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Research Article

MOLECULAR DOCKING STUDY OF BOHECO DESIRE (AN AYURVEDIC PROPRIETARY MEDICINE)

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ABSTRACT

BOHECO DESIRE is an Ayurvedic proprietary medicine formulated in capsule form, recommended for enhancing sexual health, libido, stamina, and energy. **Objectives:** This study aims to explore the molecular binding interactions of the major phytocompounds present in BOHECO DESIRE with a target protein and also to understand binding affinity and bioavailability, using advanced computational tools. **Methodology:** Molecular docking studies were performed using ChemDraw 20.1.1. Glide extra precision (XP) scoring tools were employed to calculate the docking scores. The binding energy of the receptor-phytoconstituent complexes was calculated using the Molecular Mechanics-Generalized Born Surface Area (MM-GBSA) method. Additionally, the QikProp module from Schrödinger was used to predict the ADME (Absorption, Distribution, Metabolism, Excretion) and physicochemical properties of the phytoconstituents. **Results:** Docking scores for L-DOPA, Cannabidiol, and Delta-9 Tetrahydrocannabinol suggest strong binding affinity with the target protein 1XOJ, with scores ranging from -9.4 to -4.1 kcal/mol. The Van der Waals energy (Glide evdw) between -42.5 and -24.11kcal/mol indicates favorable ligand-protein interactions. Glide energy, which includes Van der Waals, electrostatic, and solvation energies, ranged from -45.07 to -26.53kcal/mol, reinforcing the potential for stable complexes. Binding free energy values (-76.6 to -35.73kcal/mol) suggest energetically favorable interactions. ADME predictions showed high oral absorption for Withanolide A, Delta-9 THC, and Cannabidiol, with the highest Caco-2 permeability for Delta-9 THC. **Conclusion:** The phytoconstituents demonstrated a strong binding affinity with 1XOJ with favorable ADME profiles. This indicates that BOHECO DESIRE's phytocompounds may have beneficial effects in sexual health.

INTRODUCTION

BOHECO DESIRE is a proprietary Ayurvedic formulation comprises of cannabis leaf, *Ashwagandha* root extract, *Kaunch* seeds extract, *Shatavari* root extract, *Gokshura* fruit extract. It works on the body's Endocannabinoid System (ECS) to maintain and/or improve sexual and reproductive health for both women and men. The full spectrum of cannabinoids in this *Vijaya* leaf-based medication provides a natural treatment for symptomatic relief [1].

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The Endocannabinoid System (ECS) is present in every human being. A cell-signaling system spread across the body, it comprises molecules which act as neurotransmitters. The phyto cannabinoids bind with the CB1 and CB2 receptor which helps stimulate the cell signaling system and regulates sexual function in addition to improving libido by reducing anxiety about sexual performance.

Cannabinoids present in Cannabis a.k.a. *Vijaya* are known to help regulate sexual function. *Kaunch beej* is an aphrodisiac, restorative and invigorating agent which increases sperm count and quality, boosts sexual desire with its anti-depressant properties, and increases testosterone levels. Clinical studies also support that *Kaunch beej* increases sperm concentration and motility in infertile men. It is also

known to increase libido and boost sexual desire among women as well [2-3].

Cannabinoids may improve libido by reducing anxiety about sexual performance. *Gokshura* stimulates testosterone levels in men and boosts sexual drive among both men and women. It also aids in strengthening muscles and treating sexual disorders for better sexual performance. The aphrodisiac properties of *Gokshura* stimulate blood flow which aids in erection. *Gokshura* also helps manage menopausal symptoms, viz., hot flashes, night sweats which may also improve libido[4-5].

Ashwagandha is considered an aphrodisiac, used to improve sexual desire, pleasure or performance in males and females. Clinical studies support that *Ashwagandha* significantly improves spermatogenic activity, sperm count, sperm motility and serum hormone levels in infertile men [6].

