Trop J Nat Prod Res, October 2025; 9(10): 4909 - 4914 **ISSN 2616-0684 (Print)**
ISSN 2616-0692 (Electronic)

Tropical Journal of Natural Product Research

Available online at https://www.tjnpr.org

Original Research Article

Leaf-derived Bioactive Compounds of *Elaeocarpus ganitrus* as a Natural Antidepressant Agent Through Glycogen Synthase Kinase 3 Beta (GSK3β) and Serotonin 6 (5-HT6) Receptor: *In silico* Approach

Cicilia N. Primiani[1,2]*, Pujiati Pujiati[1], Weka S. Bhagawan[2], Gabriella C. Krisnamurti[3], Anak A.S.A Sukmaningsih[4]

[1]*Department of Biology Education, Faculty of Teacher Training and Education 63118, Universitas PGRI Madiun, Indonesia.*
[2]*Department of Pharmacy, Faculty of Health and Science, Universitas PGRI Madiun 63118, Indonesia.*
[3]*Biotechnology Program, School of Bioresources and Technology, King Mongkut's University of Technology Thonburi, Bang Khun Thian 10150, Thailand.*
[4]*Biology Study Program, Faculty of Mathematics and Natural Sciences, Udayana University 80361, Bali, Indonesia.*

ARTICLE INFO

Article history:
Received 28 August 2025
Revised 03 October 2025
Accepted 11 October 2025
Published online 01 November 2025

ABSTRACT

Depression is related to molecular and cellular abnormalities that interact with genetic and environmental factors. This condition was traditionally treated by Rudraksha beads of *Elaeocarpus ganitrus*, also known as natural tranquillizers. Glycogen Synthase Kinase 3 Beta (GSK3β) and Serotonin 6 receptor (5-HT6) played a significant role in mood regulation through Wnt and Akt signalling pathways, respectively. Therefore, this study aims to identify the antidepressant mechanism of *E. ganitrus* bioactive compounds through GSK3β and 5-HT6 using molecular docking. Bioactive compounds were virtually predicted for drug-likeness properties, ADME/T, and biological activity with PASS Way2Drug. 4-phenylpiperidine and medifoxamine had potent biological activity related to antidepressant mechanisms (Pa > 0.7) and satisfied the criteria of drug-likeness as Lipinski's rule of five. These compounds were subjected to molecular docking with GSK3β (1UV5) and 5-HT6 (7XTB) using AutoDock Vina integrated in PyRx 0.8. Furthermore, 4-phenylpiperidine and medifoxamine tended to perform antidepressant activity through GSK3β. These bioactive compounds occupied the same binding site as native ligand BRW on GSK3β, but the binding energy of 4-phenylpiperidine (-7.4 kcal/mol) and medifoxamine (-7 kcal/mol) was lower than BRW (-9.7 kcal/mol). Bioactive compounds were bound to the same site on 5-HT6 as the native ligand SRO. Compared to SRO (-6.5 kcal/mol), 4-phenylpiperidine (-6.3 kcal/mol) exhibited weaker binding, while medifoxamine (-6.7 kcal/mol) was stronger. These results supported the traditional use of Rudraksha beads as antidepressants. However, further studies were essential to validate the therapeutic utility of *E. ganitrus*.

Keywords: Antidepressant, docking, *E. ganitrus*, glycogen synthase kinase 3 beta, serotonin 6 receptor

Introduction

Depression is a prevalent psychiatric disorder, significantly affecting quality of life. It clinically presented as a change of mood and cognition, also loss of interest, persisting for more than 2 weeks.[1] World Health Organization (WHO) declared depression as the most significant disorder to consider as a result of the rising worldwide impact in 2020.[2] In Indonesia, the prevalence of depression in 2013 was 5.1% and 5.6% in adolescents and young adults, respectively. In 2023, the prevalence of people with mental disorders increased to approximately 20% of the Indonesian population. This was the second most significant contributor to non-communicable disease, after cardiovascular disease, and caused premature death.[3] Stress is a major contributor to depression, characterized by specific neurobiological changes.[4] Hypothesis states that depression may be associated with molecular and cellular abnormalities triggered by genetic and environmental factors.[1]

*Corresponding author. Email: primiani@unipma.ac.id
Tel: +6281556541989

Citation: Primiani CN, Pujiati P, Bhagawan WS, Krisnamurti GC, Sukmaningsih AASA. Leaf-derived bioactive compounds of *Elaeocarpus ganitrus* as a natural antidepressant agent through Glycogen Synthase Kinase 3 Beta (GSK3β) and Serotonin 6 (5-HT6) receptor: *in silico* approach. Trop J Nat Prod Res. 2025; 9(10): 4909 – 4914 https://doi.org/10.26538/tjnpr/v9i10.30

Official Journal of Natural Product Research Group, Faculty of Pharmacy, University of Benin, Benin City, Nigeria

