and Discussion-

Molecular docking analysis was performed to assess the binding affinity and interaction mechanisms of selected phytoconstituents (Table 2, 3, and Figure 1-14) and a reference drug (Table 4 and figure – 15-16) with the Dopamine D2 receptor (D2R) (Table 1), which plays a crucial role in cognition modulation and neuroprotection in Alzheimer's disease (AD).

Binding affinity and inhibition potential. The binding affinities of docked ligands to the D2 receptor, measured in kcal/mol, demonstrated considerable variability in interaction strengths (Table 5). Dihydroergotoxine, a recognized dopaminergic agent, exhibited the highest binding energy of –11.91 kcal/mol, alongside an inhibition constant (Ki) of 1.87 nM. The high intermolecular energy (–13.4 kcal/mol) and ligand efficiency (–0.28) validate the docking protocol and establish a benchmark for comparison (Table 5 and 6). Tropigline, , demonstrated the highest binding affinity of –7.4 kcal/mol, with an inhibition constant of 17.16 μM and a ligand efficiency of –0.41. Benzo[b]thiophene-3-carboxylic acid exhibited moderate binding affinity (–6.8 kcal/mol), with a Ki of 20.19 μM and a ligand efficiency of –0.49, closely paralleling the performance of Tropigline. Additional phytoconstituents, including β-myrcene, D-limonene, β-bisabolene, and succinic acid derivatives, exhibited comparatively weaker binding affinities (–4.08 to –6.1 kcal/mol) and elevated Ki values, indicating diminished stability and reduced binding efficacy with the receptor (Table 7 and 8).

Analysis of Hydrogen Bonding and Key Residue Interactions - The study focused on hydrogen bonding and non-covalent interactions to elucidate the mechanisms underlying ligand-receptor stabilization. Table 10 illustrates that Tropigline established two conventional hydrogen bonds with residues THR119 and SER193, alongside three hydrophobic interactions with VAL115, CYS118, and PHE189 (Table 5). The interactions play a crucial role in stabilizing ligands within the D2R active site. Benzo[b]thiophene-3-carboxylic acid exhibited a π-cation interaction with ARG132 and a π-sigma interaction with ILE212, along with hydrophobic contacts with LEU375 and ALA371, suggesting a moderately stable ligand-receptor complex. In contrast, β-myrcene, β-bisabolene, and D-limonene did not form any hydrogen bonds and depended solely on non-specific hydrophobic interactions with residues such as TRP386, PHE389, and ARG104, which likely restricts their receptor affinity and selectivity.

Ligand efficiency and structure-activity relationships - Ligand efficiency (LE) is an essential metric in lead optimization, representing the binding energy per non-hydrogen atom. Tropigline and Benzo[b]thiophene-3-carboxylic acid exhibited high LE values of –0.41 and –0.49, respectively, suggesting effective receptor binding relative to their molecular size (Table 7). The values were similar to those of Dihydroergotoxine (–0.28), a significantly larger molecule, highlighting the drug-like properties of these natural scaffolds (Table 8). The structure–activity relationship (SAR) analysis indicated that hydrophilic functional groups, including carboxylic acids and hydroxyl groups, in Tropigline and Benzo[b]thiophene derivatives facilitate polar interactions with D2R, essential for stable binding. In contrast,

hydrocarbon-based terpenoids, such as β-myrcene and β-bisabolene, lack polar substituents, which diminishes their ability to engage in specific interactions and, as a result, lowers their docking scores.

Comparative Binding Profile with Standard Medication- The standard reference drug Haloperidol exhibited a docking score of –9.3 kcal/mol in its interaction with D2R, characterized by the formation of three hydrogen bonds with THR412, ASP114, and PHE389 (Table 8). These interactions validate its strong affinity and clinically confirmed efficacy as a D2 receptor antagonist. Tropigline demonstrated comparable hydrogen bond interactions with conserved D2R residues and showed significant ligand efficiency, indicating its potential as a natural alternative or adjunct to current dopaminergic therapies.

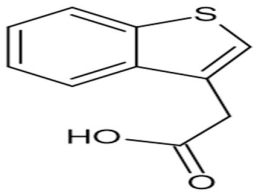
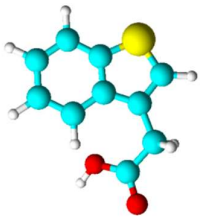
Consequences for Alzheimer's Disease Therapeutics The dopaminergic system, especially through D2 receptor signaling, significantly influences working memory, attention, executive function, and motor control, all of which are compromised in Alzheimer's disease (Missale *et al*., 1998; Cordella *et al*., 2022). Altered D2R activity has been associated with cognitive dysfunction and neuropsychiatric symptoms related to Alzheimer's disease, such as apathy and psychosis.

The findings indicate the therapeutic significance of targeting D2R with plant-derived ligands that possess multi-target and neuroprotective capabilities. Tropigline and Benzo[b]thiophene-3-carboxylic acid exhibited moderate and consistent binding affinity to D2R, with interaction profiles akin to those of established drugs, thereby supporting their potential as lead compounds for subsequent preclinical evaluation.

Table 1- taget proteins , their Id and related diseases

S. No	Protein target	Target ID	Synonyms	Related Disease
1	**Dopamine D 2 receptor**	T67162	Dopamine receptor 2; D(2) dopamine receptor	Alzheimer disease

Table 2- List of compounds with their 2D and 3D structures.

S.No	Compound Name	2D	3D
1	Benzo[b]thiophene-3-carboxylicacid,7-acetoxy-2-acet		

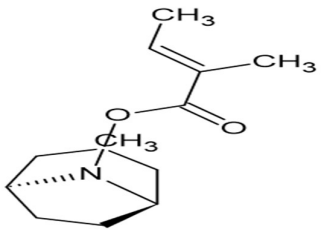
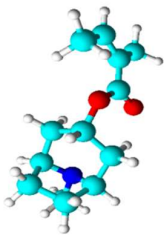
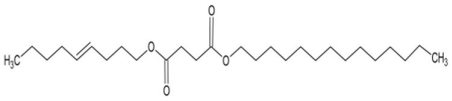
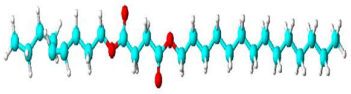
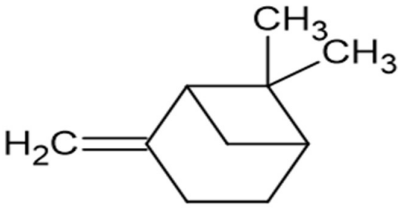
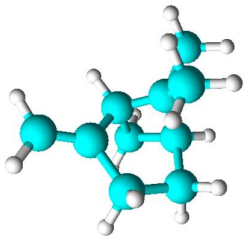
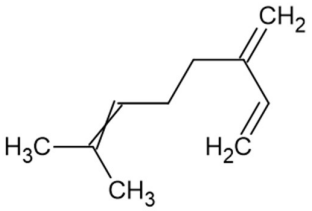
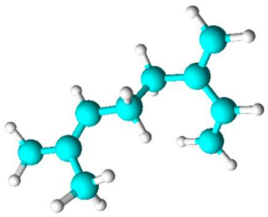
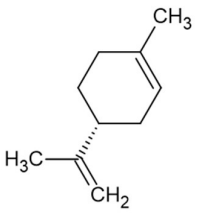
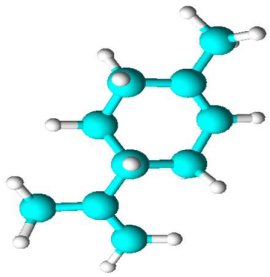
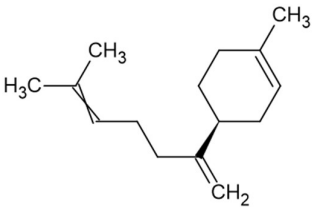
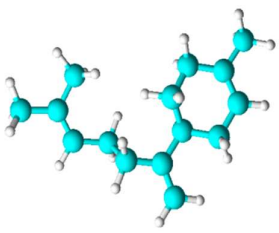
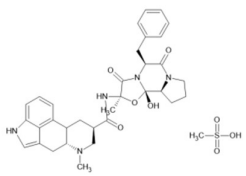
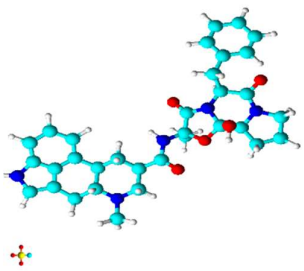
2	Tropigline		
3	Succinicacid,non-4-enyltetradecyl ester		
4	Bicyclo[3.1.1]heptane, 6,6-dimethyl-2-		
5	beta.-Myrcene		
6	D-Limonene		
7	beta.-Bisabolene		

