Current Trends in Pharmacology and Clinical Trials
ISSN: 2642-0848

Academic Strive
Researcher's perception is our reality

Research Article *Volume 8 Issue 1*

In Silico Screening of Commercial Terpenoids as Potential Antidepressant Agents

Thulasingam M[1]*, Chakraborty A[2], Mariam A[2], Balaji S[2] and Dawod Hasaballah BA[2]

[1]Department of Pharmacology, Chettinad School of Pharmaceutical Sciences, Chettinad Hospital and Research Institute, Chettinad Academy of Research and Education, India

[2]Department of Pharmacology, College of Pharmaceutical Sciences, Dayananda Sagar University, Deverakeggahalli, India

***Corresponding author:** T Muthukumaran M.Pharm., M.Sc., (Ph.D), Assistant Professor, Department of Pharmacology, Chettinad School of Pharmaceutical Sciences, Chettinad Hospital and Research Institute, Chettinad Academy of Research and Education, Kelambakkam-603103, Tamilnadu, India, Email: muthukumarant48@gmail.com

Received Date: January 23, 2025; **Published Date:** January 31, 2025

Abstract

Depression is recognized as one of the most prevalent global health issues, ranking second only to aging in its impact on the population. Terpenoids, a class of naturally occurring compounds, have shown promise in treating depression, particularly through their inhibition of two key enzymes: Monoamine Oxidase (MAO) and Indoleamine 2,3-Dioxygenase (IDO), both of which play significant roles in the condition. This study aimed to evaluate terpenoids as potential antidepressants by assessing their molecular properties and conducting docking studies based on ADMET (Absorption, Distribution, Metabolism, Excretion, and Toxicity) properties. 56 terpenoids were analyzed using Molinspiration for their molecular characteristics and bioactivity. Of these, 48 compounds complied with Lipinski's Rule of Five, suggesting they were suitable for further investigation. The compounds were subsequently modeled in Chemsketch and their ADME properties were evaluated using PreADMET, with special attention paid to their blood-brain barrier (BBB) permeability and toxicity profiles. From the initial set, 25 terpenoids demonstrated promising antidepressant potential, with no carcinogenic activity observed, indicating their safety for therapeutic use. These findings suggest that terpenoids are effective candidates for the development of new antidepressant therapies. The study highlights the potential for commercially available terpenoids to be explored further as novel treatments for depression, offering new avenues for drug development in this critical area of mental health.

Keywords: Depression; Molecular Docking; In Silico; Admet; Terpenoids; Monoamine Oxidase; Indoleamine 2,3-Dioxygenase

Abbreviations

RCSB: Research Collaborative for Structural Bioinformatics; MAO: Monoamine Oxidase; BBB: Blood-Brain Barrier; KYN: Kynurenine; HK: Hydroxykynurenine.

Introduction

Depression

Depression is defined as a common mental disorder characterised by depressed mood, loss of interest, feelings

of guilt and low self-worth, disturbed sleep or appetite, low energy and poor concentration, according to WHO [1]. The second strongest factor causing disability and health issues in the world is known to be depression. It is also known to be the leading cause for suicide [2].

Many studies have concluded that depression is linked with increased risk of cardiovascular disease and heart failure. In addition, depression is associated with many other chronic illnesses. Approximately one in every 20 individuals being affected, major depressive disorder shows high prevalence. In low-income and middle-income countries, more than 85% affected do are deprived of treatment for mental disorders. Hence, many preventive and treatment strategies are required to overcome depression [3,4]. There are many known antidepressants such as Tricyclic antidepressants, Selective serotonin reuptake inhibitors and Serotonin/ norepinephrine reuptake inhibitors, but their inability to produce complete recovery, in addition to side effects, lack to access and high cost has urged scientists and researchers to find alternatives that are natural and easily available with less side effects [5,6].

Target enzymes in this study

Mono Amine Oxidase: The first contemporary psychopharmacological drugs to be demonstrated to be effective in reducing the symptoms of clinical depression were monoamine oxidase inhibitors (MAOIs), and this finding resulted in notable modifications in the management of mood disorders [7]. Iproniazid's beneficial effects on mood were initially noted in tuberculosis patients, and around the same time, other researchers discovered that iproniazid inhibited MAO. Iproniazid, dubbed a "psychic energizer" and authorized as an antidepressant, was later reported to boost mood in people with clinical depression [8]. These medical breakthroughs sparked the creation of numerous other monoamine oxidase inhibitors and the study of the "monoamine theory of depression."