An imbalance of key neurotransmitters, such as norepinephrine, serotonin, and dopamine, is shown to be a contributing factor to the symptoms of depression.[5,6] The complex causes of depression make it difficult to define and diagnose. Although antidepressants are prescribed for depression and mood-related disorders, the limitations include a slow therapeutic response and unwanted side effects.[7,8]
Studies need to focus on obtaining antidepressant agents with high safety and optimum therapeutic effect to optimize therapeutic effect and eliminate unwanted side effects. Natural bioactive compounds are potential candidates for this purpose, offering broad therapeutic properties and pharmacological benefits with good safety and tolerability.[5,9] The ethnobiology study showed that Rudraksha is a very important and spiritual herbal plant with medicinal purposes.[10] *Elaeocarpus ganitrus* or genitri is the source of Rudraksha beads, which have been used traditionally as a natural tranquilizer. It has magnetic properties that regulate heart rate and blood pressure, also showing antidepressant effect in reducing anxiety and stress.[11] *E. ganitrus* showed potent antibacterial activity against *S. aureus* and *E. coli*,[12] which was traditionally used to treat skin infection, pimples, and fever.[10] The traditional uses of *E. ganitrus* may reflect on its pharmacological activity. Therefore, this study will predict the antidepressant mechanism of *E. ganitrus* through molecular docking.
Among antidepressant signaling pathways, Glycogen Synthase Kinase 3 Beta (GSK3β) and Akt signaling are shown to be important in mood regulation. GSK3β was identified as the downstream target for disruption in schizophrenia 1 (DISC1), and there is evidence of increased depression, schizophrenia, and bipolar disorder.[13] Meanwhile, Serotonin 6 (5-HT6) is a serotonin receptor that plays a

crucial role in mood regulation and memory processing.[6] Limited studies have reported antidepressant action of bioactive compounds on GSK3β and 5-HT6. In this study, the importance of the receptors in modulating antidepressant mechanism was recognized. Furthermore, the potency of bioactive compounds from *E. ganitrus* as natural antidepressant agents was evaluated by targeting GSK3β and 5-HT6, through molecular docking. This evaluation was carried out by comparing the active site of bioactive compounds with native ligands. Molecular docking is a representative method to predict the interaction of proteins and small molecules at the atomic level.[14] It allows for the study of *E. ganitrus* bioactive compounds binding in the binding site of GSK3β and 5-HT6. This bond is crucial for understanding antidepressant action and provides scientific evidence supporting the traditional use of Rudraksha as a natural tranquilizer.

Materials and Methods

Screening of compounds according to Lipinski's rule and ADME/T

Bioactive compounds of *E. ganitrus* were acquired from a study conducted by Khansa *et al*.[15] using UPLC-MS analysis. A total of 6 out of 20 bioactive compounds were deposited with CID in the PubChem database (https://pubchem.ncbi.nlm.nih.gov/). The Canonical SMILES was used for drug-likeness according to Lipinski's rule of five and ADME/T prediction with SwissADME (https://www.swissadme.ch/index.php) and pkCSM (https://biosig.lab.uq.edu.au/pkcsm/prediction). Lipinski's rule of five was considered as standard criteria for drug-likeness of bioactive compounds that comprised molecular weight (MW < 500 Da), octanol-water partition coefficient (logP < 5), rotatable bonds (RotB < 10), hydrogen bond donors (H donor < 5), and acceptors (H acceptor < 10). The selected bioactive compounds showed efficient absorption in the gastrointestinal (GI) tract and permeability across the blood–brain barrier (BBB), with no evidence of toxicity.

Bioactivity prediction

The possible bioactivity of *E. ganitrus* compounds was analyzed with the PASS prediction tool (http://way2drug.com/PassOnline/predict.php).[16] Analysis was based on Pa (probability of activity) and Pi (probability of inactivity), while bioactivity with Pa>Pi was considered as potentially possible. Selected bioactivity was related to anti-depression and stress-release activity.

Molecular docking studies

Ligand retrieval and preparation

Based on criteria for drug-likeness, ADME/T, and bioactivity, two *E. ganitrus* compounds were selected for a molecular docking study. The 3D structure of 4-Phenylpiperidine (CID69873) and medifoxamine (CID36109) were retrieved as SDF format from the PubChem database. Native ligand 6-Bromoindirubin-3'-Oxime (BRW) and serotonin (SRO) were acquired from the protein. Ligands were prepared by minimizing the energy and converted into PDB format by PyRx Virtual Screening Tool, Version 0.8 (released in 2010).

Protein retrieval and preparation

An anti-depression and stress release protein was selected as the target. The 3D structure of protein was retrieved in PDB format from the PDB database (https://www.rcsb.org), Glycogen Synthase Kinase 3 Beta (GSK3β PDB ID:1UV5), and Serotonin 6 (5-HT6) receptor-Gs-Nb35 (5-HT6 PDB ID: 7XTB).[6,17] Protein was prepared with Discovery Studio, Version 2024 (released in 2024), by removing water molecules and ligands. Protein structure was saved in PDB format and converted into macromolecules in PyRx 0.8 for molecular docking.[18]

Docking

The binding energy of ligands to the targeted protein was assessed by molecular docking with AutoDock Vina integrated in PyRx 0.8. The bioactive compounds, identified as potential based on PASS prediction tool, were subjected as ligands for molecular docking. This analysis was validated by redocking the native ligands, BRW and SRO, which were originally co-crystallized with GSK3β (1UV5) and 5-HT6 (7XTB) proteins, to confirm the accuracy of the docking protocol. Potential bioactive compounds assessed from biological activity prediction were subjected to molecular docking. Ligands from protein PDB Docking were adjusted with an exhaustiveness of 50 and grid box of 1UV5 (center_x = 87.6562; center_y = 62.0938; center_z = 0.1366 and size_x = 59.9990487671; size_y = 50.7123617554; size_z = 63.3317881012) also 7XTB (center_x = 115.9507; center_y = 95.5215; center_z = 117.3673; size_x = 97.1337247467; size_y = 86.2073929977; size_z = 97.5222940445). The least binding energy was used in the selection of a model for docking, which was RMSD < 2.[18] The interaction between protein and ligand was visualized using Discovery Studio 2024.

