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In Silico Evaluation of *Guiera senegalensis* Phytochemicals as Multi-Target Modulators of Anxiety and Depression-Related Proteins

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Abstract

Depression and anxiety are prevalent neuropsychiatric disorders with complex etiologies involving multiple neurotransmitter systems. Despite available treatments, limitations such as delayed efficacy, adverse effects, and treatment resistance necessitate the search for safer and more effective alternatives. *Guiera senegalensis*, a plant widely used in traditional West African medicine, has shown promise for neurological applications, though its bioactive compounds remain underexplored in this context. This study aimed to investigate the antidepressant and anxiolytic potential of phytochemicals from *Guiera senegalensis* through a comprehensive in silico approach targeting key CNS receptors. Twenty-five bioactive compounds were selected using the IMPPAT and PubChem databases. Target proteins; GABA-A receptor (6HUO), serotonin transporter (5I6X), monoamine oxidase A (2Z5X), and mGluR5 receptor (6FFH), were retrieved from the Protein Data Bank. Molecular docking was conducted using PyRx with AutoDock Vina. SwissADME and ProTox-II were used to evaluate pharmacokinetic properties and predict toxicity endpoints, respectively. Compounds such as Ergostanol (−8.2 kcal/mol), Myricetin (−7.4 kcal/mol), Isorhamnetin (−7.0 kcal/mol), and Quercetin (−7.2 kcal/mol) exhibited strong binding affinities to GABA-A and MAOA, surpassing standard drugs like Zolpidem and Phenelzine. These compounds interacted with key receptor residues essential for neuroactivity. ADME analysis revealed high gastrointestinal absorption and drug-likeness for most candidates, while toxicity predictions indicated favorable safety profiles, with only Myricetin and Quercetin flagged for potential genotoxicity. The findings support the neuropharmacological potential of *Guiera senegalensis*, identifying several compounds with multi-target affinity, acceptable pharmacokinetics, and low predicted toxicity. These results justify further experimental validation and offer a strong foundation for developing novel phytotherapeutics for anxiety and depression.

Keywords: *Guiera senegalensis*; antidepressant; anxiolytic; molecular docking; in silico pharmacology; toxicity prediction

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Introduction

Depression and anxiety disorders are among the most prevalent and disabling neuropsychiatric conditions globally, affecting about 280 and 301 million people, respectively, contributing significantly to the global burden of disease (Javaid et al., 2023; WHO, 2023). Current pharmacotherapies, including selective serotonin reuptake inhibitors (SSRIs), benzodiazepines, and monoamine oxidase inhibitors (MAOIs), are associated with limitations such as delayed onset of action, poor patient compliance, high relapse rates, and undesirable side effects including sedation, dependence, and sexual dysfunction (Bandelow et al., 2017). These challenges underscore the urgent need for safer, more effective, and faster-acting therapeutics with multi-target potential.

Natural products, particularly those derived from medicinal plants, continue to serve as valuable leads for central nervous system (CNS) drug discovery. Their structural diversity, biocompatibility, and multitarget capabilities make them particularly suited for treating complex disorders such as anxiety and depression, which involve multiple neurotransmitter systems (Chaachouay & Zidane, 2024). *Guiera senegalensis*, a plant widely used in West African traditional medicine, has shown therapeutic potential in inflammatory, antimicrobial, and neurological conditions, although its neuropsychopharmacological mechanisms remain largely unexplored (Dirar & Devkota, 2021; Hassan et al., 2025). Previous phytochemical studies have identified flavonoids, alkaloids, and terpenoids within *Guiera senegalensis* that exhibit CNS-modulating properties (Damo et al., 2022). However, systematic studies evaluating its interaction with validated molecular targets of depression and anxiety, such as GABA-A receptors, serotonin transporters (SERT), monoamine oxidase A (MAOA), and metabotropic glutamate receptor 5 (mGluR5), are lacking. Modern drug discovery tools now enable in silico modeling to predict the interaction of natural ligands with biological targets, assess pharmacokinetic properties, and estimate toxicity, thus streamlining early-stage screening and lead optimization (Chang et al., 2022).

In this study, we employed an integrative computational approach to identify potential antidepressant and anxiolytic compounds from *Guiera senegalensis*. Using molecular docking, ADME (absorption, distribution, metabolism, and excretion) analysis, and toxicity prediction, we evaluated the interactions of selected phytochemicals with major CNS targets. This approach aims to uncover multi-target natural ligands with favorable pharmacokinetic profiles and minimal toxicity, thereby supporting the traditional use of *Guiera senegalensis* and advancing its potential in neuropsychiatric drug discovery.

Materials and Methods

Selection and Preparation of Phytocompounds

Phytochemical constituents of *Guiera senegalensis* were identified using the IMPPAT database (https://cb.imsc.res.in/imppat), a curated repository of Indian medicinal plants and their bioactive phytochemicals (Vivek-Ananth et al., 2023). Twenty-five compounds were obtained from the database, and their corresponding 3D chemical structures were retrieved in .sdf format from PubChem database (https://pubchem.ncbi.nlm.nih.gov), a widely used chemical database maintained by the National Center for Biotechnology Information.

Target Protein Selection and Preparation

Four CNS protein targets associated with anxiety and depression were selected for molecular docking based on their therapeutic relevance: GABA-A receptor (PDB ID: 6HUO), serotonin transporter, SERT (PDB ID: 5I6X), metabotropic glutamate receptor 5, mGluR5 (PDB ID: 6FFH), and monoamine oxidase A, MAOA (PDB ID: 2Z5X). These 3D structures were obtained from the Protein Data Bank (https://www.rcsb.org), an authoritative source for biomolecular structures (Burley et al., 2022). Protein preparation involved the removal of co-crystallized ligands, heteroatoms, water molecules, and the addition of polar hydrogens using Discovery Studio 2024 (BIOVIA).

