

Original Research Article

Nootropic property of *Punica granatum* extract as BDNF4 stimulant for treatment of major depressive disorder

Abstract

In 2008, the World Health Organization (WHO) stressed major depressive disorder (MDD) as the third most important cause of disease burden worldwide. Based on their projections, it is expected that by 2030, MDD will take the lead among the rest of the world's health concerns. Brain derived neurotrophic factor 4 (BDNF4), a protein of neurotrophins family play pivotal role in maintaining neural plasticity. Reduced levels of BDNF4 in the hippocampus and plasma have been reported in patients with MDD. Nootropic drugs serve as therapeutic interventions in mitigating MDD through diverse molecular mechanisms. *Punica granatum* (pomegranate) is acknowledged for its nutritional and medicinal properties, currently under medical scrutiny for its potential as a natural antidepressant. Various computational methodologies, including molecular docking, pharmacokinetics, ADME profile assessment, toxicological analysis, and prediction of biological activity, were employed to identify promising compounds among the phytochemicals present in *Punica* extract, focusing on their potential BDNF4-stimulating, nootropic, and antidepressant properties. The comprehensive examination of docking scores, interactions between proteins and ligands, pharmacological and toxicological attributes, along with the forecasting of biological activities, collectively underscores the potential attributes of M-Cymene, Flavylium, 2-(4-Methylphenyl)propan-2-ol, Thymol, and Pelletierine as prospective drug candidates targeting human BDNF4 for alleviating MDD.

Keywords: Major depressive disorder, BDNF4, Nootropic, antidepressant, in silico, drug

1. Introduction

Major depressive disorder (MDD) is a common mental health condition that affects millions of people worldwide, with a 50% higher prevalence among women than men[1]. It is defined by long-term feelings of sadness, helplessness and loss of interest in activities that were

previously enjoyable [2]. It imposes major influence on everyday life such as work, learning, and even maintaining relationships [3]. Several theories on depression have been presented so far [4] such as monoamine hypothesis, neuroendocrine, neuroimmune and cytokine hypothesis [5]. Nevertheless, these theories have not been sufficient to fully explain the pathology and treatment of depression. [6]. Recently, neuroplasticity hypothesis of depression has gain considerable attention and thus, widely studied[7]. The dysfunction of neural plasticity is closely linked with onset of depression[8]. Neurotrophins are small molecules of polypeptides which bind to tyrosine kinase receptors and regulate various cellular processes including calcium homeostasis and also, inhibit free radical formation by increasing the levels of antioxidant enzymes[9]. Prominent examples of neurotrophins include brain-derived neurotrophic factor (BDNF), nerve growth factor (NGF), neurotrophin-3 (NT-3), and neurotrophin-4 (NT-4)[10]. BDNF is associated with depression, while other neurotrophins are linked to mood disorders[11]. BDNF plays a crucial role in the development, survival and plasticity of neurons in the nervous system[12]. It is involved in various processes such as neuronal maturation, neuroprotection, neurogenesis and synaptic plasticity, which are essential for learning and memory[13]. The precursor peptide pro-BDNF is encoded by the BDNF gene, which is located in the complementary reverse strand of chromosome 11p13. The pre mature form of this protein is synthesized in an inactive state as a pre-pro-neurotrophin precursor, which undergoes posttranslational modifications and forms a homodimeric protein [14]. After binding of mature BDNF or neurotrophins, including neurotrophin-4 (NT-4) and neurotrophin-3 (NT-3), to the extracellular domain of TrkB, the receptor's intracellular domain dimerizes and undergoes autophosphorylation at one of these three distinct The phosphorylation at all these residues initiates specific signaling pathways, such as Ras-PI3K-Akt, Ras-MAP kinase-Erk, or phospholipase C γ [15]. These signaling pathways activate transcription factors, such as CREB, culminating in cellular responses such as cell proliferation, survival, synaptogenesis, and memory formation[16]. Several studies have reported an observation of unusually diminished serum or plasma BDNF levels in individuals suffering from MDD[17]. Reduced BDNF level is also linked to neurological disorders like Alzheimer's disease[18] and migraine[19]. Nootropic drugs are class of drugs that are claimed to enhance cognitive function[20]. Nootropic drugs such as piracetam, phenotropil and semax have shown to stimulate BDNF level[21]. Still there remains a void of nootropic drugs which could act as BDNF stimulants and subsequently serve as potential therapeutic for major depression disorder. *Punica granatum* (Pomegranates), renowned for their substantial polyphenol concentration, have garnered recognition for their notable

nutritional and medicinal characteristics. Current investigations are underway to explore their potential efficacy as natural antidepressants[22].

The objective of the study is to elucidate potent phytochemicals present in pomegranate extract which could serve as drug candidate for treatment of MDD. Various computational methodologies, encompassing molecular docking, pharmacokinetics, ADME profile evaluation, toxicological scrutiny, and forecasting of biological activity, were utilized to discern compounds within the phytochemicals found in *Punica* extract. Emphasis was placed on identifying substances with potential stimulatory effects on BDNF4, as well as their cognitive-enhancing (nootropic) and antidepressant properties.