Ayurvedic practitioners believed that *Vijaya* could improve ejaculatory function and sexual performance. *Shatavari* helps improving sexual function by increasing the blood circulation thus helping fight erectile dysfunction. In some males, *Shatavari* has even assisted in solving impotence related issues. *Ashwagandha* may reduce stress and increase androgens in women, which may address sexual dysfunction [7-8].

The present study is an attempt to understand the binding of major phytocompounds present in an Ayurvedic proprietary formulation, BOHECO DESIRE towards the target protein and to predict its ADMET properties.

METHODOLOGY

In Silico platform

Using Maestro 12.3 version programmed on DELL Inc.27" workstation on Intel Core i7-7700 CPU@ 3.60 GHz x8 processor with 1000 GB hard disk and 8GB RAM, all the *in-silico* analysis was performed. The operating system used was Linux –x86_64.

Molecular docking studies

Using ChemDraw 20.1.1 application, the 2D structures and Canonical SMILES of the phytoconstituent compounds were obtained which were converted into 3D images using the Ligprep module on the Schrödinger. The imported phytoconstituents were energy minimized. The proteins PDB ID: 1XOJ obtained from the protein data bank (https://www.rcsb.org/) were pre-processed, refined, optimized, and minimized using the protein preparation wizard of Schrödinger. The protein's active site was identified, and a grid was generated using the grid generation module. Finally, using Glide extra precision (XP) scoring tools, the protein and phytoconstituents were docked. The docking scores were compared with a standard drug Tadalifil [9-10].

Prime MM-GBSA binding free energy calculation

The molecular mechanics- generalised born surface area (MM-GBSA) method was employed to calculate the binding energy of the receptor-phytoconstituent complex. By considering the solvation model for polar and non-polar solvation as well as molecular mechanics energies, Schrodinger's Prime module determined the ΔG bind in kcal/mol[9-10].

ADMET and physicochemical properties determination

Using the QikProp module of the Schrödinger, the ADMET and physicochemical parameters of the phytoconstituent molecules were predicted. Validation of rule of five was also carried out using the QikProp module. Absorption, distribution, metabolism, and excretion of the administered molecule play an important role in the bioactivity of a molecule. Lipinski's rule of five helps in predicting oral bioavailability of any molecules[9-10].

RESULTS AND DISCUSSION

Molecular Docking

The docking study you conducted with the phytoconstituent molecules against the target protein (1XOJ) provides valuable insights into their potential binding affinity and interaction dynamics. Docking scores represent the estimated free energy of binding; lower (more negative) values suggest stronger binding affinity. A score of -9.4kcal/mol indicates a highly favorable interaction, while -4.1kcal/mol is less favorable but still indicates potential activity. This range suggests that some phytoconstituents (L-DOPA, Cannabidiol, Delta-9 Tetrahydrocannabinol) may have significant potential as inhibitors or modulators of the protein target (Figures 1 to 3).

The Van der Waals energy value (Glide evdw) was found to be in the range of -42.5 to -24.11 kcal/mol. The Van der Waals energy component reflects the strength of the non-covalent interactions between the ligand and the protein. More negative values indicate stronger interactions due to close packing and favorable steric arrangements. The observed range suggests that the most favorable binding modes likely involve multiple Van der Waals interactions, contributing to the overall binding affinity.

Glide energy encompasses Van der Waals energy, electrostatic interactions, and solvation energy. It serves as a comprehensive measure of binding affinity. Glide energy in range of -45.07 to -26.53 kcal/mol. The substantial negative values indicate that the phytoconstituents can form stable complexes with the target protein, reinforcing the potential for biological activity.

