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Targeting Dopamine Receptors with Costunolide: A Computational Approach Toward Selective Neuroprotection

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ABSTRACT

Background: Costunolide, a neuroprotective and anti-inflammatory sesquiterpene lactone, may be utilized for tailored dopaminergic therapy. Molecular docking studies show that, in contrast to Tetrandrine, Eudesmol, and Spathulenol, costunolide possesses high binding receptor receptor and beneficial ADMET characteristics. The most effective modulator of dopaminergic transmission is costunolide because of its low pharmacokinetic risk and high efficiency.

Aim: To evaluate the therapeutic potential and receptor selectivity of costunolide as a dopaminergic modulator through in-silico analysis, including ADMET profiling and molecular docking, for potential application in Parkinson's disease and related neuropsychiatric disorders.

Methods: An in-silico approach was employed to evaluate costunolide, eudesmol, spathulenol, and tetrandine drug-likeness and receptor interaction profile. ADMET analysis of the drug properties was conducted through SwissADME and the ESOL cheminformatics platform. Molecular docking simulations performed through AutoDock Tools examined receptors dopamine D1 (PDB ID: 7X2D and D2 (PDB ID: 7JVR). Protein and ligand structures were prepared, optimized, and docked, and binding affinities and BIOVIA Discovery Studio facilitated detection of interaction patterns.

Results: The ADMET characteristics of costunolide, eudesmol and spathulenol show excellent absorption, solubility, permeability through blood brain barrier without violating the Lipinski's Rule. These compounds additionally demonstrated a distinct absence of PAINS alerts. Out of the four compounds, three exhibited CYP inhibition freedom, while spathulenol exhibited inhibition of CYP2C19. Docking simulations of costunolide eudesmol, spathulenol, and tetrandine show -6.1, -5.7, -6.0, and -6.5kcal/mol respectively against D1 receptor and -5.3, -5.5, -6.3, and -7.0kcal/mol respectively against D2 receptor.

Conclusion: Costunolide demonstrates promising therapeutic attributes and moderate selectivity for the dopamine D1 receptor, supported by robust in-silico ADMET and docking analyses. Future investigations including both in vivo efficacy assessments and chemical structure improvements are warranted to unveil therapeutic potency and receptor binding accuracy.

Keywords: *Costunolide, ADMET, in-silico, receptor, CYP2C19, molecular docking.*

1. INTRODUCTION

The central nervous system (CNS) functions, such as motor control, cognition, motivation, and reward processing, are dependent on dopaminergic signaling, which is primarily mediated through dopamine D1 and D2 receptors (1). A spectrum of neurodegenerative and mental diseases including Parkinson's disease, schizophrenia, and addiction is highly correlated

with dysregulation of these pathways. As such, the development of efficient dopamine receptor modulators presents a vital therapeutic strategy for controlling these complicated diseases. Finding molecules that not only efficiently alter receptor activity but also have good safety and pharmacokinetic characteristics fit for therapeutic use is still difficult, though (2).

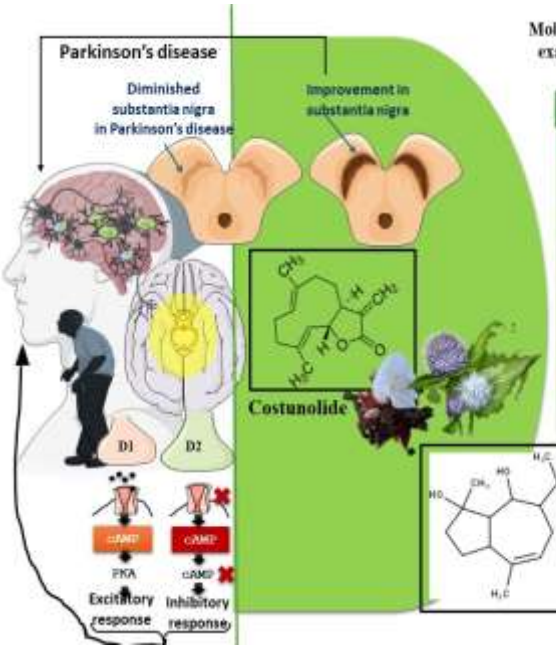
Natural substances with their varied chemical structures and multifarious pharmacological effects have attracted more and more interest as possible modulators of dopamine receptors (3, 4). Unlike many synthetic medicines, natural bioactives typically show extra neuroprotective, anti-inflammatory, and antioxidant actions that are favorable in fighting CNS diseases defined by oxidative stress and neuroinflammation (5, 6). Many natural compounds have important limitations including poor bioavailability, metabolic instability, limited ability to penetrate the blood-brain barrier (BBB), and possible toxicity notwithstanding these advantages. These difficulties greatly limit their translocation into practical treatments, thereby stressing the requirement of thorough assessment of both their pharmacokinetic characteristics and receptor binding capacity (7, 8).