2. MATERIAL AND METHODS

2.1 Protein preparation

The investigation employed the Protein Database (<https://www.rcsb.org/>) to obtain the PDB file associated with the Crystal Structure of Brain-derived neurotrophic factor, neurotrophin-4 (BDNF4), identified by its distinct PDB ID: 1B8M. The Protein Data Bank (PDB) acts as a comprehensive repository housing information on experimentally determined structures of proteins and nucleic acids. In the subsequent phases of analysis, procedures were executed to prepare the protein, which included the elimination of water molecules and associated ligands. This task was effectively performed using PyMOL[23], an open-source software tool renowned for its efficacy in generating molecular visualizations. The strategic application of PyMOL rendered it an optimal choice for streamlining the docking preparation process.

2.2 Evaluation of phytochemicals present in *P. granatum* extract

The analysis of phytochemicals in *P. granatum* was carried out using the Indian Medicinal Plants, Phytochemistry And Therapeutics 2.0 (IMPPAT 2.0) database[24]. IMPPAT is a carefully curated database, created by digitizing information from over 100 traditional Indian medicine books, 7000+ published research articles, and various other relevant resources. IMPPAT 2.0 is currently the most extensive digital repository of phytochemical information in Indian medicinal plants, representing a significant enhancement and expansion compared to its predecessor, IMPPAT 1.0.

2.3 Ligand retrieval and preparation

The molecular configurations of the chosen phytochemicals were acquired in sdf file format from the PubChem database, a valuable resource offering comprehensive details on chemical compounds, encompassing structures, formulas, and molecular weights. For ligand preparation in the subsequent analysis, the OpenBabel tool[25] within PyRx 0.8[26] was utilized. OpenBabel is a widely employed tool in molecular docking investigations for ligand preparation. The ligand energy was minimized using the mmff94 force field, a method selected for its efficacy in achieving stable and dependable ligand structures. Following this, the sdf file format of the ligands was transformed into pdbqt format, making the ligands executable and ready for docking. This conversion step played a crucial role in ensuring compatibility and streamlining the subsequent exploration of ligand-receptor interactions in molecular modeling.

2.4 Molecular Docking

A molecular docking analysis was conducted to investigate the interactions between the phytochemicals and BDNF4. To perform molecular docking, the AutoDock Vina[27] tool integrated with PyRx 0.8 was utilized. This facilitated a thorough examination of potential binding interactions between the ligands and the macromolecule, providing valuable insights into their binding affinities and orientations.

2.5 Visualization of Docking Results

Following the execution of the molecular docking analysis, we pinpointed the protein-ligand complex distinguished by the most favorable negative score, indicative of a robust affinity. This optimal binding configuration was then chosen for in-depth exploration using Discovery Studio 4.5[28]. The software facilitated the visualization and examination of the binding mode, allowing for a detailed analysis of ligand-receptor interactions. Through this thorough investigation, we unveiled crucial molecular interactions governing the high binding affinity of the ligand to BDNF4. Our emphasis was particularly on visualizing phytochemicals exhibiting both a commendable docking score and possessing drug-like properties.

2.6 Molecular descriptors of chosen phytochemicals

Properties such as the physicochemical nature, lipophilicity, water solubility, and drug-likeness of the chosen compounds underwent analysis utilizing the SWISS ADME webserver[29]. Key factors considered for assessing physicochemical properties included the number of hydrogen acceptors, number of hydrogen donors, and topological polar surface

area (TPSA). For evaluating lipophilicity and water solubility, XLOGP3 and ESOL values were taken into account, respectively. Drug-likeness properties were evaluated based on the Veber rule[30] and Lipinski rule[31].

2.7 Prediction of absorption, distribution, metabolism, and toxicity

To evaluate predictions related to absorption, distribution, metabolism, and toxicity of the selected compound, we utilized admetSAR[32]. An online tool, available at <http://lmmmd.ecust.edu.cn/admetSar2/>, was employed to analyze a variety of parameters. These parameters played a pivotal role in the prediction process, enhancing our comprehensive understanding of the compound's attributes concerning absorption, distribution, metabolism, and toxicity.

2.8 Prediction of biological activity of the compound

In the assessment of the biological activity of the identified compounds, PASS web server (<http://www.pharmaexpert.ru/passonline>)[33] was utilized. Employing atom neighbor descriptors, PASS analysis played a key role in elucidating the potential effects of each compound based solely on its molecular formula. This underscores the correlation between the chemical arrangement and biological function of the substances under investigation.

3. RESULTS

3.1 Docking score of the compounds

The docking study involved utilizing the Crystal Structure of human BDNF4, identified by its PDB ID: 1B8M. Autodock Vina, accessed through PyRx 0.8, was the tool employed for analysis. To prepare both the protein and the ligand for docking, the Dockprep feature in UCSF Chimera was utilized. The protein underwent transformation into a macromolecule, and the selected compounds underwent initial minimization using the mmff94 forcefield. Subsequently, the compounds were converted to pdbqt format using OpenBabel within PyRx. For the docking procedure, a grid box with dimensions of 27.61 Å × 58.21 Å × 50.68 Å was employed, centered at coordinates (16.10, 2.20, 9.79). The exhaustiveness level was set to the default value of 8. Detailed information regarding the ligands or compounds and their corresponding docking scores is provided in Table 1.