Table 3 - Compounds list, their Pubchem id, SMILES and their reported applications.

S.No	Compound Name	Pubchem id and SMILES	Applications
1	**Benzo[b]thiophene-3-carboxylicacid,7-acetoxy-2-acet**	Pub chem. Id- 70799 C1=CC=C2C(=C1)C(=CS2)CC(=O)O	anti-cancer, Anti-microbial, anti-oxidant, anti-inflammatory, , anti-diabetic, anti-convulsant and anti-tubercular activity
2	**Tropigline**	Pub chem. Id-12444363 C/C=C(\C)/C(=O)OC1C[C@H]2CC[C@@H](C1)N2C	Alkaloid found in Withania somnifera, it can bind with SARS CoV -2 and human targeted proteins.
3	**Succinicacid,non-4 enyl tetradecylester**	O=C(OCCCCCCCCCCCCCC)CCC(=O)OCCC\C=C\CCCC	Used as neutraceutical, radiation protective and anti ulcer drug
4	**Bicyclo[3.1.1]heptane, 6,6-dimethyl-2-**	Pub chem. Id- 14896 CC1(C2CCC(=C)C1C2)C	Neuroprotective compound, anti Parkinson and anti Alzheimer's activity. Selective Prostaglandin D_2 Receptor
5	**beta.-Myrcene**	Pub chem. Id-31253 CC(=CCCC(=C)C=C)C	Anti oxidant, anti inflammatory, anti-aging, analgesic effects , Cardio protective effect
6	**D-Limonene**	Pub chem. Id- 440917 CC1=CC[C@@H](CC1)C(=C)C	Effective against cancer, bronchitis and obesity
7	**beta.-Bisabolene**	Pub chem. Id- 10104370 CC1=CC[C@H](CC1)C(=C)CCC=C(C)C	Anti cancer , can be used to treat breast cancer

Table 4- Approved drugs for Alzheimers's disease treatment with their SMILES structure, 2D and 3D structure.

Drug Name	SMILES	2D	3D
Dihydroergotoxine-	C[C@@]1(C(=O)N2[C@H](C(=O)N3CCC[C@H]3[C@@]2(O1)O)CC4=CC=CC=C4)NC(=O)[C@@H]5CC6[C@@H](CC7=CNC8=CC=CC6=C78)N(C5)C.CS(=O)(=O)O		

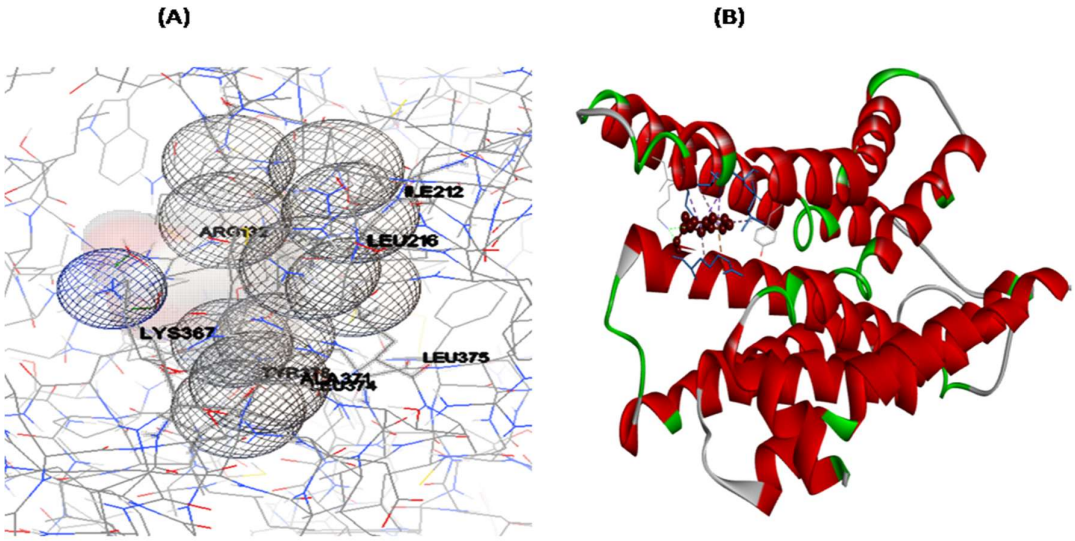


Figure 1 (A and B)- Benzo[b]thiophene-3-carboxylicacid,7-acetoxy-2-acet and Dopamine D 2 receptor interaction.

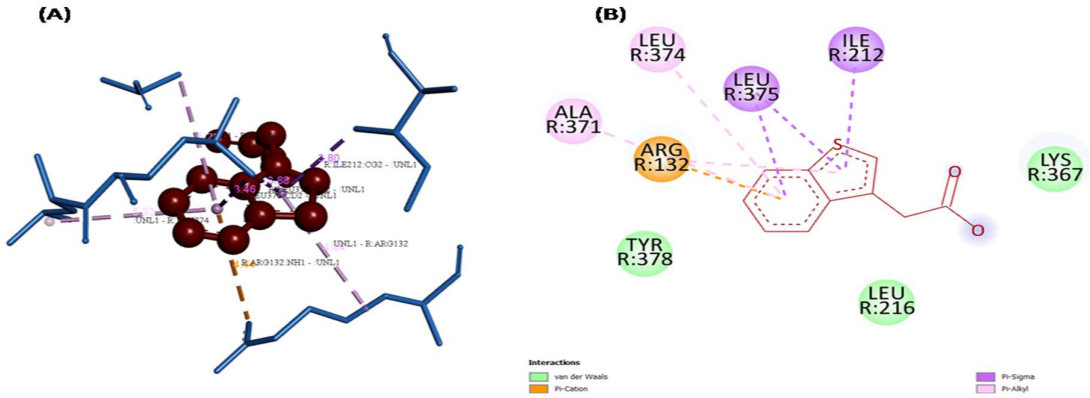


Figure 2 (A)- Dopamine D 2 receptor: Stick model (blue colour)- Benzo[b]thiophene-3-carboxylicacid,7-acetoxy-2-acet -Scaled ball and stick model (red colour) visualized using Biovia Discovery studio visualizer. (B)- 2D Diagram – Benzo[b]thiophene-3-carboxylicacid,7-acetoxy-2-acet and key amino acid residue interactions