Predicting the binding affinity and interaction patterns of small molecules with dopamine receptors requires the fundamental computational tool that is the molecular docking method. This method has gained significance since it offers a molecular level insight of the expected potency of several medications (9, 10). Moreover, these approaches give an early-stage, all-encompassing evaluation of drug candidates in concert with *in-silico* ADMET (Absorption, Distribution, Metabolism, Excretion, and Toxicity) profiling. This then allows one to select molecules with the most favorable safety and therapeutic profiles. In the field of neuropharmacology, where effective BBB penetration and low toxicity are prerequisites for the development of drugs for the central nervous system, this combined technique is quite important (11, 12).

This research examines four naturally occurring chemicals known for their neuroprotective and anti-inflammatory properties: Costunolide, Tetrandrine, Eudesmol (13), and Spathulenol (14). Costunolide (15, 16), a sesquiterpene lactone, is a notable contender owing to its recognized anti-inflammatory and neuroprotective characteristics, making it suitable for CNS-targeted therapy. The immunosuppressive and neuroprotective characteristics of tetrandrine (17), which is a bisbenzylisoquinoline alkaloid, are already well recognized (17). Eudesmol and Spathulenol, which are both sesquiterpenoids, have qualities that are protective against oxidative damage and inflammation, which are important for maintaining brain function (13, 18-20).

Although receptor binding affinity offers a first clue of therapeutic value, it cannot establish the clinical feasibility of any chemical. Successful drug development depends on their pharmacokinetic and toxicological profiles, assessed using ADMET criteria, equally importantly (21, 22). In vivo chemical behavior including absorption efficiency, distribution patterns, metabolic stability, elimination pathways, and toxicity risks is predicted by ADMET profiling. Especially, drugs with weak ADMET profiles usually fail in clinical development phases even if they demonstrate interesting receptor interactions in vitro or *in-silico* (9, 10, 21).

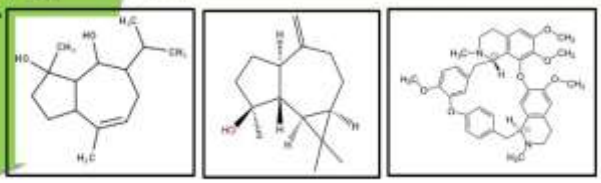
This work attempts to clarify the balance between molecular efficacy and pharmacokinetic appropriateness by methodically analyzing Costunolide, Tetrandrine, Eudesmol, and Spathulenol, so guiding future drug development efforts aiming at dopamine receptors. Knowing the molecular interactions and ADMET properties of these natural compounds would help one to find lead candidates with the maximum translational potential. In the end, this combined assessment helps to progress safer and more efficient treatments for neurological diseases connected to dopamine (23).



Molecular docking simulations performed through AutoDock Tools examined receptors dopamine D1 (PDB ID: 7X2D) and D2 (PDB ID: 7JVR)

ADMET Studies:

Parameter
Molecular weight
Donor HB
Acceptor HB
Lipophilicity Log P o/w
Log S (ESOL)
Water Solubility
GI Absorption
BBB Permeation
CYP Inhibitor (1A2, 2C19, 2C9, 3A4)
Lipinski Rule
Bioavailability
PAIN



2. MATERIAL AND METHODS

ADMET Studies:

