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Original Research Article

In silico evaluation of the antipsychotic potential of phytoconstituents from *Cymbopogon citratus* and *Rauwolfia vomitoria*

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Abstract

Introduction: Antipsychotic medications are essential in managing schizophrenia and bipolar disorder. However, current therapies often fail to adequately address negative symptoms and cognitive deficits, necessitating the exploration of new treatment candidates.
Purpose: This study aims to evaluate the antipsychotic potential of phytoconstituents from *Cymbopogon citratus* and *Rauwolfia vomitoria* using *in silico* approaches
Methods: Phytoconstituents of the two plants and standard reference drugs were retrieved in structure data file (SDF) format from PubChem and subjected to molecular docking using Maestro 12.8 against target receptors; dopamine D2 (PDB ID: 7DFP) and serotonin 5-HT2A (PDB ID: 7VOE). Pharmacokinetic and toxicity properties of promising ligands were assessed using SwissADME and ProTox-II webserver respectively.
Results: *Rauwolfia vomitoria* compounds including CID 1548910, 73073, 44592554, 445154 demonstrated strong binding affinity to the serotonin 5-HT2A receptor, with some outperforming standard antipsychotic drugs. Conversely, Compounds of *Cymbopogon citratus* including CID 87839, 7462 exhibited potent binding to the dopamine D2 receptor, with selected compounds exceeding the binding affinity of known antipsychotics. ADMET profiles revealed favorable pharmacokinetic and toxicity parameters for most of the tested compounds.
Conclusion: This study suggests that Compounds from *Rauwolfia vomitoria* and *Cymbopogon citratus* with CID: 73073, 445154, 158910, 87839 and others contain promising sources of novel antipsychotic agents. Further *in vitro* and *in vivo* investigations, including molecular dynamics simulations, are recommended to validate these findings and support the development of safer and more effective treatments for psychotic disorders.

Keywords: Antipsychotics, *Cymbopogon citratus, Rauwolfia vomitoria*, molecular docking, dopamine, serotonin, receptors

Indexing: Index Copernicus, African Index Medicus

Introduction

Psychosis is a devastating symptom of mental disease that is distinguished by a deep distortion in perception, poor functioning, and radical personality changes. Individuals with psychosis are unable to distinguish between subjective and objective reality, resulting in hallucinations, delusions, and disorganized thinking. Hallucinations are erroneous sensory sensations, such as hearing, seeing, or feeling things that are not there, whereas delusions are incorrect beliefs that impair functioning, such as paranoia or grandiosity [1]. Psychosis is not a separate diagnosis, but rather a symptom of several mental health conditions, including schizophrenia, bipolar disorder, schizoaffective disorder, psychotic depression, and substance-induced psychotic disorders. It is also a distinguishing trait of schizophrenia,

where symptoms such as thinking abnormalities and emotional withdrawal are common. The World Health Organization (WHO) estimates that some 450 million people worldwide suffer from mental or neurological diseases, with neuropsychiatric disorders accounting for 17.6% of disability-adjusted life years in Africa [2]. According to surveys, 12.1% of Nigeria's population has had a mental disorder at some point in their lives, indicating the substantial burden of these conditions.

Despite progress in understanding psychosis, gaps exist in tackling its global prevalence, particularly in low-resource contexts like Nigeria, where access to mental health care. Psychosis arises from the complex interplay of biological (such as genetic, neurodevelopmental abnormalities and substance use), psychosocial (stress and trauma), and environmental factors. These factors influence the onset and progression of psychotic disorders, including schizophrenia and other psychoses.

Management of psychosis encompasses pharmacological treatments, psychosocial interventions, and supportive care tailored to the patient's specific needs. Antipsychotic drugs are the cornerstone of psychosis treatment, effectively reducing symptoms like hallucinations, delusions, and agitation in various psychotic disorders. Typical antipsychotics such as chlorpromazine and haloperidol, primarily block dopamine D2 receptors, effectively treating positive symptoms but often causing extrapyramidal side effects (EPS). Despite their efficacy, their use is limited by side effects such as tardive dyskinesia, which affects up to 20% of long-term users [3].

Atypical antipsychotics like clozapine, risperidone, and olanzapine target both dopamine and serotonin receptors, offering broader symptom relief with fewer EPS [4]. However, they are associated with metabolic side effects, such as weight gain and diabetes, which require careful monitoring [5]. Despite their efficacy, antipsychotics present several challenges. Approximately 20–30% of patients show inadequate responses to antipsychotic therapy, particularly for negative symptoms and cognitive deficits [6]. This highlights the need for alternative treatment strategies, such as adjunctive therapies or novel pharmacological targets. Non-pharmacological management such as Cognitive Behavioral Therapy (CBT) which helps patients identify and challenge distorted thinking, resulting in improved coping skills. Family therapy involving family members in treatment increases support while decreasing stigma. Family treatments have been found to lower relapse rates in patients with schizophrenia by up to 50% [7].

Electroconvulsive Therapy (ECT) is used in treatment-resistant instances or severe psychosis to provide quick symptom alleviation. However, its usage is restricted by side effects such as memory loss, which can last for months. Supportive Care: Creating a safe atmosphere, addressing co-occurring illnesses, and encouraging good nutrition and sleep hygiene are all essential for recovery [8]. Sleep disruptions are common in psychosis and can exacerbate symptoms, hence sleep hygiene should be a focus of supportive therapy [9].

