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Short Communication

# *In-silico* investigation of the antischizophrenic activity of phytochemical constituents of *Hymenocardia acida* Tul. (Phyllantaceae)

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ABSTRACT

*Hymenocardia acida* is a medicinal plant used in the treatment of schizophrenia. Previous studies have shown that *H. acida* possessed anti-schizophrenic activity *in vivo*. This plant was reported to contain several phytochemical constituents, and the pharmacological activities of the plant might be related to its phytochemical constituents. Therefore, this study aimed to investigate the *in-silico* anti-schizophrenic activity of the phytochemical compounds of *H.acida*. The phytochemical constituents of *H.acida* were examined for their anti-schizophrenic activity using *in-silico* molecular docking studies. Sixteen compounds were docked against three receptors namely, D1 dopamine receptor (PDB I.D 7JOZ), D2 dopamine receptor (PDB I.D 6CM4), and serotonin receptor $5HT_{1A}$ (PDB I.D 7E2Y). The results obtained from molecular docking studies proved that phytochemical compounds present in *H. acida* have adequate affinity for both dopaminergic and serotonergic receptors. Therefore, this study demonstrates that *H. acida* possesses antipsychotic properties, which may be attributed to its phytochemical compounds due to their strong binding affinity to the respective dopaminergic and serotonergic receptors.

**Keywords**: *In-silico*, Docking, Phytochemical, Anti-schizophrenic, *H. acida*

## Introduction

Schizophrenia is a multifactorial disorder with a complex origin, resulting from the interplay of various factors across different life stages. Its pathogenesis is strongly linked to excessive dopaminergic activity.[1] Individuals with schizophrenia inherit genetic factors that contribute to structural abnormalities in the brain, which may be further exacerbated by early environmental influences. Consequently, some children who are predisposed to schizophrenia may display mild developmental delays, cognitive difficulties, or challenges in social interactions. These individuals are vulnerable to dopamine dysregulation, which serves as the ultimate pathway to the emergence of psychotic disorders. Research on animals has shown that stress can trigger dopamine release, while epidemiological studies indicate that social stressors can act as catalysts for schizophrenia onset.[2] All antipsychotic drugs for schizophrenia act by blocking dopamine D2 receptors. While effective against psychosis, they do little for negative and cognitive symptoms and cause severe side effects, including seizures, vision loss, and neuroleptic malignant syndrome. Patients often experience poor quality of life, and the high cost adds financial strain. This highlights the need for safer, more affordable alternatives. Phytochemical compounds, particularly flavonoids, were reported to exhibit central nervous system depressant activity as they can bind to $GABA_A$ receptors, producing sedative and anxiolytic effects.[3]

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A newly identified bioactive flavonoid, 3-(3,4-dimethoxy phenyl)-1-(4-methoxy phenyl) prop-2-en-1-one, isolated from *Celastrus paniculatus*, has been reported to demonstrate notable neuroprotective and anti-schizophrenic effects by regulating bioenergetic pathways disrupted in induced schizophrenia.[4] Furthermore, quercetin has been shown to exhibit strong binding affinities for both dopamine and N-methyl-D-aspartate receptors, suggesting its potential as an anti-schizophrenic agent.[5] Prior to the introduction of conventional medicine, herbal remedies served as the primary healthcare system for millions across Africa, providing essential medical care to both rural and urban populations.[6] In our previous study, the methanol leaf extract of *Hymenocardia acida* was reported to have potent anti-schizophrenic activity.[7] This study aimed to investigate the antischizophrenic activity of the phytochemical constituents of *H. acida* using *in-silico* molecular docking studies.

## Materials and Methods

*Software and servers:*

MarvinSketch, PyRx 0.8 (The Scripps Research Institute), Discovery Studio 2020, Autodock vina. Pro-Tox II server (https://tox.charite.de/protox_II/), SwissADME server (https://www.swissadme.ch/).

*Compounds Selection*

In our previous study, we conducted a comprehensive review of scholarly articles on *H. acida* from online electronic databases, and sixteen (16) different phytochemical compounds were isolated from the plant.[8] In this study, the affinity of these compounds to the dopaminergic and serotonergic receptors was investigated using *in-silico* molecular docking.

*Ligand Preparation*

Two-dimensional structures (2D) of all the steroidal compounds, including the reference drug (risperidone), were downloaded from

PubChem. However, structures of all the alkaloids and stilbenes were drawn using Mavin_window-x64_19.4. All structures were saved in SDF (Standard Drug File) format. The 2D structures were then optimized for docking by converting them to small molecules using PyRx.