The molecular weight (MW) of costunolide was determined using standard cheminformatics provided in PubChem. MW is a critical parameter in drug development as it significantly influences absorption, distribution, metabolism, excretion, and toxicity (ADMET) properties. Hydrogen bond donors (HBD) and acceptors (HBA) were calculated using molecular modeling software that identifies functional groups capable of forming hydrogen bonds, like BIOVIA Discovery Studio. HBD count represents the number of N-H and O-H bonds, while HBA count represents the number of nitrogen and oxygen atoms. Log P (octanol/water partition coefficient), signifying lipophilicity, is a fundamental physicochemical property that dictates numerous aspects of drug performance, including solubility, absorption, membrane permeability, plasma protein binding, and tissue distribution, and was found with the help of SwissADME software. The ideal Log P range for oral drugs is between 1.35-1.8, while CNS-targeting drugs benefit from values around 2.0. Water solubility was evaluated using the ESOL (Estimated Solubility) method, which calculates Log S values. Log S represents the logarithm of aqueous solubility expressed in mol/L. This parameter is essential for predicting absorption efficiency, as compounds with higher solubility (higher Log S values) generally demonstrate better absorption and distribution properties. Most marketed drugs have Log S values greater than -4. Gastrointestinal (GI) absorption and blood-brain barrier (BBB) permeation were predicted. These parameters determine the extent of drug availability at target sites and potential CNS activity. CYP inhibition potential was assessed using *in-silico* models that predict interactions with major CYP isoforms (1A2, 2C19, 2C9, 3A4). This analysis is critical for evaluating drug-drug interaction liabilities, as CYP inhibition can affect plasma levels of co-administered drugs and potentially lead to adverse effects or toxicity. Lipinski's Rule of Five compliance was evaluated by analyzing MW (<500 Da), HBD (≤5), HBA (≤10), and Log P (≤5). This rule helps predict whether compounds possess chemical and physical properties that would make them likely to be orally active drugs in humans. PAINS (Pan-Assay Interference Compounds) screening was conducted to identify potentially problematic structural features known to interfere with biological assays through non-specific interactions. This helps eliminate compounds that might give false-positive results in biological screening assays.

Table 1: Comparison of ADMET Studies of compounds

S. No.	Parameter	Costunolide	Eudesmol	Spathulenol	Tetrandine
1	Molecular weight	232.32	224.38	220.35	622.75
2	Donor HB	0	1	1	0
3	Acceptor HB	2	1	1	8
4	Lipophilicity Log P o/w	2.96	3.73	3.26	5.49
5	Log S (ESOL)	-2.60	-4.06	-3.17	-8.02
6	Water Solubility	Soluble	Soluble	Soluble	Insoluble
7	GI Absorption	High	High	High	High
8	BBB Permeation	Yes	Yes	Yes	No
9	CYP Inhibitor (1A2, 2C19, 2C9, 3A4)	No	No	Yes(CYP2C19)	No
1	Lipinski Rule	0 Violation	0 Violation	0 Violation	Yes, 1 Violation
1	Bioavailability	0.55	0.55	0.55	0.55
1	PAIN	0 alert	0 alert	0 alert	0 alert

Molecular Docking

Protein preparation:

The crystal structure of dopamine D1 receptor was fetched from the Protein Data Bank (PDB ID – 7X2D). In the case of D2 dopamine receptor was used (PDB ID: 7JVR). Protein preparation was performed for molecular docking using AutoDock

Tools through several key steps. Water molecules were removed from the structure, polar hydrogen atoms were incorporated, and Kollman charges were assigned to ensure proper atomic charge distribution throughout the protein. Following these preparation procedures, the refined protein structure was saved in pdbqt format to enable subsequent docking simulations.

Ligand Preparation:

The ligands were designed using ChemDraw software, beginning with the creation of two-dimensional conformations using Chem3D. Following this conversion, energy minimization procedures were applied to optimize the molecular geometry. The refined structures were then converted to pdbqt format using Open Babel to make it compatible with molecular docking software.

Grid Generation:

After preparing the protein and ligand structures, both were imported into the docking software for analysis. A grid box was then established surrounding the ligand's active site to encompass essential residues participating in ligand interactions. The grid box parameters were carefully optimized, including precise center coordinates (x, y, z) and appropriate dimensions (length, width, height) to contain the entire binding pocket properly. This optimization process ensured the ligand had adequate space for conformational exploration within the binding site while maintaining computational efficiency for accurate docking simulations. Initially, the grids were validated by performing molecular docking of the respective co-crystallized ligands of D1 and D2 receptors, followed by the docking of Costunolide, Eudesmol, Spathulenol, and Tetrandine.