Nigerian medicinal plants have long been used in traditional medicine for various ailments, including neurological disorders [16]. Among these, several plants have demonstrated antipsychotic potential of which *Rauwolfia vomitoria* was found to contain reserpine, an alkaloid with antipsychotic properties [10]. While reserpine was historically used to treat psychosis, its use declined due to side effects such as depression and hypotension. *Cymbopogon citratus* was found to contain citral, an essential oil with neuropharmacological properties [11].

Citral has been shown to modulate dopamine and serotonin levels, suggesting its potential for treating psychosis [17]. While these plants show promise, their use is limited by a lack of potential toxicity, and insufficient clinical evidence. The aim of this study was to evaluate the antipsychotic potential of the compounds from *Rauwolfia vomitoria* and *Cymbopogon citratus* using computational methods.

Methods

Selection of phytochemicals and target proteins

Phytoconstituents, including natural products and metabolites from *Rauwolfia vomitoria* and *Cymbopogon citratus* were identified and their SDF format were retrieved from PUBCHEM database. Target proteins relevant to antipsychotic activity were also retrieved from the Protein Data Bank (PDB). The selected protein targets included: Dopamine Receptor, PDB ID: 7DFP (Human dopamine D2 receptor in complex with spiperone) and serotonin Receptor, PDB ID: 7VOE (Crystal structure of 5-HT2AR in complex with aripiprazole).

Protein preparation

Protein structures were prepared using the Protein Preparation Wizard in Maestro 12.8 (Schrödinger Suite) by assigning bond orders with reference to the Chemical Component Dictionary (CCD), addition of hydrogen atoms and creating zero-order bonds to metals**,** formation of disulfide bonds where applicable and generation of protonation states via Epik at physiological pH (7 ± 2) as well as energy minimization using the OPLS4 force field.

Ligand preparation

The 3D SDF format for each phytoconstituents of *Rauwolfia vomitoria* and *Cymbopogon citratus* as well as that of the standard reference were retrieved from the PubChem database. Ligand preparation was done using the ligprep panel in Maestro 12.8, employing an OPLS4 force field at pH 7.0 +/- 2.0. Desalting and tautomer generation options were selected, while stereoisomer computation was configured to generate a maximum of 2 per ligand. The output format remained as maestro.

Binding site identification

Active binding sites on each target protein were identified using the SiteMap tool in Maestro. Known binding pockets corresponding to co-crystallized ligands were analyzed, and critical active-site residues were delineated for subsequent docking studies.

Receptor grid generation

The receptor grid file was generated via the receptor grid generation panel, delineating the active sites of the receptors for glide ligand docking jobs. The ligand-binding site was defined by selecting the co-crystallized ligand spiperone of the dopamine receptor on the workspace. Van der Waals radii of the receptor atoms with partial atomic charges were set with a scaling factor of 1.0 and partial cutoff of 0.25 to soften the potential for nonpolar receptor regions. The grid box dimensions were set for outer and internal at x= 20 Å, y= 20 Å, z= 20 Å with a grid space of 1 Å. This procedure was also repeated using the ligand aripiprazole of serotonin receptor.

Molecular docking

Prepared phytochemical ligands were docked into the predefined active sites using Glide in standard precision (SP) mode. Docking results were evaluated based on Glide docking scores and detailed ligand–receptor interaction profiles. To validate the docking protocol, co-crystallized ligands and reference standards were redocked and compared to their original poses.

ADMET prediction and drug-likeness assessment

Pharmacokinetic and toxicity profiles were predicted using SwissADME and ProTox-II, providing *in silico* evaluation of absorption, distribution, metabolism, excretion, and toxicity (ADMET) properties. Drug-likeness was assessed against Lipinski's Rule of Five and other physicochemical filters to evaluate suitability as potential drug candidates.

Results

The results of the docking scores/binding affinities of phytocompounds of *Cymbopogon citratus and Rauwolfia vomitoria* are shown in Tables 1-4.

Docking scores/binding affinities

The docking scores were gotten from maestro 12.8 by docking *Cymbopogon citratus and Rauwolfia vomitoria* with dopamine and serotonin receptor proteins and were subjected to an elimination process to streamline the docking scores to those with similar or closer scores to those of the standards olanzapine and risperidone with PubChem CID 135398745 and 5073, respectively (Tables 1-4).

Table 1: Docking score of *Cymbopogan citratus* with serotonin receptor

S/N	PubChem CID	Docking score (kcal/mol)
1	5073**	-9.389
2	135398745**	-8.802
3	165266	-7.851
4	14525	-7.378
5	11463	-7.323
6	6987	-7.273
7	87839	-7.27
8	7462	-7.248
9	1254	-7.158
10	2537	-7.152

** = standard ligand

Table 2: Docking score of *Cymbopogon citratus* with dopamine receptor

S/N	PubChem CID	Docking score (kcal/mol)
1	5073**	-5.655
2	135398745**	-6.372
3	87839	-6.14
4	6987	-5.704
5	26447	-5.693
6	443159	-5.615
7	1254	-5.586
8	7462	-5.528
9	17100	-5.525
10	11463	-5.514

** = standard ligand

The standard compounds (CIDs 5073 and 135398745) showed docking scores of -5.655 and -6.372 kcal/mol, respectively, with 135398745 having the highest affinity overall. Among the test compounds, CID 87839 showed the best binding (-6.140 kcal/mol), followed closely by 6987 and 26447, indicating moderate potential compared to the standards (Table 1 and 2).