Drug-Likeness Evaluation

The drug-likeness of all compounds were assessed using SwissADME (http://www.swissadme.ch), an online tool that predicts pharmacokinetic properties and drug-likeness based on molecular descriptors (Daina et al., 2017). Drug-likeness was evaluated using Lipinski's Rule of Five, which stipulates acceptable thresholds for molecular weight (<500 Da), lipophilicity (LogP <5), hydrogen bond donors (<5), hydrogen bond acceptors (<10), and molar refractivity (40–130). Compounds violating more than one criterion were excluded from further analysis.

Toxicity Risk Assessment

To evaluate the safety profile of the shortlisted compounds, toxicity predictions were performed using ProTox-II (https://tox.charite.de/protox3), a web-based platform that predicts various toxicity endpoints, including LD_{50}, hepatotoxicity, carcinogenicity, immunotoxicity, and mutagenicity, using machine-learning models trained on experimental data (Banerjee et al., 2024).

Molecular Docking and Virtual Screening

Prepared protein structures and phytoligands were subjected to molecular docking using PyRx version 0.8, an integrated virtual screening tool that incorporates AutoDock Vina for docking calculations (Trott & Olson, 2010). The grid box for each target was centered on the active site as defined by the crystallized ligand or reported literature. Docking simulations were performed under uniform parameters, and binding affinities were recorded in kcal/mol. For each target, five phytoligands with the highest binding affinity were selected and compared with known ligands. Each ligand's interaction profile was further visualized and analyzed using Discovery Studio Visualizer.

Results

Phytocompounds Isolated from *Guiera senegalensis*

A diverse array of bioactive compounds including polyphenols, flavonoids, alkaloids, and terpenes were isolated from *Guiera senegalensis*. Table 1 presents a comprehensive list of 25 phytochemical compounds isolated from *Guiera senegalensis*, each accompanied by its respective PubChem Compound Identifier (CID). These compounds encompass various classes, including flavonoids, alkaloids, phenolic acids, and terpenoids, reflecting the plant's rich phytochemical diversity.

Drug-Likeness Evaluation

Table 2 below summarizes the ADME-related parameters of the 25 phytocompounds, including molecular weight, LogP, hydrogen bond donors (HBD) and acceptors (HBA), molar refractivity, gastrointestinal (GI) absorption, blood-brain barrier (BBB) permeability, and Lipinski's rule violations.

Table 1. Phytochemical compounds isolated from *Guiera senegalensis* with corresponding PubChem identifiers

S/No.	Phytocompounds	PubChem CID	S/No.	Name	PubChem CID
1.	(-)-Epigallocatechin gallate	65064	14.	Hyoscyamine	154417
2.	(-)-Gallocatechin	9882981	15.	Isorhamnetin	5281654
3.	3,4,5-Tri-O-Galloylquinic Acid	127406	16.	Kaempferol	5280863
4.	3,5-Di-O-Galloylquinic Acid	460896	17.	Labdane	9548711
5.	5-Methyldihydroflavasperone	44584536	18.	Methyl gallate	7428
6.	delta-Valerolactone	10953	19.	Myricetin	5281672
7.	Ergostanol	5283641	20.	Myricitrin	5281673
8.	Ethyl gallate	13250	21.	Quercetin	5280343
9.	Gallic acid	370	22.	Quinoline	7047
10	Guieranone A	639680	23.	Quinoxaline	7045
11	Harmalan	160510	24.	Solanine	262500
12	Harman	5281404	25.	Tetrahydroharman	91522
13	Hesperetin	72281			

Table 2. Physicochemical properties and Lipinski rule evaluation of selected compounds from *Guiera senegalensis*

S/No.	Phytocompounds	Mol wt	LogP (XLOGP3	HBA	HBD	Molar Refractivity	Lipinski Violation	GI Abs	BBB Perm
1.	(-)-Epigallocatechin Gallate	458.37	1.17	11	8	112.06	2	Low	No
2.	(-)-Gallocatechin	306.27	0.00	7	6	76.36	1	High	No
3.	3,4,5-Tri-O-Galloylquinic Acid	648.48	1.13	18	11	147.23	3	Low	No
4.	3,5-Di-O-Galloylquinic Acid	496.38	-0.04	14	9	111.52	2	Low	No
5.	5-Methyldihydroflavasperone	302.32	2.97	5	0	82.58	0	High	Yes
6.	delta-Valerolactone	100.12	-0.35	2	0	25.32	0	High	Yes
7.	Ergostanol	402.70	7.78	1	1	128.90	1	Low	No
8.	Ethyl gallate	198.17	1.30	5	3	48.60	0	High	No
9.	Gallic acid	170.12	0.70	5	4	39.47	0	High	No
10	Guieranone A	316.35	3.56	5	0	89.25	0	High	Yes
11	Harmalan	184.24	2.10	1	1	62.74	0	High	Yes
12	Harman	182.22	3.28	1	1	58.57	0	High	Yes
13	Hesperetin	302.28	2.60	6	3	78.06	0	High	No
14	Hyoscyamine	289.37	1.83	4	1	84.51	0	High	Yes
15	Isorhamnetin	316.26	1.87	7	4	82.50	0	High	No
16	Kaempferol	286.24	1.90	6	4	76.01	0	High	No
17	Labdane	278.52	8.59	0	0	93.51	1	Low	No
18	Methyl gallate	184.15	0.86	5	3	43.79	0	High	No
19	Myricetin	318.24	1.18	8	6	80.06	1	Low	No
20	Myricitrin	464.38	0.51	12	8	111.02	2	Low	No
21	Quercetin	302.24	1.54	7	5	78.03	0	High	No
22	Quinoline	129.16	2.03	1	0	41.74	0	High	Yes
23	Quinoxaline	130.15	1.32	2	0	39.54	0	High	Yes
24	Solanine	868.06	1.81	16	9	222.19	3	Low	No
25	Tetrahydroharman	186.25	1.89	1	2	62.45	0	High	Yes

