https://doi.org/10.48048/tis.2025.9320

Deciphering Depression-Targeted Mechanisms of *Pandanus odorifer* Leaf Extracts Based on Component Analysis and Integrated Molecular Approaches

Ersanda Nurma Praditapuspa[1,*], Farizah Izazi[2], Dita Savitri[3], Rina Andayani[1], Saipul Maulana[4], Mohammad Rizki Fadhil Pratama[5], Masteria Yunovilsa Putra[6] and Juni Ekowati[7]

[1]*Department of Pharmaceutical Chemistry, Faculty of Pharmacy, Universitas Hang Tuah, East Java 60111, Indonesia*
[2]*Department of Biology Pharmacy, Faculty of Pharmacy, Universitas Hang Tuah, East Java 60111, Indonesia*
[3]*Bachelor Program of Pharmacy, Faculty of Pharmacy, Universitas Hang Tuah, East Java 60111, Indonesia*
[4]*Department of Pharmacy, Faculty of Mathematics and Natural Sciences, Universitas Tadulako, Central Sulawesi 94148, Indonesia*
[5]*Department of Pharmacy, Faculty of Health Science, Universitas Muhammadiyah Palangkaraya, Kalimantan Tengah 73111, Indonesia*
[6]*Research Center for Vaccine and Drugs, National Research and Innovation Agency, West Java 16911, Indonesia*
[7]*Department of Pharmaceutical Sciences, Faculty of Pharmacy, Universitas Airlangga, East Java 60115, Indonesia*

([*]Corresponding author's e-mail: ersanda.nurma@hangtuah.ac.id)

Received: 12 November 2024, Revised: 30 January 2025, Accepted: 6 February 2025, Published: 28 February 2025

Abstract

Introduction: Mental health is a worldwide health problem. Antidepressants have therapeutic effects but after prolonged use, they can cause unwanted side effects. Seeing the great potential of coastal plants such as sea pandanus (*Pandanus odorifer*) attracts attention in creating a more effective and safe treatment. The aim of this study is to identify the compounds contained in sea pandanus and elucidate the molecular mechanism in the target proteins of depressive diseases. Materials and methods: LC-MS has been used to identify compounds in sea pandanus. The network pharmacology approach used Cytoscape 3.9.1, OMIM, Disgenet, SEA, SwissTarget, STRING 2.0.0, Metascape, and Kyoto Encyclopedia of Genes and Genomes (KEGG) to predict the molecular antidepressant mechanism of the metabolite compounds. Validation was achieved using MOE with MAOA receptor (PDB ID: 2Y5Z). Molecular dynamics simulation using Maestro Schrödinger 2020-1 software. Results and discussion: A total of 19 active compounds were identified through LC-MS. Network pharmacology analysis showed that the MAOA target was the most influential protein target in the network pharmacology study of antidepressants from metabolite compounds of sea pandanus methanol extract. The results of *in silico* validation and molecular dynamics simulation support the network pharmacology findings. Benzylcarbonyl-Lys-Dab-Arg-NH2 compound showed higher affinity to MAOA receptor target compared to standard drug (fluoxetine) with S score −10.7455 kcal/mol and MMGBSA value −68.0669 kcal/mol. Conclusions: The compound Benzylcarbonyl-Lys-Dab-Arg-NH2 showed higher binding affinity towards MAOA compared to the native ligand and drug fluoxetine, also maintaining a s2interaction within the MAOA active site, indicating that *Pandanus odorifer* has significant promise as a novel antidepressant agent. These findings provide a strong basis for further investigation into its efficacy and safety in a clinical setting, potentially leading to the development of more effective and targeted treatments for depression.

Keywords: Network pharmacology, *In silico*, Depression, Molecular dynamics, *Pandanus odorifer*

Introduction

Mental health is a global health problem. Depression is the 4th most common disease in the world [1]. In Indonesia, the prevalence of depression cases is 3.7 % or around 9,162,886 people. Every year, Indonesia's population increases by more than 3,000,000 people/year, so the number of depressed people in the future will be much higher [2]. Some of the consequences of depression are decreased work productivity and the frequency of suicide which is increasing from year to year [3]. Depression can be treated with medication therapy that can improve mood such as antidepressants that help reduce symptoms of depression [2]. Antidepressants have therapeutic effects but after prolonged use, they can cause unwanted side effects. One class of antidepressant drugs that is often used is selective serotonin reuptake inhibitors (SSRIs). Among SSRIs, fluoxetine shows the least specific binding to serotonin transporter (SERT) and at high doses, can increase synaptic norepinephrine and dopamine levels [4]. Fluoxetine tends to be associated with potential cardiovascular side effects and worsen heart failure in patients, especially geriatric patients, because it can inhibit Ca^{2+} channels, attenuate myogenic constriction of resistance arterioles so as to increase orthostatic hypotension and worsen microvascular damage [5]. In addition, a side effect of using antidepressant drugs is dependence because many drugs in circulation are psychotropic groups [6]. Therefore, the development of severe side effects limits the use for the treatment of depressed patients. Hence, it is necessary to develop new drugs, especially from natural products.

Sea pandanus (*Pandanus odorifer*) is a wild plant mainly vegetated in seminatural coastal habitats throughout the tropics and subtropics of the Pacific where it can withstand drought and strong winds [7]. Sea pandanus grows in coastal areas, especially the coastal area of Panceng Gresik Beach, but many local coastal communities still do not know the benefits of these plants. The existence of sea pandanus in Indonesia has not been widely appreciated, in addition to the minimal amount of research on the plant. Sometimes there are still coastal communities who think that the plant is only a nuisance because of its spiny leaves and damages the beauty of the beach because the fruit produced falls and rots and makes a pile of garbage.

Several studies have been conducted on *Pandanus odoratissimus*, including the biological potential reported to contain chemical compounds, antioxidant activity [8-10], chemoprotective [8], antidepressant [11], antidiabetic [9], anti-inflammatory [12], and hepatoprotective [13,14]. However, there are few reports on marine pandanus of the species *Pandanus odorifer*, especially regarding its chemical content and activities. *Pandanus odorifer* contains several secondary metabolites including flavonoids, alkaloids, tannins, saponins, and terpenoids [3]. Some flavonoid compounds increase serotonin, norepinephrine, and BDNF levels, and decrease monoamine oxidase activity [15]. The mechanism of action of alkaloids is by inhibiting the monoamine oxidase enzyme, increasing serotonin levels, BDNF levels, and modulating the HPA axis [16,17]. Tannin compounds increase monoamine levels in the brain and provide neuroprotective effects. Saponin compounds can affect the BDNF signalling pathway, HPA axis, and increase monoamine levels. Terpenoids act on dopamine receptors and increase norepinephrine and serotonin levels in the brain [15]. The ability of *Pandanus odoratissimus* to reduce anxiety and depression because it has anxiolytic effects [18]. Previous studies, conducted by Sathasivampillai *et al.* [19]; Son *et al.* [20], have explored the pharmacological activities and secondary metabolites of *Pandanus odorifer*. However, these studies do not address the molecular mechanisms underlying its antidepressant effects. This research focuses on bridging this gap through network pharmacology, molecular docking, and molecular dynamics**.** Therefore, this research is aimed at developing metabolite compounds from *Pandanus odorifer* as potential drug candidates in depression therapy.

Materials and methods

Materials and instrumentation

Computational study in this work was conducted using Cytoscape 3.9.1, Molecular Operating Environment (MOE) version 2020, Biovia Discovery Studio 2017, ChemDraw 19.1, and Desmond integrated in the Maestro Schrödinger 2020-1 on Dell Workstation Linux Ubuntu 20.04.3 LTS OS, Intel Xeon W-2223

CPU @ 3.60 GHz octacore, 16 GB RAM, and NVIDIA RTX 4060 TI GPU.

Network pharmacology

Identification of *Pandanus odorifer* compound-associated gene targets

The identification of potential gene targets commenced with the analysis of active compounds derived from *Pandanus odorifer* using LC-MS data in **Figure 1** and **Table 1**. These compounds were then translated into SMILES (Simplified Molecular Input Line Entry System) representations using ChemDraw. Subsequently, the SMILES data were imported using SEA (https://sea.bkslab.org/search), targetnet (http://targetnet.scbdd.com/), and SwissTarget (http://www.swisstargetprediction.ch/) databases to predict potential gene targets. To maintain consistency in gene nomenclature across these platforms, the identified genetic targets were standardized following the guidelines of the HUGO Gene Nomenclature Committee (HGNC), facilitated via the UniProt webserver (https://www.uniprot.org/id-mapping) [21-23].

Identification of gene targets associated to depression

identification of target proteins related to depression involved a comprehensive search across several genomic databases including Online Mendelian Inheritance in Man (OMIM) (https://omim.org/) and DisGeNET (https://www.disgenet.org/), employing the keyword “Depression” to identify relevant genes target. Subsequently, we standardized the target proteins according to the Uniprot webserver (https://www.uniprot.org/id-mapping), following a similar approach as described in previous step [21-23].

Construction network of protein-protein interaction (PPI)

The protein-protein interaction (PPI) network was constructed to explore the connections between genes derived from *Pandanus odorifer* active compounds and target proteins associated with depression using the STRING database (https://string-db.org/), stringent parameters were applied, including a high confidence level of 0.700 and a false discovery rate (FDR) of 5 %. The interaction network of similar genes among the targets was then visualized and analyzed using Cytoscape 3.9.1. In this network, proteins are represented as nodes, while the interactions between genes or proteins are depicted as edges. The analysis incorporated parameters, such as degree, betweenness, and centrality (BC), to identify significant nodes within the PPI network. Particularly, nodes with high degree values, which correspond to the highest-ranked target proteins, were considered crucial in understanding the mechanisms of plant compounds in treating depression [21-23].

