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In silico evaluation of antipsychotic potential of phytoconstituents from *Aframomum melegueta* and *Piper guineense*

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ABSTRACT

Background*:* Antipsychotic drugs are crucial for treating conditions like schizophrenia and bipolar disorder. However, many existing treatments are inadequate in managing cognitive impairments and negative symptoms, highlighting the need for alternative therapeutic options. This research aims at investigating the antipsychotic potential of bioactive compounds from Aframomum melegueta and Piper guineense through computational methods,

Methods: Phytochemicals of *Aframomum melegueta* and *Piper guineense* were obtained from PubChem in SDF format and docked against dopamine D2 (PDB ID: 7DFP) and serotonin 5-HT2A receptors (PDB ID: 7VOE) using Maestro version 12.8. Their binding affinities were compared with those of established antipsychotic drugs. Additionally, pharmacokinetic and toxicity characteristics were predicted using ADMET analysis.

Results: Compounds from both plants demonstrated strong binding affinity, particularly towards the dopamine D2 receptor, with several outperforming standard antipsychotics with CID 11000257 (–7.921 kcal/mol), CID 442879 (–8.334 kcal/mol), and CID 90472536 (–7.718 kcal/mol) exhibited serotonin receptor affinities comparable to reference drugs. CID 6989 (–6.381 kcal/mol), CID 615800 (–5.712 kcal/mol), and CID 6987 (–5.704 kcal/mol) also showed favourable dopamine receptor binding, similar to olanzapine (CID 135398745; serotonin: –8.802, dopamine: –6.372 kcal/mol) and risperidone (CID 5073; serotonin: –9.389, dopamine: –5.655 kcal/mol). ADMET evaluations indicated favourable absorption, distribution, metabolism, excretion, and toxicity profiles for most compounds analyzed

Conclusion: *Piper guineense* and *Aframomum melegueta* show potential as sources of novel antipsychotic agents. Further laboratory and preclinical studies, including molecular dynamics simulations, are warranted to confirm their therapeutic promise and advance their development into safer, more effective antipsychotic medications.

Keywords: ADMET, Antipsychotic, Docking, Dopamine, Serotonin.

1.0 INTRODUCTION

Psychosis is a severe and debilitating manifestation of mental illness, marked by a profound disruption in the perception of reality, impaired daily functioning, and significant changes in personality. Individuals affected by psychosis often struggle to differentiate between internal thoughts and external reality, which leads to symptoms such as hallucinations, delusions, and disorganized thinking [1]. Hallucinations involve false sensory experiences like seeing, hearing, or feeling things that are not present, while delusions are unfounded beliefs that negatively impact functioning, including paranoid thoughts or exaggerated self-importance [2]. Rather than being a standalone diagnosis, psychosis represents a feature of several psychiatric conditions, including schizophrenia, bipolar disorder, schizoaffective disorder, major depressive disorder with psychotic features, and substance-induced psychosis. It is notably a hallmark of schizophrenia, where cognitive disorganization and emotional detachment are frequent. According to the World Health Organization (WHO), approximately 450 million individuals globally suffer from mental or neurological conditions, with neuropsychiatric disorders accounting for 17.6% of disability-adjusted life years in Africa [3]. In Nigeria, research shows that 12.1% of the population has experienced a mental illness at some