Most compounds have molecular weights below 500 Da, aligning with Lipinski's criteria. However, solanine (868.06 Da) and 3,4,5-tri-O-galloylquinic acid (648.48 Da) exceed this threshold, potentially affecting their permeability and absorption. LogP values, indicating lipophilicity, vary across the compounds. While many fall within the acceptable range ($LogP \leq 5$), labdane (8.59) and ergostanol (7.78) exhibit higher values, suggesting increased lipophilicity, which may impact solubility and bioavailability. The number of HBA and HBD influences a compound's solubility and permeability. Compounds like 3,4,5-tri-O-galloylquinic acid (HBA: 18, HBD: 11) and myricitrin (HBA: 12, HBD: 8) have high counts, potentially reducing membrane permeability. Molar refractivity values, reflecting the volume occupied by the molecule, range from 25.32 (delta-valerolactone) to 222.19 (solanine), indicating diversity in molecular sizes.

The majority of compounds comply with Lipinski's Rule of Five, suggesting favorable oral bioavailability. Notable exceptions include 3,4,5-tri-O-galloylquinic acid and solanine, each violating multiple criteria, which may limit their drug-likeness. Compounds such as (-)-gallocatechin and harman exhibit high GI absorption, indicating potential for effective oral delivery. Conversely, compounds like (-)-epigallocatechin gallate and myricitrin show low GI absorption. Regarding BBB permeability, most compounds are predicted not to cross the BBB, with exceptions like 5-methyldihydroflavasperone and harman.

Toxicity Risk Assessment

Table 3 presents the predicted acute toxicity (LD_{50}), toxicity classifications, and organ-specific toxicities of selected phytochemicals from *Guiera senegalensis*. Most compounds exhibit LD_{50} values ranging from 159 to 10,000 mg/kg, placing them in toxicity classes 3 to 6, indicative of low to moderate toxicity. Notably, (-)-gallocatechin demonstrates the highest LD_{50} (10,000 mg/kg), whereas myricetin and quercetin have lower LD_{50} values (159 mg/kg). Organ-specific toxicity predictions reveal that several compounds, including hyoscyamine and harmalan, are potentially neurotoxic and may pose risks to the nervous system. Additionally, compounds such as hesperetin and isorhamnetin show potential hepatotoxicity and nephrotoxicity, respectively.

Table 3. Predicted LD_{50}, toxicity classifications, and organ-specific toxicities of selected phytochemicals

S/No.	Phytocompounds	Predicted LD_{50}	Toxicity Class	Hepatoxicity	Neurotoxicity	Nephrotoxicity	Respiratory Toxicity	Cardiotoxicity
1.	(-)-Gallocatechin	10000 mg/kg	6	Inactive (0.72)	Inactive (0.90)	Active (0.62)	Active (0.79)	Inactive (0.99)
2.	Ergostanol	500 mg/kg	4	Inactive (0.79)	Inactive (0.56)	Inactive (0.84)	Active (0.79)	Inactive (0.71)
3.	Harmalan	175 mg/kg	3	Inactive (0.85)	Active (0.72)	Inactive (0.88)	Active (0.88)	Inactive (0.83)
4.	Harman	1000 mg/kg	4	Inactive (0.58)	Active (0.57)	Inactive (0.88)	Inactive (0.72)	Inactive (0.93)
5.	Hesperetin	2000 mg/kg	4	Inactive (0.70)	Inactive (0.87)	Active (0.67)	Active (0.86)	Active (0.99)
6.	Hyoscyamine	380 mg/kg	4	Inactive (0.98)	Active (0.93)	Active (0.54)	Active (0.93)	Inactive (0.72)
7.	Isorhamnetin	5000 mg/kg	5	Inactive (0.72)	Inactive (0.88)	Active (0.64)	Active (0.85)	Active (0.82)
8.	Kaempferol	3919 mg/kg	5	Inactive (0.68)	Inactive (0.89)	Active (0.62)	Active (0.83)	Inactive (0.94)
9.	Myricetin	159 mg/kg	3	Inactive (0.69)	Inactive (0.89)	Active (0.62)	Active (0.83)	Inactive (0.99)
10.	Quercetin	159 mg/kg	3	Inactive (0.69)	Inactive (0.89)	Active (0.62)	Active (0.83)	Inactive (0.99)

Table 4 presents the predicted toxicity endpoints of selected phytochemicals from *Guiera senegalensis*, focusing on carcinogenicity, immunotoxicity, mutagenicity, and cytotoxicity. A status of "active" or "inactive" denotes whether the compound is predicted to express the respective toxicity. Scores closer to 1.00 indicate stronger predictive confidence. Most compounds are predicted to be non-carcinogenic. However, myricetin and quercetin are exceptions, with predictions indicating potential carcinogenicity (probability: 0.68). Several compounds, including ergostanol, harmalan, hesperetin, and isorhamnetin, exhibit predicted immunotoxicity, with probabilities ranging from 0.58 to 0.99. Harman, myricetin, and quercetin are predicted to be mutagenic, with probabilities of 0.85, 0.51, and 0.51, respectively. All evaluated compounds are predicted to be non-cytotoxic, with probabilities indicating low cytotoxic potential.