Indoleamine 2,3 Dioxygenase

Tryptophan (TRP), an important amino acid, is a precursor in the manufacture of the neurotransmitter serotonin [9]. A pathophysiological explanation for MDD has been hypothesized as a reduction in the serotonin route, despite the fact that the majority of the readily accessible TRP is metabolized by the kynurenine (KYN) pathway. The enzyme indoleamine-2,3-dioxygenase 1 (IDO1) is one of the two. Tryptophan 2,3-dioxygenase (TDO) utilizes TRP via the KYN route and is the other enzyme [10]. A few pro-provocative cytokines, such as TNF-, IL-1, and IFN-, as well as lipopolysaccharide (LPS), activate IDO1. Inflammation accelerates the KYN pathway by increasing levels of neuroactive metabolites including 3-hydroxykynurenine (HK) and 3-hydroxy anthranilic acid (HAA) [11].

Materials and Methods

Selection of Phytoconstituents: Based on literature survey, 56 terpenoids from medicinal plants were selected and reported to have Anti-depressant activity.

Molecular Properties and Bioactivity Screening of Selected Drugs

Molecular Properties of 56 numbers of Phytoconstituents were calculated using Molinspiration Chemoinformatics server to make sure that the compounds hold appropriate molecular properties to be a potential drug candidate. The evaluation of the compounds' molecular characteristics and druglikeness is based on "Lipinski's Rule of Five," which highlights molecular characteristics important for a drug's pharmacokinetics in the human body.

After filtering compounds based of violations, the selected compounds were further subjected for bioactivity screening using Molinspiration Chemoinformatics server [12,13].

ADMET Screening of Drugs

The selected drugs with no violations were further screened for ADME and toxicity respectively. Compounds that crossed the blood brain barrier were subjected for toxicity studies. The server used for this is Pre-ADMET online software tool [14,15].

Selection of Drug Target

Usually, Target of the drugs is macromolecule which plays an important role in the occurrence of disease. Selection of drug target is made after thoroughly understanding the role of it in the pathological condition undertaken for the study [16,17]. In our work, Mono amine oxidase and Indole amine 2,3 Dioxygenase were selected as the target proteins.

Molecular Docking

AutoDockTools software, which does virtual screening using P.M.V open-source software, was used to conduct docking studies. In which the docking score is determined by how well a ligand binds to a protein [18,19]. The potency of the ligand is shown by the target's increased negative binding energy. The best feasible structural position for a molecule is the one with the best scores and the least amount of energy [20]. By taking into account the hydrogen bond interaction and hydrophobic interactions that were noticed between the amino acid residues and the functional group of the small molecules, the binding affinity between the ligand and protein was investigated [21,22].

Results

Sl.no	Terpenoids	Log P	Molecular weight	noN	nOHNH	nviolations
1	Artemisininin	3.32	282.336	5	0	0
2	Cryptotanshinone	3.83	296.366	3	0	0
3	Sclareol	4.93	308.506	2	2	0
4	Bisabolol	4.68	222.372	1	1	0
5	Maaliol	4.08	222.372	1	1	0
6	Linalyl acetate	3.92	196.29	2	0	0

Table 1: Calculation Of Molecular Properties.

Sl no	Terpenoid	GPCR ligand	Ion channel inhibitor	Kinase inhibitor	Nuclear receptor ligand	Protease inhibitor	Enzyme inhibitor
1	Linalyl acetate	-0.48	-0.43	-1.5	-0.62	-0.85	-0.34
2	Bisabolol	-0.06	0.26	-0.78	0.37	0.17	0.19
3	Sclareol	0.14	0.3	-0.37	0.74	-0.18	0.43
4	Artemisinin	-0.17	-0.31	-0.65	0	-0.19	0.39
5	Cryptotanshinone	0.24	0.36	-0.07	0.31	-0.14	0.46
6	Maaliol	-0.36	-0.2	-0.67	-0.08	-0.33	0.02

Table 2: Bioactivity.

Sl no	Terpenoids	BBB	HIA	MDCK	Skin Permeability	CaCO2
1	Linayl acetate	1.05	100	189.29	-0.841	25.25
2	Artemisinin	1.49	100	204.401	-1.86	22.81
3	Cryptotanshinone	1.49	100	204.401	-1.86	22.28
4	Sclareol	8.28	92.37	144.509	0.988	46.8
5	Maaliol	7.42	100	221.29	-1.33	54.39
6	Bisabalool	10.55	100	103.55	-0.179	51.106

Table 3: Admet Properties.