Docking:

The molecular docking assessments allowed each ligand to test flexible conformations to identify suitable binding postures. Computations of binding energy values in kilocalories per mole (kcal/mol) provided quantitative measures of binding affinity for each ligand-protein complex. Lower (more negative) binding energy values correspond to stronger interactions between the ligand and protein target.

3. RESULT AND DISCUSSION

Analysis of Docking

An analysis of the ligand-protein complex was conducted to characterize multiple interaction types, including hydrogen bonds, hydrophobic interactions, and Van der Waals interactions. These molecular interactions were examined and visually represented using Biovia Discovery Studio, which provides comprehensive tools for interpreting and displaying protein-ligand binding patterns.

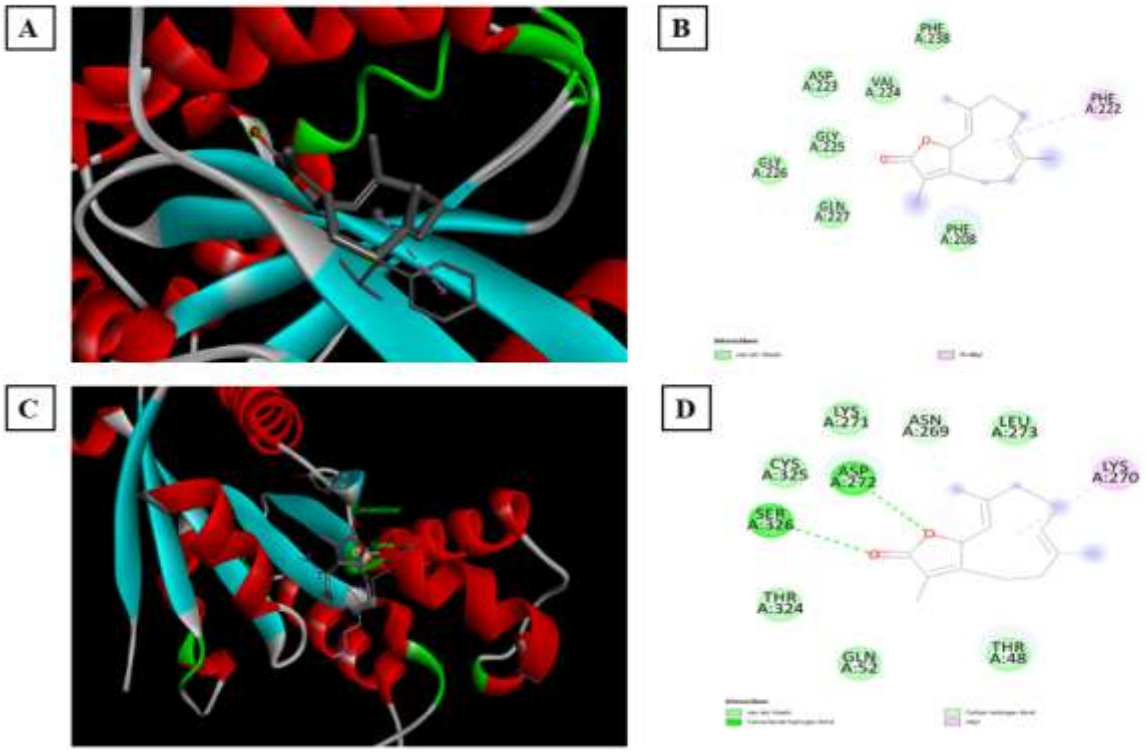


Figure 1. Represent 3D and 2D Docking Pose (A) 3D docking pose of constuloide with protein 7X2D, (B) 2D docking pose of constuloide with protein 7X2D (C) 3D docking pose of constuloide with protein 7JVR, (D) 2D docking pose of constuloide with protein 7JVR.