Results and Discussion

Screening of E. ganitrus bioactive compounds

Six bioactive compounds were identified for drug-likeness properties (Table 1) and ADME/T (Table 2), focusing on chemical properties, such as molecular size, hydrogen binding, lipophilicity, and pharmacophoric features. These parameters enabled the efficient screening of potential drug candidates.[19] The results expected bioactive compounds with similar properties as drugs, efficient GI and BBB absorption, and no toxicity. According to Table 1, all bioactive compounds matched the criteria of Lipinski's rule of five. Among four bioactive compounds, 4-phenylpiperidine and medifoxamine showcased BBB permeability, which was suitable for antidepressant therapy. These bioactive compounds also had toxicity and were cleared from the body at a moderate rate (total clearance 0.672 log/mol/min/kg). The analysis from PASS (Figure 1) showed the specific biological activity related to antidepressants and stress release. In this case, cyanamide was absent due to the minimum carbon chain, and it could not be predicted in PASS prediction. PASS analysis is effective for predicting biological activities that possess therapeutic potential.[16]

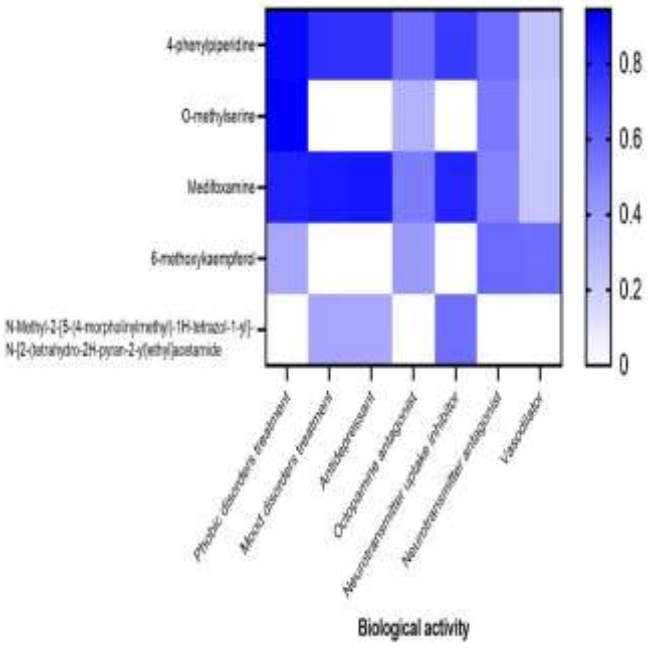

Figure 1: Prediction of biological activity from PASS Way2Drug

The intense blue color in Figure 1 represented the strong chance of activity. Among four bioactive compounds, 4-phenylpiperidine and medifoxamine showed a more intense blue color. Meanwhile, 4-phenylpiperidine and medifoxamine had Pa > 0.7 in phobic disorders treatment, mood disorders treatment, antidepressant, and neurotransmitter uptake inhibitor. In the PASS prediction tool, a Pa score > 0.7 was preferable, showing a high chance of the compounds performing the necessary activity, and was frequently selected for further testing. The 0.7 > Pa > 0.5 score and Pa < 0.5 showed moderate and low chance of activity, respectively.

Table 1: Bioactive compounds' properties according to Lipinski's rule of five

Bioactive	PubchemID	MW(g/mol) (< 500)	LogP (<5)	RotB (< 10)	H-acceptor (< 10)	H- donor (< 5)	Surface Area (Å2) (≤ 140 Å2)
4-Phenylpiperidine	69873	161.248	2.1536	1	1	1	73.8
Medifoxamine	36109	257.333	3.0321	6	3	0	113.935
Cyanamide	9864	42.041	-0.57382	0	2	1	18.472
O-Methylserine	88250	119.12	-0.9553	3	3	2	47.243
6-Methoxykaempferol	5377945	316.265	2.291	2	7	4	128.792
N-Methyl-2-[5-(4-morpholinylmethyl)-1H-tetrazol-1-yl]-N-[2-(tetrahydro-2H-pyran-2-yl)ethyl]acetamide	45253022	352.439	-0.0771	7	8	0	147.786

Table 2: Bioactive compounds' properties according to ADME/T

Bioactive	Pubchem ID	GI absorption	BBB permeant	Total Clearance (log ml/min/kg)	AMES toxicity	Max. tolerated dose (human) (log mg/kg/day)	Oral Rat Acute Toxicity (LD50) (mol/kg)
4-Phenylpiperidine	69873	High	Yes	0.672	No	0.216	2.455
Medifoxamine	36109	High	Yes	0.672	No	0.666	2.463
Cyanamide	9864	High	No	0.812	No	1.3	2.449
O-Methylserine	88250	High	No	0.48	No	1.155	2.017
6-Methoxykaempferol	5377945	High	No	0.458	No	0.52	2.39
N-Methyl-2-[5-(4-morpholinylmethyl)-1H-tetrazol-1-yl]-N-[2-(tetrahydro-2H-pyran-2-yl)ethyl]acetamide	45253022	High	No	0.99	No	0.044	2.431

This result suggested that 4-phenylpiperidine and medifoxamine had potential for further analysis. These bioactive compounds consistently showed the preferable chemical properties, ADME/T, as well as the bioactivity. Therefore, 4-phenylpiperidine and medifoxamine were effective as antidepressant agents.