Table 4. Predicted Toxicity Endpoints of Selected Phytocompounds from *Guiera senegalensis*

S/No.	Phytocompounds	Carcinogenicity	Immunotoxicity	Mutagenicity	Cytotoxicity
1.	(-)-Gallocatechin	Inactive (0.51)	Inactive (0.92)	Inactive (0.55)	Inactive (0.84)
2.	Ergostanol	Inactive (0.77)	Active (0.97)	Inactive (0.87)	Inactive (0.88)
3.	Harmalan	Inactive (0.75)	Active (0.99)	Inactive (0.65)	Inactive (0.77)
4.	Harman	Inactive (0.67)	Inactive (0.93)	Active (0.85)	Inactive (0.98)
5.	Hesperetin	Inactive (0.70)	Active (0.90)	Inactive (0.87)	Inactive (0.86)
6.	Hyoscyamine	Inactive (0.86)	Inactive (0.99)	Inactive (0.76)	Inactive (0.66)
7.	Isorhamnetin	Inactive (0.68)	Active (0.58)	Inactive (0.94)	Inactive (0.95)
8.	Kaempferol	Inactive (0.72)	Inactive (0.96)	Inactive (0.52)	Inactive (0.98)
9.	Myricetin	Active (0.68)	Inactive (0.86)	Active (0.51)	Inactive (0.99)
10.	Quercetin	Active (0.68)	Inactive (0.87)	Active (0.51)	Inactive (0.99)

Molecular Docking and Virtual Screening

Table 5 presents the molecular docking results of selected phytochemicals from *Guiera senegalensis* with the GABAA receptor. Ergostanol exhibited the strongest binding affinity at –8.2 kcal/mol, surpassing the reference drug zolpidem (–7.4 kcal/mol). Flavonoids such as myricetin, quercetin, isorhamnetin, and kaempferol demonstrated binding affinities ranging from –7.4 to –6.9 kcal/mol. Interaction analyses revealed that ergostanol and kaempferol engage with key residues including TRP412, ILE223, VAL227, and LEU416, which are associated with the benzodiazepine binding site of the GABAA receptor (Figure 1). Myricetin and quercetin interacted with residues such as TYR160, PHE100, and ASN103, suggesting potential modulation at the orthosteric site.

Table 5. Binding affinities, interaction coordinates and key residues involved in ligand binding to GABA-A receptor

S/No.	Ligands	Binding Affinity (kcal/mol)	Binding co-ordinates (XYZ)	Receptor Interaction Residues
1.	Ergostanol	-8.2	115.683567 122.154033 127.593333	TRP 412 (A), ILE 223 (A), LYS 222 (A), VAL 227 (A)
2.	Zolpidem	-7.4	117.471435 120.327435 122.149652	TRP 412 (A), VAL 227 (A), LEU 416 (A) ILE 223 (A), ASN 408 (A), ILE 235 (A)
3.	Myricetin	-7.4	134.864414 119.655103 162.493793	SER 205 (A), TYR 160 (A), PHE 100 (A), PHE 101 (A), ASN 103 (A), GLY 104 (A), HIS 102 (A)
4.	Quercetin	-7.2	129.463815 110.996926 116.410481	PHE 296 (A), VAL 292 (A), VAL 410 (A), PHE 407 (A), ILE 406 (A)
5.	Isorhamnetin	-7	115.411667 139.230889 170.164926	LEU 118 (A), ASN 88 (A), ASN 87 (A)
6.	Kaempferol	-6.9	135.359320 112.755120 105.712600	TRP 412 (A), VAL 227 (A), LEU 416 (A), ILE 223 (A), ASN 408 (A), ILE 235 (A)