Enrichment analysis

The enrichment analysis was employed to identify bioactive compounds and their corresponding targets as well as the mechanisms underlying depression treatment utilizing Metascape (https://metascape.org/), WebGestalt (https://webgestalt.org/), and Enrichr (https://maayanlab.cloud/Enrichr). These platforms facilitated the identification of significantly enriched biological processes, pathways, and gene ontology terms, offering insights into the molecular mechanisms involved in the therapeutic effects of the *Pandanus odorifer* compounds as antidepressant [24,25].

Molecular docking

In this study, we focused on Monoamine Oxidase A (MAOA) (PDB ID: 2Y5Z) as a potential target for depression therapy, based on network pharmacology. To investigate the interactions between ligands and MAOA, we employed molecular docking procedures using the Molecular Operating Environment (MOE) software (version 2020). Initially, we refined the crystal structures of MAOA by adding hydrogen atoms and protonating the receptors. The AMBER 99 force field was then applied to minimize the energy of the macromolecules prior to docking simulations. Our test compounds, initially constructed in 2 dimensions using ChemDraw software (version 19.1, Perkin Elmer Informatics), were imported into the MOE database. We converted these 2D structures into 3-dimensional conformations by appending hydrogen atoms (both polar and nonpolar) and optimizing them using the MMFF94x force field. The docking process allowed us to analyze their potential interactions within the receptor’s active site. We selected docking coordinates based on the native ligand’s binding pose. To confirm

our docking protocol, we evaluated the post-docking results of the native ligand by calculating the Root Mean Square Deviation (RMSD) compared to the original conformation. A valid docking protocol showed an RMSD value below 2 Å. Additionally, we assessed the stability of ligand-receptor interactions, including both native ligands and test compounds, using a scoring function that reflects binding energy (Score, S).

Molecular dynamics

In this work, the molecular dynamics (MD) simulations were utilized to evaluate the stability of ligand-protein complexes using Desmond. Initially, the system is prepared by generating ligand-protein complexes through a docking process. These complexes are then immersed in a simple point charge (SPC) water box, ensuring a 10 Å distance between the solute and the edges of the box. To replicate physiological conditions, the system's charges are neutralized by adding counter ions and salts, specifically sodium and chloride, at a concentration of 0.15 M. The simulation employs the OPLS_2005 force field and is conducted under NPT (constant Number of particles, Pressure, and Temperature) conditions, maintaining a temperature of 310 K and a pressure of 1.63 bar. The MD simulation is run for 100 ns, with energy measurements recorded every 1.2 ps and trajectory data every 20 ps. This approach allows for the detailed observation of the dynamic behavior of the ligand-protein complexes and the evaluation of their stability. The stability is assessed through various parameters, including Root Mean Square Deviation (RMSD), Root Mean Square Fluctuation (RMSF) and the MMGBSA (Molecular Mechanics Generalized Born Surface Area) value using *thermal_mmgbsa.py* script.

Results and discussion

Protein-protein interaction (PPI) network

The monoamine hypothesis has been the predominant framework for understanding the neurobiological underpinnings of depression for several decades, positing that the disorder is associated with deficiencies in key neurotransmitters such as serotonin, norepinephrine, and dopamine [26]. While this hypothesis has garnered widespread acceptance, recent research has questioned its comprehensiveness, as studies have found a correlation between serotonin levels and depression, suggesting the need to explore alternative pathways involved in the disorder [27]. Previous studies have predominantly focused on the role of impairments in central monoaminergic function in mood disorders. However, a major limitation of these studies is that they have not examined multiple compounds within a pathway or multiple interconnected pathways simultaneously. The application of metabolomics technology has enabled researchers to map biochemical pathways implicated in central nervous system disorders, including depression, schizophrenia, and Parkinson's disease [28].

Interestingly, elevated levels of the enzyme monoamine oxidase A have been observed in individuals with major depressive disorder, leading to an accelerated breakdown of these critical neurotransmitters and a subsequent reduction in their availability, which may exacerbate depressive symptoms [28-30]. Given that MAOA plays a central role in regulating the availability of these mood-modulating neurotransmitters, this enzyme represents a promising target for the development of novel therapeutic interventions that could address the underlying neurochemical imbalances associated with depression [30,31]. Indeed, a growing body of evidence supports the importance of MAOA in the pathophysiology of depression. Elevated MAOA levels have been linked to greater severity of depressive episodes, as well as the presence of reversed neurovegetative symptoms, such as increased appetite and sleep disturbances. Moreover, metabolomic studies have revealed distinct metabolic profiles associated with the remission state of mood disorders, highlighting the dynamic nature of the neurochemical systems involved and the potential for targeted interventions [28]. As our understanding of the complex interplay between various neurotransmitter systems and associated enzymes, such as MAOA, continues to evolve, the development of more nuanced and personalized therapeutic approaches for depression may become increasingly feasible [28-31].

Although monoamine oxidase inhibitors have proven effective in the treatment of depression, they are hindered by substantial limitations that constrain their broader clinical application [32], due to stringent dietary, potential drug interactions, and risk of side effects like xerostomia, dry mouth, nausea, and sexual

dysfunction [33,34]. Consequently, these drawbacks have driven research for safer and alternative treatments for depression. To address these challenges, we have conducted a research study that integrates network pharmacology, molecular docking, and simulation techniques. This multifaceted approach enables us to determine the molecular mechanisms of key targets, predict their interactions, and simulate drug binding to these targets under dynamic conditions to investigate potential anti-depressive agents.

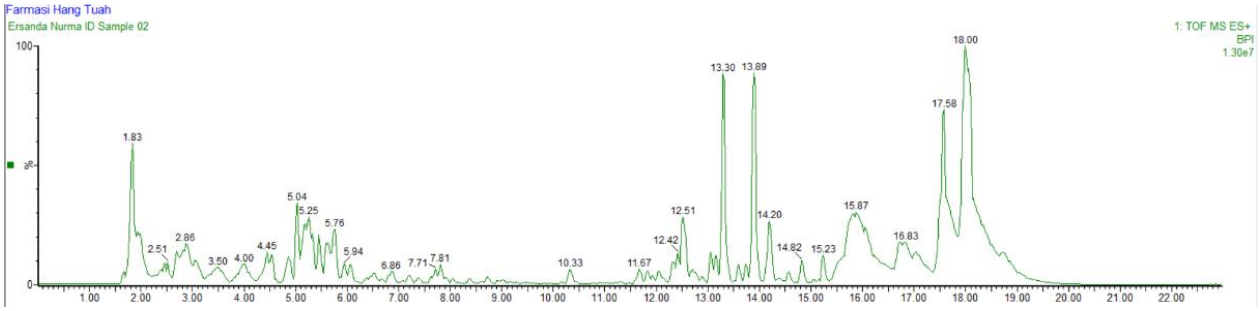
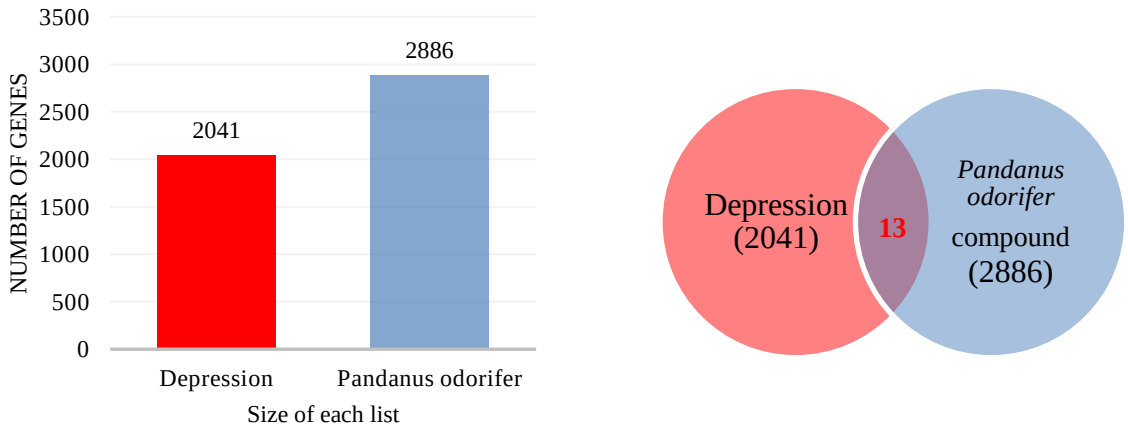


Figure 1 Chromatogram of LC-MS results.

Table 1 Metabolite compounds from *Pandanus odorifer* using the LC-MS instrument.