In Table 3, the standard compounds (CIDs 5073 and 135398745) showed strong binding affinities with docking scores of -9.389 and -8.802 kcal/mol, respectively. Among the test ligands, CID 16038898 (-9.230 kcal/mol) and CID 72193635 (-9.141 kcal/mol) closely matched or exceeded the standards, indicating high potential. Other notable compounds include 16040016, 1548910, and 445154, all with scores better than -8.3 kcal/mol, suggesting promising binding activity.

Table 3: Docking score of *Rauwolfia vomitoria with serotonin receptor*

S/N	PubChem CID	Docking score (kcal/mol)
1	5073**	-9.389
2	135398745**	-8.802
3	16038898	-9.23
4	72193635	-9.141
5	16040016	-8.682
6	1548910	-8.306
7	445154	-8.29
8	10130775	-7.913
9	5281727	-7.911
10	73073	-7.623
11	162888779	-7.297
12	137795317	-7.279
13	72193635	-7.255
14	441979	-7.231
15	24188474	-7.231

** = standard ligand

Table 4: Docking score of *Rauwolfia vomitoria* with dopamine receptor

S/N	PubChem CID	Docking score (kcal/mol)
1	5073**	-5.655
2	135398745**	-6.372
3	162888779	-7.17
4	14237653	-6.741
5	10130775	-6.281
6	13752000	-6.268
7	169853	-6.164
8	445154	-6.093
9	626317	-6.012
10	14237653	-5.985
11	14237653	-5.764
12	16038898	-5.715
13	72193635	-5.625
14	44592554	-5.594
15	72193635	-5.585
16	1548910	-5.564

** = standard ligand

Table 4 showed standard compounds (CIDs 5073 and 135398745) had docking scores of -5.655 and -6.372 kcal/mol, respectively. Several test compounds outperformed these, with CID 162888779 showing the strongest binding (-7.170 kcal/mol), followed by 14237653 (-6.741 kcal/mol) and 10130775 (-6.281 kcal/mol). These results suggest that multiple test ligands exhibit better binding affinities than the standards and may serve as promising candidates for further study.

ADME analysis

The ADME results were obtained by inputting the SMILES of the compounds gotten from PubChem into SWISSADME as shown in Tables 5 and 6

All compounds demonstrated favourable drug-likeness with zero Lipinski violations and a consistent bioavailability score of 0.55. Most ligands showed high gastrointestinal (GI) absorption and were blood-brain barrier (BBB) permeant. None were predicted to be P-gp substrates or CYP enzyme inhibitors, except the standards (CIDs 5073 and 135398745), which are P-gp substrates and inhibit CYP1A2, CYP2D6, and CYP3A4, indicating potential for drug-drug interactions. The rest showed a clean ADME profile, supporting their potential as safe oral drug candidates.

Toxicity profiles

Results from the toxicity profiling of the phytocompounds are shown in Tables 7 and 8. Most compounds exhibited a favourable toxicity profile, with no hepatotoxicity, nephrotoxicity, cardiotoxicity, or carcinogenicity observed across the board. However, neurotoxicity was noted in a few compounds, including the standards (CIDs 5073 and 135398745), as well as 7462, 6987, 2537, and 14525. Additionally, CID 5073 and 1254 showed respiratory toxicity. CIDs 165266, 11463, 87839, 26447, 17100, and 443159 were completely inactive across all assessed toxicity endpoints, indicating a safer toxicological profile for further development.

All tested compounds were non-hepatotoxic and non-carcinogenic, which is favourable. However, neurotoxicity was consistently present across all compounds, including the standards (CIDs 5073 and 135398745). Several test compounds - such as 1548910, 445154, 441979, 5281727 and 24188474 also showed multiple toxicities, including nephrotoxicity, respiratory toxicity, and cardiotoxicity. Only CIDs 10130775, 5073, and 135398745 had fewer toxicity flags, suggesting a relatively safer profile compared to the others, though neurotoxicity remains a common concern.

Table 5: ADME analysis of *Cymbopogon citratus* using SWISSADME

S/N	PubChem CID	GI absorption	BBB permeant	Pgp substrate	CYP1A2 inhibitor	CYP2D6 inhibitor	CYP3A4 inhibitor	Lipinski violations	Bioavailability score
1	165266	High	Yes	No	No	No	No	0	0.55
2	14525	High	Yes	No	No	No	No	0	0.55
3	11463	Low	Yes	No	No	No	No	0	0.55
4	6987	High	Yes	No	No	No	No	0	0.55
5	87839	High	Yes	No	No	No	No	0	0.55
6	7462	Low	Yes	No	No	No	No	0	0.55
7	1254	High	Yes	No	No	No	No	0	0.55
8	2537	High	Yes	No	No	No	No	0	0.55
9	443159	High	Yes	No	No	No	No	0	0.55
10	17100	High	Yes	No	No	No	No	0	0.55
11	26447	High	Yes	No	No	No	No	0	0.55
12	5073	High	Yes	Yes	Yes	Yes	Yes	0	0.55
13	135398745	High	Yes	Yes	Yes	Yes	Yes	0	0.55