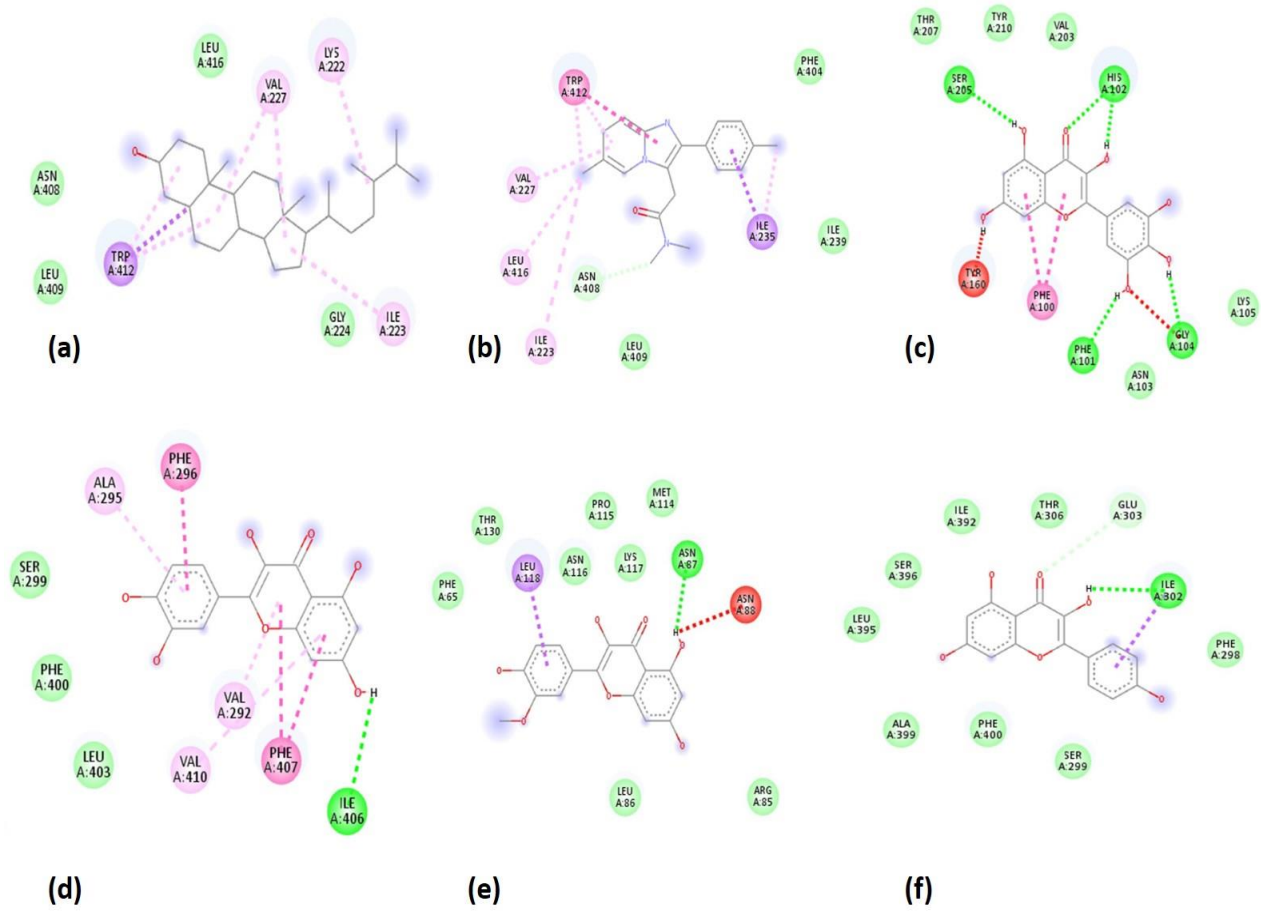

Figure 1: Pharmacophore of the drugs showcasing their spatial arrangement and key amino acids residues for interactions with GABA-A Receptor; (a) Ergostanol, (b) Zolpidem, (c) Myricetin, (d) Quercetin, (e) Isorhamnetin, (f) Kaempferol.

Table 6 summarizes the molecular docking results of selected phytochemicals from *Guiera senegalensis* with MAO-A. Hesperetin and isorhamnetin exhibited the highest binding affinities (–9.8 kcal/mol), surpassing the reference inhibitor phenelzine (–6.8 kcal/mol). Other flavonoids, including myricetin, quercetin, and (–)-gallocatechin, demonstrated strong binding affinities ranging from –9.3 to –8.8 kcal/mol. Interaction analyses revealed that these compounds engage with key residues within the MAO-A active site, such as ASP328, GLU327, ASN179, and PRO186 (Figure 2).

Table 6. Binding affinities, interaction coordinates and key residues involved in ligand binding to MAOA receptor

S/No.	Ligands	Binding Affinity (kcal/mol)	Binding co-ordinates (XYZ)	Receptor Interaction Residues
1.	Hesperetin	-9.8	38.645600 10.046440 -12.340640	ASP 328 (A), GLU 327 (A), ASN 179 (A), PRO 186 (A)
2.	Isorhamnetin	-9.8	53.135185 29.367259 -18.117444	VAL 210 (A), VAL 93 (A), GLY 110 (A), SER 209 (A), ALA 111 (A), THR 211 (A), VAL 484 (A), GLU 485 (A)
3.	Myricetin	-9.3	53.533759 23.418621 -21.058414	PHE 112 (A), ALA 111 (A), GLU 492 (A), THR 487 (A), THR 205 (A)
4.	Quercetin	-9.1	38.792333 10.203444 -11.860000	LEU 118 (A), ASN 88 (A), ASN 87 (A)
5.	(-)-Gallocatechin	-8.8	39.841500 9.311179 -10.056000	GLU 329 (A), ASP 328 (A), GLU 327 (A)
6.	Phenelzine	-6.8	53.454462 20.366000 -19.740154	TYR 124 (A), GLU 492 (A), PHE 112 (A), ALA 111 (A)