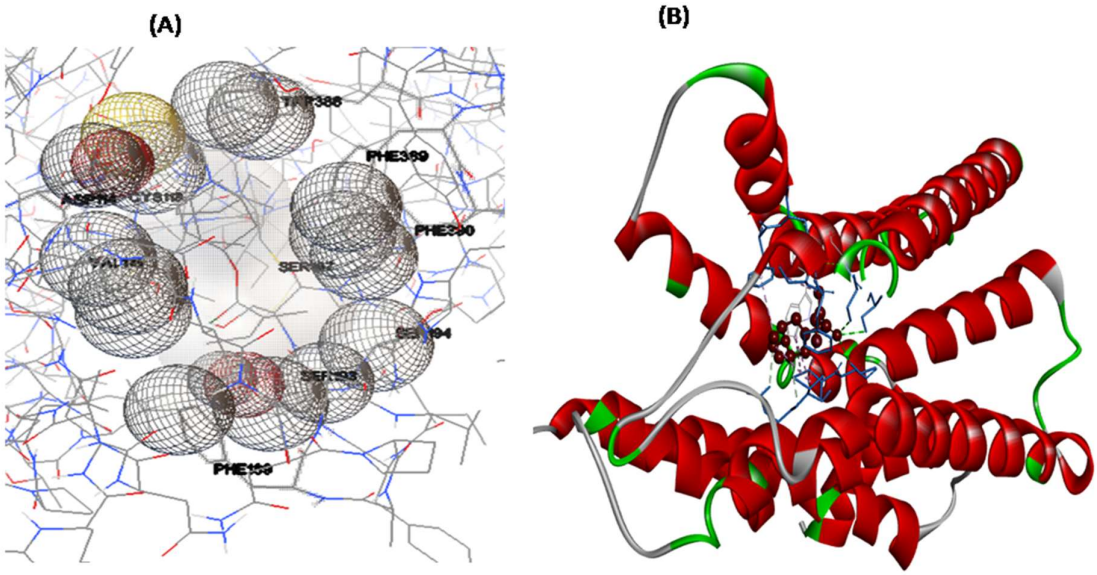


Figure 3 (A and B)- Tropigline and Dopamine D 2 receptor interaction.

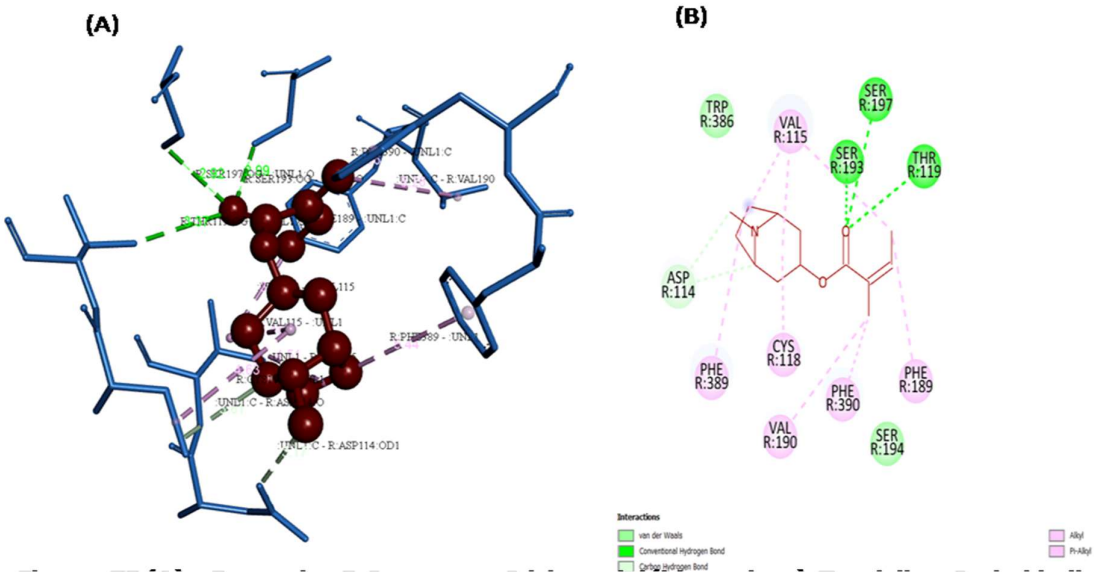


Figure 4 (A) - Dopamine D 2 receptor: Stick model (blue colour)- Tropigline -Scaled ball and stick model (red colour) visualized using Biovia Discovery studio visualizer. (B)- 2D Diagram – Tropigline and key amino acid residue interactions

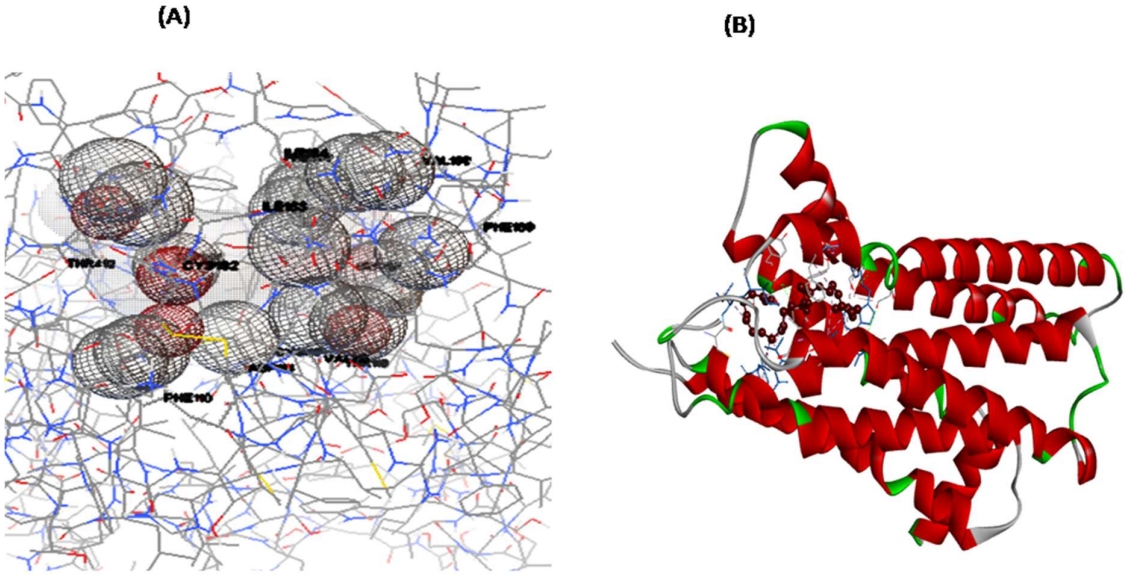


Figure 5 (A and B) - Succinicacid, non-4-enyltetradecyl ester and Dopamine D 2 receptor