Identification of molecular interaction

Molecular interactions of atoms and amino acid residues of bioactive compounds and proteins were the key components in drug discovery.[20] These components predicted the molecular mechanism and the possible effect of compound binding towards the protein.[21] To validate the docking of *E. ganitrus* bioactive compounds, this study redocked the native ligands, SRO and BRW, obtained from the PDB structure of proteins. Native ligands were used as a control to predict the mechanism of targeted compounds. For analysis, only docking models that satisfied the validation criteria (RMSD < 2.0 Å) were selected for further analysis. More specifically, the selected models exhibited an RMSD of 0.0 Å, which was effective for accurately predicting the ligand-protein interaction.[14] Docking analysis predicted that medifoxamine performed stronger binding to 5-HT6 than the native ligand with -6.7 kcal/mol and -6.5 kcal/mol, respectively (Table 3). Furthermore, 4-phenylpiperidine performed less strongly binding to 5-HT6 with -6.3 kcal/mol. This compound posed strong binding toward GSK3β with -7.4 kcal/mol, which was stronger than medifoxamine with -7 kcal/mol. The results further showed that bioactive compounds had less strong binding than BRW with -9.7 kcal/mol. The binding energy score was a key parameter to determine the potency of the compound toward protein and the system.[16]

SRO, a neurotransmitter, was a known antidepressant that essentially regulated mood, appetite, and behavior connected to stress release. This antidepressant was synthesized in the central nervous system (CNS) and stored in secretory vesicles until triggered by neuronal depolarization to release into the synaptic cleft.[22] BRW was a potent GSK3β inhibitor, which influenced downstream processes, specifically in mood regulation and stress release.[23]

Table 3: Binding energy score of bioactive compounds and core target

Receptor	Ligand	Energy score (kcal/mol)	Bond	
			Hydrogen	Hydrophobic
5-HT6 (7XTB)	Serotonin	-6.5	N:Thr104, A:Asp106, A:Arg232, B:Asp246	N:Ala101, A:Arg232, A:Lys280
	4-Phenylpiperidine	-6.3	R:Ala157	R:Pro187;Phe188, R:Val191
	Medifoxamine	-6.7	N:Phe108, N:Thr111	A:Ala48, A:Ala268, A:Ala269, A:Lys271, A:Leu272
GSK3β (1UV5)	6-Bromoindirubin-3'-Oxime	-9.7	A:Ile62, A:Asp133, A:Val135, A:Cys199	A:Ile62, A:Val70, A:Ala83, A:Lys85, A:Leu132, A:Leu188, A:Cys199

ISSN 2616-0684 (Print)
ISSN 2616-0692 (Electronic)

4-Phenylpiperidine	-7.4	-	A:Val70, A:Ala83, A:Leu188
Medifoxamine	-7	A:Asn64, A:Cys199, A:Asp200	A:Ile62, A:Val70, A:Lys85, A:Val110, A:Leu132, A:Leu188

The binding mechanism and potency of *E. ganitrus* bioactive compounds toward targeted proteins were evaluated by comparing with native ligands. The binding analysis showed that both compounds occupied binding sites distinct from the native ligand SRO on 5-HT6. Specifically, 4-phenylpiperidine interacts with Ala157, Pro187, Phe188, and Val191 through hydrogen bonding and hydrophobic forces. Medifoxamine binds through residues Phe108, Thr111, Ala48, Ala268, Ala269, Lys271, and Leu272, none of which were used by SRO (Figure 2).