Sl.no	Name	Ames test	Carcino Mouse	Carcino rat	hERG Inhibition
1	Bisabolol	NMU	-ve	-ve	LR
2	Linyl acetate	MU	+ve	+ve	LR
3	Sclareol	MU	-ve	+ve	LR
4	Artemisinin	MU	-ve	+ve	LR
5	Cryptotinsinone	MU	-ve	+ve	MR
6	Maaliol	NMU	-ve	+ve	LR

MU- MUTAGEN
NMU- NON MUTAGEN
+ve- POSITIVE
-ve- NEGATIVE
LR- LOW RISK
MR- MEDIUM RISK
Table 4: Toxicity Prediction.

Sl.no	Compounds	Binding Energy (kcal/mol)	Inhibition Constant (nm/um)	Intermolecular Energy (kcal/mol)	Internal Energy (kcal/mol)
1	Alpha phellandrene	-5.49	94.3	-5.79	-0.2
2	Alpha pinene	-5.55	84.88	-5.55	0
3	Beta pinene	-5.66	71.39	-5.66	0
4	1,8-cineole	-5.59	79.63	-5.59	0
5	Citronellol	-4.35	650.75	-6.14	-0.32
6	Linalyl acetate	-5.57	83	-7.36	-0.66
7	3-carene	-5.5	93.15	-5.5	0
8	Borneol	-5.65	72.54	-5.95	0.04
9	Sclareol	-9.27	159.42	-11.06	-1.33
10	Maaliol	-7.83	1.83	-8.13	0.03
11	Artemisininin	-8.43	667.1	-8.43	0
12	Cryptotanshinone	-9.06	230.01	-9.06	0
13	Tanshinone IIA	-9.79	66.26	-9.79	0
14	Geosmin	-6.59	14.7	-6.89	0.09
15	Isopulegol	-5.79	57.31	-6.38	-0.2
16	Myrcene	-4.79	309.79	-5.98	-0.28
17	Longifolene	-5.3	129.66	-5.3	0
18	Thymol	-4.57	446.04	-5.17	-0.18
19	Rose oxide	-4.81	299.11	-5.11	-0.19
20	Pipertone	-4.29	764.79	-4.55	-0.12
21	Menthol	-5.83	53.25	-6.43	-0.11
22	Terpeniol	-5.42	105.95	-6.62	-0.16
23	Linalool	-5.21	151.02	-5.7	-0.27
24	D limonene	-5.47	97.41	-5.77	-0.14
25	Bisabolol	-8.14	1.07	-9.64	-0.54

Table 5: Docked Compounds Against The Enzyme Monoamine Oxidase (Pdb Id: 1o5w).

Sl.no	Compounds	Binding Energy (kcal/mol)	Inhibition Constant (nm/um)	Intermolecular Energy (kcal/mol)	Internal Energy (kcal/mol)
1	Alpha phellandrene	-7.02	7.1	-7.32	-0.2
2	Alpha pinene	-6.73	11.57	-6.73	0
3	Beta pinene	-6.97	7.77	-6.97	0
4	1,8-cineole	-6.89	8.87	-6.89	0
5	Citronellol	-6.68	12.8	-8.46	-0.34
6	Linalyl acetate	-7.56	2.88	-9.35	-0.71
7	3-carene	-6.85	9.54	-6.85	0
8	Borneol	-6.37	21.46	-6.67	0
9	Sclareol	-7.43	3.56	-9.22	-0.55
10	Maaliol	-7.97	1.44	-8.27	0.03

11	Artemisinin	-10.58	17.67	-10.58	0
12	Cryptotanshinone	-6.95	7.99	-6.95	0
13	Tanshinone IIA	-6.43	19.37	-6.43	0
14	Geosmin	-7.38	3.9	-7.68	0.03
15	Isopulegol	-7.06	6.74	-7.65	-0.15
16	Myrcene	-6.27	25.19	-7.47	-0.24
17	Longifolene	-7.39	3.83	-7.39	0
18	Thymol	-7.18	5.5	-7.77	-0.18
19	Rose oxide	-7.4	3.79	-7.69	-0.3
20	Pipertone	-4.25	764.79	-4.55	-0.12
21	Menthol	-5.83	53.25	-6.43	-0.11
22	Terpeniol	-6.73	11.66	-7.92	-0.16
23	Linalool	-5.21	151.02	-6.7	-0.27
24	D limonene	-5.47	97.41	-5.77	-0.14
25	Bisabolol	-9.16	193.97	-10.65	-0.84

Table 5.1: Docked Compounds Against The Enzyme Indoleamine 2,3 Dioxygenase (PDB ID: 6E35).