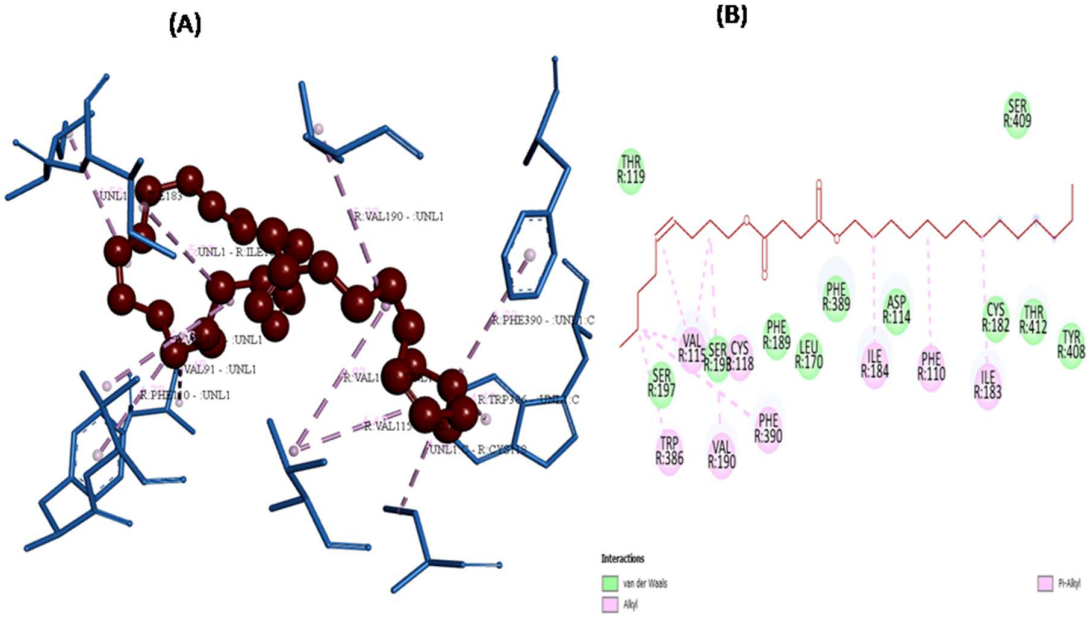


Figure 6 (A)- Dopamine D 2 receptor: Stick model (blue colour)- Succinic acid, non-4-enyltetradecyl ester -Scaled ball and stick model (red colour) visualized using Biovia Discovery studio visualizer. (B) - 2D Diagram – Succinic acid, non-4-enyltetradecyl ester and key amino acid residue interactions

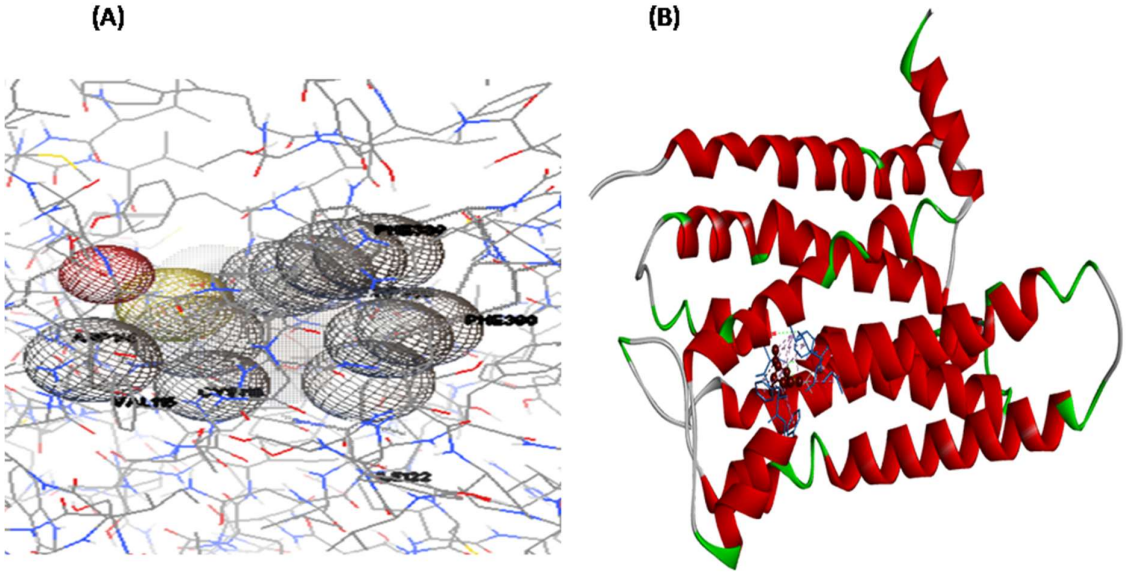


Figure 7 (A and B) - Bicyclo[3.1.1]heptane, 6,6-dimethyl-2- and Dopamine D 2 receptor interaction.

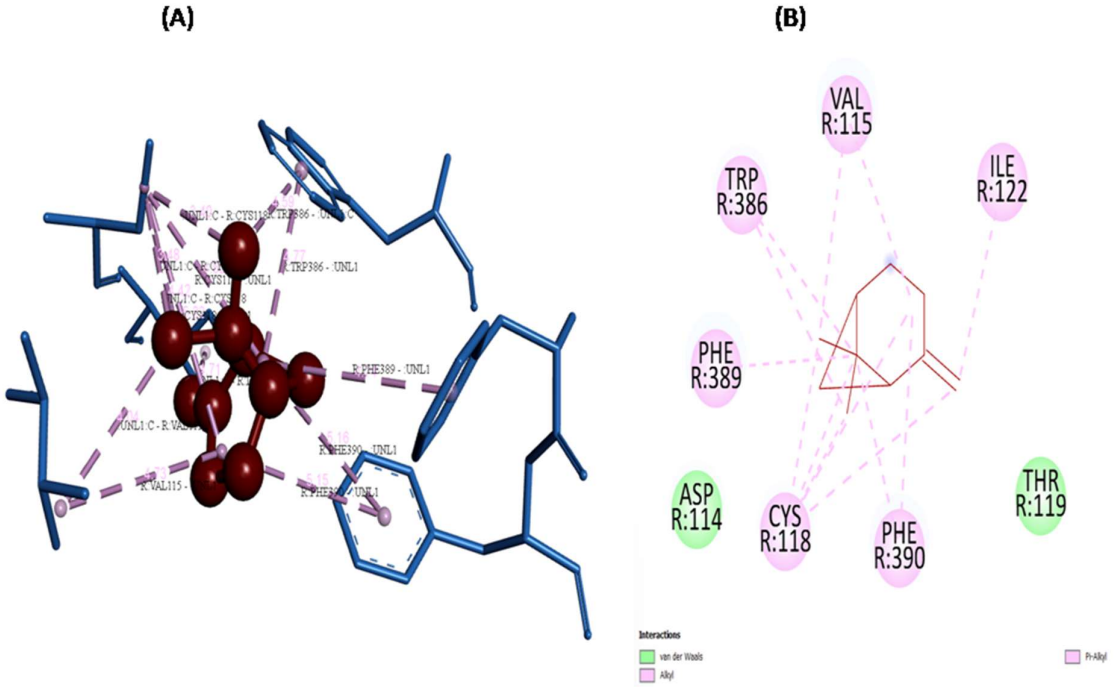


Figure 8 (A)- Dopamine D 2 receptor: Stick model (blue colour)- Bicyclo [3.1.1]heptane, 6,6-dimethyl-2- -Scaled ball and stick model (red colour) visualized using Biovia Discovery studio visualizer. (B) - 2D Diagram – Bicyclo [3.1.1]heptane, 6,6-dimethyl-2- and key amino acid residue interactions