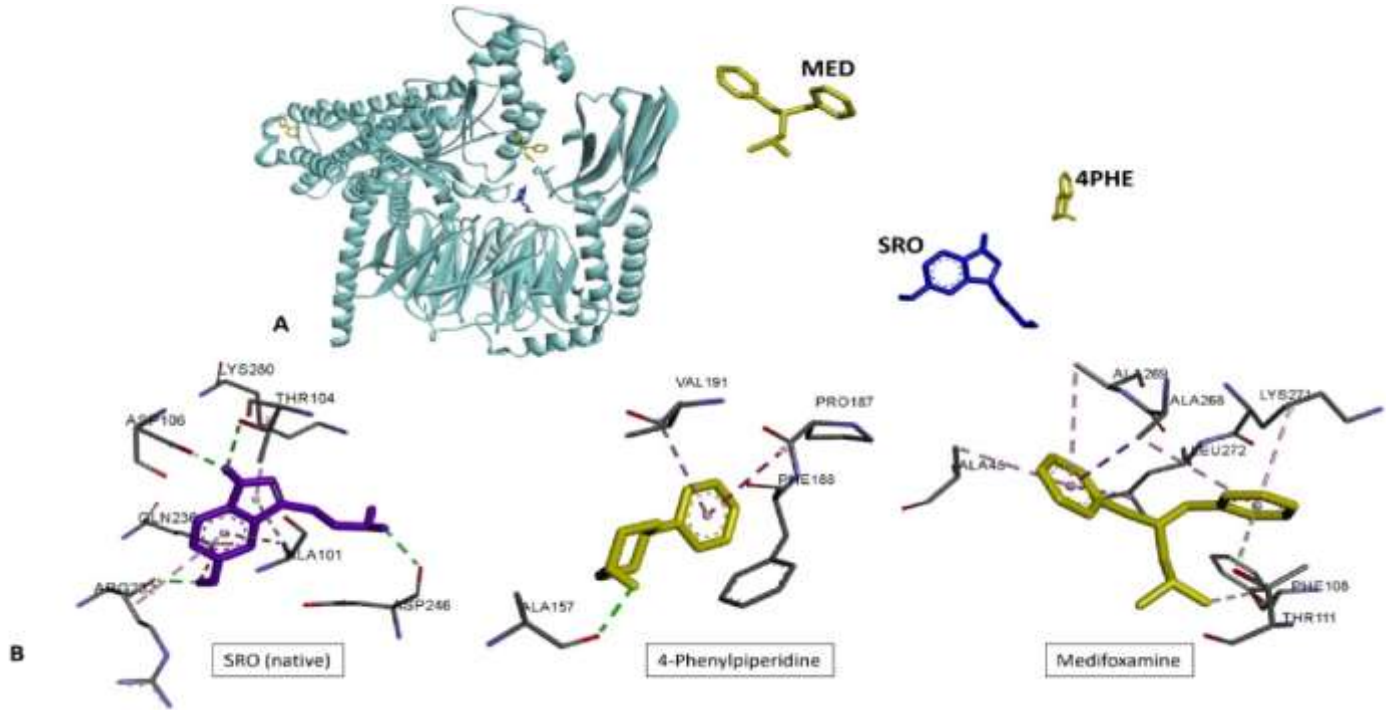

Figure 2: Interacting atom of *E. ganitrus* bioactive compounds on 5-HT6 (7XTB): A) complex on protein with ligand (MED: medifoxamine, 4PHE: 4-phenylpiperidine, SRO: serotonin), B) interaction of ligand on amino acid residues of protein

This result suggested that both 4-phenylpiperidine and medifoxamine were able to interact with 5-HT6 but did not perform antidepressant activity, such as SRO. Different from 5-HT6, bioactive compounds of *E. ganitrus* were predicted to actively interact with GSK3β at the similar active sites of native ligand BRW (Figure 3).

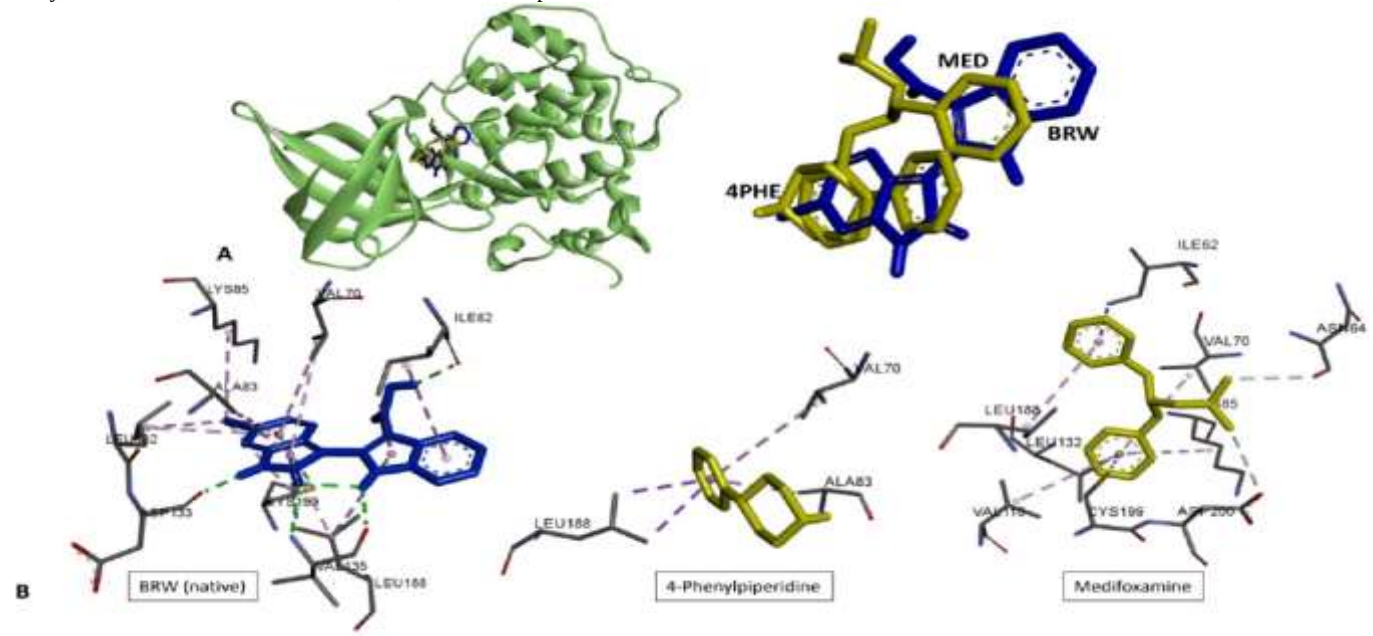

Figure 3: Interacting atom of *E. ganitrus* bioactive compounds on GSK3β (1UV5): A) complex on protein with ligand (MED: medifoxamine, 4PHE: 4-phenylpiperidine, BRW: 6-Bromoindirubin-3'-Oxime), B) interaction of ligand on amino acid residues of protein