Table 1: Displays the molecular docking scores of phytochemicals in *P. grantum*, along with their corresponding PubChem ID and molecular weight.

LIGANDS	PubChem ID	Molecular weight (g/mol)	Docking score (kcal/mol)
9-Azabicyclo(3.3.1)nonan-3-one, 9-methyl-	6602484	153.22	-4.4
9-Methyl-9-azabicyclo[3.3.1]nonan-3-amine	14403175	154.25	-4.4
9-Azabicyclo[3.3.1]nonan-3-one	145745	139.19	-4.5
Methylisopelletierine	86786	155.24	-4.5
Pelletierine	92987	141.21	-6.2
Friedelin	91472	426.7	-5.9
Ellagic acid	5281855	302.19	-5.1
Ursolic acid	64945	456.7	-5.2
3-Methyl-2-buten-1-OL	11173	86.13	-4.7
M-Cymene	10812	134.22	-6.8
Flavylium	145858	207.25	-6.5
Nonanal	31289	142.24	-5.3
Thymol	6989	150.22	-7.0
Eucalyptol	2758	154.25	-4.9
Hexyl acetate	8908	144.21	-5.3
2-Heptanol	10976	116.2	-4.8
2-(4-Methylphenyl)propan-2-ol	14529	150.22	-7.1

3.2 Protein-ligand interaction

The molecular interactions between various ligands and amino acids within a protein, sheds light on the specific forces that govern ligand-protein binding. M-Cymene, for instance, engages in Van der Waals interactions with Arg53, Gln56, Arg98, and Trp110, contributing to the overall stability of the ligand-protein complex. Flavylium, on the other hand, forms

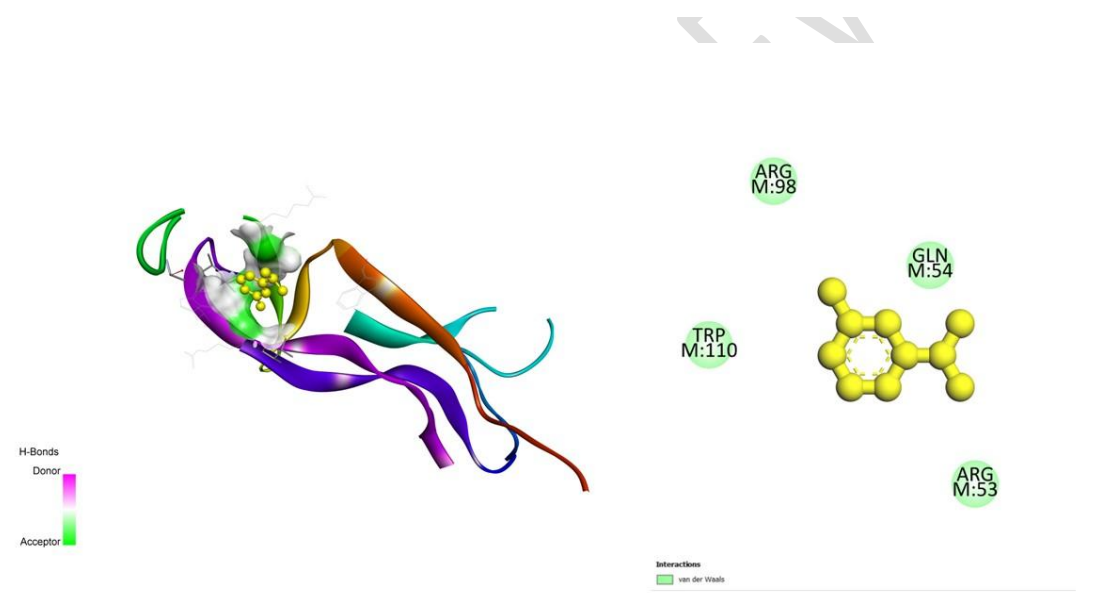
Van der Waals interactions with a range of amino acids, including Trp23, Ala47, Arg53, Gln54, Tyr55, Phe57, Arg98, Tyr110, and Ile115. 2-(4-Methylphenyl)propan-2-ol exhibits Van der Waals interactions with Arg53, Gln54, and Ala99, along with a specific hydrogen bond with Arg98, characterized by a bond length of 2.72 Å. Thymol interacts through Van der Waals forces with various amino acids (Ala47, Leu52, Arg53, Tyr55, Val97, Arg98, Ala99, Leu100) and forms a specific hydrogen bond with Gln54 (bond length: 1.96 Å). Lastly, Pelletierine engages in Van der Waals interactions with Arg53, Gln54, Tyr55, Phe56, Val97, Arg98, Ala99, and Trp110. This comprehensive analysis provides valuable insights into the molecular basis of ligand-protein interactions, crucial for drug design and understanding biological processes. Table 2 summarizes the result while Figure 1 (a-e) depicts two dimensional representation of ligand-protein interaction.