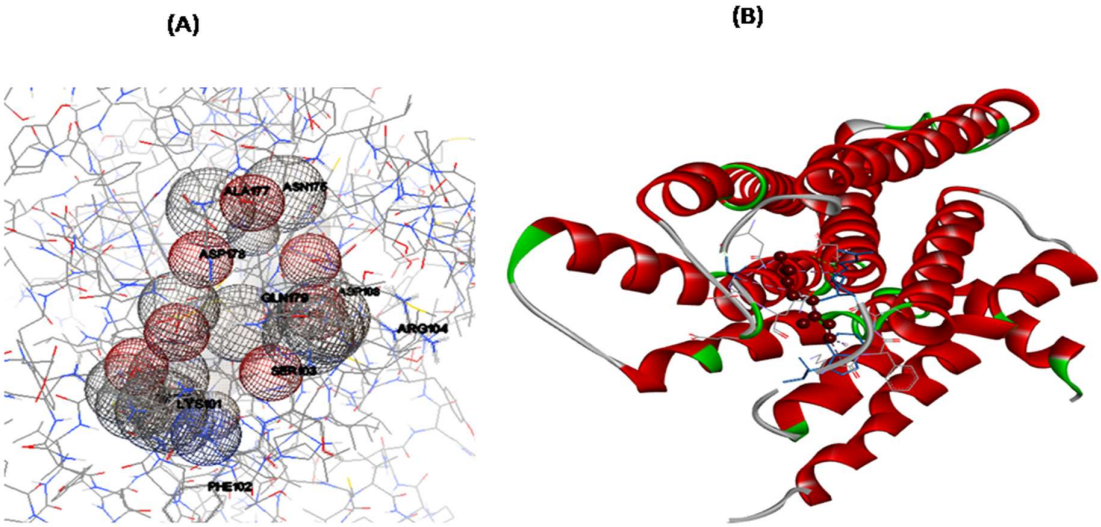


Figure 9 (A and B)- beta-Myrcene and Dopamine D 2 receptor interaction.

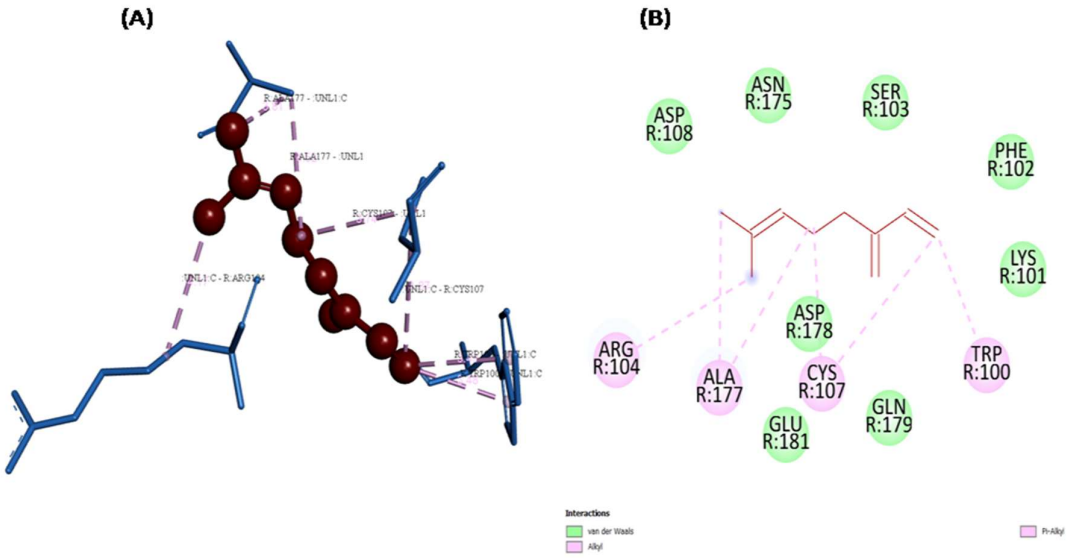


Figure 10 (A)- Dopamine D 2 receptor: Stick model (blue colour)- beta-Myrcene -Scaled ball and stick model (red colour) visualized using Biovia Discovery studio visualizer. (B)-2D Diagram – beta-Myrcene and key amino acid residue interactions

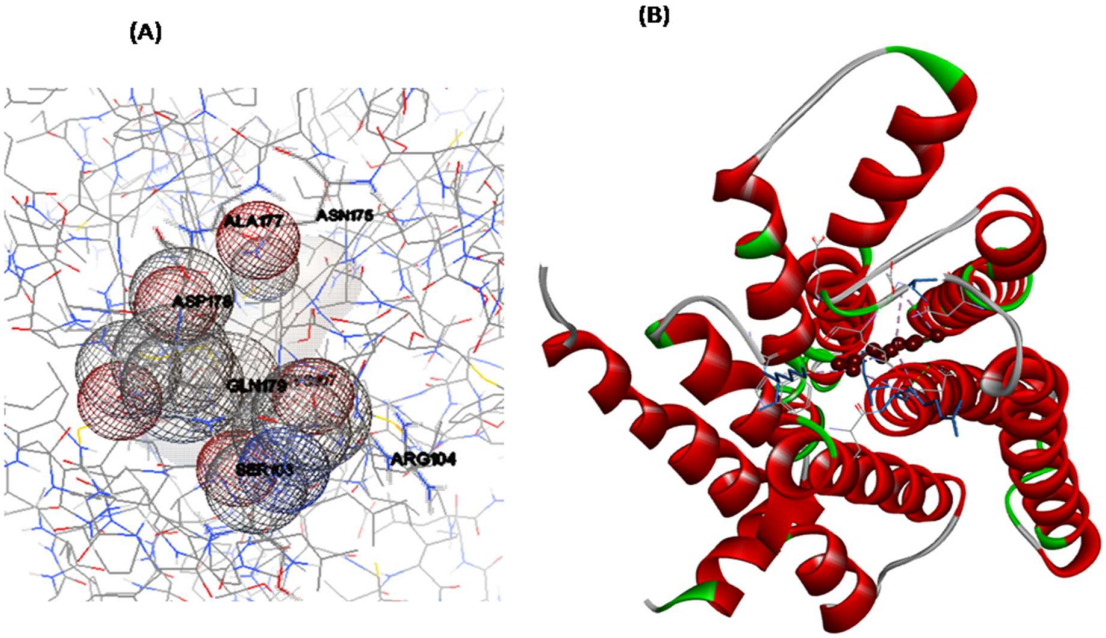


Figure 11 (A and B)- D-Limonene and Dopamine D 2 receptor interaction.