*Protein Preparation*

The protein structures Dopamine D1 (7JOZ), D2 (6CM4), and serotonin $5HT_{1A}$ (7E2Y) were obtained from the Protein Data Bank (www.rcsb.org) in PDB format. They were prepared for molecular docking using the Discovery Studio visualizer by removing water molecules and co-crystallized ligands within the protein structure. Additionally, polar hydrogens were added, and Chain A of each receptor was selected for analysis.

*Docking Study and Virtual Screening*

Molecular docking investigation was conducted separately between the three different protein receptor types; dopamine D1 (7JOZ), D2 (6CM4), and serotonin $5HT_{1A}$ (7E2Y), and the 16 selected compounds as well as the reference drug risperidone, to probe into individual ligands' binding affinity to the proteins. The proteins (D1, D2, and $5HT_{1A}$) were selected because they are implicated in schizophrenia.[9] The method was first validated by redocking the co-crystallized native ligand with its respective receptor. The docking was carried out using Autodock vina of PyRx virtual screening tool. PyRx virtual screening tool is software for screening compounds against potential drug targets.[10] In this study, the blind docking approach was adopted and the grid dimensions were predicted as x:83.20 y:59.68 z:20.22 for 6CM4, x:83.20 y:129.01 z:93.47 for 7E2Y, and x:65.94 y:109.72 z:25.00 for 7JOZ. The docking was carried out with the default parameter, and a maximum of nine (9) conformations were predicted for each compound. The more negative the binding energy becomes, the greater the chances of the potential drug candidate initiating protein biochemical action or reaction.[11,12] For each ligand, the conformation with the highest binding affinity was then saved in pdb format and was further analyzed using the Discovery Studio visualizer.

*Drug Likeness and Pharmacokinetic Studies*

The drug-likeness, pharmacokinetic, and toxicity profiles of the sixteen (16) selected compounds (five steroids, seven stilbenes, and four alkaloids) were investigated. The pharmacokinetic investigation was carried out using "admetSAR" on the SwissADME web server. Lipinski's rule of five (5) was used to assess the drug-likeness and physicochemical properties that will be imperative in the efficiency and absorption of the compounds. The acute oral toxicity was predicted using the Pro-Tox II prediction server.

## Results and Discussion

The binding scores of all the studied compounds against each of the three receptors are reported (Table 1). Moreover, all studied compounds had a high affinity to the three receptors. The higher the binding activity (greater negative value) the higher the inhibitory action of the compound,[13] hence it was observed that hymenocardine N-oxide had greater inhibitory action to 6CM4 (-9.8 kcal/mol), lupeol and hymenocardichromene F against 7JOZ (-9.3 kcal/mol) and hymenocardinol against 7E2Y (-10 Kcal/mol). However, the reference ligand risperidone had a better affinity for 7JOZ and 7E2Y with binding affinities of -10.6 and -10.4 kcal/mol, respectively. The results obtained from molecular docking studies proved that phytochemical compounds present in *H. acida* have adequate affinities for both dopaminergic and serotonergic receptors (Table 1.0). Also, it could be seen that interaction was fair across all receptors and no particular receptor had the best interaction with the studied ligands. A receptor may interact better with a particular ligand than another within the same class. The highest binding affinity to the D1 receptor was predicted to be exhibited by lupeol and hymenocardichromene F from the steroid and stilbene class, respectively. Both had an equal binding affinity of -9.3 kcal/mol, which is higher than the binding affinity of all the other tested compounds but considerably lower than that of risperidone (-10.6 kcal/mol) (Table **1.**). The co-crystallized ligand (native ligand) redocked into the dopamine D1 receptor PDB ID 7JOZ shows a similar binding interaction with the complex downloaded from the protein data bank (Figure 1A and Figure 1B). The reference molecule risperidone was predicted to interact with the receptor via both hydrogen (Ser277), hydrophobic (His62, Met188, Ala231, Cys148, Met101) as well as pi-cation (Arg150) bonds (Figure 2). Lupeol was predicted to interact through three hydrophobic bonds of the alkyl and pi-alkyl types at Val234, Ala255, and Phe232 (Figure 3). Likewise, the interaction profile of hymenocardichromene F showed interaction via hydrophobic bonds at Trp90, Trp99, Cys186, and Lys581 which were majorly of the alkyl and pi-pi T-shaped types. More so, there was also a pi-sulfur bond interaction at cys96 for hymmenocardichromene F (Figure 4). Similarly, the result of docking validation of both redocked and downloaded complexes showed similar binding interactions. The native/reference ligand risperidone interacted with 6CM4 via both hydrogen and hydrophobic bonds. Two hydrogen bonds at Arg1096, Asp1072 and seven hydrophobic bonds majorly of the alkyl and pi alkyl type at Arg220, Ile10003, Ala1097, Ala1093, Lys221, Val1075, and Leu1079. Other interactions include a carbon-hydrogen bond at Asp1072 and an unfavourable acceptor bond at Tyr1088 (Figure 5A and Figure 5B).