RT	% Area	Measured mass	Calculated mass	Molecular formula	Compound name
1.83	0.7864 %	365.1066	365.1084	$C_{14}H_{20}O_{11}$	2,3,4,5-Tetra-O-acetyl- d-gluconic acid
2.51	0.1251 %	268.1056	268.1093	$C_8H_{13}N_9S$	N,N-dimethyl-6-{[(1-methyl-1H-tetrazol-5-yl)thio]methyl}-1,3,5-triazine-2,4-diamine
2.86	0.2276 %	276.1457	276.1447	$C_{12}H_{21}NO_6$	Glutarylcarnitine
3.50	0.0973 %	144.0665	144.0661	$C_6H_9NO_3$	Methyl 5-oxopyrrolidine-2-carboxylate
4.00	0.1138 %	310.1300	310.1291	$C_{15}H_{19}NO_6$	Domoate(2-)
4.45	0.1818 %	240.1611	240.1600	$C_{13}H_{21}NO_3$	2,5-Dimethoxy-4-ethoxyamphetamine
5.04	0.4522 %	595.1678	595.1663	$C_{27}H_{30}O_{15}$	Kaempferol-3-O-rutinoside
5.25	0.3777 %	565.1569	565.1557	$C_{26}H_{28}O_{14}$	Apigenin-7-apioglucoside (Apiin)
5.76	0.3092 %	433.1142	433.1135	$C_{21}H_{20}O_{10}$	Genistin
5.94	0.1135 %	463.1251	463.1240	$C_{22}H_{22}O_{11}$	Thermopsoside (Chrysoeriol 7-O-glucoside)
6.86	0.0734 %	133.1023	133.1017	$C_{10}H_{12}$	1,2,3,4-Tetrahydronaphthalene
7.71	0.0875 %	478.3379	478.3380	$C_{24}H_{47}NO_8$	Hexosylsphingosine
7.81	0.1117 %	478.3380	478.3393	$C_{25}H_{43}N_5O_4$	(3S)-4-[(2S)-2-[2-(1-carbamimidoylpiperidin-4-yl)oxyethyl]piperidin-1-yl]-3-[cyclohept-4-en-1-yl(methyl)amino]-4-oxobutanoic acid
10.33	0.0883 %	181.1236	181.1229	$C_{11}H_{16}O_2$	2-tert-Butyl-4-methoxyphenol
12.51	0.3760 %	300.2920	300.2903	$C_{18}H_{37}NO_2$	D-Sphingosine

RT	% Area	Measured mass	Calculated mass	Molecular formula	Compound name
13.30	1.1674 %	520.3400	520.3360	$C_{24}H_{41}N_9O_4$	Benzylcarbonyl-Lys-Dab-Arg-NH2
13.89	1.1745 %	496.3406	496.3387	$C_{26}H_{45}N_3O_6$	(2R,4S,5S,7S)-5-amino-N-(2-carbamoylethyl)-4-hydroxy-7-{[4-methoxy-3-(3-methoxypropoxy)phenyl]methyl}-2,8-dimethylnonanamide
17.58	0.9723 %	766.5738	766.5734	$C_{46}H_{75}N_3O_6$	(3R)-N-[(1S,4S)-1-cyclohexyl-4-[(5R,8S)-8-[(3R)-6-cyclopropyl-4-hydroxy-5-oxo-3-propylhexanoyl]-10,10-dimethyl-7-azadispiro[3.0.45.14]decane-7-carbonyl]-5,5-dimethyl-2-oxohexyl]-1-ethylpiperidine-3-carboxamide
18.00	1.3237 %	766.5737	766.5694	$C_{41}H_{75}N_5O_8$	N-[1-amino-6-[[2-[3-[4-[3-(3-tert-butyl-2,5-dioxopyrrolidin-1-yl)propanoylamino]-2-methylbutan-2-yl]oxy-2,2-dimethylpropoxy]acetyl]amino]-1-oxohexan-2-yl]dodecanamide



(A) (B)

Figure 2 Number of predicted genes in each set (*Pandanus odorifer* and depression) (A). Venn diagram illustrating overlapping and specific genes among *Pandanus odorifer* and depression (B).

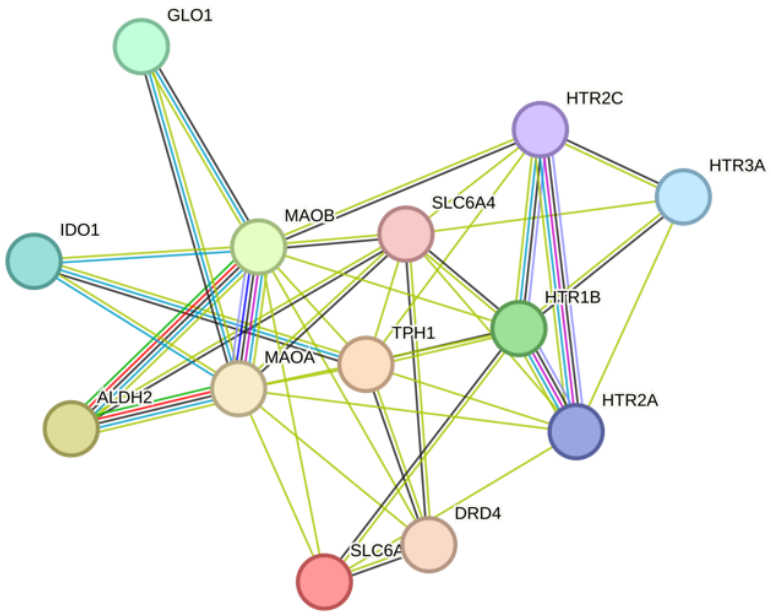


Figure 3 Visualization of a protein-protein interaction (PPI) network comprising 13 target genes, constructed using the STRING database.

Table 2 Topological analysis of the protein-protein interaction (PPI) network based on 13 shared target genes among active compounds from *Pandanus odorifer* and gene related to depression. The data were sorted by degree value.

Name	Degree	Closeness centrality	Betweenness centrality
MAOA	14	0.341463	0.061172
SLC6A4	14	0.310345	0.035888
SLC6A3	13	0.339623	0.074823
MAOB	12	0.324742	0.03598
HTR2A	9	0.307317	0.020081
TPH1	8	0.312655	0.012505
HTR3A	8	0.307317	0.042438
HTR1B	8	0.293706	0.004745
DRD4	8	0.293706	0.019097
HTR2C	6	0.283784	0.001619
IDO1	6	0.363112	0.082361
ALDH2	4	0.270968	0.019056
GLO1	2	0.256098	0

The network pharmacology approach employed in this study successfully identified 13 target genes (**Figure 2**), with monoamine oxidase A as the primary target due to its highest degree making it prominent within the interaction network (**Figure 3** and **Table 2**), signifying MAOA's central role in the target network and its potential significance in the anti-depressive mechanism of *Pandanus odorifer* compounds (**Figure 3**). The protein-protein interaction analysis was further evaluated through enrichment analysis, which was conducted using Metascape to elucidate the pathways associated with depression for the 13 identified genes. This analysis unveiled 3 primary functional activities of the selected protein group; "amine binding", "serotonergic synapse", and "ADHD and autism ASD linked metabolic pathways and SNP" (**Figure 4**).

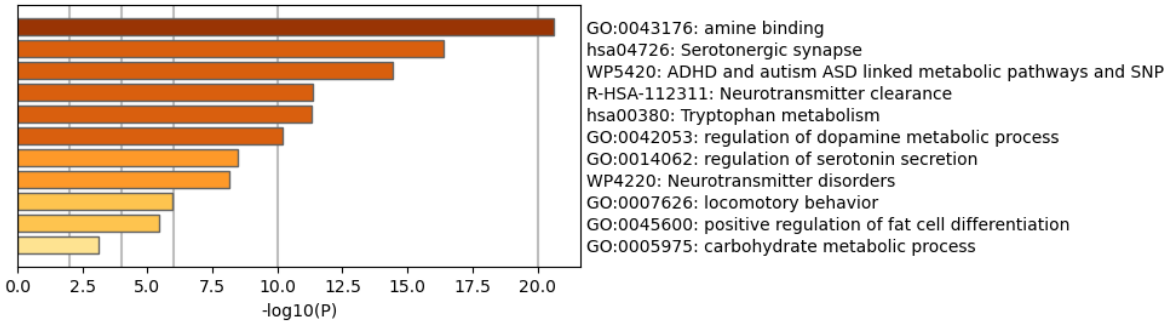
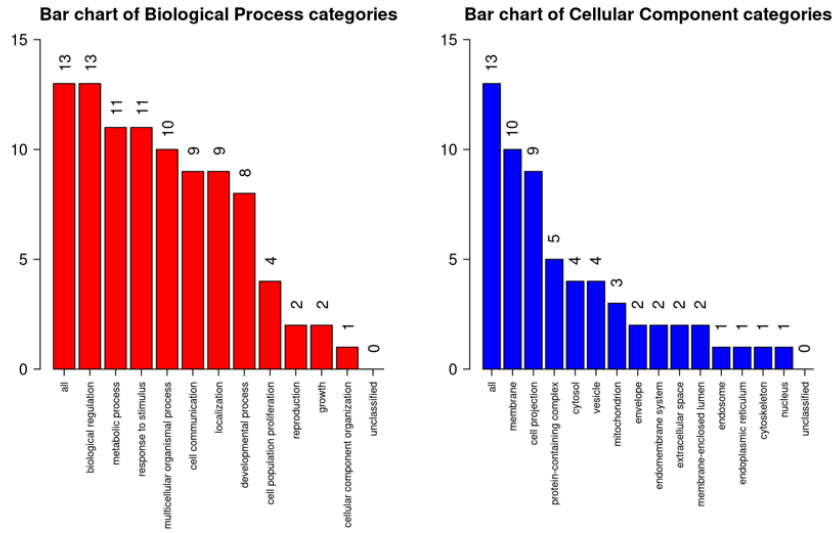
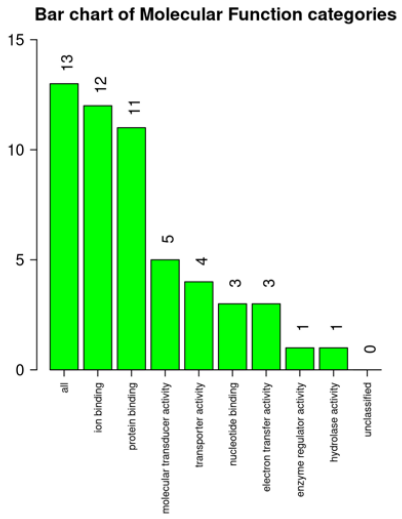


Figure 4 Pathway analysis of 13 shared genes using the Metascape database reveals significant biological processes in depression. These processes include the ‘amine binding’, ‘Serotonergic synapse’, ‘ADHD and autism ASD linked metabolic pathways and SNP’ and ‘Neurotransmitter clearance’.