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stage, underscoring the significant burden these disorders pose [4]. Despite advances in the understanding of psychosis, major challenges remain, particularly in under-resourced settings such as Nigeria, where mental health services are limited. Psychosis emerges from a multifaceted interaction of biological (e.g., genetics, neurodevelopmental issues, substance use), psychosocial (e.g., stress, trauma), and environmental influences. These elements collectively affect both the onset and development of psychotic illnesses, including schizophrenia and related disorders. Managing psychosis involves a combination of pharmacological interventions, psychological therapies, and supportive strategies personalized to the individual's needs. Antipsychotic medications form the foundation of treatment, effectively mitigating symptoms like hallucinations, delusional thinking, and agitation across various psychotic conditions. Typical antipsychotics, such as chlorpromazine and haloperidol, exert their effects by blocking dopamine D2 receptors, which help manage positive symptoms but are often associated with extrapyramidal side effects (EPS) [5]. Long-term use can lead to conditions like tardive dyskinesia, affecting up to 20% of patients [6]. Atypical antipsychotics, including clozapine, risperidone, and olanzapine, act on both dopamine and serotonin receptors, offering relief across a broader range of symptoms and typically causing fewer EPS [7]. However, they carry metabolic risks such as weight gain and diabetes, necessitating vigilant monitoring [8]. Despite their benefits, antipsychotics are not universally effective; around 20–30% of individuals do not respond adequately, especially with respect to negative symptoms and cognitive impairments [9]. This gap underscores the importance of exploring new treatment avenues, including adjunct therapies and novel pharmacological approaches. Non-pharmacological treatments such as Cognitive Behavioral Therapy (CBT) support patients in recognizing and correcting distorted thought patterns, thereby enhancing coping mechanisms [10]. Family therapy, which includes relatives in the treatment process, promotes a supportive environment and reduces stigma [11]. Such interventions have been shown to decrease relapse rates in schizophrenia by up to 50% [12]. Electroconvulsive Therapy (ECT) is another option, used for severe or treatment-resistant cases to provide rapid symptom relief [13], although it may cause lasting side effects such as memory impairment [14]. Supportive care including the creation of a stable living environment, treatment of coexisting conditions, and promotion of healthy habits like proper nutrition and sleep is essential to recovery [15]. Since sleep disorders are common and can worsen psychotic symptoms, improving sleep hygiene should be prioritized [16]. In Nigeria, traditional medicine has long utilized indigenous plants to treat various health problems, including mental and neurological disorders. Some of these plants have shown potential antipsychotic effects. For instance, *Piper guineense* was found to contain β-sesquiphellandren, which has antipsychotic effects [17]. Another example is *Aframomum melegueta* Traditionally used for its therapeutic properties, with flavonoids and terpenoids contributing to antipsychotic-like actions [18-19]. Despite these promising findings, limitations such as unclear dosing standards, potential toxicity, and limited clinical data constrain their current therapeutic use. Future research should aim to isolate these bioactive compounds, conduct rigorous clinical trials, and find ways to integrate traditional remedies with contemporary psychiatric practices. The aim of this study is to evaluate the antipsychotic potential of the phytoconstituents of *Aframomum melegueta* and *Piper guineense* using *in silico* studies.

2.0 MATERIALS AND METHOD

2.1 *Materials*: The materials for the *in silico* investigation of antipsychotic activities include a Computer System, Databases (PubChem, Protein Data Bank (PDB), Webservers such as SwissADME, ProTox-II, Maestro software (Schrödinger Suite 12.8)

2.2 *Method*: To perform *in silico* screening of phytochemicals from *Piper guineense* and *Aframomum melegueta* for potential antipsychotic activity, the following methods including and involving selection of phytochemicals and targets, selection target proteins relevant to the disease or condition of interest from Protein Data Bank (PDB) database, preparation of ligands and proteins, virtual screening/molecular docking and ADMET analysis.

3.0 RESULTS

The results presented below are those of the docking scores/binding affinities and ADMET analysis of phytocompounds of *Aframomum melegueta and Piper guineense*.