Hymenocardine N-oxide, hymenocardichromene D, and lupeol were predicted to have the highest negative binding energy for the dopamine D2 receptor (6CM4) as shown in Table 1. All three compounds were predicted to possess docking scores higher than the other studied compounds including the native/reference ligand; risperidone. Hymenocardine N-oxide had the highest negative docking energy (-9.8 kcal/mol) to the D2 receptor among all studied compounds. Hymenocardine N-oxide interacted via conventional hydrogen bonds at Tyr408; Ser409 and hydrophobic bonds of the pi-pi T shaped and pi alkyl types at Trp100, Leu94, and Phe389 (Figure 6). Hymenocardichromene D had the second highest docking energy -9.3 kcal/mol and was predicted to interact with the receptor via six hydrophobic interactions of the pi alkyl, alkyl, and pi sigma types at Ala378, Ala379, Ile383, Leu206, Phe202, Ile210 and one conventional hydrogen bond at Ala122 (Figure 7). Interestingly, lupeol with a docking energy of -9.1 kcal/mol was predicted to interact with the 6CM4 receptor via a single hydrophobic interaction at Ile383 (Figure 8). The native ligand redocked into the $5HT_{1A}$ binding site showed a similar interaction with the complex downloaded from pdb (Figure 9A and Figure 9B). Among all the studied compounds, hymenocardinol, betulinic acid, and friedelan-3-one had the highest negative docking energies for the $5HT_{1A}$ receptor. Hymenocardinol (alkaloid) was predicted to have the highest negative affinity (-10 kcal/mol) to $5HT_{1A}$. Betulinic acid (-9.9 kcal/mol) and friedelan-3-one (-9.8 kcal/mol) both steroidal compounds had second and third highest negative binding energies, respectively. However, all three compounds had docking energies considerably lower than the docking energy for risperidone (-10.4 kcal/mol) as seen in Table 1.0. The interaction profile of hymenocardinol revealed protein-ligand interaction via conventional hydrogen bonds at Gly192; Asn84, carbon-hydrogen bond at Ile193, hydrophobic bonds of the pi sigma and pi alkyl types at Pro238; Leu192; Arg150; His62 and finally a pi sulfur bond at Cys233 (Figure 10). Though betulinic acid was one of the compounds with the highest negative binding energy its interaction profile showed no prediction of hydrophobic or hydrogen bond interactions with the receptor (Figure 11). Friede-lan-3one however, interacted with the $5HT_{1A}$ receptor via one conventional hydrogen bond at ARG 150 (Figure 12). Risperidone with the highest predicted binding affinity to $5HT_{1A}$ receptor interacted via the hydrophobic bond of pi-pi stacked, alkyl, and pi alkyl at His62, Ala23. Others include Pi sulfur and pi-cation bonds at Arg150 and Met180 (Figure 13).

It is noteworthy that other docked compounds also had very good binding energies (Table 1.0) as well as interactions with key amino acid residues. Additionally, the presence of both substituted and un-substituted aromatic groups in the structural framework of the stilbenes and alkaloids was found to be of significance in the forming of pi interactions with key amino acid residues of the proteins. The steroidal framework lacked both substituted and un-substituted aromatic groups; however, they still had good binding interaction with the proteins via hydrogen and hydrophobic bonds as well as pi bonds with key amino acid residues. The results of drug-likeness properties, including the

**Table 1:** Binding affinity of steroids and alkaloids from *H. acida* and reference drug (risperidone) with dopamine and serotonin receptors.