Compounds	Binding Energy (kcal/mol)	Inhibition Constant (nm,um)	Inter-Molecular Energy (kcal/mol)	Internal Energy (kcal/mol)
Scalerol	-9.27	159.42	-11.06	-1.33
Cryptotanshinone	-9.06	230.01	-9.06	0
Artemisinin	-8.43	667.1	-8.43	0
Bisabolol	-8.14	1.07	-9.64	-0.54
Maaliol	-7.83	1.83	-8.13	0.03
Moclobemide	-7.82	1.84	-9.02	-0.43

Table 6: Terpenoids And Standard Against Monoamine Oxidase (Pdb Id: 1o5w).

Compounds	Binding Interaction with Amino Acid Residue Against Monoamine
Scalerol	MET350, LED337, PHE352, ILE207, TYR444, FHE206, PHE208
Cryptotanshinone	LEU337, ILE335, THR338, ILE180, GLN215, PHE208
Artemisinin	MET350, ILE335, PHE352, ILE207, PHE208
Bisabolol	ALA68 , TYR69 , GLY67 , GLY66, TRP397, LYS305, PHE352, VAL303, GLY443 TYR407 , CYS406, TYR444
Maaliol	MET350, LED337, ILE335, PHE352, ILE180, GLN215, VAL210, PHE208
Moclobemide	ILE23, MET445, ARG51, THR52, GLY67, ALA68, TYR69, TYR407, TYR444, GLY443

Table 6.1: Binding Interaction With Amino Acid Residue Of Terpenoids And Standard With Monoamine Oxidase (Pdb Id: 1o5w).

Compounds	Binding Energy (kcal/mol)	Inhibition Constant (nm/um)	Inter-Molecular Energy (kcal/mol)	Internal Energy (kcal/mol)
Artemisinin	-10.58	17.67	-10.58	0
Bisabolol	-9.16	193.79	-10.65	-0.84
Maaliol	-7.97	1.44	-8.27	0.03
Linalyl acetate	-7.56	2.88	-9.35	-0.71
Sclareol	-7.43	3.56	-9.22	-0.55
Moclobemide	-8.06	1.23	-9.26	0.61

Table 7: Terpenoids And Standard Against Indoleamine 2,3-Dioxygenase. (PDB ID: 6E35).

Compounds	Binding Interaction with Amino Acid Residue Against Indoleamine
Artemisinin	SER187, SER263, HEM501 , PHE163, PHE226 , CYS129 , TYR126 , ALA264 GLY262, THR379, LEU234
Bisabolol	GLY262, PHE163, SER263 , ALA264 , HEM501 , TYR126 , CYS129 , VAL130, SER167
Maaliol	SER167, PHE163 , CYS129 , HEM501 , TYR126 , ALA284, SER263 GLY262, LEU234, THR379
Linalyl acetate	THR379 , , PHE226, HEM501 , GLY262, LEU234, PHE163 SER263 , ALA264 TYR126 CYS129, VAL130,
Sclareol	PRO300, HIS303, ARG77, LEU131, ALA132, ASN27, PRO28, LYS74
Moclobemide	THR379, SER263, ALA264, TYR126, SER167, HEM501, VAL130 CYS129, ARG331, PHE226, PHE164, PHE163

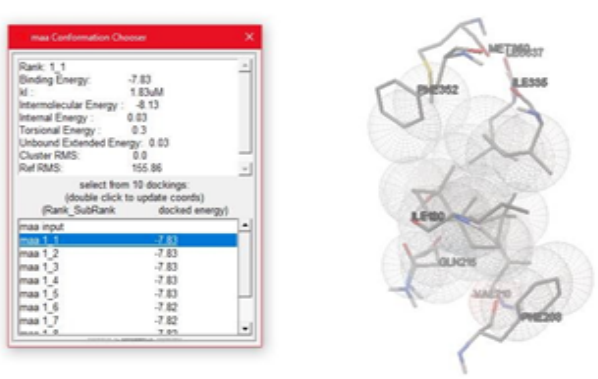
Table 7.1: Binding Interaction with Amino Acid Residue of Terpenoids and Standard with Indoleamine 2,3-Dioxygenase (Pdb Id: 6e35).