3.1 *Docking scores/Binding affinities.*

The docking scores were gotten from maestro 12.8 by docking *Aframomum melegueta* and *Piper guineense* with dopamine and serotonin receptor proteins and these scores 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 (in *)

Table 1: Docking Score of *Aframomum melegueta* with Serotonin Receptor

S/N	PUBCHEM CID	docking score (kcal/mol)
1	**5073***	**-9.389**
2	**135398745***	**-8.802**
3	11000257	-7.921
4	61130	-7.628
5	7461	-7.253
6	615800	-7.205
7	6989	-7.185
8	88302	-7.094
9	92284339	-7.082
10	86707	-7.068

*= Reference ligands

Table 2: Docking Score of *Aframomum melegueta* with Dopamine Receptor

S/N	PUBCHEM CID	docking score (kcal/mol)
1	**5073***	**-5.655**
2	**135398745***	**-6.372**
3	163183900	-5.728
4	615800	-5.712
5	73174	-5.685
6	6989	-6.381
7	10582	-5.565
8	17100	-5.525
9	7461	-5.315

*= Reference ligands

Table 3: Docking Score of *Piper guineense* with Serotonin Receptor

S/N	PUBCHEM CID	docking score (kcal/mol)
1	**5073***	**-9.389**
2	**135398745***	**-8.802**
3	**11463***	**-7.323**
4	442879	-8.334
5	90472536	-7.718
6	92037727	-7.718
7	163186488	-7.516
8	5281772	-7.402
9	11142	-7.338

10	6987	-7.273
11	7461	-7.253
12	384877	-7.217
13	101821165	-7.202
14	7460	-7.188
15	5320621	-7.186
16	2537	-7.152

*= Reference ligands

Table 4: Docking Score of *Piper guineense* with Dopamine Receptor

S/N	PUBCHEM CID	docking score (kcal/mol)
1	**5073***	**-5.655**
2	**135398745***	**-6.372**
3	6987	-5.704
4	17100	-5.525
5	11463	-5.514
6	7461	-5.315
7	11142	-5.298
8	7460	-5.237
9	384877	-5.175
10	5320621	-5.06

*= Reference ligands

3.2 ADME analysis.

The ADME results were obtained by inputting the SMILES of the compounds gotten from PUBCHEM into SWISSADME.

Table 5: ADME Analysis of *Aframomum melegueta* using SWISSADME

S/N	PUBCHEM CID	GI absorption	BBB permeant	Pgp substrate	CYP1A2 inhibitor	CYP2D6 inhibitor	CYP3A4 inhibitor	Lipinski #violations	Bioavailability Score
1	11000257	High	Yes	No	Yes	Yes	No	0	0.55
2	61130	High	Yes	No	No	No	No	0	0.55
3	7461	Low	Yes	No	No	No	No	0	0.55
4	615800	High	Yes	No	Yes	No	No	0	0.55
5	6989	High	Yes	No	Yes	No	No	0	0.55
6	88302	High	Yes	No	No	No	No	0	0.55
7	92284339	High	Yes	No	No	No	No	0	0.55
8	86707	High	Yes	No	No	No	No	0	0.55
9	163183900	High	Yes	Yes	No	Yes	No	0	0.55
10	17100	High	Yes	No	No	No	No	0	0.55
11	10582	High	Yes	No	No	No	No	0	0.55
12	73174	High	Yes	No	No	No	No	0	0.55
13	163183900	High	Yes	Yes	No	Yes	No	0	0.55
14	**5073***	High	Yes	Yes	Yes	Yes	Yes	0	0.55
15	**135398745***	High	Yes	Yes	Yes	Yes	Yes	0	0.55

Table 6: ADME Analysis of *Piper guineense* using SWISSADME

S/N	PUBCHEM CID	GI absorption	BBB permeant	Pgp substrate	CYP1A2 inhibitor	CYP2D6 inhibitor	CYP3A4 inhibitor	Lipinski #violations	Bioavailability Score