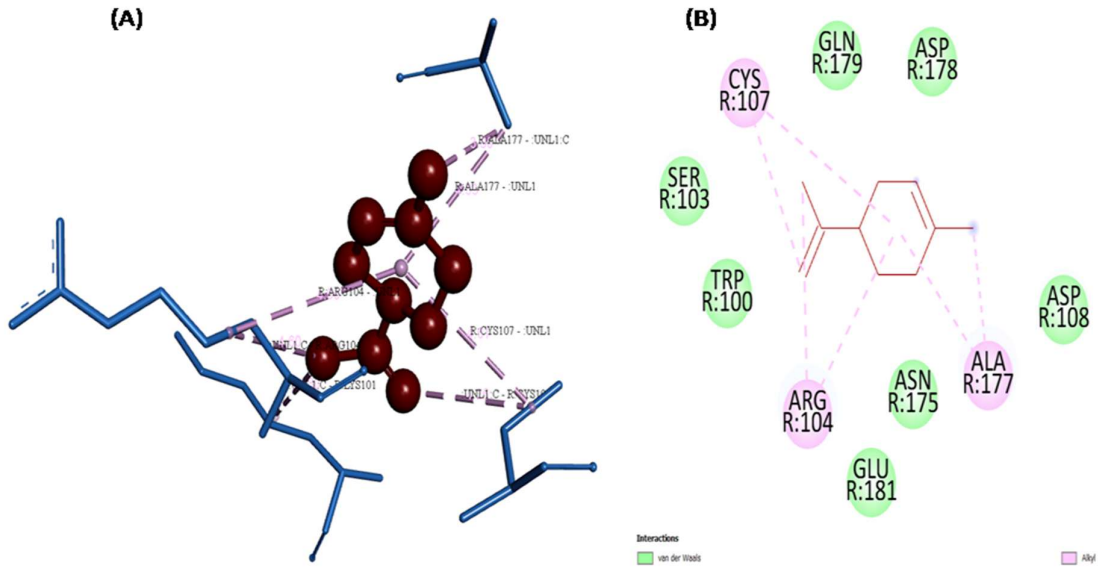


Figure 12 (A)- Dopamine D 2 receptor: Stick model (blue colour)- D-Limonene -Scaled ball and stick model (red colour) visualized using Biovia Discovery studio visualizer. (B) - 2D Diagram – D-Limonene and key amino acid residue interactions

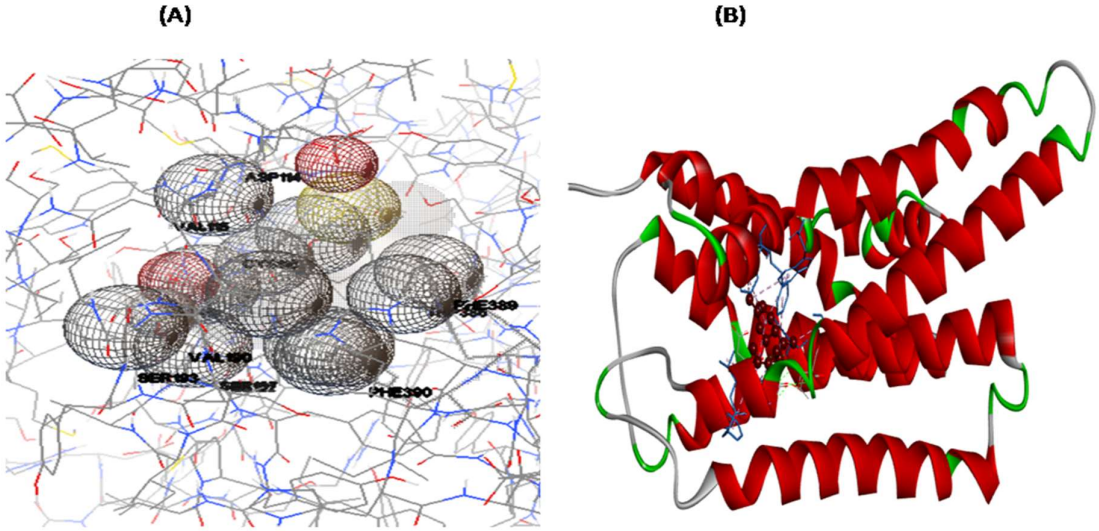


Figure 13 (A and B)- beta-Bisabolene and Dopamine D 2 receptor interaction.

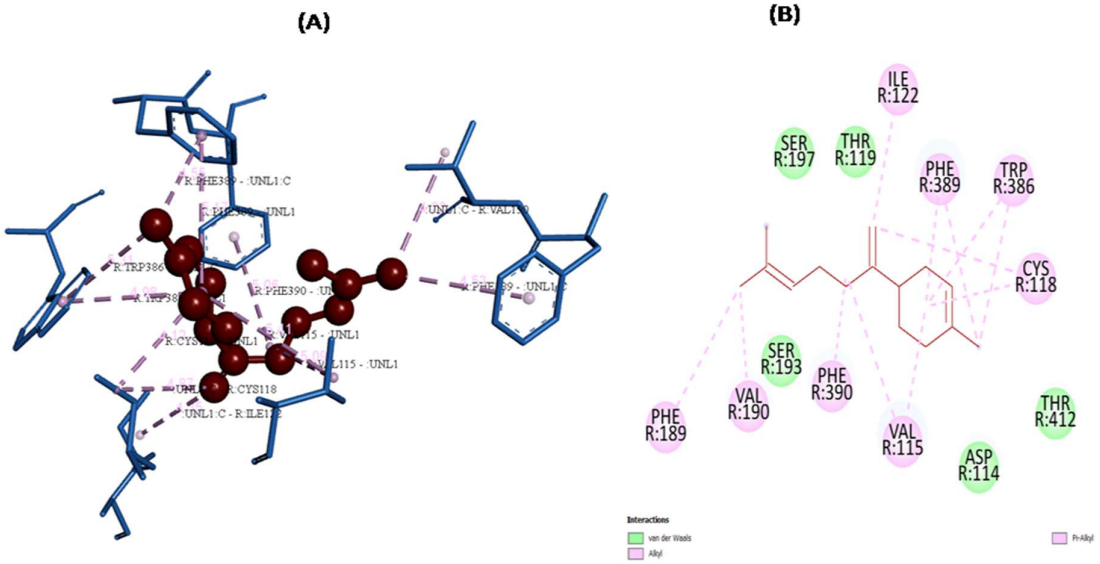


Figure 14 (A)- Dopamine D 2 receptor: Stick model (blue colour)- beta-Bisabolene - Scaled ball and stick model (red colour) visualized using Biovia Discovery studio visualizer. (B)- 2D Diagram – beta-Bisabolene and key amino acid residue interactions

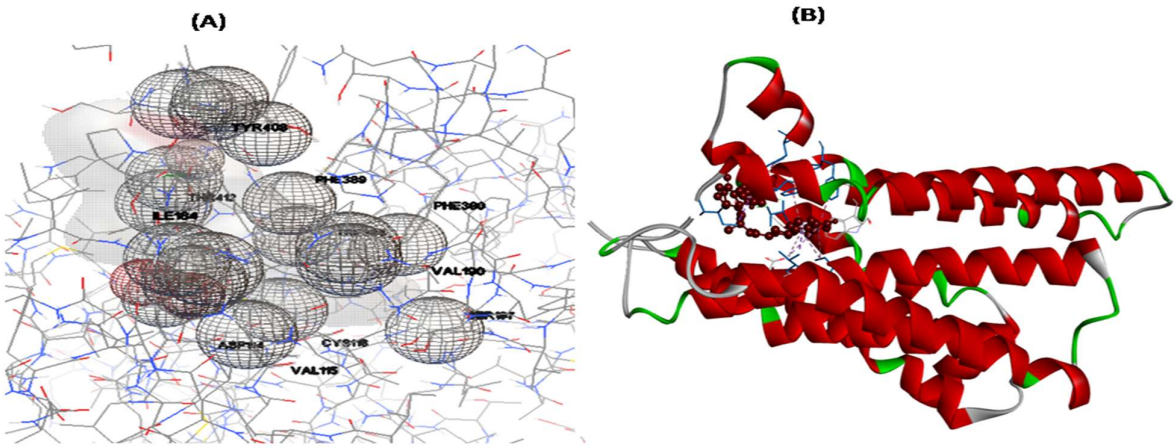


Figure 15 (A and B)- Dihydroergotoxine and Dopamine D2 receptor (D2R)interaction.