Discussion

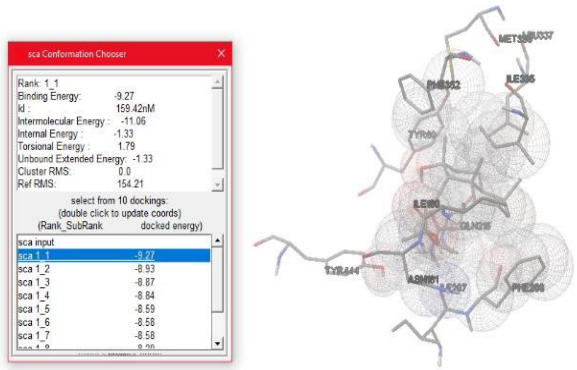
Depression is a psychological condition of low state of mind and repugnance for movement. Terpenoids have shown to be effective in the treatment of Depression, particularly, shows inhibition towards Mono amine oxidase and Indole amine 2,3 dioxygenase enzyme which are two main enzyme targets in depression. In this study, several Terpenoids obtained from medicinal plants were explored for their potential treatment of Depression.

The terpenoids were first studied for their molecular properties and bioactivity using Molinspiration to obtain the data. A total of 56 compounds from various plant sources were studied using the SMILES of each compound taken from PubChem. These 56 compounds were investigated for their molecular properties (Lipsinki's rule of 5) and bioactivity using the Molinspiration Cheminformatics online software tool. Out of 56 compounds 47 compounds were found to have no violations and 9 compounds were found to have more than 2 violations. The compounds were then examined for their ADMET (Absorption, Distribution, Metabolism, Excretion and Toxicity) properties using PreADMET, using Chemsketch to draw the compounds. The compounds having BBB (Blood Brain Barrier) value greater than or equal to 1 were further examined for Toxicity studied using PreADMET. A total of 36 compounds were considered from toxicity studies and 25 compounds which passed all the selection criterias were taken for molecular docking studies. Docking was performed using Autodock 4.2. The enzymes were taken from Research Collaborative for Structural Bioinformatics (RCSB). Using BIOVIA Discovery Studio, the enzymes were visualized and refined. The ligands were obtained by using Online SMILES translator to convert the ligand to .pdb file. The docking procedure was then conducted for the compounds and checked for their binding energies. Out of 25 compounds docked against Monoamine Oxidase (PDB ID: 1O5W) and Indoleamine 2,3- dioxygenase (PDB:6E35) five

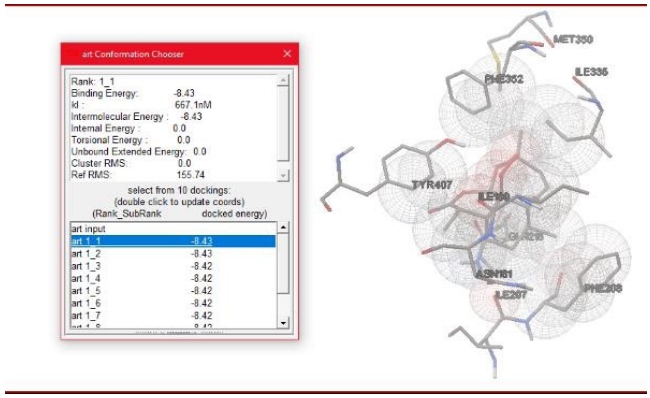
best compounds were found to have relatively higher binding energy compared to the standard drug Moclobemide. The compounds are Sclareol, Cryptotanshinone, Artemisinin, Bisabolol, Maaliol for the former enzyme and Artemisinin, Bisabolol, Maaliol, Linalyl acetate, Sclareol for the latter enzyme. Sclareol, a diterpene, against MAO and Artemisinin, a sesquiterpene, against IDO were found to have highest binding energies -9.27 and -10.58 respectively compared to the standard drug Moclobemide with binding energy -7.82 and -8.06 for the respective enzymes.