| Ligand | Protein Ligand-Interaction (Kcal/mol) | | |
|---|---|---|---|
| | D1 PDB I.D: (7JOZ) | D2 PDB I.D: (6CM4) | $5HT_{1A}$ PDB I.D: (7E2Y) |
| Friedlan-3-One | -8.9 | -8.2 | -9.8 |
| Betulinic acid | -8.8 | -8.4 | **-9.9** |
| Lupeol | **-9.3** | -9.1 | -9.6 |
| Beta-Sitosterol | -8.1 | -8.1 | -8.9 |
| Stigmasterol | -8.8 | -8.4 | -8.6 |
| Hymenocardinol | -8.5 | -7.3 | -10 |
| Hymenocardine N-Oxide | -8.4 | **-9.8** | -8.9 |
| Hymenocardine-H | -8.1 | -7.5 | -8.4 |
| Hymenocardine | -8.3 | -8.7 | -9.4 |
| Hymenocardichromene A | -7.4 | -7.8 | -7.7 |
| Hymenocardichromene B | -7.6 | -7.6 | -8.3 |
| Hymenocardichromene C | -7.7 | -8.8 | -8.5 |
| Hymenocardichromene D | -8.0 | -9.2 | -9.3 |
| Hymenocardichromene E | -7.4 | -7.5 | -8.9 |
| Hymenocardichromene F | **-9.3** | -7.9 | -9.0 |
| Hymenocardichromanic Acid | -9.1 | -8.4 | -9.4 |
| Risperidone | -10.6 | -8.4 | -10.4 |

**Table 2:** Predicted drug-likeness properties of selected compounds and reference risperidone analyzed with SwissADME

| Compound | Molecular weight (g/mol) | LogP | nHBD | nHBA | TPSA | MR | Log $k_p$ (cm/s) | Log S | nRotB | Lipinski's violation | Inference |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Friedelan-3-one | 426.7 | 6.92 | 0 | 1 | 17.07 | 134.39 | -1.94 | -10.08 | 0 | 1 | **Pass** |
| Betulinic acid | 456.7 | 5.82 | 2 | 3 | 57.53 | 136.91 | -3.26 | -9.28 | 2 | 1 | **Pass** |
| Lupeol | 412.69 | 6.73 | 1 | 1 | 20.23 | 130.59 | -2.09 | -9.81 | 1 | 1 | **Pass** |
| Beta-sitosterol | 414.7 | 6.73 | 1 | 1 | 20.23 | 133.23 | -2.2 | -9.67 | 6 | 1 | **Pass** |
| Stigmasterol | 412.67 | 6.62 | 1 | 1 | 20.23 | 132.75 | -2.74 | -8.86 | 5 | 1 | **Pass** |
| Hymenocardinol | 676.85 | 0.5 | 6 | 7 | 164.86 | 197.01 | -7.52 | -7.26 | 12 | 3 | Fail |
| Hymenocardine-N-oxide | 690.83 | -1.35 | 5 | 7 | 187.92 | 199.64 | -7.48 | -7.94 | 12 | 2 | Fail |
| Hymenocardine-H | 653.81 | 3.53 | 5 | 8 | 174.62 | 186.13 | -7.5 | -5.62 | 18 | 2 | Fail |
| Hymenocardine | 674.83 | 3.18 | 5 | 7 | 161.73 | 196.27 | -7.04 | -7.88 | 12 | 2 | Fail |
| Hymenocardichromene A | 346.46 | 5.50 | 1 | 2 | 29.46 | 111.68 | -3.66 | -7.11 | 4 | 1 | **Pass** |
| Hymenocardichromene B | 390.47 | 5.70 | 2 | 4 | 66.76 | 118.64 | -3.88 | -7.97 | 4 | 0 | **Pass** |
| Hymenocardichromene C | 404.5 | 4.32 | 2 | 4 | 66.76 | 123.28 | -3.69 | -8.37 | 7 | 1 | **Pass** |
| Hymenocardichromene D | 420.50 | 3.50 | 3 | 5 | 86.99 | 124.45 | -4.49 | -7.77 | 8 | 0 | **Pass** |
| Hymenocardichromene E | 420.50 | 3.50 | 3 | 5 | 86.99 | 124.48 | -4.95 | -7.1 | 7 | 0 | **Pass** |
| Hymenocardichromene F | 418.48 | 3.42 | 2 | 5 | 83.83 | 123.48 | -4.73 | -7.33 | 8 | 0 | **Pass** |
| Hymenocardichromanic acid | 376.44 | 4.06 | 2 | 4 | 66.76 | 109.3 | -4.52 | -6.91 | 3 | 0 | **Pass** |
| Risperidone | 410.80 | 3.19 | 0 | 6 | 64.16 | 117.71 | -6.87 | -3.72 | 4 | 0 | **Pass** |

Linpinski's rule of 5: (1)-MW<500Da (2)-LogP<5 (3)-nHBD<5 (4)-nHBA<10 (5)-nRotB<5Abbreviations: MW: Molecular weight, LogP: Log of octanol/water partition coefficient, nHBA: Number of hydrogen bond acceptor(s), nHBD: Number of hydrogen bond donor(s), MR-Molar refractivity, nRotB: Number of rotatable bonds, Log S: log of solubility, TPSA: Total polar surface area.