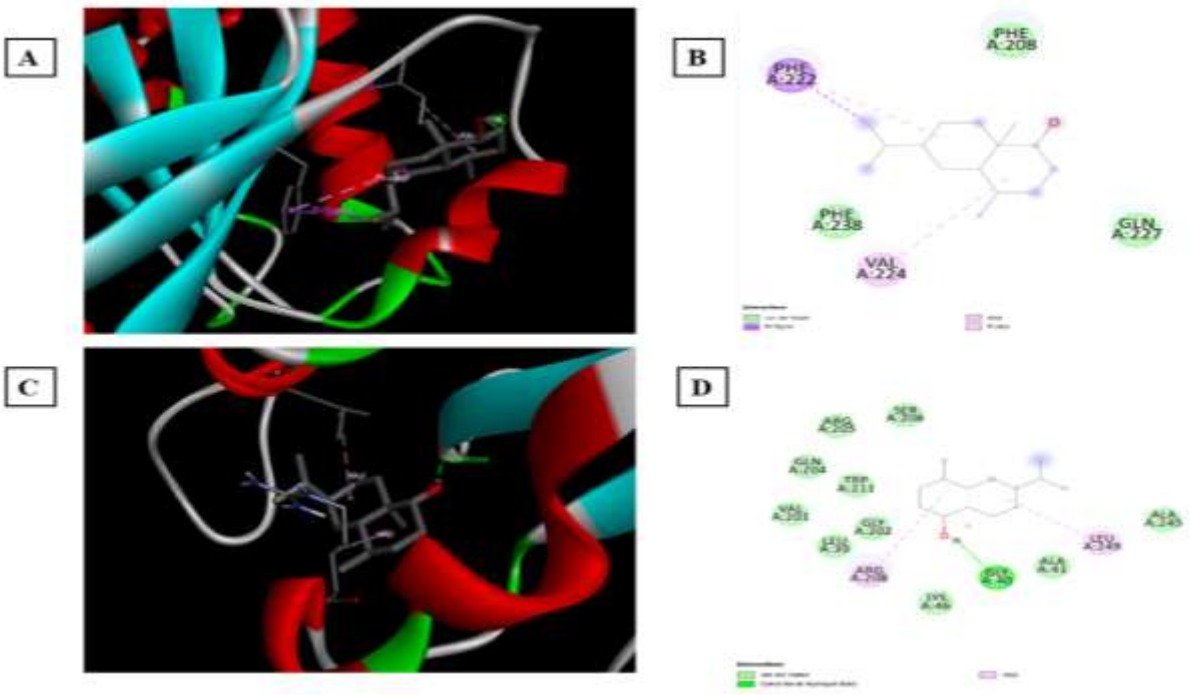


Figure 2. Represent 3D and 2D Docking Pose (A) 3D docking pose of eudesmol with protein 7X2D, (B) 2D docking pose of eudesmol with protein 7X2D (C) 3D docking pose of eudesmol with protein 7JVR, (D) 2D docking pose of eudesmol with protein 7JVR.