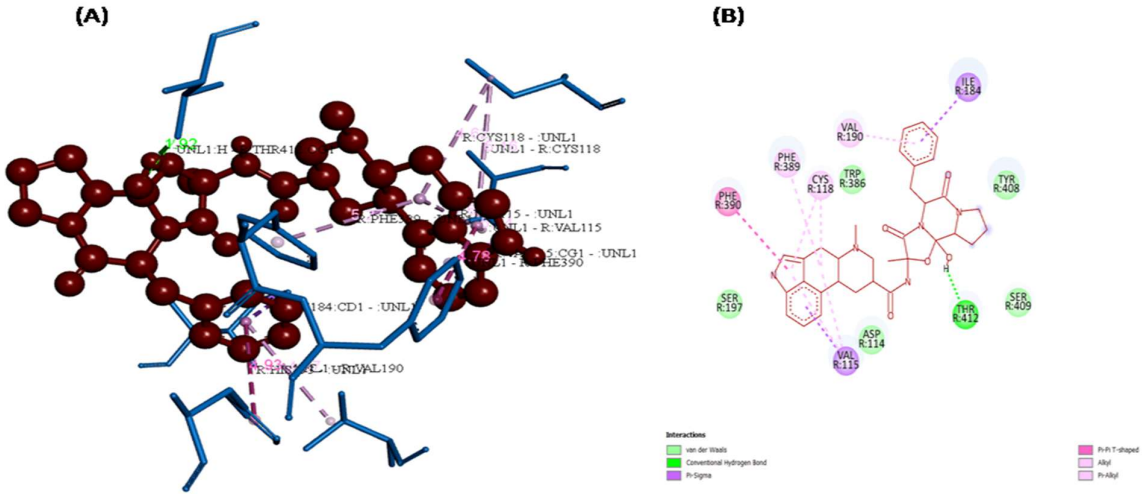


Figure 16 (A)- Dopamine D 2 receptor: Stick model (blue colour)- Dihydroergotoxine - Scaled ball and stick model (red colour) visualized using Biovia Discovery studio visualizer. (B)- 2D Diagram –Dihydroergotoxine and key amino acid residue interactions.

Table 5 : Hydrogen Bond Donor-Acceptor Linkages of Ligands with Target Proteins.

Ligand	Target Protein	Donor → Acceptor (Amino Acid - Atom → Ligand - Atom)	Distance (Å)	Bond Type
Tropigline	**Dopamine D2 Receptor**	R:THR119:OG1 → UNL1:O	3.37122	Conventional Hydrogen Bond
		R:SER193:OG → UNL1:O	2.9876	Conventional Hydrogen Bond
Benzo[b]thiophene-	**Dopamine D2**	R:ARG132:NH1 →	4.43533	Pi-Cation

3-carboxylic acid	**Receptor**	UNL1		
		R:ILE212:CG2 → UNL1	3.80428	Pi-Sigma

Table 6 - Docking scores of some important molecules against Dopamine D2 receptor

Dopamine D2 Receptor docking with compounds	**Binding Energy**	**No. Of Hdrogen bonds**	**Inhibition constant**	**Ligand efficiency**	**Intermolecular energy**	**vdW + H bond+desolv energy**	**Electrostatic energy**	**Torsional energy**	**Total internal**
Dihydroergotoxine (Approved drug)	-11.91	1	1.87	-0.28	-13.4	-12.42	-0.97	1.49	-1.29
Benzo(b) thiopene 3 carboxylic acid, 7 acetoxy2 acet	-6.4	2	20.19	-0.49	-7.3	-4.6	-2.7	0.89	-0.17
Tropigline	-6.5	1	17.16	-0.41	-7.4	-6.77	-0.63	0.89	-0.54
Succinicacid, non-4-enyltetradecyl ester	-4.08	-	1.03	-0.13	-11.53	-11.56	0.02	7.46	-2.61
Bicyclo[3.1.1]heptane, 6,6-dimethyl-2-	-5.22	-	150.42	-0.52	-5.22	-5.21	-0.01	0.0	0.0
beta.-Myrcene	-5.11	-	178.39	-0.51	-6.31	-6.31	-0.01	1.19	-0.22
D-Limonene	-5.42	-	106.28	-0.54	-5.72	-5.73	0.01	0.3	-0.13
beta.-Bisabolene	-6.76	-	11.01	-0.45	-7.96	-7.95	-0.01	1.19	-082

Table 7- Classification of Polar and Non-Polar Molecules Involved in Ligand-Protein Interactions

Ligand	**Target Protein**	**Polar Molecules Involved**	**Non-Polar Molecules Involved**
Tropigline	**Dopamine D2 Receptor**	THR119 (OG1), SER193 (OG)	VAL115, CYS118, PHE189
Benzo[b]thiophene-3-carboxylic acid	**Dopamine D2 Receptor**	ARG132 (NH1)	ILE212, LEU375, ALA371

Table 8: Comparative Binding Affinity and Molecular Interaction Analysis.

Ligand/Drug	**Target**	**Binding**	**Hydrogen**	**Hydrophobic**	**Key**

	Protein	Energy (kcal/mol)	Bonds	Interactions	Residues Involved
Tropigline	**Dopamine D2 Receptor**	**-7.4**	3	3	THR119, SER193, PHE189
Benzo[b]thiophene-3-carboxylic acid	**Dopamine D2 Receptor**	**-6.8**	1	3	ARG132, LEU375, ALA371
Succinic acid, non-4-enyltetradecyl ester	**Dopamine D2 Receptor**	**-6.1**	0	3	PHE110, ARG104
β-Myrcene	**Dopamine D2 Receptor**	**-5.7**	0	2	TRP100
D-Limonene	**Dopamine D2 Receptor**	**-5.6**	0	2	ARG104
β-Bisabolene	**Dopamine D2 Receptor**	**-5.8**	0	3	TRP386, PHE389
Haloperidol (Proven Drug)	**Dopamine D2 Receptor**	**-9.3**	**3**	**5**	THR412, ASP114, PHE389

Table 9-Binding Energy and Molecular Interaction Summary of Standard drug with target proteins.

Drug Name	Target Protein	Binding Energy (kcal/mol)	No. of Hydrogen Bonds	Inhibition Constant (Ki)	Ligand Efficiency	Intermolecular Energy	vdW + H bond + Desolv Energy	Electrostatic Energy	Torsional Energy	Unbound Energy
Dihydroergotoxine	Dopamine D2 receptor (D2R)	**-11.91**	**1** (THR412:OG1)	**1.87 nM**	**0.28**	**-13.4**	**-12.42**	**-0.97**	**1.49**	**-1.29**

Conclusion

The present *In silico* study demonstrates that *Tropigline* and *Benzo[b]thiophene-3-carboxylic acid*, exhibit favorable binding affinity and stable interactions with the Dopamine D2 receptor. Their hydrogen bonding and hydrophobic interaction profiles, along with ligand efficiency values, are comparable to those of established drugs such as Haloperidol and Dihydroergotoxine. These findings underscore their potential as natural modulators of the D2 receptor for Alzheimer's disease management.

Given the central role of the Dopamine D2 receptor in regulating cognition, behaviour, and motor function, its therapeutic relevance in neurodegenerative disorders remains significant. This study supports the potential repositioning of plant-derived compounds as safer and more accessible alternatives for dopaminergic modulation. However, further pharmacological validation—including in vitro assays, in vivo studies, and ADME-Tox profiling—is essential to substantiate their efficacy and safety, and to advance these candidates toward clinical development.