1	442879	**High**	**Yes**	**No**	**Yes**	**Yes**	**Yes**	**0**	**0.55**
2	90472536	High	Yes	No	No	Yes	Yes	0	0.55
3	92037727	High	Yes	No	No	Yes	Yes	0	0.55
4	163186488	High	Yes	No	Yes	No	No	0	0.55
5	5281772	High	Yes	No	Yes	No	No	0	0.55
6	11142	Low	Yes	No	No	No	No	0	0.55
7	11463	Low	Yes	No	No	No	No	0	0.55
8	6987	High	Yes	No	No	No	No	0	0.55
9	7461	Low	Yes	No	No	No	No	0	0.55
10	384877	High	Yes	No	No	Yes	Yes	0	0.55
11	101821165	High	Yes	No	No	Yes	Yes	0	0.55
12	7460	Low	Yes	No	No	No	No	0	0.55
13	5320621	High	Yes	No	Yes	No	No	0	0.55
14	2537	High	Yes	No	No	No	No	0	0.55
15	17100	High	Yes	No	No	No	No	0	0.55
16	**5073***	High	Yes	Yes	Yes	Yes	Yes	0	0.55
17	**135398745***	High	Yes	Yes	Yes	Yes	Yes	0	0.55

3.3 Toxicity profiles

The toxicity profiles of these compounds were obtained by inputting the SMILES of the compound gotten from PUBCHEM into PROTOX-II

Table 7: Toxicity profile of *Aframomum melegueta* using Protox-ii

S/N	PubChem CID	Hepatotoxicity	Neurotoxicity	Nephrotoxicity	Respiratory toxicity	Cardiotoxicity	Carcinogenicity
1	6989	Inactive	**Active**	**Inactive**	**Active**	**Inactive**	**Inactive**
2	88302	Inactive	Active	Inactive	Active	Inactive	Inactive
3	615800	Inactive	Inactive	Active	Active	Inactive	Inactive
4	73174	Inactive	Inactive	Inactive	Inactive	Inactive	Inactive
5	10582	Inactive	Inactive	Inactive	Inactive	Inactive	Inactive
6	7461	Inactive	Active	Inactive	Inactive	Inactive	Inactive
7	163183900	Inactive	Active	Inactive	Active	Inactive	Inactive
8	17100	Inactive	Inactive	Inactive	Inactive	Inactive	Inactive
9	61130	Inactive	Active	Inactive	Inactive	Inactive	Inactive
10	11000257	Inactive	Inactive	Inactive	Inactive	Inactive	Inactive
11	**5073***	Inactive	Active	Inactive	Inactive	Inactive	Inactive
12	**135398745***	Inactive	Active	Inactive	Inactive	Inactive	Inactive

Table 8: Toxicity Profile of *Piper guineense* using Protox-II

S/N	PUBCHEM CID	Hepatotoxicity	Neurotoxicity	Nephrotoxicity	Respiratory toxicity	Cardiotoxicity	Carcinogenicity
1	384877	**Inactive**	**Inactive**	**Active**	**Inactive**	**Inactive**	**Inactive**
2	11463	Inactive	Inactive	Inactive	Inactive	Inactive	Inactive
3	5320621	Inactive	Inactive	Active	Inactive	Active	Inactive
4	101821165	Inactive	Inactive	Active	Active	Inactive	Inactive
5	17100	Inactive	Inactive	Inactive	Inactive	Inactive	Inactive
6	7460	Inactive	Active	Inactive	Inactive	Inactive	Inactive
7	5281772	Inactive	Inactive	Active	Active	Inactive	Inactive
8	90472536	Inactive	Inactive	Inactive	Active	Inactive	Inactive
9	92037727	Inactive	Inactive	Inactive	Active	Inactive	Inactive
10	11142	Inactive	Active	Inactive	Inactive	Inactive	Inactive

11	7461	Inactive	Active	Inactive	Inactive	Inactive	Inactive
12	6987	Inactive	Active	Inactive	Inactive	Inactive	Inactive
13	5281772	Inactive	Inactive	Active	Inactive	Active	Inactive
14	163186488	Inactive	Inactive	Active	Inactive	Active	Inactive
15	2537	Inactive	Active	Inactive	Inactive	Inactive	Inactive
16	5073	Inactive	Active	Inactive	Inactive	Inactive	Inactive
17	135398745	Inactive	Active	Inactive	Inactive	Inactive	Inactive