Furthermore, 4-phenylpiperidine occupied Val70, Ala83, and Leu188 of the protein with hydrophobic interaction. Medifoxamine formed hydrogen bonds and hydrophobic interactions with Asn64, Cys199, Asp200, Ile62, Val70, Lys85, Val110, Leu132, and Leu188. A comparative analysis of the binding modes showed an overlap in the interacting amino acid residues between the compounds 4-phenylpiperidine and medifoxamine and the native ligand BRW at the GSK3β. These shared residues were Ile62, Val70, Ala83, Lys85, Leu132, Leu188, and Cys199, suggesting that the bioactive compounds may exhibit an inhibitory mechanism against GSK3β similar to the native ligand BRW, as the comparative binding analysis showed an overlap in their binding sites.[24] GSK3β is a serine/threonine kinase widely expressed in the brain, functioning in glycogen synthesis, development, proliferation, and apoptosis through phosphorylation.[25] Accordingly, it has been implicated in various pathologies, particularly neurodegeneration.[1] Protein is regulated through the Wnt signalling pathway. In antidepressant response, blocking GSK3β requires upregulation of phosphorylation, primarily through Akt signaling using 5-HT6.[23] Blocking GSK3β lead to the reduction of β-catenin phosphorylation, and the level of unphosphorylated β-catenin is successfully maintained in the cell. In the nucleus, it acts as a transcription factor, interacting with T cell factor/Lymphoid enhancer-binding factor (TCF/LEF) to turn on specific genes.[1,26] BRW is shown to inhibit GSK3β by mimicking activation of Wnt signaling.[27]

Bioactive compounds from plant extracts are often used for traditional treatment and therapy, which show promising therapeutic effects. Previously, ethanol leaf extract of *Entada africana* reduced the duration of mice immobility in the tail suspension test (TST).[28] The bioactives from the methanol extract of *Saurauia roxburghii* leaf showed potential binding toward the $GABA_A$ receptor, potassium channel receptor, and human serotonin transporter.[9] Furthermore, the 400 mg/kg dose of *Ximenia americana* extracts reduced the immobility time of the forced swim test (FST) and TST in the depressive prediction model.[5] This study predicted that 4-phenylpiperidine and medifoxamine could act as GSK3β inhibitors by activating Wnt signalling, similarly to BRW. In contrast to SRO, these bioactive compounds did not effectively modulate Akt/β-arrestin2/PP2A through 5-HT6.

Antidepressant mechanism associated with GSK3 signaling, which played a role in reducing stress, anxiety, and depression. This protein is activated in response to inflammation or stress, leading to further inflammatory processes.[29] Subsequently, the activation of GSK3 regulates inflammation-related transcription factors, such as TNFα.[30] The response is characterized by the trafficking of proinflammatory factors and immune cells from the peripheral blood circulation that led to the disruption of BBB.[29,30] Therapeutic intervention using GSK3 inhibitors typically aims to decrease TNFα level and increase tight junction (TJ) protein expression.[29] Therefore, it attenuates the prolonged learned helplessness and depressive-like behavior.[30] The potential antidepressant activity of *E. ganitrus* bioactive compounds found in this study was consistent with a previous report on potential anti-inflammatory activity through COX-2 modulation.[31] Inflammation was closely related to depressive behavior, considering that COX-2 stimulated the production of pro-inflammatory factor prostaglandin E2 (PGE2) and released other inflammatory mediators.[29,32] Antidepressant activity of 4-phenylpiperidine and medifoxamine through GSK3β is closely related to anti-inflammatory action, as GSK3β signaling is implicated in stress-induced inflammation and its activation regulated the expression of pro-inflammatory factors.[29]

Conclusion

In conclusion, this study evaluates the molecular mechanism of bioactive compounds from *E. ganitrus* toward antidepressant receptors, GSK3β, and 5-HT6. A novel validation of the traditional antidepressant activity of *E. ganitrus* was provided through a molecular docking analysis of its interactions with GSK3β and 5-HT6. Among four bioactive compounds in *E. ganitrus* leaf, 4-phenylpiperidine and medifoxamine are the most promising compounds to be developed as natural antidepressant agents. These bioactive compounds show drug-like properties, as well as potency in GI absorption and BBB permeability. PASS also predicted that 4-phenylpiperidine and medifoxamine exhibit high antidepressant activity (Pa > 0.7). In a molecular docking study, 4-phenylpiperidine and medifoxamine effectively inhibit GSK3β, binding at a similar active site as the inhibitor. Meanwhile, bioactive compounds are not bound similarly to serotonin to 5-HT6, showing that *E. ganitrus* probably performed potent antidepressant activity on GSK3β. Further studies should focus on validating this mechanism to establish GSK3β as a key therapeutic target. *In vivo* and *in vitro* studies are also required to evaluate the therapeutic and side effects of *E. ganitrus* bioactive compounds as natural antidepressant agents.

Conflict of Interest

The author`s declare no conflict of interest.

Authors' Declaration

The authors hereby declare that the work presented in this article is original and that any liability for claims relating to the content of this article will be borne by them.

Acknowledgements

We sincerely acknowledge the financial assistance from the Ministry of Higher Education, Science, and Technology of the Republic of Indonesia number 0070/C3/AL.04/2025 (23 May 2025).