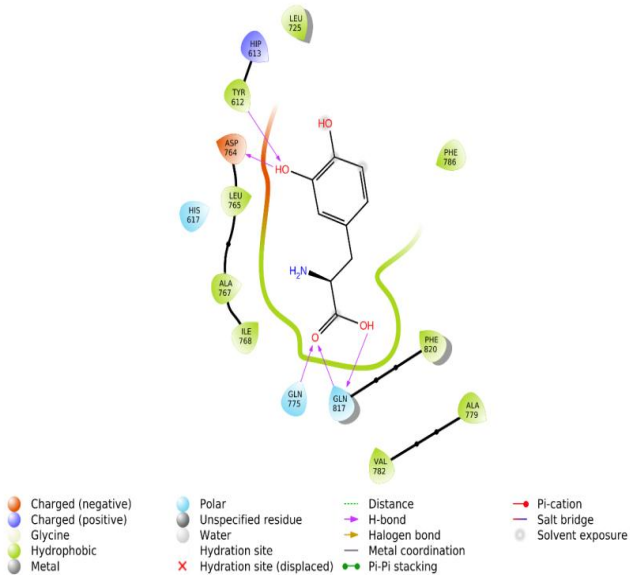

Fig. 1A. Hydrophobic interactions of L-DOPA with 1XOJ

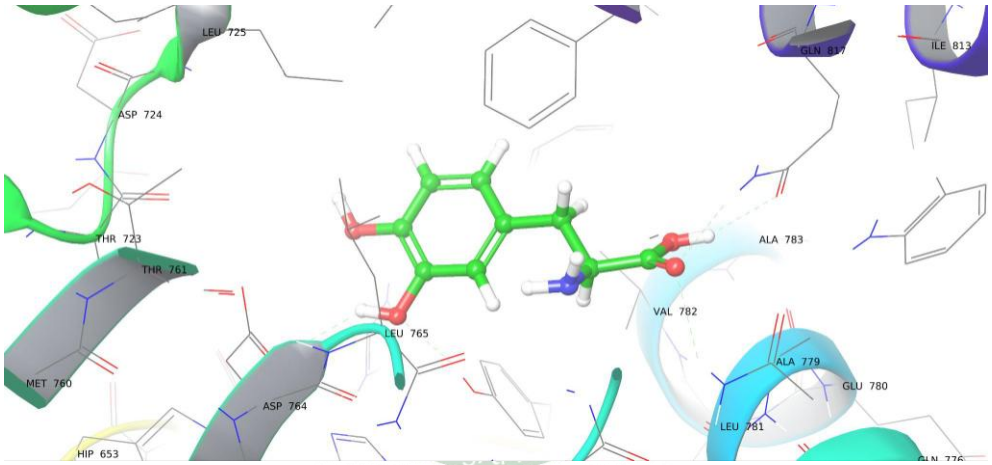

Fig. 1B. Binding mode of L-DOPA with 1XOJ

The values for 'g' rotatable bonds was in the range of 17 to 1. The number of rotatable bonds in a ligand can impact its conformational flexibility, which is crucial for binding to the target protein. A high number of rotatable bonds (17) may suggest that the molecule is more flexible and can adopt various conformations to fit the active site of the protein. Conversely, a lower number (1) indicates a more rigid structure, which may restrict its ability to adapt to the binding pocket. The variation in rotatable bonds across the docking candidates indicates diversity in their structural flexibility and potential binding modes. (Table 1 and Table 2)

Table 1: Molecular docking data with 1XOJ

S. No.	Compounds	Docking score	Glide evdw	Glide Energy	G rotatable bond
1	Delta-9-tetrahydrocannabinol	-8.722	-29.137	-29.105	5
2	Cannabidiol	-8.644	-24.427	-26.531	8
3	L-DOPA	-8.248	-24.111	-33.007	6
4	Withaferin A	-5.466	-35.262	-37.152	5
5	Shatavarin IV	-4.148	-26.044	-27.899	17
6	Withanolide A	-4.08	-32.098	-39.973	4
7	Tadalafil	-9.366	-42.503	-45.070	1