Table 2: Table summarizes the ligands, their interactions (Van der Waals or Hydrogen bonding), the involved amino acids, and the corresponding bond lengths of hit compounds with active site of BDNF4

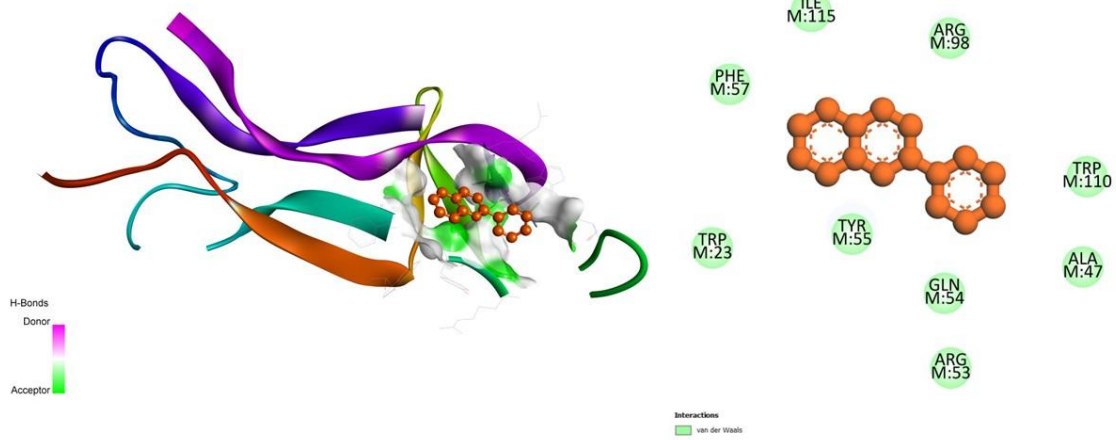
Ligands	Interaction	Amino acids	Bond length (Å)
M-Cymene	Van der Waals	Arg53, Gln56, Arg98, Trp110	---
	Hydrogen bond	---	---
Flavylium	Van der Waals	Trp23, Ala47, Arg53, Gln54, Tyr55, Phe57, Arg98, Tyr110, Ile115	---
	Hydrogen bonding	---	---
2-(4-Methylphenyl)propan-2-ol	Van der Waals	Arg53, Gln54, Ala99	---
	Hydrogen bond	Arg98	2.72
Thymol	Van der Waals	Ala47, Leu52, Arg53, Tyr55, Val97, Arg98, Ala99, Leu100	---
	Hydrogen bond	Gln54	1.96
Pelletierine	Van der Waals	Arg53, Gln54, Tyr55, Phe56, Val97, Arg98, Ala99, Trp110	---
	Hydrogen bond	---	---



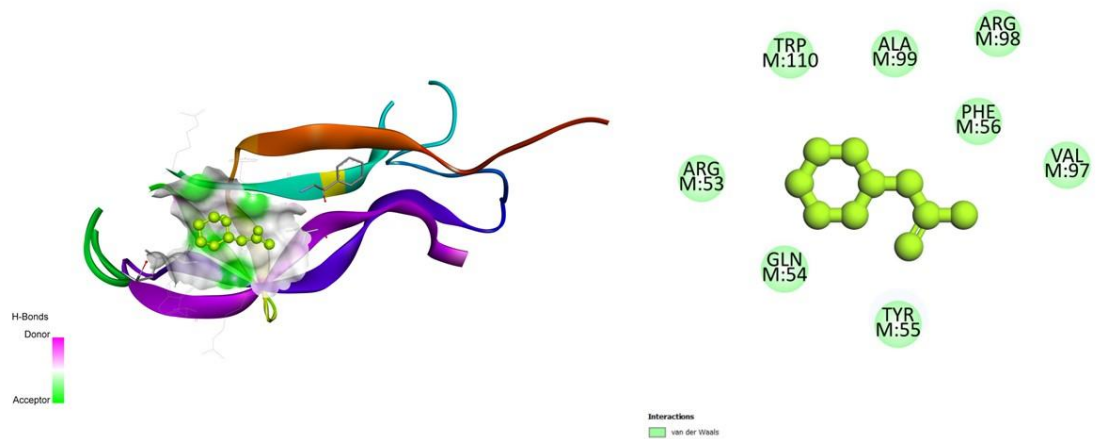
(a)



(b)



(c)



(d)