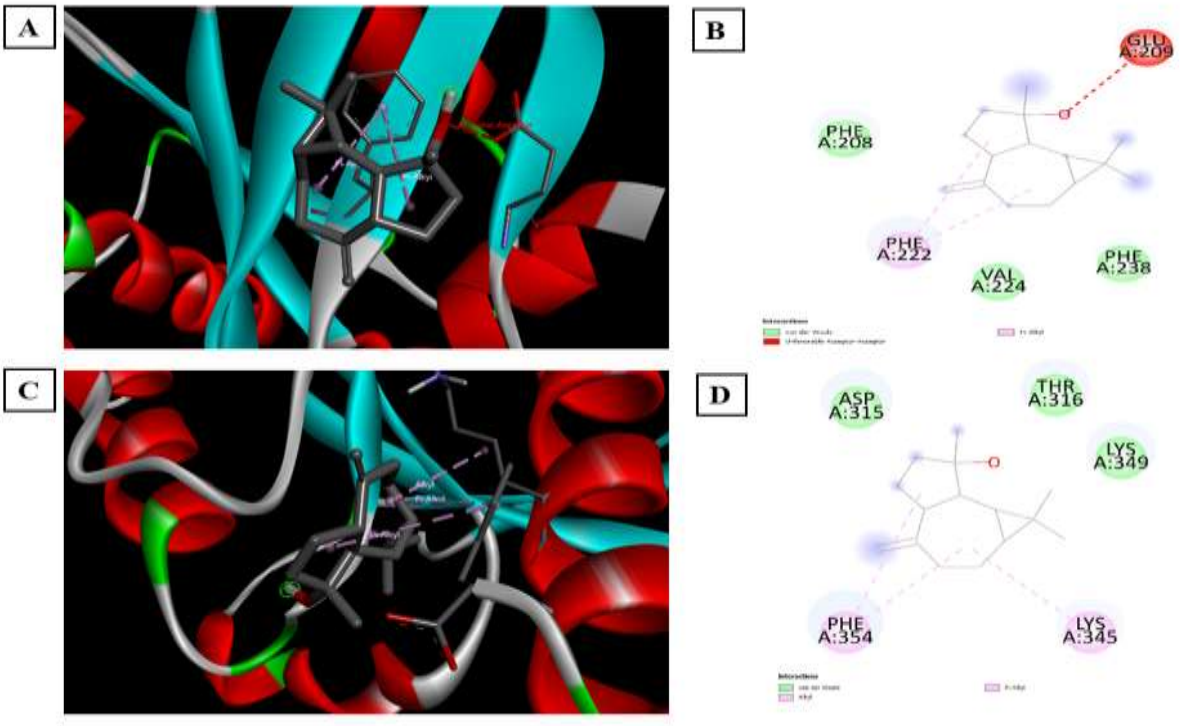


Figure 3. Represent 3D and 2D Docking Pose (A) 3D docking pose of spathulenol with protein 7X2D, (B) 2D docking pose of spathulenol with protein 7X2D (C) 3D docking pose of spathulenol with protein 7JVR, (D) 2D docking pose of spathulenol with protein 7JVR

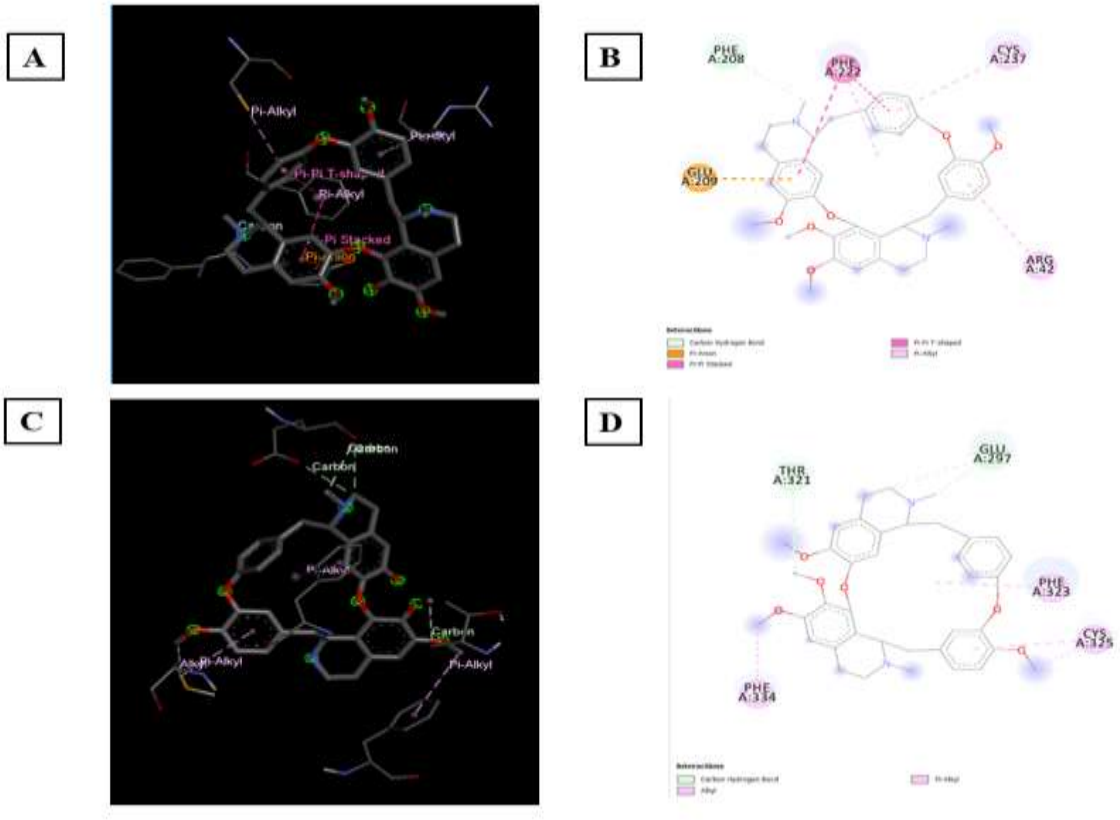


Figure 4. Represent 3D and 2D Docking Pose (A) 3D docking pose of tetrandrine with protein 7X2D, (B) 2D docking pose of tetrandrine with protein 7X2D (C) 3D docking pose of tetrandrine with protein 7JVR, (D) 2D docking pose of tetrandrine with protein 7JVR.