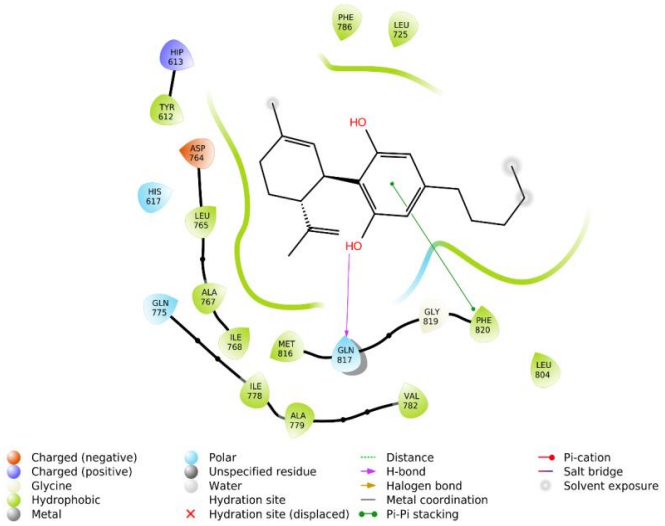

Fig. 2A. Hydrophobic interactions of Cannabidiol with 1XOJ

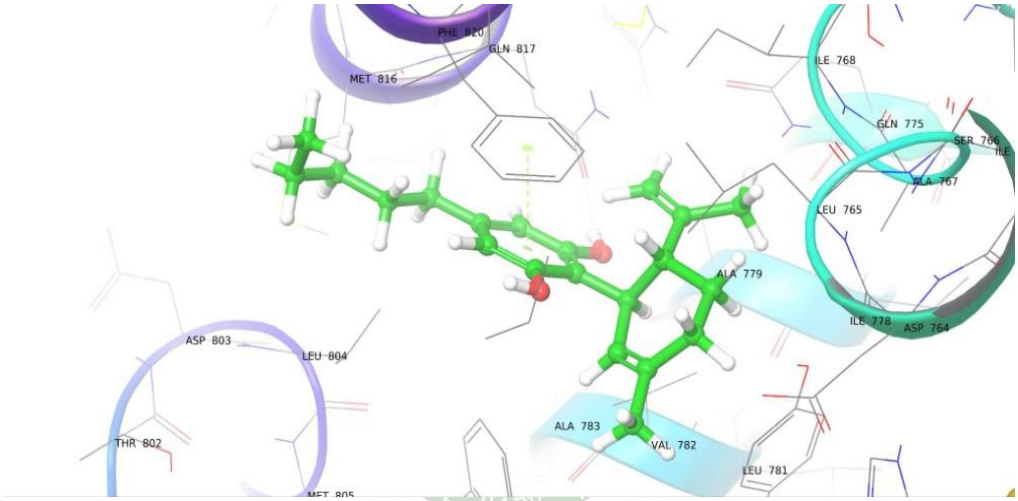

Fig. 2B. Binding mode of Cannabidiol with 1XOJ

Table 2: Molecular docking interaction with amino acid residues

S. No.	Ligand (Compound)	Hydrophobic Interaction	Polar Interaction with Ligand	Hydrogen Bonding	Pi-Pi
1	Delta-9-tetrahydrocannabinol	Ile 778, Ala779, Val782, Phe820, Leu804, Phe786, Leu725, Tyr612, Leu765, Ala767, Ile768	Gln775, Gln817, Ser766	-	Phe820
2	Cannabidiol	Phe786, Met816, Phe820, Leu804, Val782, Ala779, Ile778, Leu725, Ile768, Ala767, Leu765, Tyr612	Gln817, Gln775, His617	Gln817	Phe820
3	L-DOPA	Val782, Phe820, Ala779, Ph786, Leu725, Tyr612, Leu765, Ala767, Ile768	Gln775, Gln817, His617	Gln775, Gln817, Tyr612, Asp764	-
4	Withaferin A	Met816, Phe820, Ala823, Ile824, Leu804, Met805, Val660, Leu681, Leu725, Ala726, Ile729, Phe786	Asn662, Ser661, Hie657, Thr723	Leu725, Asp654	
5	Shatavarin IV	Ile729, Ala726, Met816, Leu804	Thr802, Ser661, Asn662, Gln663	-	-