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3.3.1 *Ligand interactions*

Molecular Interaction Analysis with Dopaminergic and Serotonergic Receptors

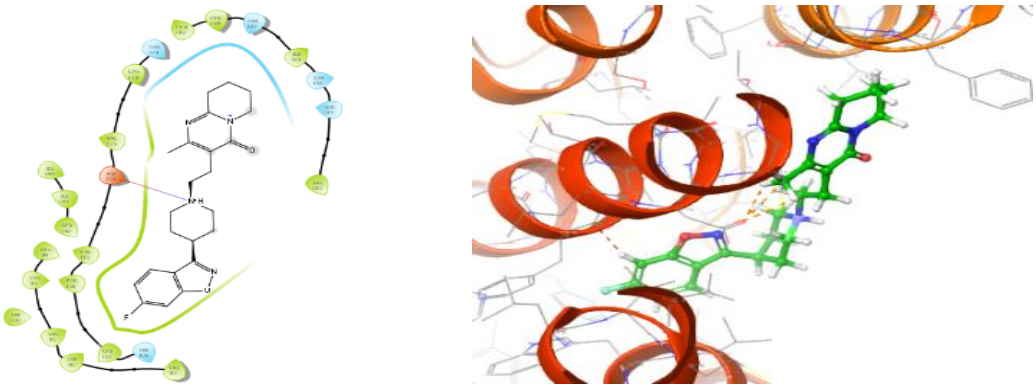

Figure 1 &2 2D(left) and 3D(right) structure of compound 5073 molecular interaction with dopamine receptor

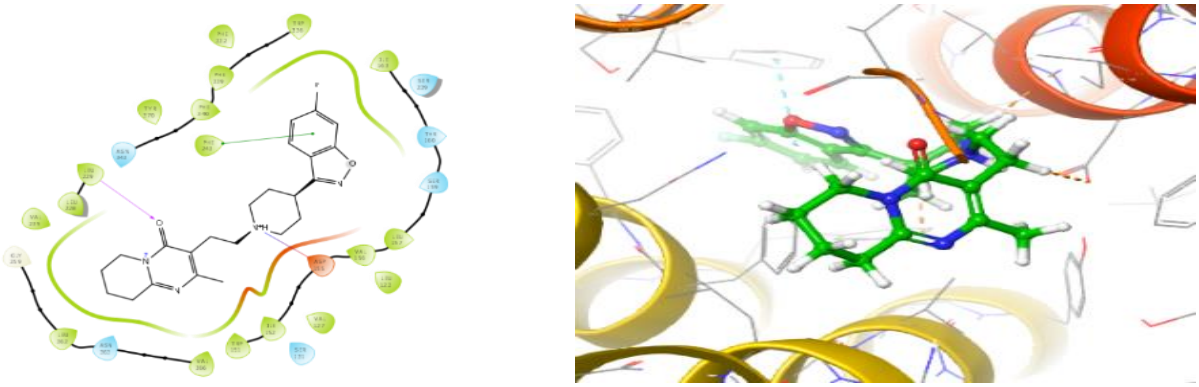

Figure 3 & 4 2D(left) and 3D(right) structure of compound 5073 molecular interaction with serotonin receptor