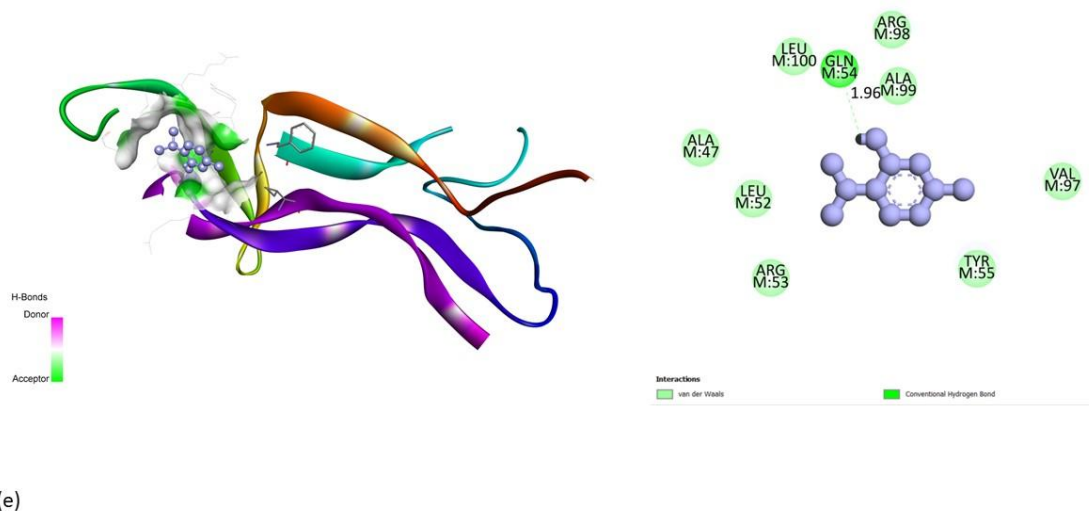


Figure 1 (a-e): Two dimensional representation of interaction between target protein (BDNF4) and chosen phytochemicals: (a) 2-(4-Methylphenyl)propan-2-ol (b) M-cymene (c) Flavylium (d) Pelletierine (e) Thymol

3.3 Evaluation of pharmacological and toxicological properties

The assessment of pharmacological and toxicological properties phytochemicals through analysis of physicochemical properties, lipophilicity, water solubility, drug-likeness and ADME/t values. The evaluation was done using SWISSADME and admetSAR. The summarized outcomes are presented in Tables 3 and 4. The pivotal criteria influencing a compound's potential as a drug candidate, encompassing topological polar surface area (TPSA), molecular weight (MW), ESOL (solubility), xlog3 value, and drug-likeness parameters such as Lipinski's rule and Veber rule were considered. M-Cymene, characterized by moderate lipophilicity (XLOGP3: 4.50) and hydrophobic nature (ESOL: -3.89), satisfies both Veber and Lipinski rules, suggesting potential drug-likeness. Flavylium, with moderate lipophilicity (XLOGP3: 3.51) and hydrophobicity (ESOL: -4.01), possesses one hydrogen bond acceptor (Accept H: 1), passing both rules for drug-likeness. 2-(4-Methylphenyl)propan-2-ol exhibits lower lipophilicity (XLOGP3: 1.99) and moderate hydrophobicity (ESOL: -2.36), with one hydrogen bond acceptor and donor each, satisfying both drug-likeness criteria. Thymol, characterized by high lipophilicity (XLOGP3: 5.29) and strong hydrophobicity (ESOL: -5.30), contains two hydrogen bond acceptors and donors, meeting Veber and Lipinski rules for drug-likeness. Pelletierine, with low lipophilicity

(XLOGP3: 0.36) and minimal hydrophobicity (ESOL: -0.81), has two acceptors and one donor, adhering to both drug-likeness rules. The significance lies in the evaluation of these properties, aiding in the prediction of ligand behavior, oral bioavailability, and potential suitability for further drug development. Balancing lipophilicity, water solubility, and adherence to established drug-likeness rules provides valuable information for researchers in the early stages of drug design and discovery.

Table 3: Physicochemical properties, lipophilicity, water solubility, and drug-likeness of selected compounds (M-Cymene, Flavylum, 2-(4-Methylphenyl)propan-2-ol, Thymol, and Pelletierine). The data include hydrogen bond acceptor/donor counts, topological polar surface area, XLOGP3 lipophilicity, and ESOL water solubility. All compounds exhibit favorable drug-likeness according to Veber and Lipinski criteria

Ligands	Physicochemical Properties			Lipophilicity	Water Solubility	Drug-likeness	
	Accept H	Donor H	TPSA (Å)			Veber	Lipinski
				XLOGP3	ESOL		
M-Cymene	0	0	0	4.50	-3.89	YES	YES
Flavylum	1	0	13.14	3.51	-4.01	YES	YES
2-(4-Methylphenyl)propan-2-ol	1	1	20.23	1.99	-2.36	YES	YES
Thymol	2	2	40.46	5.29	-5.30	YES	YES
Pelletierine	2	1	29.10	0.36	-0.81	YES	YES