6	Withanolide A	Leu725, Ala726, Met805, Leu804, Phe786, Leu681	Thr723, Gln663, Asn662, Ser661, Gln789, Hie657	Hie657	-
7	Tadalafil	Leu765, Ala767, Ile768, Tyr612, Phe820, Met816, Ile813, Leu804, Ile778, Ala779, Val782, Ala783, Phe786, Phe787, Leu725	Gln 817, Gln775	Tyr612, Gln817	Phe820, Phe786

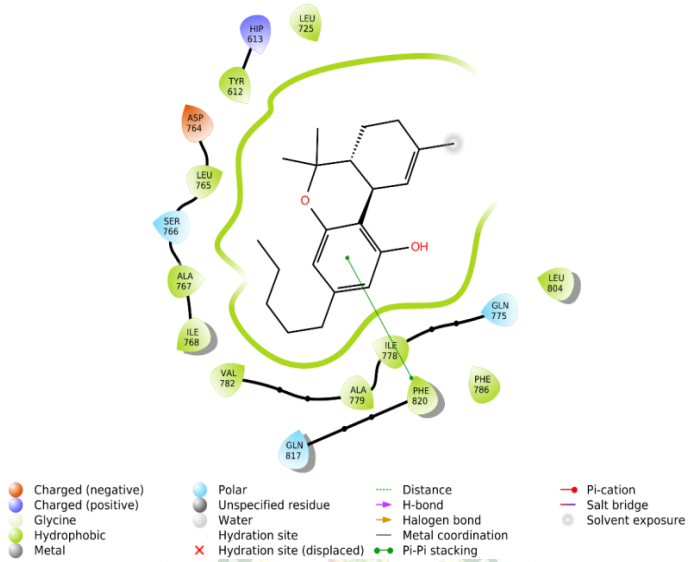

Fig. 3A. Hydrophobic interactions of Delta Tetra-9 hydrocannabinol with 1XOJ

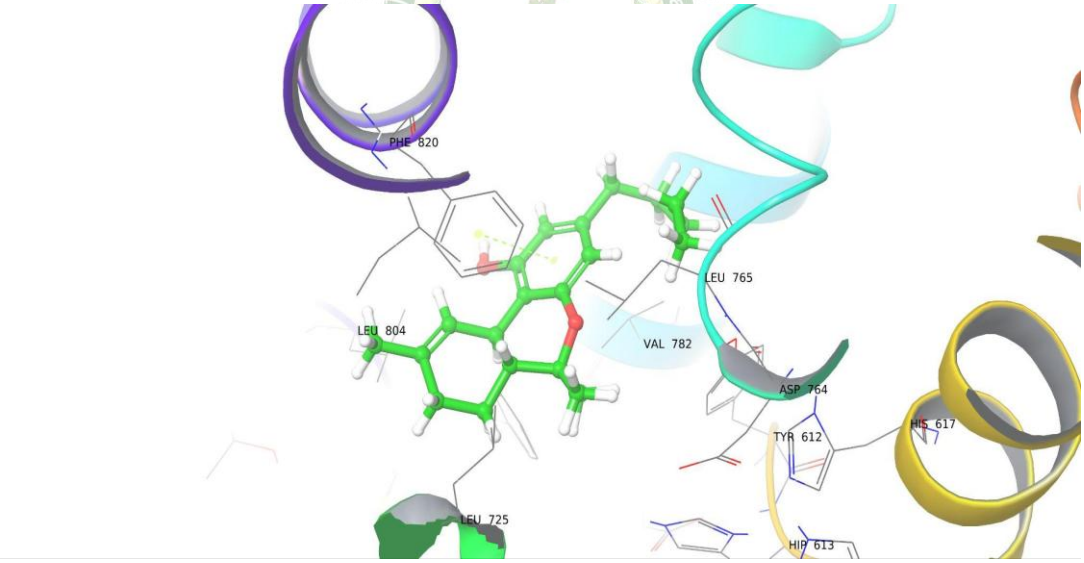

Fig. 3B. Binding mode of Delta Tetra-9 hydrocannabinol with 1XOJ

Binding free energy calculation

The docking results were validated using binding free energy analysis of the protein-phytoconstituent complexes. The ΔThe binding free energy (ΔGbind) represents the total energy change associated with the formation of the complex between the protein (1XOJ) and the phytoconstituent. The more negative the value, the stronger the interaction, indicating that the complex formation is highly favorable and stable under physiological conditions. The binding free energy values ranging from -76.6 to -35.73kcal/mol suggest that several of the docked phytoconstituents form stable and energetically favorable complexes with the protein 1XOJ (Table 3).