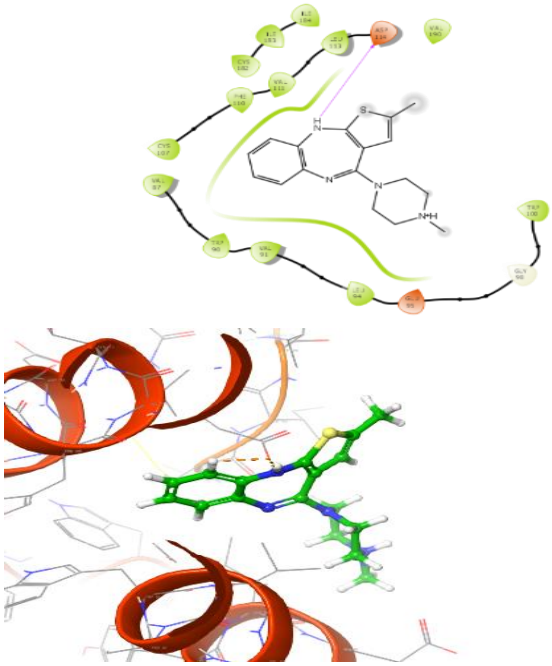

Figure 5 & 6 2D(left) and 3D(right) structure of compound 135398745 molecular interaction with dopamine receptor

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With Serotonin Receptor

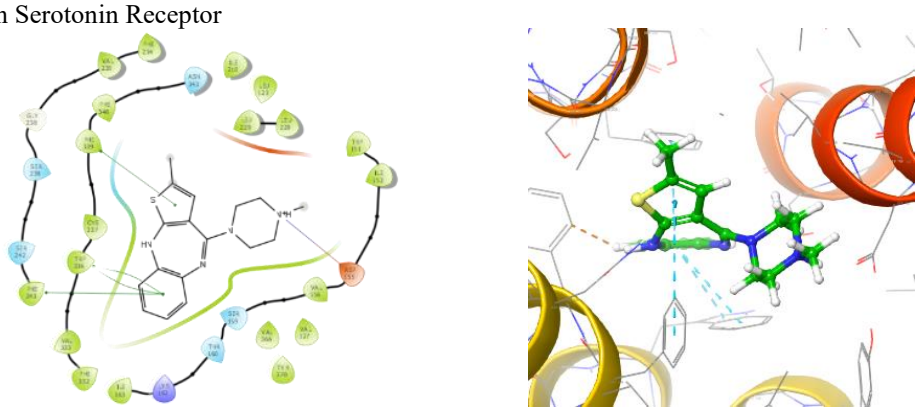

Figure 7 & 8 2D(left) and 3D(right) structure of compound 135398745 molecular interaction with serotonin receptor

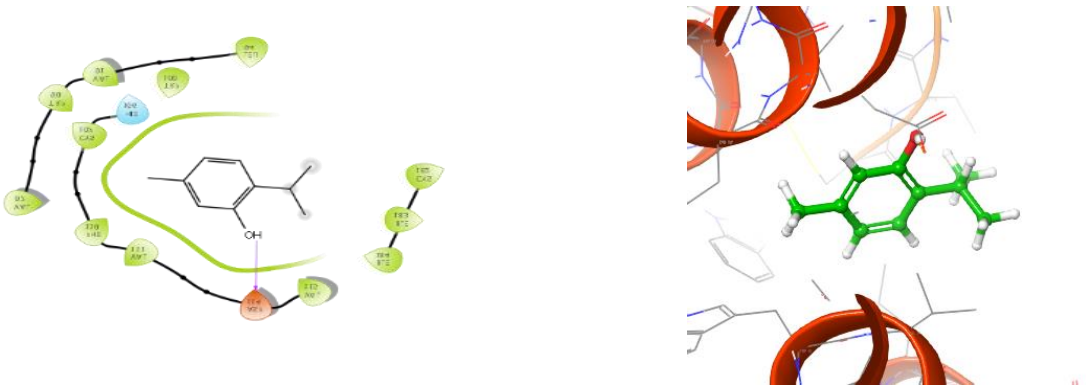

Figure 9 & 10 images of the 2D(left) and 3D(right) structure of compound 6869 molecular interaction with dopamine receptor