(A) (B)



(C)

Figure 5 Gene Ontology (GO) analysis of target-disease gene interactions for *Pandanus odorifer* compounds reveals correlations in key biological processes (BP), cellular components (CC), and molecular functions (MF). The numbers of genes involved are indicated next to the horizontal bar graph.

These findings corroborate the growing body of evidence suggesting a significant overlap in the neurobiological underpinnings of depression, attention deficit hyperactivity disorder, and autism spectrum disorders [35-38]. Furthermore, the gene ontology analysis from WebGestalt provided additional insights into the molecular underpinnings of depression. The evaluation of Biological Processes (BP) revealed a triad of predominant activities; "Biological regulation", "metabolic process", and "response to stimulus" (**Figure 5(A)**). These findings provide insight into the intricate relationships between regulatory systems, metabolic processes, and environmental responsiveness underlying the pathophysiology of depression. Our findings emphasize the prominence of metabolic processes, which aligns with recent research identifying metabolic dysregulation as a crucial factor in the pathogenesis of mood disorders [39].

Subsequently, the cellular component analysis identified "membrane", "cell projection", and "protein-containing complex" as key components (**Figure 5(B)**). The prominence of membrane-associated elements highlights the essential function that membrane-bound proteins, including neurotransmitter receptors and transporters, play in regulating synaptic activity and neurotransmission processes, and neuronal morphology and also synaptic plasticity in mood regulation [40]. On the other hand, Molecular Function analysis highlighted "ion binding", "protein binding", and "molecular transducer activity" (**Figure 5(C)**). These functions represent the role of ion homeostasis, protein-protein interactions, and signal transduction mechanisms in the pathophysiology of depression, which aligns with the notion that mood disorders involve dysregulation at multiple levels, including genes, neurons, and brain regions [41].

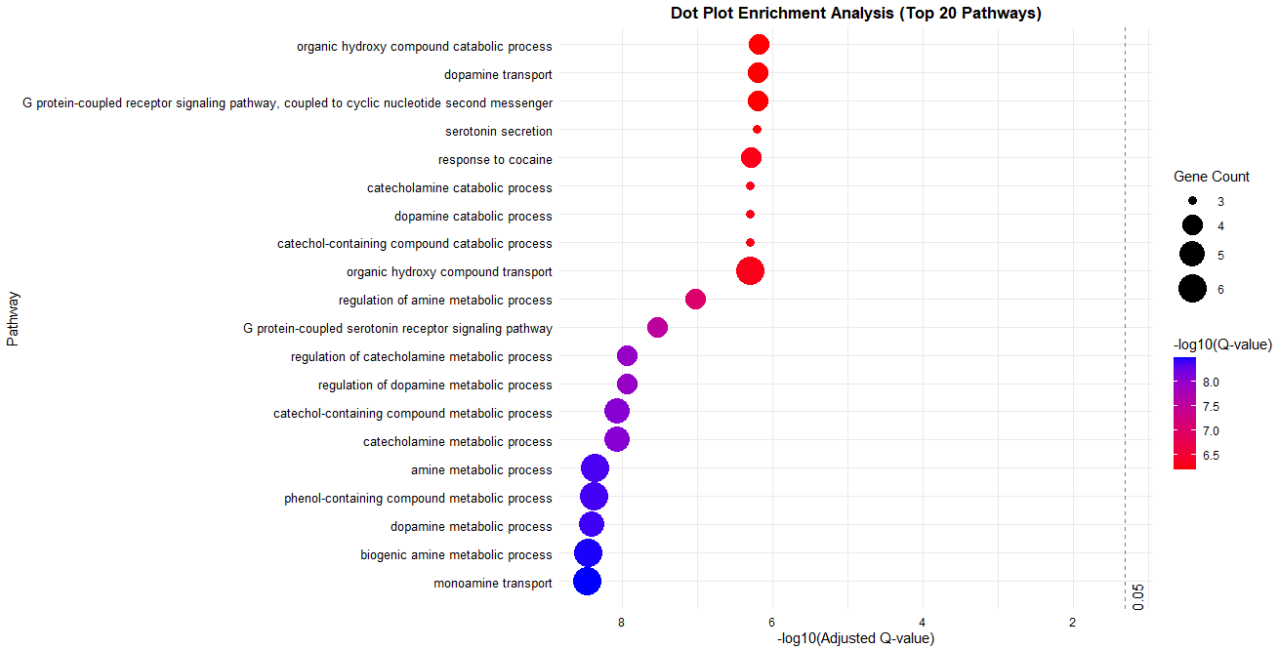


Figure 6 Twenty pathways enriched with identified target genes were determined using the ConsensusPathDB-human database analysis. The bubble plot visually represents these statistically significant pathways, where the size of the bubbles indicates the level of pathway enrichment, and the color intensity reflects the statistical significance.

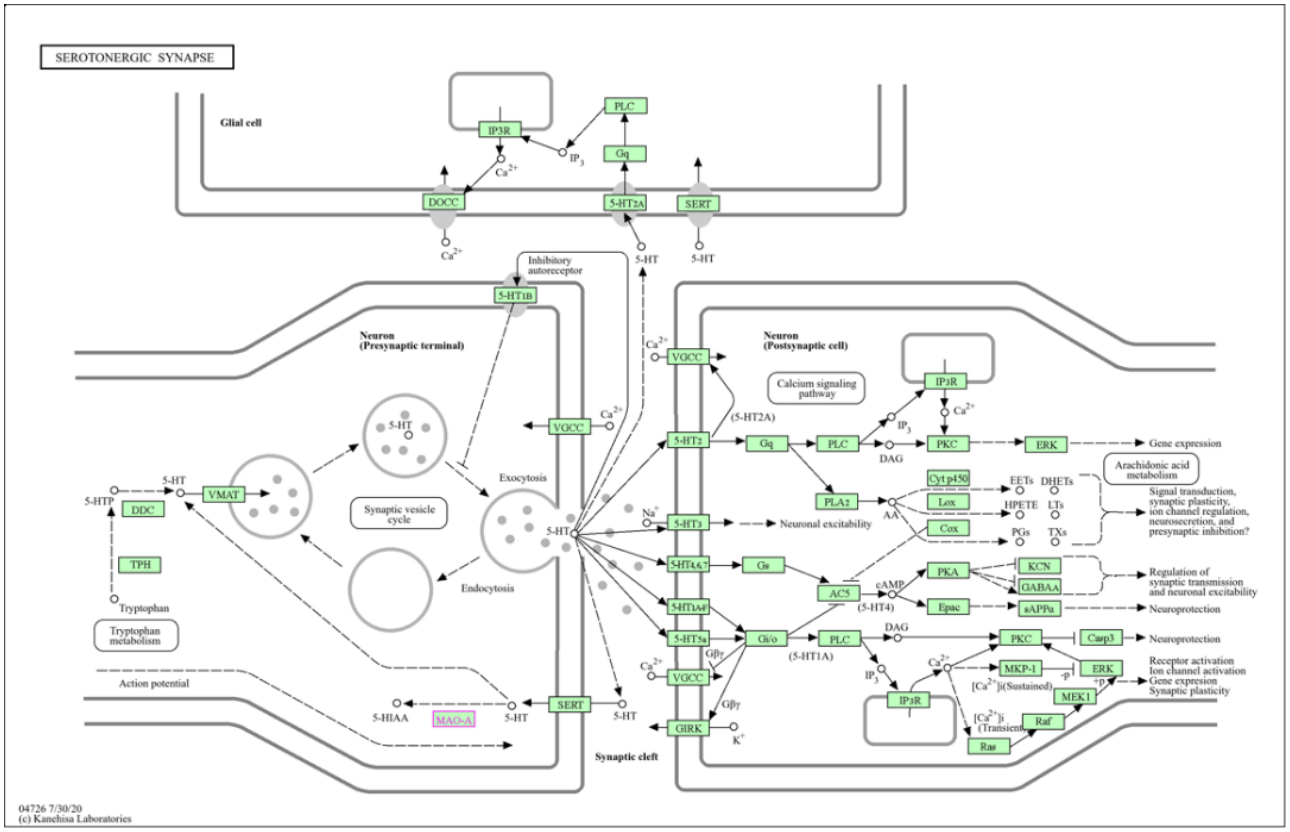


Figure 7 Detailed analysis of the serotonergic synapse signaling pathway and its role in depression prognosis.