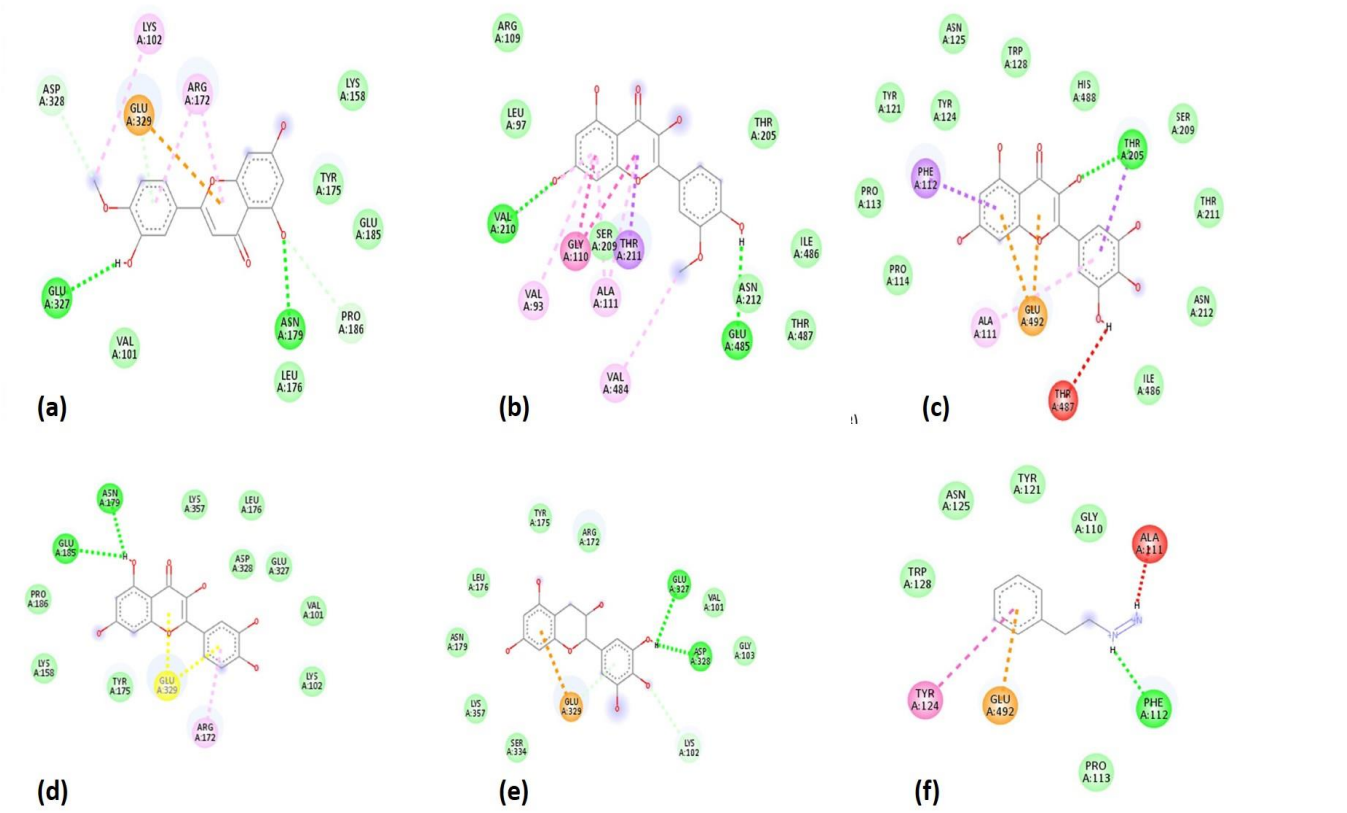

Figure 2: Pharmacophore of the drugs showcasing their spatial arrangement and key amino acids residues for interactions with MAOA Receptor; (a) Hesperetin, (b) Isorhamnetin, (c) Myricetin, (d) Quercetin, (e) (-)-Gallocatechin, (f) Phenelzine.

Table 7 presents binding affinities, coordinates, and key interacting residues for various ligands binding to the mGluR5 receptor as further depicted in Figure 3. Harman shows the highest affinity (-8.1 kcal/mol), followed by Ergostanol (-8.0 kcal/mol). Myricetin and Harmalan both have affinities of -7.9 kcal/mol, followed by Hesperetin Hyoscyamine, and Fenobam.

Table 7. Binding affinities, interaction coordinates and key residues involved in ligand binding to mGluR5 receptor

S/No.	Ligand	Binding Affinity (kcal/mol)	Binding co-ordinates (XYZ)	Receptor Interaction Residues
1.	Harman	-8.1	-27.348200 5.199533 50.291733	LEU 630 (A), CYS 631 (A), LEU 646 (A)
2.	Ergostanol	-8	-40.697433 12.695200 33.867567	PHE 596 (A), VAL 1819 (A), VAL 1822 (A), ALA 593 (A)
3.	Myricetin	-7.9	-19.006862 26.958931 14.158897	ARG 1076 (A), TYR 1088 (A), VAL 1075 (A), ASP 1072, LYS 1760 (A)
4.	Harmalan	-7.9	-21.579333 17.124000 57.917200	LYS 1798 (A), TYR 1792 (A), ILE 1799 (A), CYS 1733
5.	Hesperetin	-7.8	-24.081960 17.981520 59.200720	ILE 651 (A), ILE 1799 (A), ILE 1732, LYS 1798 (A)
6.	Hyoscyamine	-7.8	-35.908000 23.674864 56.165818	TYR 1797 (A), ALA 579 (A), ALA 582 (A), PRO 578 (A)
7.	Fenobam	-6.7	-23.216800 37.972200 -8.830500	PHE 114 (A), THR 1109 (A), GLY 1110 (A)