1. Compound 163183900 With Dopamine Receptor

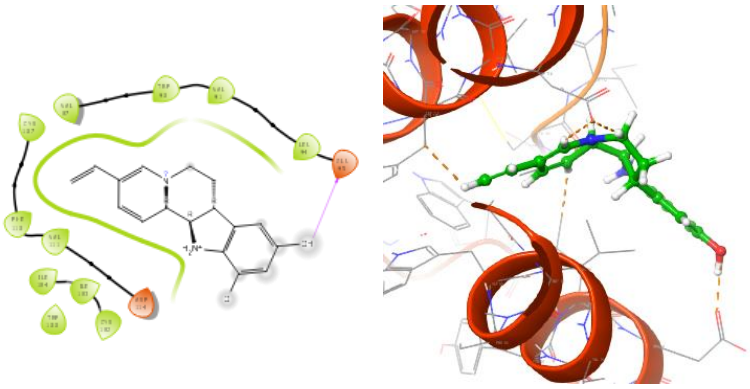

Figure 11 & 12 images of the 2D(left) and 3D(right) structure of compound 163183900 molecular interaction with dopamine receptor

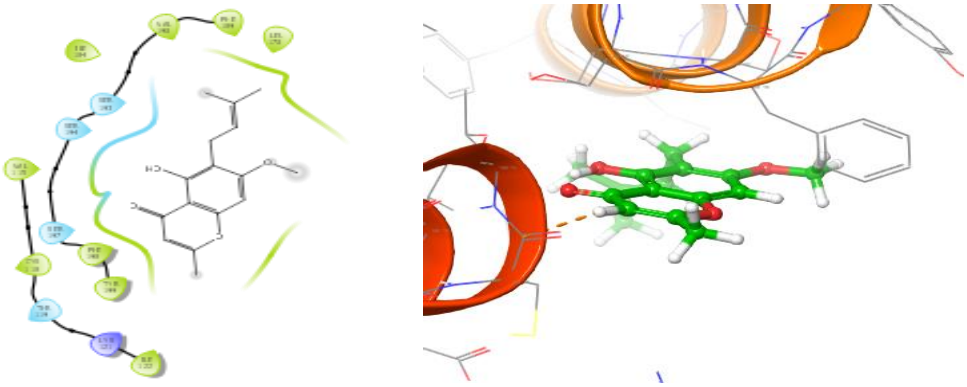

Figure 13 & 14 images of the 2D(left) and 3D(right) structure of compound 615800 molecular interaction with dopamine receptor

Molecular Interaction for some of the ligands of Piper guineense with Dopamine and Serotonin Receptor

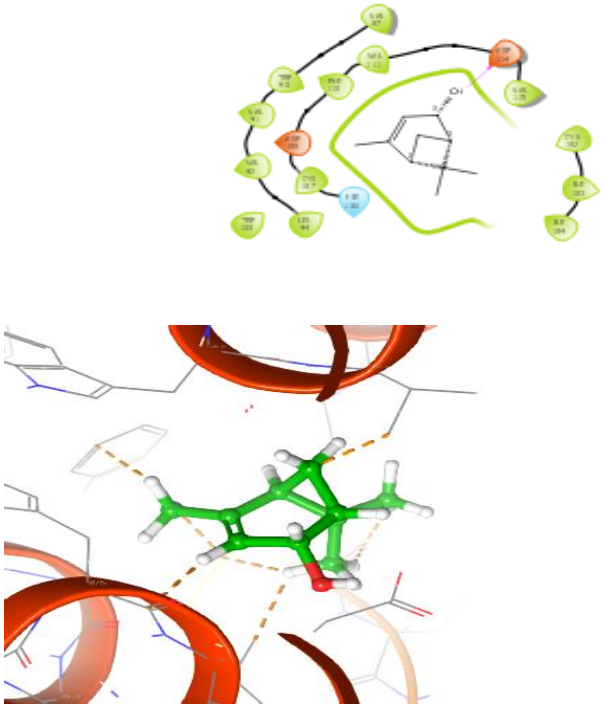

Figure 15 & 16 images of the 2D(left) and 3D(right) structure of compound 6987 molecular interaction with dopamine receptor