**Table 3:** Predicted ADME properties of the selected compounds and reference drug risperidone analyzed with SwissADME.

| Compound | Log-$K_p$ (cm/s) | GI Abs | BB Perm | P-gp substrate | CYP1A2 Inhibitor | CYP2C19 inhibitor | CYP2C9 Inhibitor | CYP2D6 inhibitor | CYP3A4 Inhibitor |
|---|---|---|---|---|---|---|---|---|---|
| Friedelan-3-one | -1.94 | Low | No | No | No | No | No | No | No |
| Betulinic acid | -3.26 | Low | No | No | No | No | Yes | No | No |
| Lupeol | -2.09 | Low | no | No | No | No | No | No | No |
| Beta-sitosterol | -2.2 | Low | no | No | No | No | No | No | No |
| Stigmasterol | -2.74 | Low | no | No | No | No | Yes | No | No |
| Hymenocardinol | -7.52 | Low | no | Yes | No | No | No | No | Yes |
| Hymenocardine N-oxide | -7.48 | Low | no | Yes | No | No | No | No | Yes |
| Hymenocardine H | -7.5 | Low | no | Yes | No | No | No | No | Yes |
| Hymenocardine | -7.04 | Low | no | Yes | No | No | No | No | Yes |
| HymenocardichromeneA | -3.66 | High | no | No | No | Yes | No | Yes | No |
| HymenocardichromeneB | -3.88 | High | no | No | No | Yes | Yes | No | Yes |
| HymenocardichromeneC | -3.69 | High | no | No | No | No | Yes | Yes | Yes |
| HymenocardichromeneD | -4.49 | High | no | No | Yes | No | Yes | Yes | Yes |
| HymenocardichromeneE | -4.95 | High | no | No | No | No | Yes | Yes | Yes |
| Hymenocardichromen F | -4.73 | High | no | No | Yes | No | Yes | Yes | Yes |
| Hymenocardichromanic acid | -4.52 | High | no | Yes | Yes | No | Yes | No | No |
| Risperidone | -6.87 | High | Yes | Yes | Yes | Yes | Yes | Yes | Yes |

Abbreviations: log Kp: Log of skin permeability; GI Abs: Gastrointestinal absorption; BBB Per: Blood-brain barrier permeability; P-gp, P-glycoprotein; CYP, cytochrome-P450.

**Table 4:** Toxicity profile of the selected compounds and reference drug risperidone predicted with Pro-Tox II server

| COMPOUND | Predicted $LD_{50}$ (mg/Kg) | Average Similarity (%) | Prediction Accuracy (%) | Predicted Toxicity Class |
|---|---|---|---|---|
| Friedelan-3-One | 500 | 100 | 100 | 4 |
| Betulinic Acid | 2610 | 77.12 | 69.26 | 5 |
| Lupeol | 2000 | 100 | 100 | 4 |
| Beta-Sitosterol | 890 | 89.38 | 70.97 | 4 |
| Stigmasterol | 890 | 89.38 | 70.97 | 4 |
| Hymenocardinol | 550 | 59.12 | 67.38 | 4 |
| Hymenocardine H | 2400 | 68.08 | 68.07 | 5 |
| Hymenocardine N-Oxide | 550 | 59.15 | 67.38 | 4 |
| Hymenocardine | 550 | 62.58 | 68.07 | 4 |
| Hymenocardichromanic Acid | 1000 | 54.77 | 67.38 | 4 |
| Hymenocardinehromen A | 500 | 57.75 | 67.38 | 4 |
| Hymenocardichromene B | 1000 | 54.83 | 67.38 | 4 |
| Hymenocardichromene C | 500 | 58.33 | 67.38 | 4 |
| Hymenocardichromene D | 500 | 59.65 | 67.38 | 4 |
| Hymenocardichromene E | 750 | 57.76 | 67.38 | 4 |
| Hymenocardichromene F | 500 | 58.35 | 67.38 | 4 |
| Risperidone | 57 | 100 | 100 | 3 |

Class 1-fatal if swallowed LD50≤5, class 2: fatal if swallowed LD50≤50, class 3: toxic if swallowed LD50≤300, class 4: harmful if swallowed LD50≤2000, class 5: may be harmful if swallowed LD50 ≤5000 and class 6: non-toxic LD50≥5000.