Last but not least, pathway enrichment analysis from the ConsensusPathDB-human database revealed several significant pathways potentially implicated in depression, with those related to "monoamine transport", "biogenic amine metabolic processes", and "dopamine metabolic processes", demonstrating the strongest enrichment (**Figure 6**). Of particular significance is the monoamine transport pathway, which is directly linked to the serotonin transporter (SERT) and regulates extracellular serotonin levels, aligning with the well-established role of serotonin dysregulation in depression and the efficacy of selective serotonin reuptake inhibitors (SSRIs) [42,43]. The notable enrichment of dopamine metabolic processes underscores the potential role of dopaminergic dysfunction in depression, consistent with recent research highlighting dopamine's crucial role in motivation, reward processing, and anhedonia [44]. Additionally, our results emphasized the activity of monoamine oxidase A (MAO-A), which significantly impacts serotonergic neurotransmission (**Figure 7**), with higher MAO-A activity leading to increased serotonin breakdown, potentially contributing to depressive symptoms [45,46]. These findings not only reinforce the monoamine hypothesis of depression but also provide a comprehensive molecular framework for understanding the complex pathophysiology of depressive disorders, potentially guiding future research and therapeutic strategies toward more personalized and effective treatments.

Molecular docking

According to our network pharmacology analysis, MAOA is a crucial target for anti-depressive action. This finding is consistent with previous research on MAOA's role in the pathophysiology of depression, given its responsibility for breaking down neurotransmitters like serotonin, norepinephrine, and dopamine [47]. Recognizing MAOA as a key target justified the subsequent molecular docking studies. The docking protocol showed high reliability, with a Root Mean Square Deviation (RMSD) of 0.8173 Å (**Figure 8**) [48,49]. The docking results of the sea pandan metabolite compounds can be seen in **Table 3**.

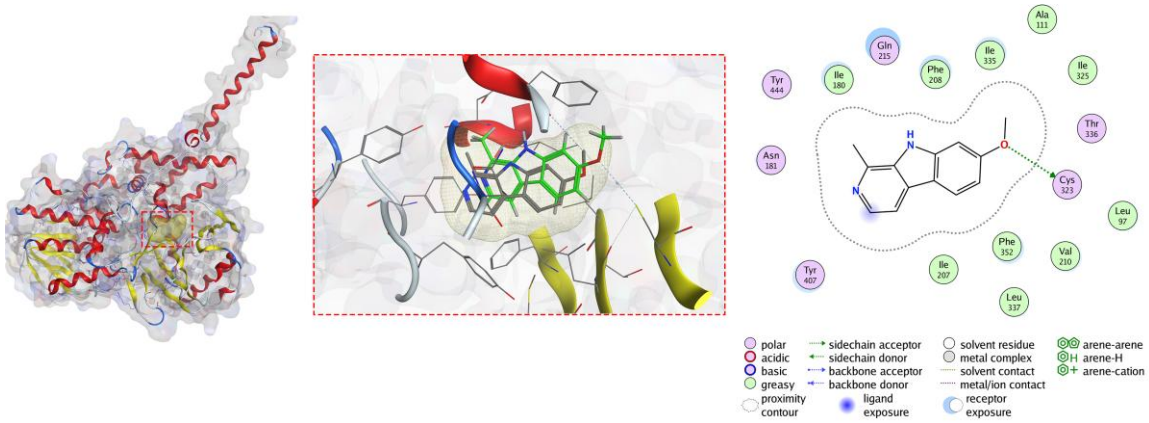


Figure 8 Molecular interactions of Harmine as native ligand with the MAOA receptor, showing an RMSD value of 0.8173 Å. The structure is depicted in gray before docking and in green post docking.

Table 3 Docking result of co-crystallized ligand, *Pandanus odorifer* compound against MAOA receptor.

No.	Compound	S Score (kcal/mol)
1.	Harmine (Native ligand)	−6.4067
2.	Fluoxetine	−7.5107
3.	2,3,4,5-Tetra-O-acetyl-d-gluconic acid	−7.3871
4.	N,N-dimethyl-6-{[(1-methyl-1H-tetrazol-5-yl)thio]methyl}-1,3,5-triazine-2,4-diamine	−7.335
5.	Glutarylcarnitine	−7.4017
6.	Methyl 5-oxopyrrolidine-2-carboxylate	−5.0828
7.	Domoate(2-)	−7.5234
8.	2,5-Dimethoxy-4-ethoxyamphetamine	−7.0972
9.	Kaempferol-3-O-rutinoside	−7.4814
10.	Apigenin-7-apioglucoside (Apiin)	−8.9045
11.	Genistin	−9.7436
12.	Thermopsoside (Chrysoeriol 7-O-glucoside)	−8.9292
13.	1,2,3,4-Tetrahydronaphthalene	−5.1383
14.	Hexosylsphingosine	−9.5296
15.	(3S)-4-[(2S)-2-[2-(1-carbamimidoylpiperidin-4-yl)oxyethyl]piperidin-1-yl]-3-[cyclohept-4-en-1-yl(methyl)amino]-4-oxobutanoic acid	−9.6649
16.	2-tert-Butyl-4-methoxyphenol	−5.7954
17.	D-Sphingosine	−9.079
18.	Benzylcarbonyl-Lys-Dab-Arg-NH2	−10.7455
19.	(2R,4S,5S,7S)-5-amino-N-(2-carbamoylethyl)-4-hydroxy-7-{[4-methoxy-3-(3-methoxypropoxy)phenyl]methyl}-2,8-dimethylnonanamide	−9.1419
20.	(3R)-N-[(1S,4S)-1-cyclohexyl-4-[(5R,8S)-8-[(3R)-6-cyclopropyl-4-hydroxy-5-oxo-3-propylhexanoyl]-10,10-dimethyl-7-azadispiro[3.0.45.14]decane-7-carbonyl]-5,5-dimethyl-2-oxohexyl]-1-ethylpiperidine-3-carboxamide	13.9
21.	N-[1-amino-6-[[2-[3-[4-[3-(3-tert-butyl-2,5-dioxopyrrolidin-1-yl)propanoylamino]-2-methylbutan-2-yl]oxy-2,2-dimethylpropoxy]acetyl]amino]-1-oxohexan-2-yl]dodecanamide	−5.6535

The low RMSD value validates the reliability of our molecular docking protocol, indicating its potential to accurately predict the inhibitory activity of compounds from *Pandanus odorifer* against the MAOA target for antidepressant activity. The molecular docking analysis demonstrated that Benzylcarbonyl-Lys-Dab-Arg-NH2 exhibited a particularly potent binding affinity to the MAOA target, with a binding energy of −10.7455 kcal/mol. This binding energy surpassed that of the native ligand Harmine as well as the standard antidepressant drug fluoxetine. The superior binding energy of Benzylcarbonyl-Lys-Dab-Arg-NH2 suggests it may have a higher affinity for MAOA and, consequently, a potentially greater anti-depressive activity. Moreover, the molecular interactions between the ligands and the active site of the target protein reveal intricate binding mechanisms that contribute to their potential therapeutic effects. **Figure 8** illustrates the interaction between hermaine and the protein's active site, where the ligand is surrounded by various amino acid residues forming the binding pocket. The primary interaction observed is a hydrogen bond between the -OH group of hermaine and the Cys323 residue, depicted by a green dashed line. The binding site is predominantly composed of hydrophobic residues such as Ile180, Ile207, Ile325, Ile335, Phe208, Phe352, Leu97, Leu337, Val210 and Ala111, which contribute to hydrophobic interactions. Polar residues like Tyr407, Tyr444, Asn181 and Thr336 are also present, potentially forming electrostatic interactions. In contrast, fluoxetine's structure consists of 2 benzene rings connected by an oxygen bridge, with 1 ring bearing a trifluoromethyl (CF3) substituent and the other end possessing a tertiary amino group.