Table 6: ADME analysis of *Rauwolfia vomitoria* using SWISSADME

S/N	PubChem CID	GI absorption	BBB permeant	Pgp substrate	CYP1A2 inhibitor	CYP2D6 inhibitor	CYP3A4 inhibitor	Lipinski violations	Bioavailability score
1	1548910	High	Yes	No	Yes	No	Yes	0	0.55
2	445154	High	Yes	No	Yes	No	Yes	0	0.55
3	10130775	High	Yes	No	Yes	No	Yes	0	0.55
4	5281727	High	Yes	No	Yes	Yes	No	0	0.55
5	73073	High	Yes	No	No	Yes	Yes	0	0.85
6	441979	High	Yes	No	No	Yes	Yes	0	0.85
7	24188474	High	Yes	Yes	Yes	Yes	Yes	0	0.85
8	44592554	High	Yes	Yes	No	Yes	No	0	0.55
9	5073	High	Yes	Yes	Yes	Yes	Yes	0	0.55
10	135398745	High	Yes	Yes	Yes	Yes	Yes	0	0.55

Table 7: Toxicity profile of *Cymbopogon Citratus* using PROTOX-II

S/N	PubChem CID	Hepato-toxicity	Neuro-toxicity	Nephro-toxicity	Respiratory toxicity	Cardio toxicity	Carcinogenicity
1	7462	Inactive	Active	Inactive	Inactive	Inactive	Inactive
2	6987	Inactive	Active	Inactive	Inactive	Inactive	Inactive
3	165266	Inactive	Inactive	Inactive	Inactive	Inactive	Inactive
4	11463	Inactive	Inactive	Inactive	Inactive	Inactive	Inactive
5	2537	Inactive	Active	Inactive	Inactive	Inactive	Inactive
6	87839	Inactive	Inactive	Inactive	Inactive	Inactive	Inactive
7	1254	Inactive	Inactive	Inactive	Active	Inactive	Inactive
8	26447	Inactive	Inactive	Inactive	Inactive	Inactive	Inactive
9	17100	Inactive	Inactive	Inactive	Inactive	Inactive	Inactive
10	443159	Inactive	Inactive	Inactive	Inactive	Inactive	Inactive
11	14525	Inactive	Active	Inactive	Inactive	Inactive	Inactive
12	**5073****	Inactive	Active	Inactive	Active	Inactive	Inactive
13	135398745**	Inactive	Active	Inactive	Inactive	Inactive	Inactive

** = standard ligand

Table 8: Toxicity profile of *Rauwolfia vomitoria* using PROTOX-11

S/N	PubChem CID	Hepato-toxicity	Neuro-toxicity	Nephro-toxicity	Respiratory toxicity	Cardio toxicity	Carcinogenicity
1	1548910	Inactive	Active	Active	Active	Active	Inactive
2	73073	Inactive	Active	Active	Active	Inactive	Inactive
3	44592554	Inactive	Active	Inactive	Active	Inactive	Inactive
4	445154	Inactive	Active	Active	Active	Active	Inactive
5	5281727	Inactive	Active	Active	Active	Inactive	Inactive
6	10130775	Inactive	Active	Inactive	Inactive	Inactive	Inactive
7	441979	Inactive	Active	Active	Active	Inactive	Inactive
8	24188474	Inactive	Active	Active	Active	Inactive	Inactive
9	5073**	Inactive	Active	Inactive	Inactive	Inactive	Inactive
10	135398745**	Inactive	Active	Inactive	Inactive	Inactive	Inactive

** = Standard ligand

Ligand interactions

Molecular interaction analysis with dopaminergic and serotonergic receptors

Results from the post docking analysis of some of the phytoconstituents with dopaminergic and serotonergic receptors are shown in Figures 1-26. The analysis showed that the ligands interacted with vital amino acid residues in the binding sites of various receptors. The 2D structures showed the interactions while the 3D structures revealed the ligand in the binding pockets.

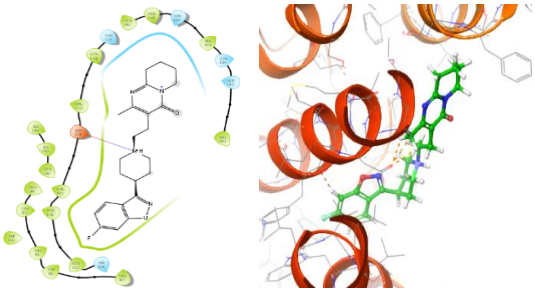

Figure 1 & 2: 2D(left) and 3D(right) structure of compound 5073 molecular interaction with dpamine receptor

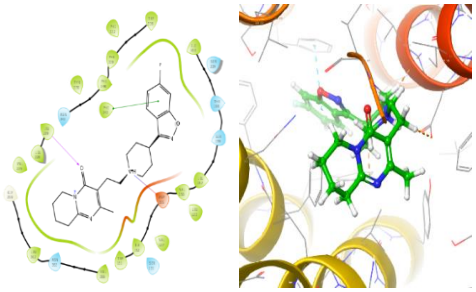

Figure 3 & 4: 2D(left) and 3D(right) structure of compound 5073 molecular interaction with serotonin receptor