In the assessment of absorption, distribution, Metabolism, and toxicological properties, phytochemicals were subjected to analysis via admetSAR server (Table 4). In terms of absorption, all five phytocompounds exhibit positive values for blood-brain permeability, suggesting a potential ability to cross the blood-brain barrier (BBB). The ability to effectively traverse the BBB is a pivotal determinant for a drug, particularly in the context of disorders associated with the brain. This factor holds significant importance in the study and treatment of brain-related disorders. All compounds display positive values for human intestinal absorption, suggesting good absorption in the gastrointestinal tract. In terms of distribution,

all compounds localize to the mitochondria, providing insights into their subcellular targets. Regarding metabolism, M-Cymene, Flavylium, 2-(4-Methylphenyl)propan-2-ol, and Thymol are identified as non-substrates for key cytochrome P450 (CYP) enzymes (CYP2C9, CYP2D6, CYP3A4). Additionally, Flavylium and Thymol function as inhibitors of CYP1A2. Overall, this information is pivotal for predicting the compounds' behavior in the human body, aiding in the selection of lead compounds with favorable pharmacokinetic profiles and predicting potential challenges related to absorption, distribution, metabolism, and excretion (ADME) in drug development.

Table 4: Summarizes the absorption, distribution, and metabolism profiles predicted by the admetSAR server for the analyzed compounds (M-Cymene, Flavylium, 2-(4-Methylphenyl)propan-2-ol, Thymol, and Pelletierine). It includes information on blood-brain permeability, human intestinal absorption, P-glycoprotein interactions, subcellular localization, and interactions with key cytochrome P450 enzymes

Parameters	M-Cymene	Flavylium	2-(4-Methylphenyl)propan-2-ol	Thymol	Pelletierine
ABSORPTION					
Blood brain permeant	Positive	Positive	Positive	Positive	Positive
Human intestinal absorption	Positive	Positive	Positive	Positive	Positive
P-glycoprotein substrate	Negative	Negative	Negative	Negative	Negative
P-glycoprotein inhibitor	Negative	Negative	Negative	Negative	Negative
DISTRIBUTION					
Subcellular localization	Mitochondria	Mitochondria	Mitochondria	Mitochondria	Mitochondria
METABOLISM					
CYP2C9 substrate	Non-substrate	Non-substrate	Non-substrate	Non-substrate	Substrate
CYP2D6 substrate	Non-	Non-substrate	Non-	Non-substrate	Substrate

CYP3A4 substrate	substrate	Non-substrate	substrate	Non-substrate	Non-substrate
CYP1A2 inhibition	Non-substrate	Inhibitor	Non-substrate	Non-inhibitor	Inhibitor
CYP2C9 inhibition	Non-inhibitor	Non-inhibitor	Non-inhibitor	Non-inhibitor	Non-inhibitor
CYP2D6 inhibition	Non-inhibitor	Non-inhibitor	Non-inhibitor	Non-inhibitor	Non-inhibitor
CYP2C19 inhibition	Non-inhibitor	Inhibitor	Non-inhibitor	Non-inhibitor	Non-inhibitor
	Non-inhibitor		Non-inhibitor		
	Non-inhibitor		Non-inhibitor		

Toxicity prediction was performed using the admetSAR server, considering parameters such as hepatotoxicity, immunotoxicity, and cytotoxicity. Strikingly, all selected compounds demonstrated an absence of such toxicities, affirming their safety for potential use, according to the assessments conducted by the admetSAR server Table 5.

Table 5: Summarizes the toxicological assessment of compounds including M-Cymene, Flavylium, 2-(4-Methylphenyl)propan-2-ol, Thymol, and Pelletierine. Results indicate no observed hepatotoxicity, immunotoxicity, or cytotoxicity for any of the analyzed compounds.

Parameters	M-Cymene	Flavylium	2-(4-Methylphenyl)propan-2-ol	Thymol	Pelletierine
Hepatotoxicity	NO	NO	NO	NO	NO
Immunotoxicity	NO	NO	NO	NO	NO
Cytotoxicity	NO	NO	NO	NO	NO

3.4 Prediction of biological activity of compounds

The PASS webserver was utilized to validate the anticipated biological effects. Biological activity such as BDNF4 stimulant, nootropic, and antidepressant were taken into consideration. Out of all assessed compounds, M-Cymene, Flavylum, 2-(4-Methylphenyl)propan-2-ol, Thymol, and Pelletierine exhibit BDNF4 stimulant property. All five aforementioned phytochemicals show nootropic properties. In context to antidepressant property, except thymol, all phytochemicals possess anti-depressant property. The Pa value for BDNF4 stimulant ranged between 0.236 to 0.493, for nootropic it ranged between 0.329 to 0.575 and for antidepressant, it was observed to range between 0.151 to 0.253. When the Pa value surpasses the Pi value, it indicates a probable presence of the specified biological activity. The summarized outcomes are presented in table 6.