**Figure 1A:** 3D/2D structures of dopamine D1 receptor PDB ID 7JOZ in complex with co-crystallize native ligand (G protein and a non-catechol agonist)

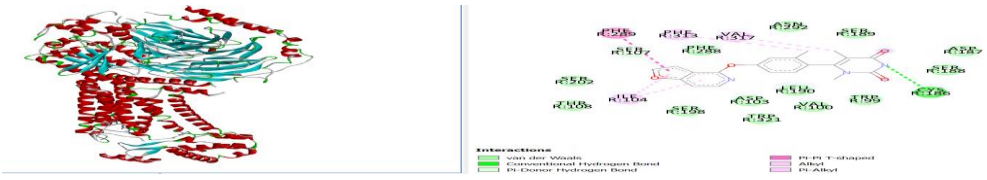

**Figure 1B**: 3D/2D structures of **redocked** native ligand (G protein and a non-catechol agonist) in complex with dopamine D1 receptor PDB ID 7JOZ

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**Figure 2:** 3D/2D structures of dopamine D1 receptor PDB ID 7JOZ in complex with Risperidone

**Figure 3**: 3D/2D structures of dopamine D1 receptor PDB ID 7JOZ in complex with Lupeol

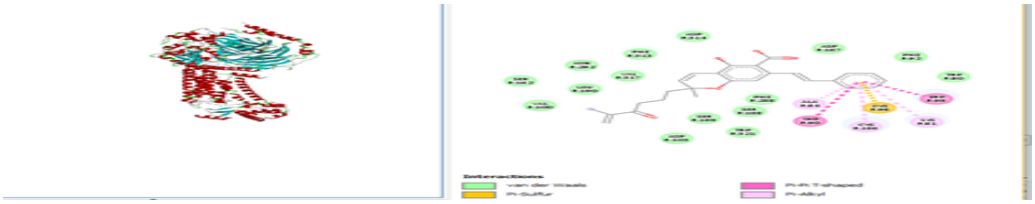

**Figure 4:** 3D/2D structures of dopamine D1 receptor PDB ID 7JOZ in complex with Hymenocardichromene F

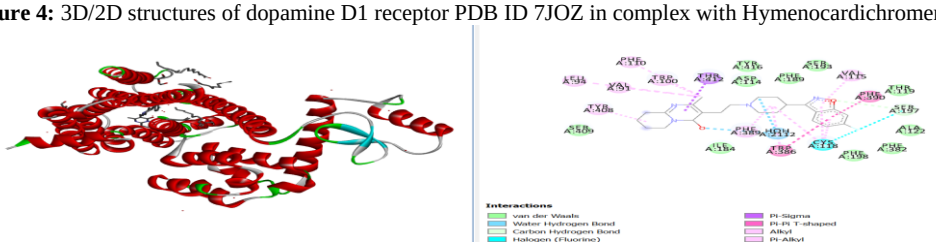

**Figure 5A:** 3D/2D structures of co-crystallized native ligand (Risperidone) in complex with receptor PDB ID 6CM4

**Figure 5B:** 3D/2D structures of redocked native ligand (risperidone) in complex with receptor PDB ID 6CM4

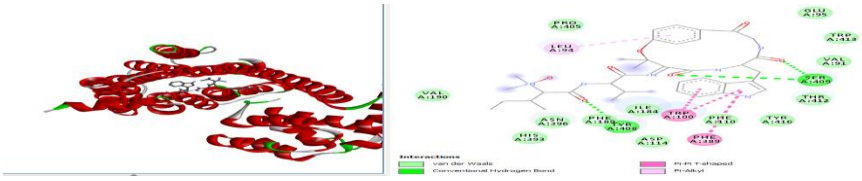

**Figure 6:** 3D/2D structures of dopamine D2 receptor PDB ID 6CM4 in complex with Hymenocardine N-oxide.

**Figure 7:** 3D/2D structures of dopamine D2 receptor PDB ID 6CM4 in complex with Hymenocardichromene D.

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**Figure 8:** 3D/2D structures of dopamine D2 receptor PDB ID 6CM4 in complex with Lupeol

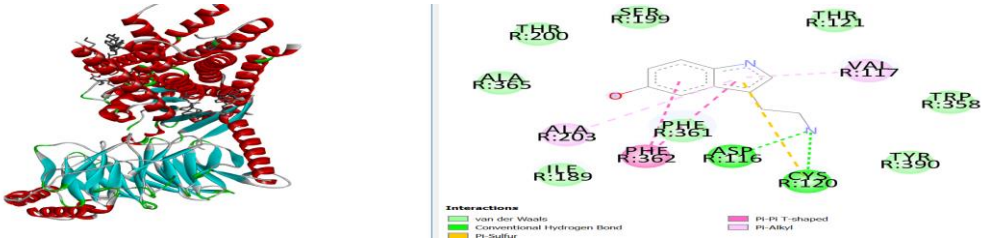


**Figure 9A**: 3D/2D structures of co-crystallized native ligand (serotonin) in complex with receptor serotonin $5HT_{1A}$ receptor PDB ID 7E2Y