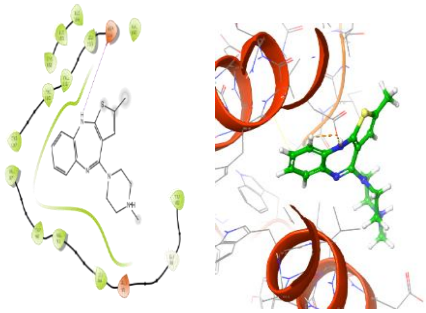

Figure 5 & 6: 2D(left) and 3D(right) structure of compound 135398745 molecular interaction with dopamine receptor

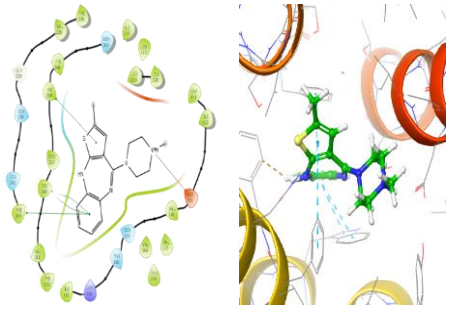

Figure 7 & 8: 2D(left) and 3D(right) structure of compound 135398745 molecular interaction with serotonin receptor

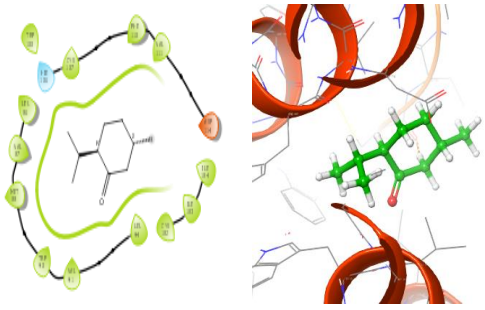

Figure 9 & 10: 2D(left) and 3D(right) structure of compound 443159 molecular interaction with dopamine receptor

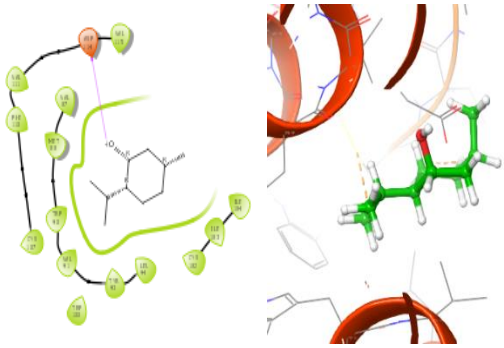

Figure 11 & 12: 2D(left) and 3D(right) structure of compound 1254 molecular interaction with dopamine receptor

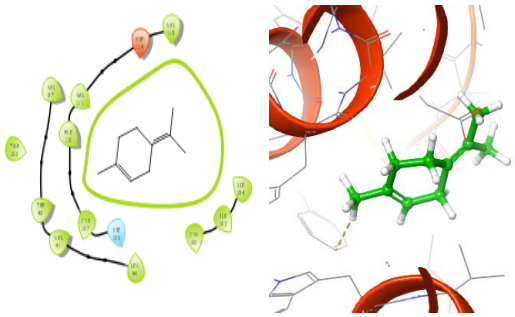

Figure 13 & 14: 2D(left) and 3D(right) structure of compound 11463 molecular interaction with dopamine receptor

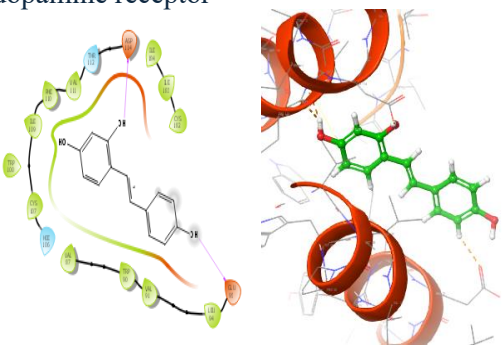

Figure 15 & 16: 2D(left) and 3D(right) structure of compound 10130775 molecular interaction with dopamine receptor

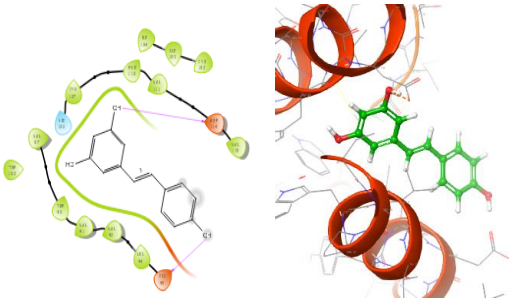

Figure 17 & 18: 2D(left) and 3D(right) structure of compound 445154 molecular interaction with dopamine receptor

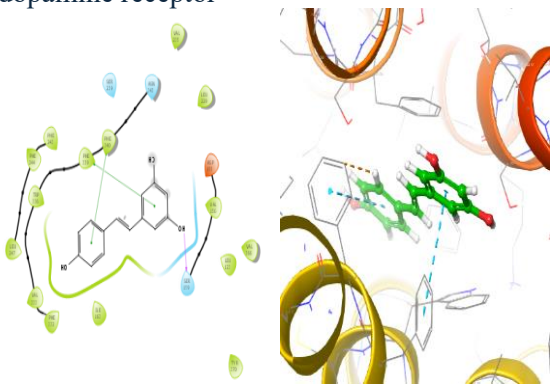

Figure 19 & 20: 2D(left) and 3D(right) structure of compound 445154 molecular interaction with dopamine receptor