References

1. Duman RS, Voleti B. Signaling pathways underlying the pathophysiology and treatment of depression: novel mechanisms for rapid-acting agents. Trends Neurosci. 2012; 35(1):47-56. Doi: 10.1016/j.tins.2011.11.004
2. Jain NK, Tailang M, Chandrasekaran B, Khazaleh NT, Thangavel N, Makeen HA, Albratty M, Najmi A, Alhazmi HA, Zoghebi K, Alagusundaram M, Jain HK. Integrating network pharmacology with molecular docking to rationalize the ethnomedicinal use of *Alchornea laxiflora* (Benth.) Pax & K. Hoffm. for efficient treatment of depression. Front Pharmacol. 2024; 15:1290398. Doi: 10.3389/fphar.2024.1290398
3. Basrowi RW, Wiguna T, Samah K, Moeloek NDF, Soetrisno M, Purwanto SA, Ekowati M, Elisabeth A, Rahadian A, Ruru B, Pelangi B. Exploring Mental Health Issues and Priorities in Indonesia Through Qualitative Expert Consensus. Clin Pract Epidemiol Ment Health. 2024; 20:e17450179331951. Doi: 10.2174/0117450179331951241022175443
4. Friedrich MJ. Depression is the leading cause of disability around the world. JAMA. 2017; 317(15):1517-1517. Doi: 10.1001/jama.2017.3826
5. Abebe T, Hymete A, Giday M, Bisrat D. Antidepressant-Like Activity and Molecular Docking Analysis of a Sesquiterpene Lactone Isolated from the Root Bark of *Ximenia americana* (L.). Evid Based Complement Alternat Med. 2024; 2024(1):6680821. Doi: 10.1155/2024/6680821
6. Marcinkowska M, Mordyl B, Siwek A, Głuch-Lutwin M, Karcz T, Gawalska A, Sapa M, Bucki A, Szafrańska K, Pomierny B, Pytka K, Kotańska M, Mika K, Kolaczkowski M. Dual molecules targeting 5-HT6 and GABA-A receptors as a new approach to combat depression associated with neuroinflammation. ACS Chem Neurosci. 2023;14(8):1474-1489. Doi: 10.1021/acschemneuro.3c00033
7. Ramic E, Prasko S, Gavran L, Spahic E. Assessment of the Antidepressant Side Effects Occurrence in Patients Treated in Primary Care. Mater Sociomed. 2020; 32(2):131–134. Doi: 10.5455/msm.2020.32.131-134
8. Braund TA, Tillman G, Palmer DM, Gordon E, Rush AJ, Harris AW. Antidepressant side effects and their impact on treatment outcome in people with major depressive disorder: an iSPOT-D report. Transl Psychiatry. 2021; 11(1):417. Doi: 10.1038/s41398-021-01533-1
9. Rahman MA, Sarkar KK, Aktaruzzaman M, Mitra T, Sarker MT, Abid MA, Mazumder K, Barman AK, Molla NU, Al Hossain,

AM. Evaluation of antioxidant, anxiolytic, and antidepressant potential of *Saurauia roxburghii* Wall. Leaves: Supported by in vitro, in vivo, and in silico approaches. Phytomedicine Plus. 2025; 5(2):100792. Doi: 10.1016/j.phyplu.2025.100792