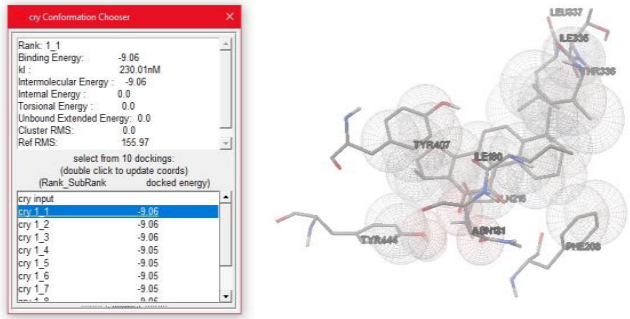
1) Sclareol



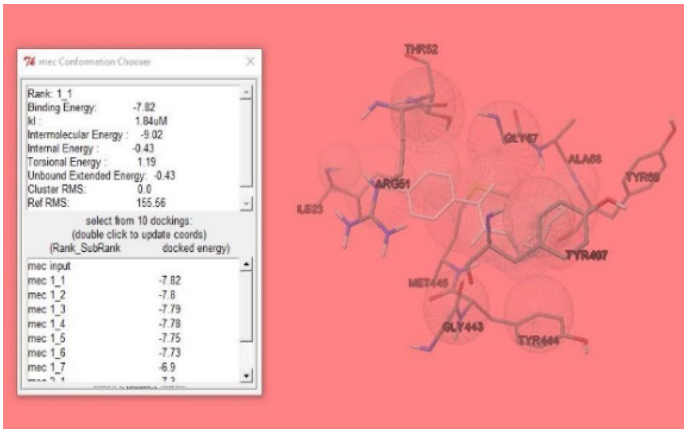
2) Maaliol



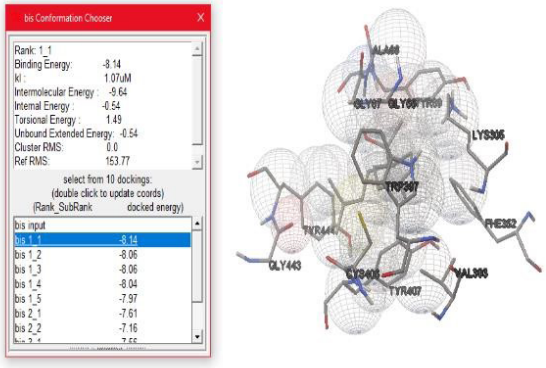
3) Artemisinin



4) Cryptotanoshinone



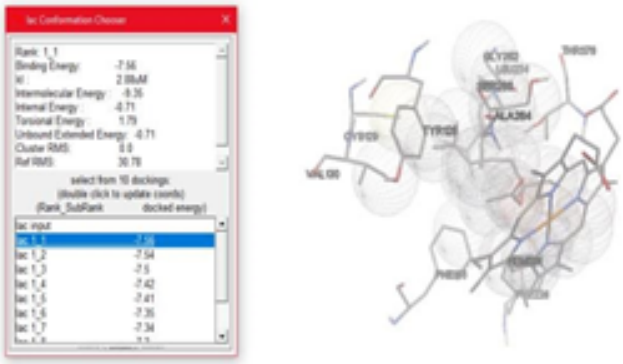
5) Bisabolol



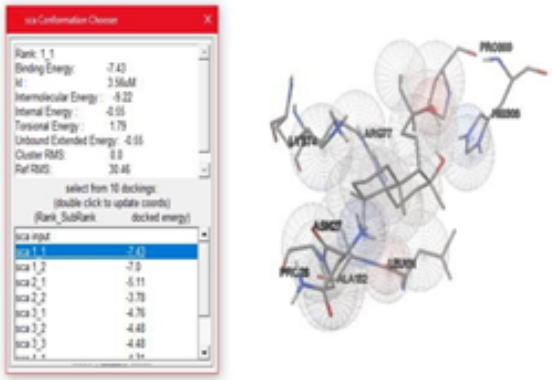
6) Moclobemide against Monoamine oxidase

Figure 1: Molecular Docking of Terpenoids Against the Enzyme – Monoamine Oxidase (Pdb Id: 1o5w)