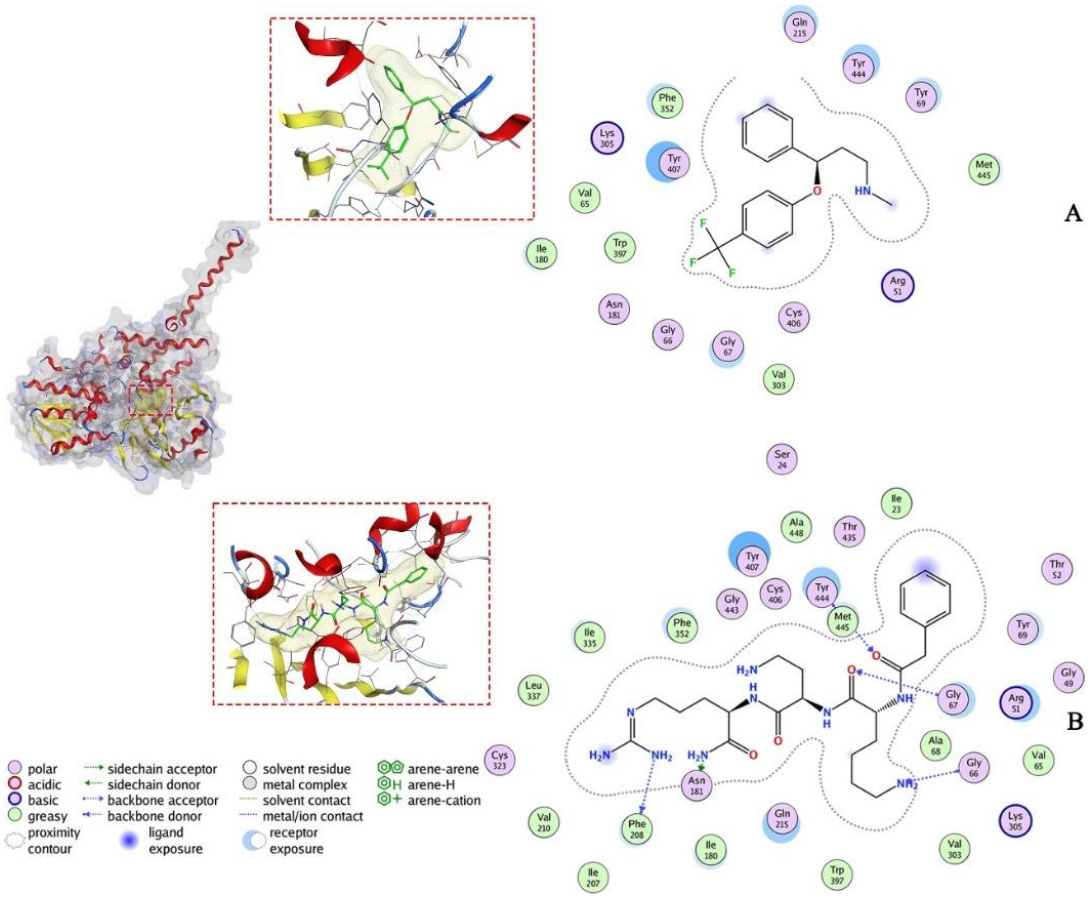


Figure 9 Molecular interactions of fluoxetine (A) and benzylcarbonyl-Lys-Dab-Arg-NH2 (B) from *Pandanus odorifer* with the MAOA receptor.

The benzylcarbonyl-Lys-Dab-Arg-NH2, which has the best binding energy, exhibits a more complex structure. It consists of a benzyl carbonyl group at the N-terminal end, followed by lysine (Lys), aminobutyric acid (Dab), and arginine (Arg) residues, with an amide group at the C-terminal end. As shown in **Figure 9(A)**,

the main interaction observed is a hydrogen bond between fluoxetine's amino group and the Gly67 residue, indicated by a blue dashed line. The binding site is similarly dominated by hydrophobic residues such as Val65, Val303, Ile180, Trp397, Phe352 and Met445, contributing to hydrophobic interactions. Polar residues, including Tyr69, Tyr407, Tyr444, Asn181, Gln215 and Cys406, are also present, potentially forming electrostatic interactions. Basic residues Lys305 and Arg51 are observed in the vicinity of the ligand. The Benzylcarbonyl-Lys-Dab-Arg-NH2, which has the best binding energy, exhibits a more complex structure. It consists of a benzyl carbonyl group at the N-terminal end, followed by lysine (Lys), aminobutyric acid (Dab), and arginine (Arg) residues, with an amide group at the C-terminal end. The primary interaction observed is a hydrogen bond between the C-terminal amide group of the ligand and the Gly67 residue, depicted by a blue dashed line in **Figure 9(B)**. The binding site is characterized by a mix of hydrophobic residues (Ile23, Ile180, Ile207, Ile335, Phe208, Phe352, Leu337, Val210, Val303, Ala68, Ala111 and Ala448) and polar residues (Tyr69, Tyr407, Tyr444, Asn181, Gln215, Thr52, Thr336, Thr435 and Gly443). Charged residues such as Lys305 and Arg51 are also present, potentially contributing to ionic interactions. Additionally, Cys323 and Cys406 are also observed near the ligand, possibly involved in sulfur-π interactions or hydrogen bonding. Based on the molecular interaction results, the ligand Benzylcarbonyl-Lys-Dab-Arg-NH2 interacts mainly with the residues of the MAO-A active site. This interaction enhances the specificity and affinity of the ligand-enzyme binding, effectively inhibiting the enzyme's catalytic region [50,51].

Molecular dynamics

Since molecular docking is a computational method widely used for predicting ligand-protein interactions, including binding affinities and binding orientations. However, it has inherent limitations that can hinder its predictive performance. One major drawback of docking is its treatment of the receptor as a rigid state, which fails to capture the dynamic nature of proteins in physiological conditions [52]. In reality, proteins are flexible molecules that can undergo conformational changes upon ligand binding, a crucial aspect that is often neglected in docking simulations. Moreover, the scoring functions used in docking are based on approximations and may not accurately account for key thermodynamic factors contributing to the binding energy, such as entropic changes and solvation effect. To overcome the limitations, we combined it with molecular dynamics simulations. MD simulations make both the ligand and the protein in a flexible state, allowing the receptor binding site to adapt around the ligand [53]. This dynamic representation can simulate the time-dependent motions and conformational changes of biomolecules, providing valuable insights into the binding mechanism dynamically [53,54]. The RMSD plot post 100 ns simulation times revealed distinct stability profiles for each ligand (**Figure 10**).

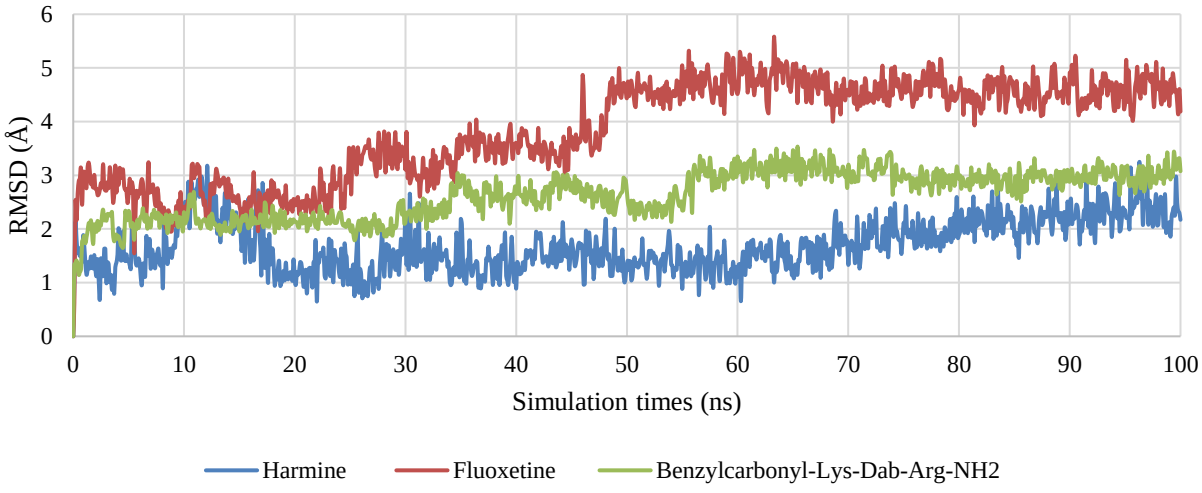


Figure 10 Root Mean Square Deviation (RMSD) over 100 ns of molecular dynamics simulations for native, Fluoxetine, and Benzylcarbonyl-Lys-Dab-Arg-NH2 complexes with the MAOA receptor.

Harmine demonstrated the most favorable RMSD profile, with values predominantly ranging between 1 - 2 Å, indicating a highly stable binding mode. However, a slight increase to about 2.5 Å was observed after 70 ns. Benzylcarbonyl-Lys-Dab-Arg-NH2 exhibited moderate stability, with RMSD values initially around 2 Å, increasing to 2.5 - 3 Å after 30 ns, and stabilizing around 3 - 3.5 Å for the remainder of the simulation. Fluoxetine showed the highest RMSD values and most significant changes, starting around 2.5 - 3 Å, increasing to 3.5 - 4 Å between 20 - 40 ns, and then sharply rising to 4.5 - 5 Å after 50 ns. These results suggest that Harmine maintains the most consistent and low RMSD, indicating the most stable binding. Benzylcarbonyl-Lys-Dab-Arg-NH2 demonstrates intermediate stability, while Fluoxetine's higher and more variable RMSD values imply substantial conformational changes during binding, particularly after the 50 ns. Besides RMSD plot, the RMSF analysis provided crucial insights into the flexibility of specific residues in the MAOA active site (**Figure 11**).

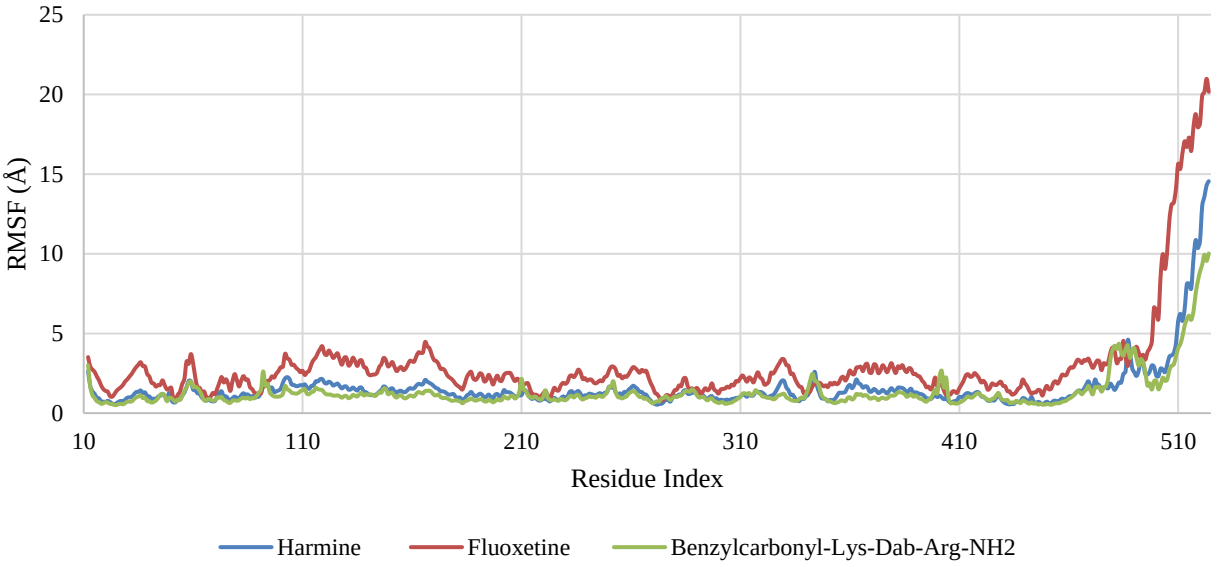


Figure 11 Root Mean Square Fluctuation (RMSF) over 100 ns of molecular dynamics simulations for native, Fluoxetine, and Benzylcarbonyl-Lys-Dab-Arg-NH2 complexes with the MAOA receptor.