Table 6: Biological activity prediction of compounds (Pa = probability to be active; Pi = probability to be inactive)

Ligands	Biological activity					
	BDNF stimulant		Nootropic potential		Antidepressant activity	
	Pa	Pi	Pa	Pi	Pa	Pi
M-Cymene	0.284	0.018	0.555	0.098	0.186	0.067
Flavylum	0.236	0.036	0.329	0.298	0.253	0.035
2-(4-Methylphenyl)propan-2-ol	0.245	0.032	0.383	0.227	0.151	0.088
Thymol	0.493	0.004	0.411	0.205	---	---
Pelletierine	0.259	0.009	0.575	0.088	0.177	0.072

4. Discussion

The comprehensive analysis of the docking scores, protein-ligand interactions, pharmacological and toxicological properties, and the prediction of biological activities provides valuable insights into the potential of the selected phytochemical compounds as drug candidates targeting human BDNF4. Firstly, the docking study using Autodock Vina revealed the binding affinities of the compounds to the Crystal Structure of human BDNF4. The detailed docking scores serve as an initial indicator of the compounds' ability to interact with the target protein. Understanding the specific amino acids involved in ligand-protein

interactions sheds light on the forces contributing to the stability of the ligand-protein complexes. Such information is crucial for rational drug design, allowing researchers to optimize compounds for enhanced binding and efficacy. Evaluation of pharmacological and toxicological properties using SWISSADME and admetSAR provides a comprehensive overview of key parameters influencing drug-likeness. Lipophilicity, water solubility, and adherence to drug-likeness rules are crucial factors for a compound's potential as a drug candidate. The balanced properties of M-Cymene, Flavylium, 2-(4-Methylphenyl)propan-2-ol, Thymol, and Pelletierine suggest their potential suitability for further drug development. The absorption, distribution, metabolism, and toxicological properties (ADME/T) analysis further supports the drug development potential of the compounds. Positive values for blood-brain permeability and human intestinal absorption indicate favorable characteristics for drug delivery, especially in the context of brain-related disorders. The compounds' localization to mitochondria and non-substrate status for key cytochrome P450 enzymes, except for specific inhibitory effects, provide insights into their subcellular targets and metabolic stability. Toxicity prediction using the admetSAR server is reassuring. The absence of hepatotoxicity, immunotoxicity, and cytotoxicity suggests the safety of the selected compounds, reinforcing their potential for therapeutic use. The prediction of biological activities using the PASS webserver adds another layer of information. The compounds exhibiting BDNF4 stimulant, nootropic, and antidepressant properties align with the potential therapeutic targets for mental health condition like major depression. The Pa values indicating the probability of biological activity further support the potential efficacy of these compounds.

5. Conclusion

The integrated analysis of docking scores, protein-ligand interactions, pharmacological and toxicological properties, and the prediction of biological activities collectively highlights the promising characteristics of M-Cymene, Flavylium, 2-(4-Methylphenyl)propan-2-ol, Thymol, and Pelletierine as drug candidates targeting human BDNF4 in context to major depression. This information is valuable for guiding further experimental validation and optimization processes in drug discovery and development.

Ethical approval: Not Applicable

References

1. India State-Level Disease Burden Initiative Mental Disorders Collaborators. The burden of mental disorders across the states of India: the Global Burden of Disease Study 1990-2017. *Lancet Psychiatry*. 2020;7(2):148-161.
2. Marx W, Penninx BWJH, Solmi M, Furukawa TA, Firth J, Carvalho AF, Berk M. Major depressive disorder. *Nat Rev Dis Primers*. 2023;9(1):44.
3. Steger MF, Kashdan TB. Depression and Everyday Social Activity, Belonging, and Well-Being. *J Couns Psychol*. 2009:289-300.
4. Alam M, Abbas K, Abdullah M, Ahmed K, Khan S. Herbal Interventions as Promising Therapeutic for Alleviating Depression. *International Journal of Current Science Research and Review*. 2023;06. doi: 10.47191/ijcsrr/V6-i11-17.
5. Corrigan M, O'Rourke AM, Moran B, Fletcher JM, Harkin A. Inflammation in the pathogenesis of depression: a disorder of neuroimmune origin. *Neuronal Signal*. 2023;7(2):NS20220054.
6. Yang T, Nie Z, Shu H, Kuang Y, Chen X, Cheng J, Yu S, Liu H. The Role of BDNF on Neural Plasticity in Depression. *Front Cell Neurosci*. 2020;14:82.
7. Price RB, Duman R. Neuroplasticity in cognitive and psychological mechanisms of depression: an integrative model. *Mol Psychiatry*. 2020;530-543.
8. Kuhn M, Höger N, Feige B, Blechert J, Normann C, Nissen C. Fear extinction as a model for synaptic plasticity in major depressive disorder. *PLoS One*. 2014;9(12):e115280
9. Razavi S, Nazem G, Mardani M, Esfandiari E, Salehi H, Esfahani SH. Neurotrophic factors and their effects in the treatment of multiple sclerosis. *Adv Biomed Res*. 2015;4:53.
10. Vega JA, García-Suárez O, Hannestad J, Pérez-Pérez M, Germanà A. Neurotrophins and the immune system. *J Anat*. 2003;203(1):1-19.
11. Castrén E. Neurotrophins and psychiatric disorders. *Handb Exp Pharmacol*. 2014;220:461-79.
12. Alam M, Abbas K, Harina, Verma AK. "An Insight into Neurodegenerative Disorders, their therapeutic approaches and drugs available for tackling with Neurodegeneration: A Review". 2021;2:55-62.