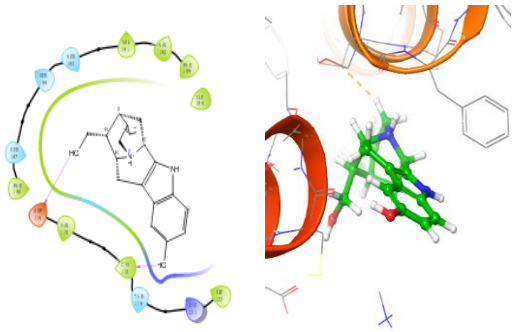

Figure 21 & 22: 2D(left) and 3D(right) structure of compound 44592554 molecular interaction with dopamine receptor

Figure 23 & 24: 2D(left) and 3D(right) structure of compound 1548910 molecular interaction with dopamine receptor

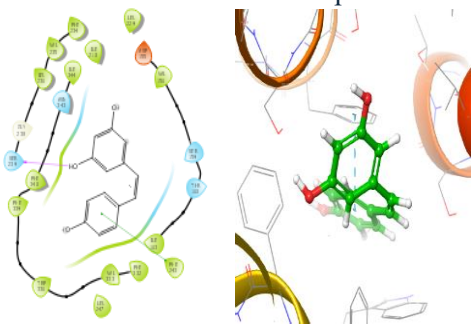

Figure 25 & 26: 2D(left) and 3D(right) structure of compound 1548910 molecular interaction with serotonin receptor

Discussion

In silico research has provided critical insights into the binding affinities of potential pharmacological active compounds. Binding scores, typically expressed in kcal/mol, are used to classify ligand-protein interactions into high, moderate, and low affinity categories. High-affinity interactions (scores <-9 kcal/mol) are particularly promising for drug development, as they indicate strong binding and potential therapeutic efficacy Scores ranging from -7 to -9 kcal/mol are typically classified as moderate affinity. These interactions are significant but not as strong as those in the high affinity category. Scores greater than -7 kcal/mol are usually considered low affinity. These interactions are weaker and may not be sufficient for effective binding in a biological context [12-13].

Molecular docking

Docking scores are predictive values used to assess receptor-ligand interactions and potential effects. A more negative Docking score typically indicates a stronger binding affinity, suggesting a higher likelihood of stable interactions between the ligand and receptor [14-16]. The strength of receptor-ligand interactions is estimated based on Docking scores, where lower values suggest better binding potential.

Cymbopogon citratus

This study utilized high-throughput virtual screening (HTVS) and standard precision (SP) docking to evaluate 155 natural products and 57 metabolites from *Cymbopogon citratus* against dopamine (7DFP) and serotonin (7VOE) receptors. The docking results from Table 1 showed several compounds exhibited strong binding affinities, with several matching or exceeding the dopamine receptor binding of standard antipsychotics. Notably, compound 87839 (Figure 27) with binding affinity of -6.14 Kcal/mol outperformed olanzapine (-5.655 Kcal/mol) and approached risperidone (-6.372 Kcal/mol). However, on Table 2, none of the *Cymbopogon citratus* compounds demonstrated serotonin receptor binding comparable to the standard benchmark suggesting that while some phytochemicals may exhibit dopaminergic activity, their serotonergic interaction is insufficient for dual-receptor antipsychotic potential.

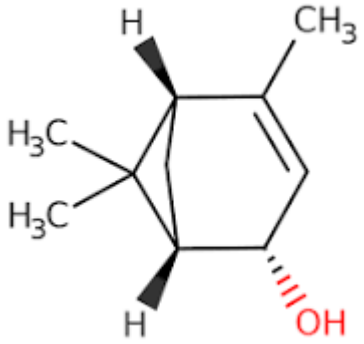

Figure 27: Structure of compound CID 87839

Rauwolfia vomitoria

A total of 316 natural products and one metabolite from *Rauwolfia vomitoria* were screened using HTVS and SP docking, identifying several compounds with significant binding affinities. Several exhibited strong serotonin receptor interactions, particularly compound 16038898 (Figure 28) with binding affinity of -9.23 Kcal/mol were also equivalent to that of olanzapine -9.389 Kcal/mol as seen in Table 3. Other notable serotonin-binding compounds included 16040016 (-8.682 Kcal/mol), 1548910 (-8.306 Kcal/mol), and 445154 (-8.29 Kcal/mol). In contrast, compound 162888779 displayed the highest dopamine receptor affinity (-7.17 Kcal/mol), outperforming risperidone (-6.372 Kcal/mol) and olanzapine (-5.655 Kcal/mol). Other promising dopamine-binding compounds included 14237653 (-6.741 Kcal/mol), 10130775 suggesting potential dual-receptor activity akin to standard antipsychotics seen in Table 4. These results show that *Cymbopogon citratus* could be seen as a potential source of dopaminergic compounds, while *Rauwolfia vomitoria* exhibits promising dual-receptor interactions. Further experimental validation is necessary to confirm their antipsychotic potential.