Benzylcarbonyl-Lys-Dab-Arg-NH2 consistently demonstrated the lowest fluctuations across key residues, indicating more stable interactions. The RMSF values on several important residues were as follows: Ile180 (Harmine: 1.013 Å, Fluoxetine: 1.817 Å, Benzylcarbonyl-Lys-Dab-Arg-NH2: 0.812 Å), Ile207 (1.048, 2.011 and 0.916 Å), Phe208 (1.058, 2.162 and 1.03 Å), Cys323 (1.023, 1.989 and 0.951 Å), Ile335 (0.926, 2.142 and 0.766 Å), Phe352 (0.793, 1.789 and 0.677 Å), and Tyr407 (0.72, 1.367 and 0.649 Å). These results highlight the better affinity of Benzylcarbonyl-Lys-Dab-Arg-NH2 in maintaining stable interactions with crucial hydrophobic residues in the active site. The MM-GBSA further analysis validated these findings, providing binding free energy estimations that offer insights into the thermodynamics of the protein-ligand interactions. The binding free energies were −68.0669 kcal/mol for Benzylcarbonyl-Lys-Dab-Arg-NH2, −56.9483 kcal/mol for Fluoxetine, and −41.7675 kcal/mol for Harmine (**Figure 12**).

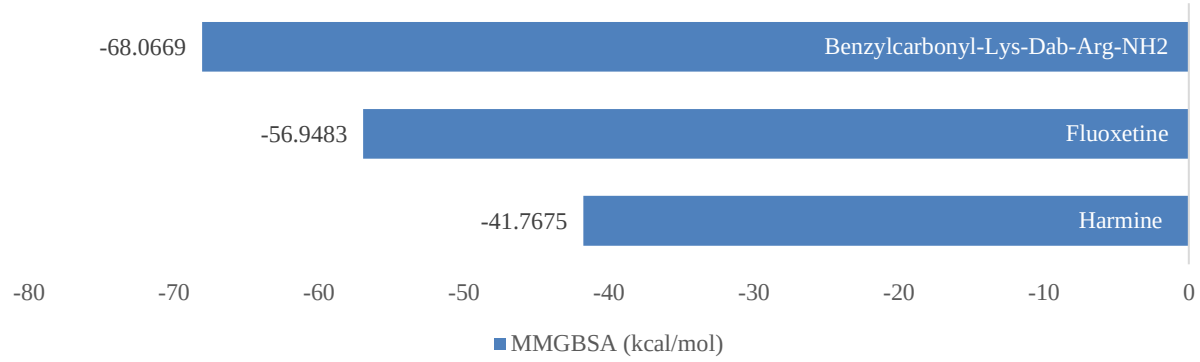


Figure 12 The binding energy post molecular dynamic simulations presented in (Molecular Mechanics Generalized Born Surface Area (MMGBSA) comparison for native, Fluoxetine, and Benzylcarbonyl-Lys-Dab-Arg-NH2 complexes with the MAOA receptor.

Conclusions

This study successfully identified 13 target genes, with monoamine oxidase A as the primary target in antidepressant mechanism. Molecular docking and dynamics simulations demonstrated that Benzylcarbonyl-Lys-Dab-Arg-NH2, a compound from *Pandanus odorifer*, exhibited superior binding affinity to MAOA compared to the native ligand Harmine and the standard antidepressant fluoxetine. It also maintained stable interactions within the MAOA active site, suggesting that *Pandanus odorifer* holds significant promise as a novel antidepressant agent. The findings provide a strong groundwork for further investigation into its efficacy and safety in clinical settings, potentially leading to the development of more effective and targeted treatments for depression.

Acknowledgements

The researchers expressed their gratitude to Ministry of Research and Technology for Higher Education (Kemendikbudristek), Indonesia who has funded this investigation with contract number 0036/SP2H/PT/LL7/2024; B/11/HIB-EX/PL/UHT.C7/VI/2024, so that it can run well and get results that can benefit the academic world.

References

[1] SC Parija. World suicide prevention day: Creating hope through action. *Pondicherry Journal of Nursing* 2022; **15(3)**, 50.

[2] Kementerian Kesehatan Republik Indonesia. *Topik kesehatan depresi* (*in Indonesian*). Kementerian Kesehatan Republik Indonesia, Jakarta, Indonesia, 2019.

[3] L Puspitasari. Ekstrak etanol daun pandan wangi (*Pandanus amaryllifolius* R.) 10 % menurunkan immobility time dan kadar kortisol tikus jantan galur wistar yang depresi (*in Indonesian*). *Intisari Sains Medis* 2017; **8(1)**, 24-30.

[4] FP Bymaster, W Zhang, PA Carter, J Shaw, E Chernet, L Phebus, DT Wong and KW Perry. Fluoxetine, but not other selective serotonin uptake inhibitors, increases norepinephrine and dopamine extracellular levels in prefrontal cortex. *Psychopharmacology* 2002; **160**, 353-361.

[5] Z Ungvari, S Tarantini, A Yabluchanskiy and A Csiszar. Potential adverse cardiovascular effects of treatment with fluoxetine and other selective serotonin reuptake inhibitors (SSRIs) in patients with geriatric depression: Implications for atherogenesis and cerebromicrovascular dysregulation. *Frontiers in Genetics* 2019; **10**, 455576.

[6] SP Rahma and D Suzana. Uji aktivitas antidepresan minyak atsiri daun kemangi (*Ocimum basilicum* L.) dengan metode open field test (OFT) (*in Indonesian*). *Jurnal Farmasi dan Farmakoinformatika* 2024; **2(1)**, 9-22.

[7] I Rochmadi and S Rohmah. Pemanfaatan buah pandan laut sebagai pangan olahan pada

masyarakat pesisir (*in Indonesian*). *Jurnal Riset Ekonomi Pembangunan* 2019; **4(2)**, 161-173.

[8] R Londonkar and A Kamble. Evaluation of free radical scavenging activity of *Pandanus odoratissimus*. *International Journal of Pharmacology* 2009; **5(6)**, 377-380.

[9] S Venkatesh, R Kusuma, V Sateesh, MB Reddy and R Mullangi. Antidiabetic activity of *Pandanus odoratissimus* root extract. *Indian Journal of Pharmaceutical Education and Research* 2012; **46(4)**, 340-345.

[10] TT Jong and SW Chau. Antioxidative activities of constituents isolated from *Pandanus odoratissimus*. *Phytochemistry* 1998; **49(7)**, 2145-2148.

[11] S Raju, NV Subbaiah, KS Reddy, A Das and KB Murugan. Potential of *Pandanus odoratissimus* as a CNS depressant in Swiss albino mice. *Brazilian Journal of Pharmaceutical Sciences* 2011; **47**, 629-634.

[12] RL Ramesh Londonkar, AK Abhaykumar Kamble and VC Reddy. Anti-inflammatory activity of *Pandanus odoratissimus* extract. *International Journal of Pharmacology* 2010; **6(3)**, 311-314.

[13] A El-Shaibany, ALH Molham, S Al-Massarani, Ali Al-Ajami and A Al-Adhl. Hepatoprotective effect of *Pandanus odoratissimus* l inflorescence extracts in acetaminophen-treated guinea pigs. *Tropical Journal of Pharmaceutical Research* 2016; **15(2)**, 259-267.

[14] G Mishra, RL Khosa, P Singh and KK Jha. Hepatoprotective potential of ethanolic extract of *Pandanus odoratissimus* root against paracetamol-induced hepatotoxicity in rats. *Journal of Pharmacy and Bioallied Sciences* 2015; **7(1)**, 45-48.

[15] R Bahramsoltani, MH Farzaei, MS Farahani and R Rahimi. Phytochemical constituents as future antidepressants: A comprehensive review. *Reviews in the Neurosciences* 2015; **26(6)**, 699-719.

[16] JJ Fortunato, GZ Réus, TR Kirsch, RB Stringari, GR Fries, F Kapczinski, JE Hallak, AW Zuardi, JA Crippa and J Quevedo. Effects of β-carboline harmine on behavioral and physiological parameters observed in the chronic mild stress model: Further evidence of antidepressant properties. *Brain Research Bulletin* 2010; **81(4-5)**, 491-496.

[17] QQ Mao, YF Xian, SP Ip and CT Che. Involvement of serotonergic system in the antidepressant-like effect of piperine. *Progress in Neuro-Psychopharmacology and Biological Psychiatry* 2011; **35(4)**, 1144.