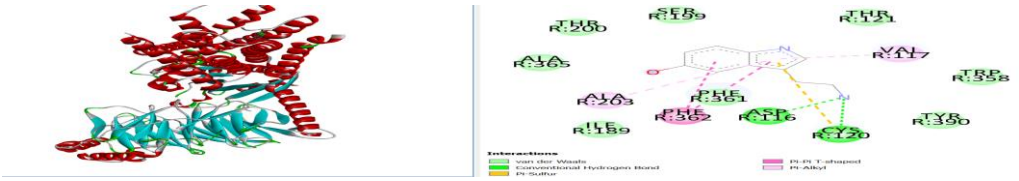


**Figure 9B:** 3D/2D structures of redocked native ligand (serotonin) in complex with receptor serotonin $5HT_{1A}$ receptor PB ID 7E2Y

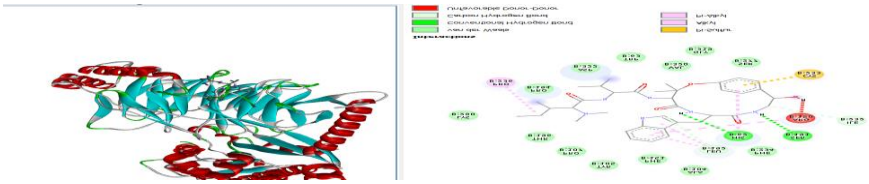

**Figure 10**: 3D/2D structures of serotonin $5HT_{1A}$ receptor PDB ID 7E2Y in complex with Hymenocardinol

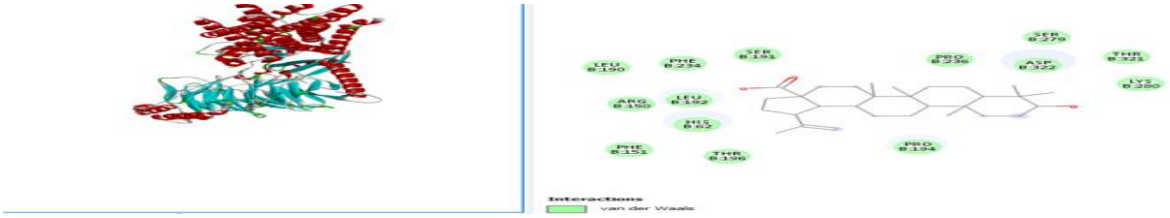


**Figure 11**: 3D/2D structures of serotonin $5HT_{1A}$ receptor PDB ID 7E2Y in complex with Betulinic acid

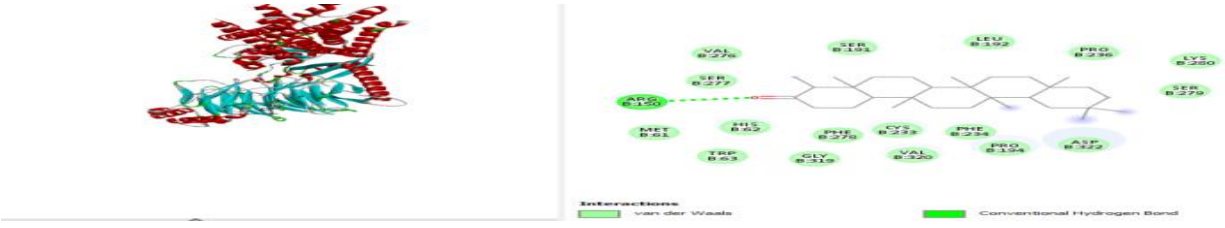


**Figure 12:** 3D/2D structures of serotonin $5HT_{1A}$ receptor PDB ID 7E2Y in complex with Friedelan-3-one

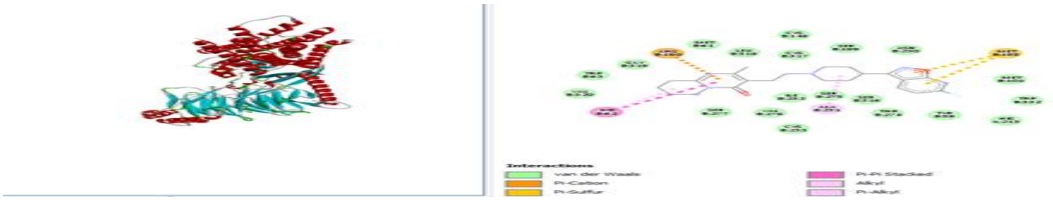


**Figure 13**: 3D/2D structures of serotonin $5HT_{1A}$ receptor PDB ID 7E2Y in complex with Risperidone

absorption, distribution, metabolism, excretion, and toxicity (ADMET) profiles, are presented in Tables 2, 3, and 4. All the studied alkaloids (hymenocardinol, hymenocardine, hymenocardine H, and hymenocardine N-oxide) were seen to have violated at least two (2) rules from Lipinski's Rule of 5, indicating that these compounds are likely to have poor oral bioavailability as well as absorption properties and will be poor choices for oral drug formulations. All the other studied compounds (stilbenes and steroids) obeyed Lipinski's Rule of 5 since they satisfied at least four, of the five requirements. The only violation resulted from the compounds having mLOGp of greater than 4.15 that is for the selected steroids and also hymenocardichromene A and C. Moreover, the predicted ADME properties show that stilbenes and reference drug (risperidone) had better intestinal absorption than steroids and alkaloids (Table 2). For the drug-likeness study, all the stilbenes and steroids obeyed Lipinski's RO5. However, all the studied alkaloids (hymenocardinol, hymenocardine, hymenocardine H, and

hymenocardine N-oxide) failed to obey Lipinski's RO5. Lipinski's rule of five or just rule of five (RO5) is a rule used to evaluate drug likeness or determine if a compound with biological or pharmacological effects has characteristics that would make it likely an orally active drug in humans.[14] The rule states that for oral-bioavailability, a drug molecule is more likely to have good absorption or permeation when it has a Hydrogen Bond Donor of not more than 5 (HBD<5), hydrogen bond acceptor of not more than 10 (HBA <10), molecular weight less than 500 daltons (MW < 500), octanol-water partition coefficient log P not greater than 5 (MLOGP < 4.15 or WLOGP <5) and rotatable bonds less than 10. Compounds that obey at least four of the five requirements are said to be orally bioavailable.[14]