10. Choudhary S, Kaurav H. Elaeocarpus ganitrus (Rudraksha): A drug with spiritual and medicinal properties. Int J Pharm Biol Sci. 2009; 11(3):242-253.
11. Sudradjat SE, Timotius KH. Pharmacological properties and phytochemical components of Elaeocarpus: A comparative study. Phytomedicine Plus. 2022; 2(4):100365. Doi: 10.1016/j.phyplu.2022.100365
12. Primiani CN, Bhagawan WS, Pujiati P, Sari DRT. Phytochemical screening, in vitro and in silico antibacterial investigation of *Elaeocarpus ganitrus* extract. J.Biota. 2024; 10(1):1-14. Doi: 10.19109/Biota.v10i1.20038
13. Mao Y, Ge X, Frank CL, Madison JM, Koehler AN, Doud MK, Tassa C, Berry EM, Soda T, Singh KK, Biechele T, Petryshen TL, Moon RT, Haggarty SJ, Tsai LH. Disrupted in schizophrenia 1 regulates neuronal progenitor proliferation via modulation of GSK3beta/beta-catenin signaling. Cell. 2009;136(6):1017–1031. Doi: 10.1016/j.cell.2008.12.044
14. Agu PC, Afiukwa CA, Orji OU, Ezeh EM, Ofoke IH, Ogbu CO, Ugwuja EI, Aja PM. Molecular docking as a tool for the discovery of molecular targets of nutraceuticals in disease management. Sci Rep. 2023 13(1):13398. Doi: 10.1038/s41598-023-40160-2
15. Khansa NM, Pujiati P, Bhagawan WS, Primiani CN. Phytochemical profile of Genitri (Rudraksha) leaf (*Elaeocarpus ganitrus*) in the Gunungpati, Semarang area using the UPLC-MS method [Profil fitokimia daun genitri (*Elaeocarpus ganitrus*) pada daerah Gunungpati Semarang dengan metode UPLC-MS]. In Prosiding Seminar Nasional Program Studi Farmasi UNIPMA (SNAPFARMA). 2023 October; 1(1):192-196.
16. Eva MA, Mia E, Al Hasan MS, Chowdhury R, Yana NT, Rakib IH, Akter SM, Situ SG, Islam MT. Fruit-derived bioactive compounds of *Malus domestica* as novel therapeutic inhibitors against Monkeypox and Marburg virus: A computational-based drug discovery study. Food Chem. Adv. 2025; 7:100998. Doi: 10.1016/j.focha.2025.100998
17. Zareei S, Pourmand S, Eskandarzadeh M, Massahi S. In silico anti-alzheimer study of phytochemicals from Lamiaceae family through GSK3-β inhibition. Sci Rep. 2024; 14(1): 834. Doi: 10.1038/s41598-023-47069-w
18. Krisnamurti GC, Sari DRT, Bare Y. Capsaicinoids from *Capsicum annuum* as an Alternative fabh Inhibitor of *Mycobacterium tuberculosis*: in silico study. Makara J. Sci. 2021; 25(4): 195−202. Doi:10.7454/mss.v25i4.1248
19. Giordano D, Biancaniello C, Argenio MA, Facchiano A. Drug design by pharmacophore and virtual screening approach. Pharmaceuticals. 2022; 15(5): 646. Doi: 10.3390/ph15050646
20. Krisnamurti GC, Fatchiyah F. The biological function prediction of the 10-gingerol compound of ginger in inhibiting cyclooxygenase-2 activity. Doi: J. pure appl. chem. res. 2020; 9(3):222-232. Doi: 10.21776/ub.jpacr.2020.009.03.547
21. Ferdausi N, Islam S, Rimti FH, Quayum ST, Arshad EM, Ibnat A, Islam T, Arefin A, Ema TI, Biswas P, Dey D, Al Azad S. Point-specific interactions of isovitexin with the neighboring amino acid residues of the hACE2 receptor as a targeted therapeutic agent in suppressing the SARS-CoV-2 influx mechanism. J Adv Vet Anim Res. 2022; 9(2): 230-240. Doi: 10.5455/javar.2022.i588
22. Ślifirski G, Król M, Turło J. 5-HT Receptors and the Development of New Antidepressants. Int J Mol Sci. 2021; 22(16):9015. Doi: 10.3390/ijms22169015
23. Ragozzino E, Brancaccio M, Di Costanzo A, Scalabrì F, Andolfi G, Wanderlingh LG, Patriarca EJ, Minchiotti G, Altamura S, Summa V, Varrone, F. 6-Bromoindirubin-3'-oxime intercepts GSK3 signaling to promote and enhance skeletal muscle differentiation affecting miR-206 expression in mice. Sci Rep. 2019; 9(1):18091. Doi: 10.1038/s41598-019-54574-4
24. Marliana E, Danova A, Hairani R, Ruga R, Hermawati E, Yulvia A. In vitro Evaluation and Molecular Docking Study of the Antibacterial Potential of *Macaranga hullettii* King ex Hook. f. Leaf Extract. Trop. J. Nat. Prod. Res. 2025; 9(7):3050 -3057. Doi: 10.26538/tjnpr/v9i7.15
25. Duda P, Akula SM, Abrams SL, Steelman LS, Martelli AM, Cocco L, Ratti S, Candido S, Libra M, Montalto G, Cervello M, Gizak A, Rakus D, McCubrey JA. Targeting GSK3 and associated signaling pathways involved in cancer. Cells. 2020; 9(5): 1110. Doi: 10.3390/cells9051110
26. Li X, Jope RS. Is glycogen synthase kinase-3 a central modulator in mood regulation?. Neuropsychopharmacology. 2010; 35(11): 2143-2154. Doi: 10.1038/npp.2010.105
27. Wang LL, Li J, Gu X, Wei L, Yu SP. Delayed treatment of 6-Bromoindirubin-3′-oxime stimulates neurogenesis and functional recovery after focal ischemic stroke in mice. Int J Dev Neurosci. 2017; 57: 77-84. Doi: 10.1016/j.ijdevneu.2017.01.002
28. Bebeji MY, Yaro AH. Evaluation of antidepressant activity of ethanol leaf extract of *Entada africana* Guill. & Perr. (Fabaceae) in mice. Trop. J. Nat. Prod. Res. 2024; 8(2):6446-6450.
29. Welcome MO. Cellular mechanisms and molecular signaling pathways in stress-induced anxiety, depression, and blood–brain barrier inflammation and leakage. Inflammopharmacol. 2020; 28:643–665. Doi: 10.1007/s10787-020-00712-8
30. Cheng Y, Desse S, Martinez A, Worthen RJ, Jope RS, Beurel E. TNFα disrupts blood brain barrier integrity to maintain prolonged depressive-like behavior in mice. Brain Behav Immun. 2018; 69:556-567. Doi: 10.1016/j.bbi.2018.02.003.
31. Primiani CN, Sari DR, Krisnamurti GC, Pujiati P, Setiawan MA. Anti-Inflammatory Potentials of *Elaeocarpus sphaericus* Schum Fruit Compounds by Molecular Docking Approach. Trop. J. Nat. Prod. Res. 2021; 6(10):1775-1781. Doi: doi.org/10.26538/tjnpr/v5i10.13
32. da Silva DMA, Sales ISL, Oliveira JVS, dos Santos Júnior MA, de Oliveira Rebouças M, Valentim JT, de Carvalho Vale L, Capibaribe VCC, de Carvalho MAJ, de Aquino PEA, Macêdo DS, de Sousa FCF. Cyclooxygenase-2 inhibitors alleviated depressive and anxious-like behaviors in mice exposed to lipopolysaccharide: Involvement of oxidative stress and neuroinflammation. Pharmacol. Biochem. Behav. 2024; 240:173778. Doi: 10.1016/j.pbb.2024.173778