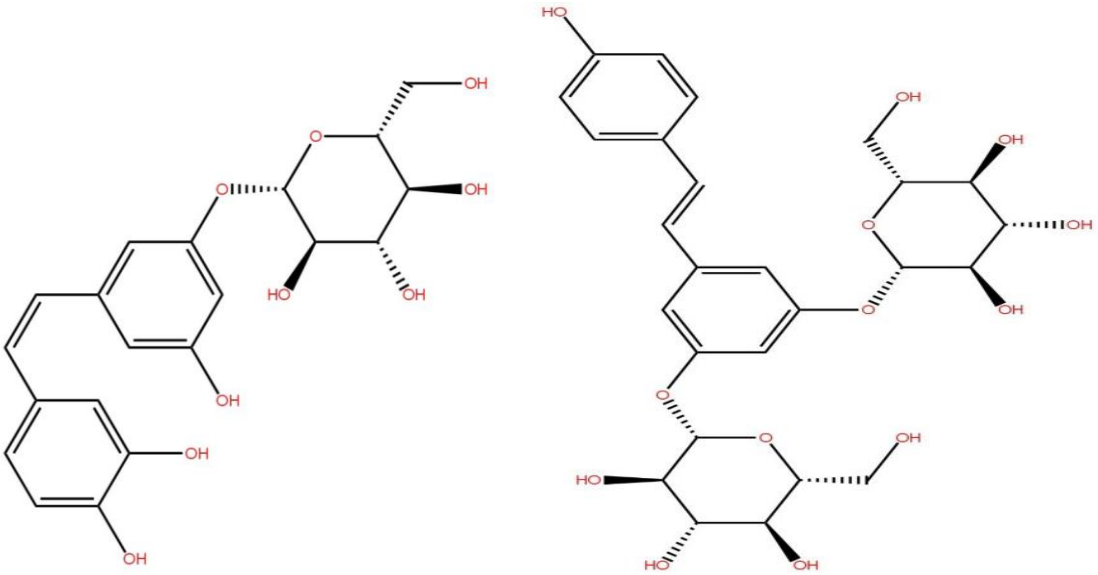

Figure 28: Structures of compound CID 16038898 (left) and 1604016 (right)

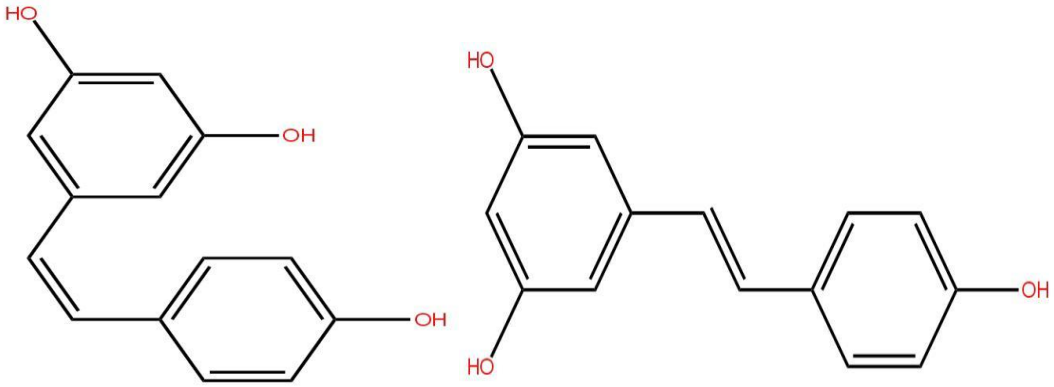

Figure 29: Structures of compound CID 1548910 (left) and 445154 (right)

Drug likeness and ADME profile

Pharmacokinetic profile

The pharmacokinetic evaluation of the selected phytochemicals from *Cymbopogon citratus* and *Rauwolfia vomitoria* revealed high gastrointestinal (GI) absorption for most compounds as shown in Table 5 and 6, except for CID 7462 in *Cymbopogon citratus*. Both sets of compounds demonstrated the ability to cross the blood-brain barrier (BBB), which is a critical feature for central nervous system (CNS)-acting drugs. Regarding interactions with P-glycoprotein (P-gp), none of the *Cymbopogon citratus* compounds were identified as substrates, which is beneficial for brain penetration. However, some *Rauwolfia vomitoria* compounds were found to be P-gp substrates, suggesting that their CNS bioavailability might be reduced due to efflux mechanisms. In terms of cytochrome P450 (CYP) enzyme interactions, most *Cymbopogon citratus* compounds did not inhibit key metabolic enzymes. On the other hand, several *Rauwolfia vomitoria* compounds inhibited CYP1A2, CYP2D6, and CYP3A4. The inhibition of CYP1A2 (by CID 1548910, CID 137795317, and CID 72318) raises concerns for interactions with caffeine and theophylline. CYP2D6 inhibition (by CID 445154, CID 10130775, and CID 137795317) may influence the metabolism of psychiatric drugs and cardiovascular agents, while CYP3A4 inhibition (by CID 1548910 and CID 137795317) could impact the clearance of statins, benzodiazepines, and calcium channel blockers.