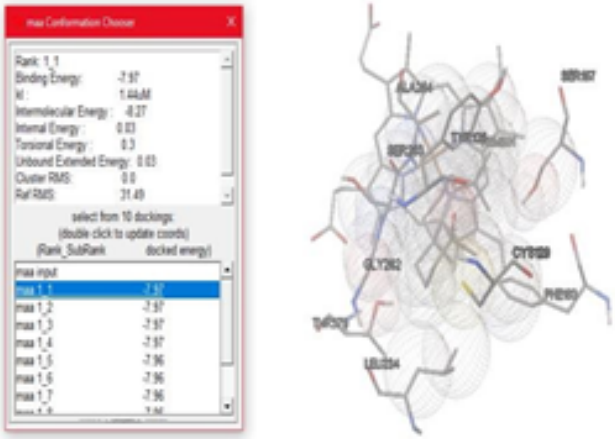
1) Linalyl acetate



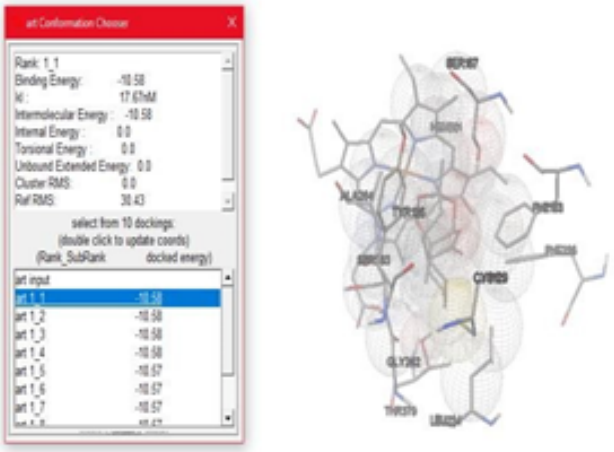
2) Sclareol



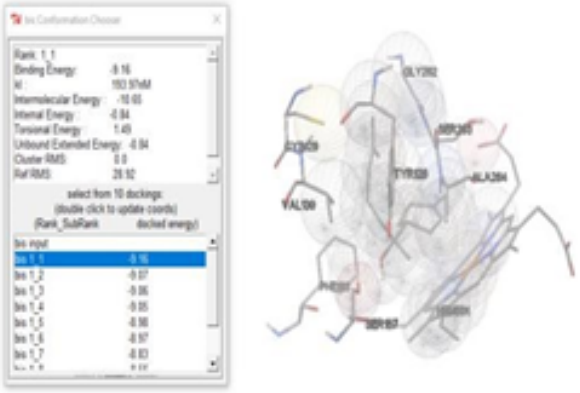
3) Maaliol



4) Artemisinin



5) Bisabolol



Moclobemide against Indoleamine 2,3-dioxygenase

Figure 2: Docked Images for the Enzyme – Indoleamine 2,3 Dioxygenase (Pdb Id: 6e35).

The amino acids in Moclobemide against Monoamine Oxidase A (PDB ID : 1O5W): ILE23, MET445, ARG51, THR52, GLY67, ALA68, TYR69, TYR407, TYR444, GLY443

Comparing the amino acids present in the standard Sclareol - MET350, LED337, PHE352, TYR69, ILE190, GLN215, ASN181, ILE207, TYR444, FHE206, PHE208

Sclareol has TYR69, TYR444 as common amino acids from the standard drug Moclobemide.
Bisabolol has the maximum amino acids matching the standard drug Moclobemide

ALA68, TYR69, GLY67, GLY66, TRP397, LYS305, PHE352, VAL303, TYR407, CYS406, TYR444, GLY443

The amino acids matching the standard drug Moclobemide are ALA68, TYR69, GLY67, TYR407, TYR444, GLY443

The amino acids in Moclobemide against Indoleamine 2,3 Dioxygenase (PDB ID : 6E35): THR379, SER263, ALA264, TYR126, SER167, HEM501, VAL130, CYS129, ARG331, PHE226, PHE164, PHE163 Comparing the amino acids present in the standard
Artemisinin - SER187, HEM501, PHE163, PHE226, CYS129, TYR126, ALA264, SER263, GLY262, THR379, LEU234

Artemisinin has HEM501, PHE163, PHE226, CYS129, TYR126, ALA264, SER263, THR379 as common amino acids from the standard drug Moclobemide.

Linalyl acetate has the maximum amino acid matching the standard drug Moclobemide

THR379, PHE226, HEM501, GLY262, LEU234, SER263, ALA264, TYR126, CYS129, VAL130, PHE163
The amino acids matching the standard drug Moclobemide are THR379, PHE226, HEM501, SER263, ALA264, TYR126, CYS129, VAL130, PHE163.

Conclusion

Plant phytochemicals have been shown to play an important role in the treatment of depression. This study's findings demonstrate that a variety of terpenoids have been identified and tested against specific enzyme targets linked to the potential to treat depression. Based on these in silico examinations, it is proposed here that the inhibitory activity of the terpenoids alpha-phellandrine, alpha pinene, beta pinene, 1,8-cineole, citronellol, linalyl acetic acid derivation, 3-carene, borneol, sclareol, maaliol, artemisisin, cryptotanshinone, tanshinone IIA, geosmin, isopulegol, myrcene, longifolene, thymol, rose oxide, pipertone, menthol, terpeniol, linalool, d limonene and camphor had the best docking results against monoamine oxidase and indoleamine 2,3-dioxygenase enzymes, prompting strong lead molecules for the treatment of Depression. Additionally, studies on pharmacokinetics demonstrated that the compounds possess drug-like properties and are very likely to enter the brain after crossing the blood–brain barrier. Indisputably, our research has shown that Terpenoids like are Sclareol, Cryptotanshinone, Artemisinin, Bisabolol, Maaliol and Linalyl acetate exhibit strong anti-depressant activity out of which Sclareol and Artemisinin have relatively high binding energy i.e, -9.27 and -10.58 against the enzymes monoamine oxidase and indoleamine 2,3 dioxygenase respectively.