Table 3: Binding free energy calculation (MMGBSA) with 1XOJ

S. No.	Compounds	ΔG bind	ΔGbind Columb	ΔGbind Covalent	ΔGbind Lipo	ΔGbind Solv GB	ΔGbind vdw
1	Delta-9-tetrahydrocannabinol	-51.8	0.34	16.49	-58.4	20.48	-28.19
2	Cannabidiol	-59.62	-3.94	9.65	-62.98	22.58	-23.72
3	L-DOPA	-35.73	-18.86	1.97	-16.74	23.19	-23.16
4	Withaferin A	-71.45	-9.89	5.65	-54.66	32.21	-43.75
5	Shatavarin IV	-76.6	-11.67	12.82	-64.96	28.16	-40.93
6	Withanolide A	-62.03	-28.69	3.66	-42.07	37.84	-31.98
7	Tadalafil	-72.44	-4.19	3.7	-41.15	20.65	-46.79

Predicted ADME profile

Among the tested molecules for their ADME profile, the compounds, withanolide A, Delta-9-tetrahydrocannabinol, and cannabidiol were predicted to have a high percentage of human oral absorption. The predicted apparent Caco-2 cell permeability of the compounds was found highest (QPP Caco 4343.03) for Delta-9-tetrahydrocannabinol. It was also observed that the molecules could moderately bind to the protein human serum albumin. The compounds' predicted brain/blood partition coefficient was also within the recommended range of -3 to 1.2. The predicted number of likely metabolic reactions of all the compounds was also found to be within the prescribed range (Table 4).

Table 4: Pharmacokinetic profile of compounds

S.No.	Compounds	% Human Oral Absorption	QPlogs	QPPCaco	#metab	QplogBB	CNS	QPlogKhsa	SASA	FOSA	FISA
1	Withaferin A	87.745	-4.91	253.415	4	-1.298	-2	0.329	713.039	466.226	167.887
2	Tribulosin	0	-2.182	0.843	13	-6.251	-2	-2.434	1358.448	929.271	429.177
3	Shatavarin IV	11.343	-5.153	13.685	9	-4.145	-2	-0.873	1197.551	895.996	301.555
4	L-DOPA	20.779	-0.741	2.969	6	-1.401	-2	-0.952	401.673	48.425	245.05
5	Withanolide A	100	-5.094	700.253	6	-0.751	-1	0.545	687.868	485.801	121.338
6	Delta-9-tetrahydrocannabinol	100	-6.776	4334.031	5	-0.118	0	1.25	650.63	527.217	37.858
7	Cannabidiol	100	-5.87	2408.829	8	-0.474	0	1.047	635.729	477.612	64.757

CONCLUSION

The docking results suggest that the phytoconstituents present in active blend in BOHECO DESIRE exhibit varying degrees of strong binding affinity, conformational flexibility, and stable interaction potential with the target protein 1XOJ, indicating their potential as effective inhibitors or modulators. The binding free energy analysis also confirms that the docked phytoconstituents form stable and energetically favorable complexes with the target protein 1XOJ, indicating their strong interaction potential. Furthermore, ADME profile predicts that withanolide A, Delta-9-tetrahydrocannabinol, and cannabidiol have high human oral absorption, moderate protein binding, appropriate brain/blood partition coefficients, and a manageable number of metabolic reactions, indicating their potential for good bioavailability and efficacy. This can support that BOHECO DESIRE improves and/or maintain sexual wellness in humans.

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