Drug-likeness and metabolic considerations

The compounds from *Cymbopogon citratus* demonstrated good oral bioavailability, high GI absorption, and strong BBB permeability, making them strong candidates for CNS-related applications. Additionally, the absence of P-gp interactions suggests that these compounds may have enhanced brain retention compared to conventional antipsychotics, which often face efflux-related limitations. However, *Rauwolfia vomitoria* compounds exhibited significant CYP enzyme inhibition, increasing the likelihood of drug-drug interactions. These findings suggest that careful dose adjustments and co-administration considerations are necessary when using these compounds in therapeutic settings.

Toxicity assessment

The toxicity profile of *Cymbopogon citratus* compounds was relatively favorable, with no observed cardiotoxicity or hepatotoxicity as shown in Table 7. However, one compound (CID 6987) showed potential neurotoxic effects, and compounds CID 443159 and CID 11463 were linked to respiratory toxicity. In contrast, *Rauwolfia vomitoria* compounds exhibited a higher degree of toxicity concerns. Some compounds (CID 10130775, CID 445154, and CID 44592554) showed neurotoxicity, while cardiotoxicity was observed in CID 13752000, CID 16038898, and CID 626317. Additionally, hepatotoxicity was detected in CID 1548910, and both respiratory and nephrotoxicity risks were noted for CID 1548910 and CID 16040016.

Overall, *Cymbopogon citratus* compounds show a promising pharmacokinetic profile with strong BBB penetration and minimal CYP-related metabolic concerns. These properties suggest that they could be valuable candidates for CNS-targeted therapies. However, the neurotoxic potential of CID 6987 warrants further investigation to assess its safety. On the other hand, while *Rauwolfia vomitoria* compounds (Table 8) also demonstrated strong BBB permeability, their interaction with P-gp and significant CYP enzyme inhibition poses challenges for CNS bioavailability and metabolic stability. The presence of neurotoxicity and cardiotoxicity in some compounds indicates the need for structural modifications or dose optimizations to reduce these risks while preserving therapeutic efficacy. To advance these findings, further experimental validation is necessary, particularly *in vivo* and *in vitro* studies to assess metabolic stability and safety. Additionally, prodrug strategies could be explored to mitigate the P-gp efflux of *Rauwolfia vomitoria* compounds, while structural modifications might help minimize toxicity risks.

Bond interactions

Compounds from *Cymbopogon citratus* show mixed potential for dopamine receptor modulation. Specifically, compounds CID 87839, CID 1254, and CID 17100 formed hydrogen bonds with Asp114, which suggests they may effectively modulate dopamine receptor activity. In contrast, other compounds (CID 7462, 11463, 443159, 26447, and 6987)

did not bind, indicating a limited capacity as dopamine receptor ligands. This variation in binding suggests that while some chemicals from *Cymbopogon citratus* could be pharmacologically relevant, others might need further modifications to enhance their activity. In comparison, *Rauwolfia vomitoria* demonstrated more promising interactions with dopamine receptors.

For example, compounds CID 162888779, CID 10130775, and CID 445154 all formed hydrogen bonds with both Glu95 and Asp114, reinforcing their potential for dopamine receptor binding. Moreover, compounds CID 13752000 and CID 169853 exhibited even stronger interactions by forming hydrogen bonds with Asp114, Asp80, and Tyr199, as well as engaging in π-π stacking with residue 198 and forming a salt bridge with Lys121. These enhanced interactions suggest that these compounds may have a more robust pharmacological effect. Additionally, several compounds from *Rauwolfia vomitoria* showed interactions with serotonin receptors, indicating their potential as atypical antipsychotics. For instance, CID 445154 engaged in π-π stacking with Phe339 and Phe340 and formed hydrogen bonds with Ser159.

Similarly, CID 16038898 established hydrogen bonds with Asp155 and Ile206. Further, CID 1548910 demonstrated π-π stacking with Phe243 and hydrogen bonding with Ser239, while CID 16040016 formed hydrogen bonds with Asp156 and showed π-π interactions. These interactions with serotonin receptors add another layer to the pharmacological potential of these compounds.

Conclusion

The *in-silico* experiments showed that *Rauwolfia vomitoria* exhibited the most promising dual-receptor interactions, with several compounds demonstrating superior serotonin receptor affinity compared to standard antipsychotics and others displaying high dopamine receptor binding and *Cymbopogon citratus* showed selective dopaminergic activity, making them potential sources of dopamine-modulating antipsychotic agents with many of these compounds possessing favorable pharmacokinetic and ADMET properties.

Abbreviations

3D: Three-dimensional,
ADME: Absorption, Distribution, Metabolism and Excretion,
ADMET: Absorption, Distribution, Metabolism, Excretion and Toxicity
CBT: Cognitive Behavioural Therapy
CID: Compound Identifier
CNS: Central Nervous System
CYP: Cytochrome P450
ECT: Electroconvulsive Therapy
EPS: Extrapyramidal Side Effects
HTVS: High-Throughput Virtual Screening
SDF: Structure Data File
SMILES: Simplified Molecular Input Line Entry System
SP: Standard Precision
WHO: World Health Organization

Conflict of Interest

No conflict of interest is associated with this work.

Contribution of Authors

We declare that this work was carried out by the authors named in this article all liabilities pertaining to claims relating to the content of this article will be borne by the authors. The *in silico* experiment, data administration, and manuscript writing were done by CI while UMO designed the study. Critical assessment and endorsement of final copy of manuscript by CI and UMO.

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