References-

1. Avila, J., Lucas, J. J., Perez, M., & Hernandez, F. (2004). Role of tau protein in both physiological and pathological conditions. *Physiological reviews*, *84*(2), 361–384. https://doi.org/10.1152/physrev.00024.2003.
2. Ben-Jonathan, N., & Hnasko, R. (2001). Dopamine as a prolactin (PRL) inhibitor. *Endocrine reviews*, *22*(6), 724–763. https://doi.org/10.1210/edrv.22.6.0451
3. Bezard, E., Porras, G., Blesa, J., & Obeso, J. A. (2010). *Compensatory Mechanisms in Experimental and Human Parkinsonism. Handbook of Basal Ganglia Structure and Function, 641–652. https://doi.org/10.1016/B978-0-12-374767-9.00037-8*.
4. Birks J. (2006). Cholinesterase inhibitors for Alzheimer's disease. *The Cochrane database of systematic reviews*, *2006*(1), CD005593. https://doi.org/10.1002/14651858.CD005593.
5. Cordella, A., *et al*. (2022). Dopamine dysfunction in Alzheimer's disease: A new perspective on therapeutic approaches. *Frontiers in Aging Neuroscience*, 14, 863294.
6. Emamzadeh, F. N., & Surguchov, A. (2018). Parkinson's Disease: Biomarkers, Treatment, and Risk Factors. *Frontiers in neuroscience*, *12*, 612. https://doi.org/10.3389/fnins.2018.00612.
7. Frank, M.J., & O'Reilly, R.C. (2006). A mechanistic account of striatal dopamine function in human cognition: psychopharmacological studies with cabergoline and haloperidol. *Behavioral neuroscience, 120 3*, 497-517 . https://doi.org/10.1037/0735-7044.120.3.497.
8. Francis, P. T., Palmer, A. M., Snape, M., & Wilcock, G. K. (1999). The cholinergic hypothesis of Alzheimer's disease: a review of progress. *Journal of neurology, neurosurgery, and psychiatry*, *66*(2), 137–147. https://doi.org/10.1136/jnnp.66.2.137.
9. Glickstein, S. B., & Schmauss, C. (2001). Dopamine receptor functions: lessons from knockout mice [corrected]. *Pharmacology & therapeutics*, *91*(1), 63–83. https://doi.org/10.1016/s0163-7258(01)00145-0.
10. Hardy, J. A., & Higgins, G. A. (1992). Alzheimer's disease: the amyloid cascade hypothesis. *Science (New York, N.Y.)*, *256*(5054), 184–185. https://doi.org/10.1126/science.1566067.
11. Heneka, M. T., Carson, M. J., El Khoury, J., Landreth, G. E., Brosseron, F., Feinstein, D. L., Jacobs, A. H., Wyss-Coray, T., Vitorica, J., Ransohoff, R. M., Herrup, K., Frautschy, S. A., Finsen, B., Brown, G. C., Verkhratsky, A., Yamanaka, K., Koistinaho, J., Latz, E., Halle, A., Petzold, G. C., … Kummer, M. P. (2015). Neuroinflammation in Alzheimer's disease. *The Lancet. Neurology*, *14*(4), 388–405. https://doi.org/10.1016/S1474-4422(15)70016-5.
12. Howes, O. D., & Kapur, S. (2009). The dopamine hypothesis of schizophrenia: version III--the final common pathway. *Schizophrenia bulletin*, *35*(3), 549–562. https://doi.org/10.1093/schbul/sbp006.

13. Jayaprakasam B., Zhang Y., Seeram N P., Nair M G. Growth inhibition of human tumor cell lines by withanolides from Withania somnifera leaves. Life Sci. 2003 Nov 21;74(1):125-32. doi: 10.1016/j.lfs.2003.07.007.
14. Kuboyama, N., Nabetani, T., Shibuya, K., *et al*. (2005) Relationship between Cerebral Activity and Frequency during Maximal Movement Stimulus. Journal of Physiological Anthropology and Applied Human Science, 24, 201-208. https://doi.org/10.2114/jpa.24.201.
15. Lane, C. A., Hardy, J., & Schott, J. M. (2017). *Alzheimer's disease. European Journal of Neurology, 25(1), 59–70.* https://doi.org/10.1111/ene.13439.
16. Lipton S. A. (2004). Failures and successes of NMDA receptor antagonists: molecular basis for the use of open-channel blockers like memantine in the treatment of acute and chronic neurologic insults. *NeuroRx : the journal of the American Society for Experimental NeuroTherapeutics*, *1*(1), 101–110. https://doi.org/10.1602/neurorx.1.1.101.
17. Livingston, G., Huntley, J., Sommerlad, A., Ames, D., Ballard, C., Banerjee, S., Brayne, C., Burns, A., Cohen-Mansfield, J., Cooper, C., Costafreda, S. G., Dias, A., Fox, N., Gitlin, L. N., Howard, R., Kales, H. C., Kivimäki, M., Larson, E. B., Ogunniyi, A., Orgeta, V., … Mukadam, N. (2020). Dementia prevention, intervention, and care: 2020 report of the Lancet Commission. *Lancet (London, England)*, *396*(10248), 413–446. https://doi.org/10.1016/S0140-6736(20)30367-6.
18. Mattson M. P. (2004). Pathways towards and away from Alzheimer's disease. *Nature*, *430*(7000), 631–639. https://doi.org/10.1038/nature02621.
19. Missale, C., Nash, S. R., Robinson, S. W., Jaber, M., & Caron, M. G. (1998). Dopamine receptors: from structure to function. *Physiological reviews*, *78*(1), 189–225. https://doi.org/10.1152/physrev.1998.78.1.189.
20. Selkoe, D. J., & Hardy, J. (2016). The amyloid hypothesis of Alzheimer's disease at 25 years. *EMBO molecular medicine*, *8*(6), 595–608. https://doi.org/10.15252/emmm.201606210.
21. Sevigny, J., Chiao, P., Bussière, T. weinreb PH,. Williams L., Maier M., Dunstan R., Salloway S., Chen T., Ling Y., Gorman J O., Qian F., Arastu M., Li M., Chollate S., Brennan M S., Quintero monzon O., Scannevin R H., Arnold H M., Engber T., Rhodes K., Ferrero J., Hang Y., Mikulskis A., Grimm J., Hock C., Nitsch R M.. *Sandrock A.* The antibody aducanumab reduces Aβ plaques in Alzheimer's disease. *Nature* **537**, 50–56 (2016). https://doi.org/10.1038/nature19323.
22. Scheltens, P., Blennow, K., Breteler, M. M., de Strooper, B., Frisoni, G. B., Salloway, S., & Van der Flier, W. M. (2021). Alzheimer's disease. *Lancet (London, England)*, *388*(10043), 505–517. https://doi.org/10.1016/S0140-6736(15)01124-1.
23. Surmeier, D. J., Carrillo-Reid, L., & Bargas, J. (2011). Dopaminergic modulation of striatal neurons, circuits, and assemblies. *Neuroscience*, *198*, 3–18. https://doi.org/10.1016/j.neuroscience.2011.08.051.
24. Wang, Y., Mandelkow, E. Tau in physiology and pathology. *Nat Rev Neurosci* **17**, 22–35 (2016). https://doi.org/10.1038/nrn.2015.1.
25. Volkow, N. D., Fowler, J. S., Wang, G. J., & Swanson, J. M. (2004). Dopamine in drug abuse and addiction: results from imaging studies and treatment implications. *Molecular psychiatry*, *9*(6), 557–569. https://doi.org/10.1038/sj.mp.4001507