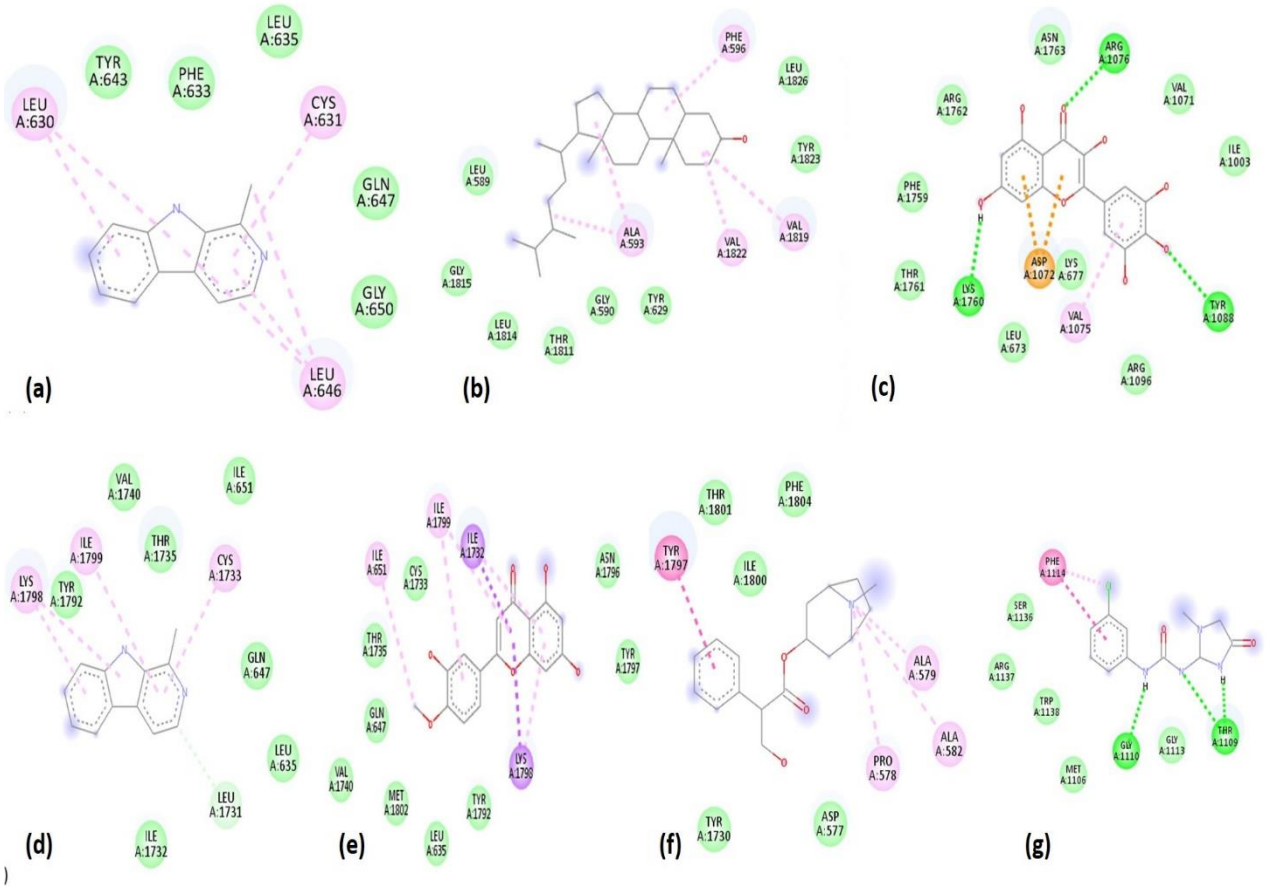

Figure 3: Pharmacophore of the drugs showcasing their spatial arrangement and key amino acids residues for interactions with mGluR5 receptor; (a) Harman, (b) Ergostanol, (c) Myricetin, (d) Harmalan, (e) Hesperetin, (f) Hyoscyamine, (g) Fenobam.

Table 8 below shows binding affinities, coordinates, and key residues for ligands interacting with SERT. Ergostanol has the strongest affinity (-9.7 kcal/mol), followed by Fluoxetine (-9.3 kcal/mol). Common interacting residues include ARG104, PHE335, ASP328, and TYR175/176 (Figure 4).

Table 8. Binding affinities, interaction coordinates and key residues involved in ligand interaction with SERT

S/No.	Ligand	Binding Affinity (kcal/mol)	Binding co-ordinates (XYZ)	Receptor Interaction Residues
1.	Ergostanol	-9.7	-46.034667 -10.770833 -0.643233	PRO 561 (A), ILE 327 (A), SER 559 (A), PHE 556 (A), PHE 335 (A), ALA 331 (A)
2.	Fluoxetine	-9.3	-45.164739 -12.453435 0.583783	ALA 331 (A), ARG 104 (A), TYR 175 (A), TYR 176 (A), THR 497 (A), PHE 335 (A), ASP 328 (A)
3.	Quercetin	-8.9	-40.488333 -17.916667 2.046852	GLU 494 (A), PHE 335 (A), GLU 493 (A), ARG 104 (A), ASP 98 (A), GLY 100 (A)
4.	Myricetin	-8.8	-40.467960 -16.314920 1.267600	ASP 328 (A), ALA 331 (A), ARG 104 (A), TYR 176 (A), TYR 175 (A), THR 497 (A), PHE 335 (A)
5.	Hesperetin	-8.8	-43.261310 -11.535517 1.097172	PHE 556 (A), SER 559 (A), ASP 328 (A), ARG 104 (A)
6.	Isorhamnetin	-8.4	-37.738370 -18.146852 1.755556	ARG 104 (A), PHE 335 (A), ILE 172 (A), PHE 341 (A)