[18] SS Mardolkar and MP Joshi. Pharmacological evaluation of *Pandanus odorifer* (Forssk.) Kuntze adminstered orally and by inhalation route in rats. *International Journal of Current Science* 2022; **12(4)**, 311-318.

[19] SV Sathasivampillai, V Shanmugalingam, PR Sebastian. Pharmacological activities of extracts and isolated phytochemical constituents of *Pandanus odorifer* (Forssk.) Kuntze. *Gümüşhane Üniversitesi Sağlık Bilimleri Dergisi*. 2021, **10(3)**, 574-80.

[20] T Son. Secondary metabolites of genus Pandanus: an aspect of phytochemistry. *Mini-Reviews in Organic Chemistry* 2019, **16(7)**, 689-710.

[21] C Jia, X Pan, B Wang, P Wang, Y Wang and R Chen. Mechanism prediction of *Astragalus membranaceus* against cisplatin-induced kidney damage by network pharmacology and molecular docking. *Evidence-Based Complementary and Alternative Medicine* 2021; **2021(1)**, 9516726.

[22] P Zhou, R Zhou, Y Min, LP An, F Wang and QY Du. Network pharmacology and molecular docking analysis on pharmacological mechanisms of *Astragalus membranaceus* in the treatment of gastric ulcer. *Evidence-Based Complementary and Alternative Medicine* 2022; **2022(1)**, 9007396.

[23] F Li, J Duan, M Zhao, S Huang, F Mu, J Su, K Liu, Y Pan, X Lu, J Li, P Wei, M Xi and A Wen. A network pharmacology approach to reveal the protective mechanism of *Salvia miltiorrhiza-Dalbergia odorifera* coupled-herbs on coronary heart disease. *Scientific Reports* 2019; **9(1)**, 19343.

[24] EY Chen, CM Tan, Y Kou, Q Duan, Z Wang, GV Meirelles, NR Clark and A Ma'ayan. Enrichr: Interactive and collaborative HTML5 gene list enrichment analysis tool. *BMC Bioinformatics* 2013; **14(1)**, 128.

[25] Y Liao, J Wang, EJ Jaehnig, Z Shi and B Zhang. WebGestalt 2019: Gene set analysis toolkit with

revamped UIs and APIs. *Nucleic Acids Research* 2019; **47(W1)**, W199-W205.

[26] O Mutlu, G Ulak, IK Celikyurt, FY Akar and F Erden. *New approaches for the therapy of treatment refractory depression*. *In*: G Rossi (Ed.). Psychology-selected papers. IntechOpen, London, 2012.

[27] JR Leheste, C Curcio, L Baldinger, S Sarwar, SM Zakhary, BH Hallas, JM Horowitz and G Torres. Glutamate-based drugs for the treatment of clinical depression. *Bentham Science Publishers* 2008; **8(3)**, 170-176.

[28] R Kaddurah-Daouk, P Yuan, SH Boyle, W Matson, Z Wang, ZB Zeng, H Zhu, GG Dougherty, J Yao, G Chen, X Guitart, PJ Carlson, A Neumeister, CA Zarate, R Krishnan, HK Manji and WC Drevets. Cerebrospinal fluid metabolome in mood disorders-remission state has a unique metabolic profile. *Nature Portfolio* 2012; **2(1)**, 667.

[29] DM Diniz, K Bosch, F Calabrese, P Brivio, MA Riva, J Grandjean and JR Homberg. BDNF overexpression in the prelimbic cortex does not reduce anxiety- and depression-like behavior in serotonin knockout rats. *Cold Spring Harbor Laboratory* 2020. https://doi.org/10.1101/2020.07.01.180604

[30] A Kaltenboeck and C Harmer. The neuroscience of depressive disorders: A brief review of the past and some considerations about the future. *Brain and Neuroscience Advances* 2018; **2**, 1-6.

[31] L Chiuccariello, S Houle, L Miler, RG Cooke, PM Rusjan, G Rajkowska, RD Levitan, SJ Kish, NJ Kolla, X Ou, AA Wilson and JH Meyer. Elevated monoamine oxidase a binding during major depressive episodes is associated with greater severity and reversed neurovegetative symptoms. *Neuropsychopharmacology* 2013; **39(4)**, 973-980.

[32] G Hasler. Pathophysiology of depression: Do we have any solid evidence of interest to clinicians? *World Psychiatry* 2010; **9(3)**, 155-161.

[33] S Chaki, Y Ago, A Palucha-Paniewiera, F Matrisciano and A Pilc. mGlu2/3 and mGlu5 receptors: Potential targets for novel antidepressants. *Neuropharmacology* 2013; **66**, 40-52.

[34] J Cookson. Side-effects of antidepressants. *The British Journal of Psychiatry* 1993; **163(S20)**, 20-24.

[35] SH Lin, LT Lee and YK Yang. Serotonin and mental disorders: A concise review on molecular neuroimaging evidence. *Clinical Psychopharmacology and Neuroscience* 2014; **12(3)**, 196-202.

[36] R Marotta, MC Risoleo, G Messina, L Parisi, M Carotenuto, L Vetri and M Roccella. The neurochemistry of autism. *Brain Sciences* 2020; **10(3)**, 163.

[37] CL Muller, AMJ Anacker and J Veenstra-VanderWeele. The serotonin system in autism spectrum disorder: From biomarker to animal models. *Neuroscience* 2016; **321**, 24-41.

[38] J Sinzig and G Lehmkuhl. What do we know about the serotonergic genetic heterogeneity in attention-deficit/hyperactivity and autistic disorders? *Psychopathology* 2007; **40(5)**, 329-337.

[39] X Yang, G Wang, X Gong, C Huang, Q Mao, L Zeng, P Zheng, Y Qin, F Ye, B Lian, C Zhou, H Wang, W Zhou and P Xie. Effects of chronic stress on intestinal amino acid pathways. *Physiology & Behavior* 2019; **204**, 199-209.

[40] NNJ Rommelse, B Franke, HM Geurts, CA Hartman and JK Buitelaar. Shared heritability of attention-deficit/hyperactivity disorder and autism spectrum disorder. *European Child & Adolescent Psychiatry* 2010; **19(3)**, 281-295.

[41] T Fan, Y Hu, J Xin, M Zhao and J Wang. Analyzing the genes and pathways related to major depressive disorder via a systems biology approach. *Brain and Behavior* 2020; **10(2)**, e01502.

[42] CB Nemeroff and MJ Owens. The role of serotonin in the pathophysiology of depression: As important as ever. *American Association for Clinical Chemistry* 2009; **55(8)**, 1578-1579.

[43] E Żmudzka, K Sałaciak, J Sapa and K Pytka. Serotonin receptors in depression and anxiety: Insights from animal studies. *Life Sciences* 2018; **210**, 106-124.

[44] P Belujon and AA Grace. Dopamine system dysregulation in major depressive disorders. *International Journal of*

Neuropsychopharmacology 2017; **20(12)**,1036-1046.

[45] Y Higuchi, T Soga and IS Parhar. Regulatory pathways of monoamine oxidase a during social stress. *Frontiers in Neuroscience* 2017; **11**, 604.

[46] JH Meyer, N Ginovart, A Boovariwala, S Sagrati, D Hussey, A Garcia, T Young, N Praschak-Rieder, AA Wilson and S Houle. Elevated monoamine oxidase a levels in the brain: An explanation for the monoamine imbalance of major depression. *Archives of General Psychiatry* 2006; **63(11)**, 1209.

[47] JPM Finberg and JM Rabey. Inhibitors of MAO-A and MAO-B in psychiatry and neurology. *Frontiers in Pharmacology* 2016; **7**, 340.

[48] J Ekowati, BA Tejo, S Maulana, WA Kusuma, R Fatriani, R Fatriani, NS Rmadhanti, N Norhayati, KA Nofianti, MI Sulistyowaty, MS Zubair, T Yamauchi and IS Hamid. Potential utilization of phenolic acid compounds as anti-inflammatory agents through TNF-α convertase inhibition mechanisms: A network pharmacology, docking, and molecular dynamics approach. *ACS Omega* 2023; **8(49)**, 46851-46868.

[49] KE Hevener, W Zhao, DM Ball, K Babaoglu, J Qi, SW White and RE Lee. Validation of molecular docking programs for virtual screening against dihydropteroate synthase. *Journal of Chemical Information and Modeling* 2009; **49(2)**, 444-460.

[50] LD Colibus, M Li, C Binda, A Lustig, DE Edmondson and A Mattevi. Three-dimensional structure of human monoamine oxidase A (MAO A): Relation to the structures of rat MAO A and human MAO B. *National Academy of Sciences* 2005; **102(36)**, 12684-12689.

[51] RM Geha, K Chen, J Wouters, F Ooms and JC Shih. Analysis of conserved active site residues in monoamine oxidase A and B and their three-dimensional molecular modeling. *Journal of Biological Chemistry* 2002; **277(19)**, 17209-17216.

[52] IA Vakser. Challenges in protein docking. *Current Opinion in Structural Biology* 2020; **64**, 160-165.

[53] J Aghajani, P Farnia, P Farnia, J Ghanavi and AA Velayati. Molecular dynamic simulations and molecular docking as a potential way for designed new inhibitor drug without resistance. *Tanaffos* 2022; **21(1)**, 1-14.

[54] V Salmaso and S Moro. Bridging molecular docking to molecular dynamics in exploring ligand-protein recognition process: An overview. *Frontiers in Pharmacology* 2018; **9**, 923.