13. Numakawa T, Odaka H, Adachi N. Actions of Brain-Derived Neurotrophin Factor in the Neurogenesis and Neuronal Function, and Its Involvement in the Pathophysiology of Brain Diseases. *Int J Mol Sci.* 2018;19(11):3650.
14. Notaras M, van den Buuse M. Brain-Derived Neurotrophic Factor (BDNF): Novel Insights into Regulation and Genetic Variation. *Neuroscientist.* 2019;25(5):434-454.
15. Gupta VK, You Y, Gupta VB, Klistorner A, Graham SL. TrkB receptor signalling: implications in neurodegenerative, psychiatric and proliferative disorders. *Int J Mol Sci.* 2013;14(5):10122-42.
16. Kaltschmidt B, Kaltschmidt C. NF-KappaB in Long-Term Memory and Structural Plasticity in the Adult Mammalian Brain. *Front Mol Neurosci.*;8:69.
17. Emon MPZ, Das R, Nishuty NL, ShalahuddinQusar MMA, Bhuiyan MA, Islam MR. Reduced serum BDNF levels are associated with the increased risk for developing MDD: a case-control study with or without antidepressant therapy. *BMC Res Notes.* 2020;13(1):83.
18. Abbas K, Alam M, Ali V, Ajaz M. Virtual screening, molecular docking and ADME/T properties analysis of neuroprotective property present in root extract of chinese skullcap against β -site amyloid precursor protein cleaving enzyme 1 (BACE1) in case of alzheimer's disease. *J PharmacognPhytochem* 2023;12(1):146-153.
19. Abbas K, Alam M, Parveen U, Zairy I. A Review on Intricate Scheme of Therapeutic Approaches Involved in Control and Prevention of Episodic Migraine. *International Journal of Current Science Research and Review.* 2023;06. doi: 10.47191/ijcsrr/V6-i1-47.
20. Raza M, Alam M, Kamal S, Abbas K. Interaction of Nootropic Drugs with Neurotransmitter Enzyme Acetylcholinesterase: An Insilico Approach: A Review. 2021;3.doi: 10.46610/JAPP.2021.v03i02.005..
21. Voronina TA. Cognitive Impairment and Nootropic Drugs: Mechanism of Action and Spectrum of Effects. *Neurochemical Journal.* 2023;17(2):180-8.
22. Zhu X, Sun-Waterhouse D, Cui C. A red pomegranate fruit extract-based formula ameliorates anxiety/depression-like behaviors via enhancing serotonin (5-HT) synthesis in C57BL/6 male mice. *Food Science and Human Wellness.* 2021;10(3):289-96. doi: <https://doi.org/10.1016/j.fshw.2021.02.020>.
23. Schrödinger L, DeLano W. PyMOL. 2020. Available from: <http://www.pymol.org/pymol>.

24. Mohanraj K, Karthikeyan BS, Vivek-Ananth RP, Chand RPB, Aparna SR, Mangalapandi P, Samal A. IMPPAT: A curated database of Indian Medicinal Plants, Phytochemistry And Therapeutics. *Sci Rep.* 2018 12;8(1):4329.
25. O'Boyle NM, Banck M, James CA, Morley C, Vandermeersch T, Hutchison GR. Open Babel: An open chemical toolbox. *J Cheminform.* 2011;3(1):1-4.
26. Dallakyan S, Olson AJ. Small-molecule library screening by docking with PyRx. *Chem Biol Methods Protoc.* 2015:243-50.
27. Trott O, Olson AJ. AutoDock Vina: improving the speed and accuracy of docking with a new scoring function, efficient optimization, and multithreading. *J Comput Chem.* 2010;31(2):455-61.
28. Discovery Studio Modeling Environment, Release 4.5. 2021. BIOVIA, Dassault Systèmes, San Diego.
29. Daina A, Michielin O, Zoete V. SwissADME: a free web tool to evaluate pharmacokinetics, drug-likeness and medicinal chemistry friendliness of small molecules. *Sci Rep.* 2017;7:42717.
30. Veber DF, Johnson SR, Cheng HY, Smith BR, Ward KW, Kopple KD. Molecular properties that influence the oral bioavailability of drug candidates. *J Med Chem.* 2002 6;45(12):2615-23.
31. Lipinski CA, Lombardo F, Dominy BW, Feeney PJ. Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings. *Adv Drug Deliv Rev.* 2001. 1;46(1-3):3-26.
32. Cheng F, Li W, Zhou Y, et al. AdMetSAR: a comprehensive source and free tool for assessment of chemical ADMET properties. *J Chem Inf Model.* 2012;52(11):3099-3105.
33. Filimonov DA, Lagunin AA, Glorizova TA, Rudik AV, Druzhilovskii DS, Pogodin PV, Poroikov VV. Prediction of the biological activity spectra of organic compounds using the PASS online web resource. *Chem Heterocycl Compd.* 2014;50:444-57.

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