Additional in vitro blood barrier models must be developed in order to verify that compounds can cross the blood-brain barrier. In addition, in order to develop a treatment for depression, it is necessary to carry out in vivo experiments to ascertain the pharmacological activities of the compounds.

- **Ethics Approval And Consent To Participate:** Not applicable.
- **Human and Animal Rights:** No animals/humans were used for studies that are the basis of this research.
- Consent For Publication: Not applicable.
- **Funding:** None.
- **Availability of Data And Materials:** not applicable.
- **Conflict Of Interest**: None.
- **Acknowledgements:** None declared.

References

1. Sharmili Banu RK, Mohana Priya I, S Azar Zochedh A (2022) Identification of novel bioactive compounds from banana fruit (Musa sapientum) as antidepressant in pregnant women: molecular docking, physiochemical and ADMET evaluation. Ajbge.

2. Bakalov D, Hadjiolova R, Pechlivanova D (2020) Pathophysiology of depression and novel sources of phytochemicals for its treatment–a systematic review. Acta Medica Bulgarica 47(4): 69-74.

3. Park SJ, Jaiswal V, Lee HJ (2021) Dietary intake of flavonoids and carotenoids is associated with anti-depressive symptoms: epidemiological study and in silico—mechanism analysis. Antioxidants 11(1): 53.

4. Ha A, Mehdi S, Kl K (2019) Medicinal herbs and phytochemicals used in the treatment of depression: A review. Asian J. Pharm Clin Res 12: 8-14.

5. Rahman J, Tareq AM, Hossain MM, Sakib SA, Islam MN, et al. (2020) Biological evaluation, DFT calculations and molecular docking studies on the antidepressant and cytotoxicity activities of Cycas pectinata Buch.-Ham. compounds. Pharmaceuticals 13(9): 232.

6. Ehigiator BE, Umana IK, Ikem CJ, Izuegbu C, Ojesebholo RO, et al. (2021) Honey: A remedy for depression. An investigation by experimental validation and molecular docking studies International Journal of Pharmacology and Pharmaceutical Sciences 3(1): 05-15.

7. Duman RS (2014) Pathophysiology of depression and innovative treatments: remodeling glutamatergic synaptic connections. Dialogues in clinical neuroscience 16(1): 11-27.

8. Wang K, Zhai Q, Wang S, Li Q, Liu J, et al. (2021) Cryptotanshinone ameliorates CUS-induced depressive-like behaviors in mice. Translational Neuroscience 12(1): 469-481.

9. Brigitta B (2002) Pathophysiology of depression and mechanisms of treatment. Dialogues in clinical neuroscience 4(1): 7-20.

10. Hirschfeld RM (2000) History and evolution of the monoamine hypothesis of depression. Journal of clinical psychiatry 61(6): 4-6.

11. Schildkraut JJ (1995) The catecholamine hypothesis of affective disorders: a review of supporting evidence. 1965. The Journal of neuropsychiatry and clinical neurosciences 7(4): 524-533.

12. Lemberger L, Fuller RW, Zerbe RL (1985) Use of specific serotonin uptake inhibitors as antidepressants. Clinical neuropharmacology 8(4): 299-317.

13. Nestler EJ, MB RJ, Eisch AJ, Stephen J (2002) Gold, and aLM Monteggia. Neurobiology of Depression. Neuron 34: 13-25.

14. Drevets WC (2000) Functional anatomical abnormalities in limbic and prefrontal cortical structures in major depression. Progress in brain research 126: 413-431.

15. Shulman KI, Herrmann N, Walker SE (2013) Current place of monoamine oxidase inhibitors in the treatment of depression. CNS drugs 27: 789-797.

16. Gold PW, Goodwin FK, Chrousos GP (1988) Clinical and biochemical manifestations of depression. Relation to the neurobiology of stress (2). The New England journal of medicine. 319(7): 413-420.

17. Wei K, Wang GQ, Bai X, Niu YF, Chen HP, et al. (2015) Structure-based optimization and biological evaluation of pancreatic lipase inhibitors as novel potential antiobesity agents. Natural Products and Bioprospecting 5: 129-157.