4. DISCUSSION

Molecular docking studies and ADMET profiling were used to assess the possible potency of costunolide, eudesmol, spathulenol, and tetrandrine, as dopaminergic receptor modulators. With a favorable molecular weight of 232.32 g/mol, modest lipophilicity (Log P = 2.96), and great aqueous solubility (Log S = -2.60), costunolide was labeled as water-soluble. Both central nervous system operations depend on high gastrointestinal absorption and efficient blood-brain barrier (BBB), which it proved to possess. Furthermore, by not inhibiting cytochrome P450, following Lipinski's guidelines, and avoiding PAINS signals, costunolide shown a favorable safety and efficacy record.

The molecular weights of eudesmol and spathulenol were comparable (~220–224 g/mol), and they both had high BBB permeability and gastrointestinal absorption. However, it was predicted that spathulenol would inhibit CYP2C19, which could be related to metabolic interactions. With no Lipinski violations, both were water soluble, but not as much as Costunolide (Log S of -4.06 and -3.17, respectively).

Tetrandrine was significantly different due to its high molecular weight (622.75 g/mol), high lipophilicity (Log P = 5.49), and poor water solubility (insoluble; Log S = -8.02). Its CNS drug potential was limited because it broke one Lipinski rule and lacked BBB penetration, despite having high gastrointestinal absorption.

To determine binding affinities, docking scores (kcal/mol) were computed for interactions with dopamine D1 and D2 receptors (Table 2). Following closely with Spathulenol (-6.0 and -6.3 kcal/mol), Tetrandrine displayed the highest binding affinities with docking scores of -6.5 kcal/mol (D1) and -7.0 kcal/mol (D2). With scores of -6.1 kcal/mol (D1) and -5.3 kcal/mol (D2), costunolide showed modestly strong binding; Eudesmol had the lowest affinities (-5.7 and -5.5 kcal/mol).

Table 2. Docking Score D1 and D2 receptors

Compound	D1 Docking Score (kcal/mol)	D2 Docking Score (kcal/mol)

Costunolide	-6.1	-5.3
Eudesmol	-5.7	-5.5
Spathulenol	-6.0	-6.3
Tetrandrine	-6.5	-7.0

Although Tetrandrine and Spathulenol showed better docking affinities, their poor ADMET profiles, especially in Tetrandrine's case, limit their therapeutic value. On the other hand, Costunolide is the most interesting candidate for dopaminergic modulation since it balances reasonable binding affinities with an outstanding ADMET profile including high BBB permeation and metabolic safety. Eudesmol shows rather less receptor binding even with a good ADMET profile.

5. CONCLUSION

The critical need of combining molecular docking with thorough ADMET profiling in the evaluation of possible dopaminergic modulators is underlined by this work. Although Tetrandrine and Spathulenol show strong binding affinities to dopamine receptors, their suboptimal pharmacokinetic and safety profiles limit their therapeutic potential. The most exciting candidate is costunolide, which shows a harmonic mix of good ADMET properties and strong receptor binding. It's ideal solubility, strong gastrointestinal absorption, blood-brain barrier permeability, and metabolic stability place it as a better lead compound for the development of safe and effective dopaminergic treatments. To progress the clinical use of Costunolide in neurological diseases, future studies should concentrate on in vitro and in vivo validation of its efficacy and safety.

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Author Contribution declaration

Ritika Sharma (RS): Drafting the original document, curating data, collecting and interpreting data; Kundan Singh Bora (KSB): Reviewing and editing writing, managing software; Handling resources, conducting formal analysis; Hitesh Kumar Dewangan (HKD): Overseeing conceptualization and supervision, gathering data, performing literature surveys.

Conflict of interest

The authors declare no competing financial or any conflict of interests.

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