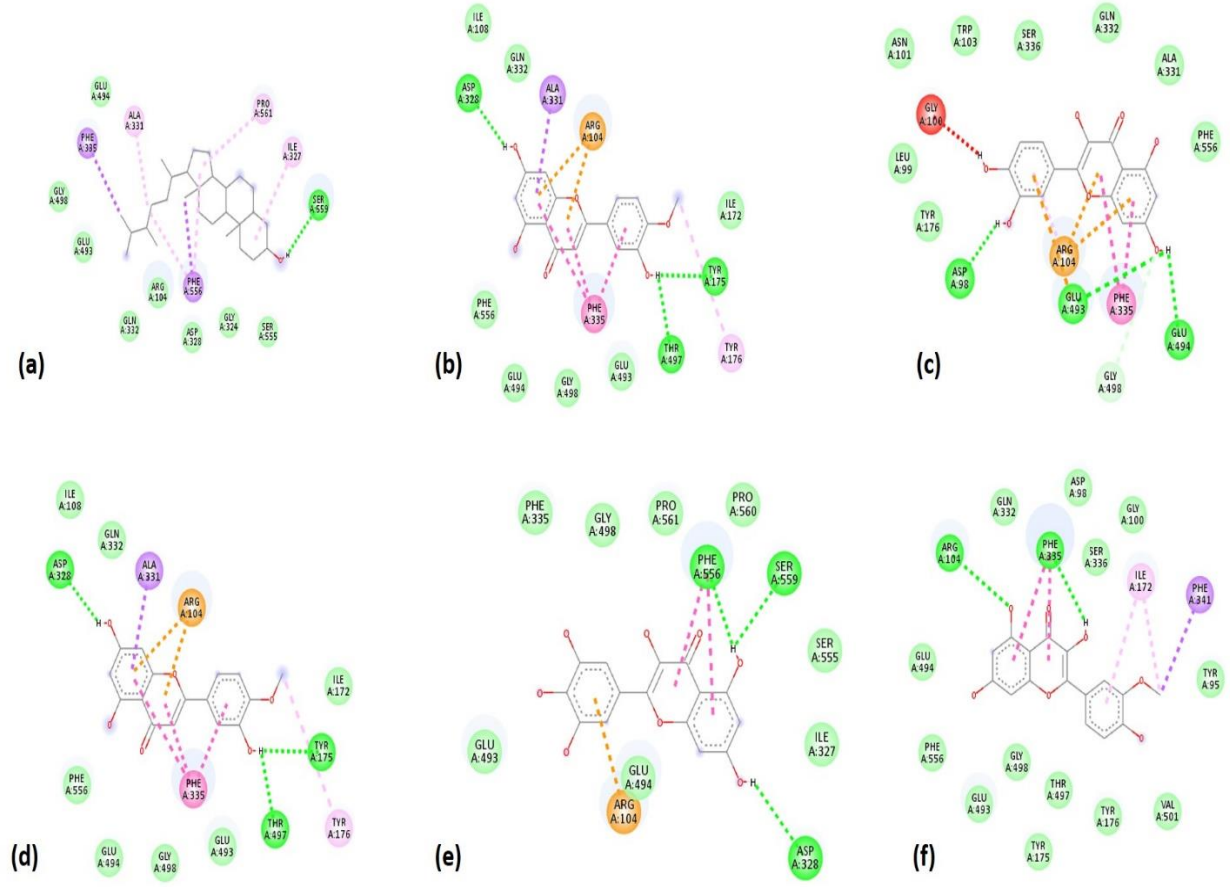

Figure 4: Pharmacophore of the drugs displaying their spatial arrangement and key amino acids residues for interactions with MAOA Receptor; (a) Ergostanol, (b) Fluoxetine, (c) Quercetin, (d) Myricetin, (e) Hesperetin, (f) Isorhamnetin.

Discussion

This study investigated the neuropharmacological potential of phytochemicals from *Guiera senegalensis* using a comprehensive in silico workflow, targeting proteins implicated in anxiety and depression: GABA-A receptor, MAOA, mGluR5, and SERT. *Guiera senegalensis* is rich in diverse phytochemicals, including flavonoids (e.g., quercetin, kaempferol), alkaloids (e.g., harman, harmalan), phenolic acids (e.g., gallic acid), and terpenoids (e.g., ergostanol). Pharmacokinetic profiling via SwissADME indicated that most lead compounds comply with Lipinski's Rule of Five, suggesting favorable oral bioavailability and drug-likeness (Benet et al., 2016). Isorhamnetin and Kaempferol, in particular, exhibited high gastrointestinal absorption and acceptable lipophilicity, consistent with prior pharmacokinetic studies (Li et al., 2012). Although Ergostanol exceeded the recommended LogP threshold, its high lipophilicity could be mitigated through advanced drug delivery systems such as nanoencapsulation, which has been shown to enhance solubility and CNS delivery of hydrophobic phytochemicals (Mittal et al., 2022).

Toxicity predictions reveal that most compounds have high LD_{50} values, indicating low acute toxicity. For instance, (-)-gallocatechin has an LD_{50} of 10,000 mg/kg, classifying it as practically non-toxic. Conversely, compounds like myricetin and quercetin have lower LD_{50} values (159 mg/kg), placing them in toxicity class 3, which denotes moderate toxicity. Organ-specific toxicity assessments show that while many compounds are inactive concerning hepatotoxicity and neurotoxicity, some exhibit potential nephrotoxic and respiratory toxic effects. Notably, myricetin and quercetin are predicted to be active in mutagenicity and carcinogenicity assays, warranting caution in their therapeutic application.

Molecular docking studies demonstrate that several phytochemicals from *Guiera senegalensis* exhibit significant binding affinities to neurological receptors. Ergostanol exhibited the highest binding affinity to the GABA-A receptor (−8.2 kcal/mol), outperforming the reference drug Zolpidem (−7.4 kcal/mol), a standard GABAergic agent for anxiety and insomnia. The predicted interactions with residues such as TRP412 and VAL227-key mediators of allosteric modulation-mirror the binding profiles of other neuroactive steroids known to enhance GABAergic transmission (Ko et al., 2020). This suggests that Ergostanol may act as a positive allosteric modulator, a mechanism increasingly recognized for its anxiolytic and sedative efficacy with potentially fewer side effects than direct agonists. Similarly, Myricetin and Quercetin, both flavonoids, demonstrated robust binding to MAOA (−9.3 and −9.1 kcal/mol, respectively), surpassing the clinically used MAO-A inhibitor Phenelzine (−6.8 kcal/mol). These findings align with accumulating evidence that dietary flavonoids can modulate monoaminergic neurotransmission and exert antidepressant-like effects in preclinical models (Ko et al., 2020).

The polypharmacological action of these compounds, capable of targeting multiple mood-related pathways, is particularly relevant given the multifactorial nature of mood disorders. Additionally, the ability of Isorhamnetin, Hesperetin, and Kaempferol to bind mGluR5 and SERT further highlights their multi-target potential, aligning with trends favoring polypharmacology over single-target interventions. This provides a mechanistic basis for the traditional use of *Guiera senegalensis* in managing neuropsychiatric symptoms, as well as supports the emerging paradigm of multi-receptor targeting for mood disorders, which is associated with enhanced therapeutic efficacy and reduced risk of tolerance or adverse effects compared to single-target agents (Henter et al., 2017; Oritsetimenyin Otimenyin & Doosuur Ior, 2022).

Conclusion

This study presents an in silico evidence highlighting the neuropharmacological promise of *Guiera senegalensis* phytochemicals as multi-target modulators of key CNS proteins implicated in anxiety and depression. These findings not only support the ethnomedicinal relevance of *G. senegalensis* but also contribute to the growing repertoire of plant-derived neurotherapeutics with multi-target efficacy. While the in silico workflow provides valuable predictive insights, future studies should prioritize in vitro and in vivo validation of these findings, including functional assays for receptor modulation, pharmacokinetic profiling in animal models, and comprehensive toxicological assessments. Furthermore, structure-activity relationship (SAR) studies and chemical optimization may enhance the efficacy and safety profiles of the lead compounds.

Ethical approval: Not applicable

Conflict of Interest: The authors declare that there are no conflicts of interests.

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Data availability: All data associated with this study are presented in the paper.

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