Among all the selected compounds, only the alkaloids, hymenocardichromanic acid, and reference molecule were predicted to be substrates of P-glycoprotein, which acts as a biological barrier by pumping toxins and foreign substances out of the cell thereby protecting the body.[15] Furthermore, hymenocardichromene A-F (stilbenes) and alkaloids as well as the reference compound risperidone were inhibitors of the selected cytochrome P450 enzyme (CYP-3A4), an essential enzyme for drug metabolism in the body (Table 3).[16] However this was not the case for the steroidal compounds as well as hymenocardichromanic acid. Also, the prediction showed that all the molecules do not readily permeate through the BBB (Blood-brain barrier) which is an important feature required for drugs with central nervous system effect. [17]Furthermore, the predicted toxicity for the compounds was found to be 'class 4' except for betulinic acid, hymenocardine H, and risperidone which had predicted toxicity of class 5, 5, and 3, respectively as shown in Table 4.0. Toxicity classes were defined by the Pro-Tox II server according to the Globally Harmonized System (GHS) of Classification of labeling of chemicals and the $LD_{50}$ values are given in mg/kg.[18] The ADMET study shows that all tested compounds are unable to cross BBB. The inability of the compounds to permeate the BBB might be a hindrance in exerting antischizophrenic activity since to reach their therapeutic target, antipsychotics have to cross the BBB.[17] The reference molecule risperidone permeates the BBB. Based on the predicted parameters, the selected compounds were said to possess relatively good pharmacokinetics profiles being that some; showed high intestinal absorption, were substrates P-glycoprotein, conformed to Lipinski's RO5 for oral bio-availability and were on the fair side of the toxicity scale with even lesser toxic effect and higher $LD_{50}$ than the reference molecule.

## Conclusion

The virtual screening results revealed that phytochemicals present in *H. acida* had good binding affinity to the respective dopaminergic and serotonergic receptors they were docked against. This study encourages further investigations such as; manipulating the structure of the studied compounds to generate a library of compounds that might possess better pharmacokinetic properties, and cross the blood-brain barrier. These compounds could serve as new entities for future development of antipsychotics.

## Conflict of Interest:

The authors declare that there is no conflict of interest. The authors alone are responsible for the content of the paper.

## Authors' Declaration:

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

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