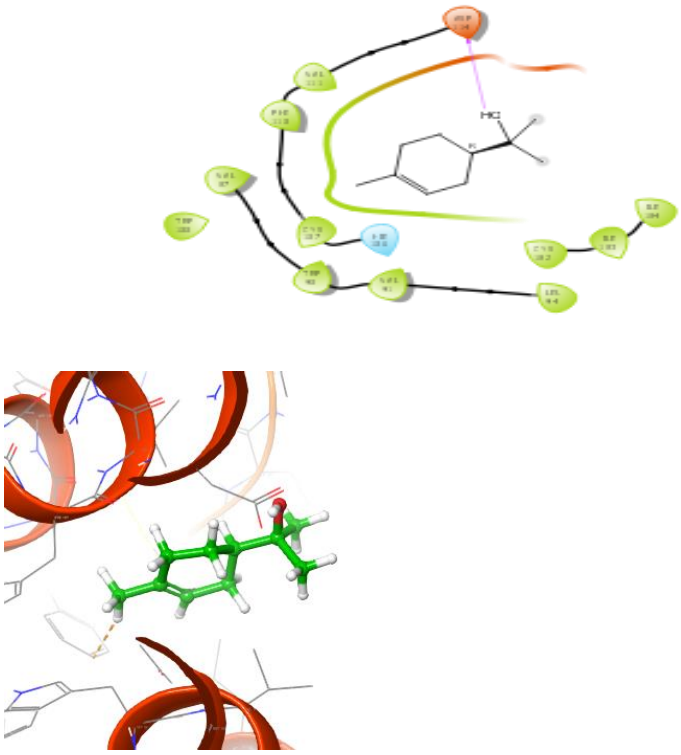

Figure 17 & 18 images of the 2D(left) and 3D(right) structure of compound 17100 molecular interaction with dopamine receptor

Figure 19 & 20 images of the 2D(left) and 3D(right) structure of compound 11463 molecular interaction with dopamine receptor

4.0 DISCUSSION

Molecular Docking studies have provided critical insights into the binding affinities of potential antipsychotic 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 [20-21]. 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 [20-21]. Identifying active binding sites on these receptors is crucial for optimizing drug design, reducing side effects, and predicting drug behavior. Understanding how ligands interact at a molecular level aid in modifying chemical structures for improved efficacy and selectivity. Additionally, targeting specific receptor subtypes or allosteric

sites can minimize unwanted pharmacological effects. Molecular docking provides insights into binding stability, potency, and receptor-ligand dynamics, which are essential for *in vitro* and *in vivo validation.*

4.1 *Aframomum melegueta*

In this study, 90 phytocompounds of *Aframomum melegueta* were obtained from PubChem and docked against dopamine (7DFP) and serotonin (7VOE) receptors using a hierarchical Docking technique. High-throughput virtual screening (HTVS) was used to filter the huge number of ligands, followed by standard precision (SP) Docking to improve and evaluate the Docking scores' correctness. The SP Docking results revealed 18 compounds with potential receptor binding affinity. To assess their therapeutic relevance, the docking scores of these phytochemicals were compared to those of standard antipsychotic drugs, namely risperidone (-6.372 for dopamine, -8.802 for serotonin), olanzapine (-5.655 for dopamine, -9.389 for serotonin), and aripiprazole.

The findings revealed that various *Aframomum melegueta* compounds had equivalent or higher affinity for the dopamine receptor, particularly compounds 6989 (-6.381), 163183900 (-5.728), and 615800 (-5.712), with compound 6989 having a better binding affinity than risperidone (-6.372). However, none of the identified phytochemicals had higher affinity for the serotonin receptor than the reference antipsychotics, indicating a more selective interaction with the dopamine receptor.

4.2 *Piper guineense*

The docking study evaluated 142 phytochemicals from *Piper guineense*, including 141 natural compounds and one metabolite. A tiered docking strategy was used, beginning with high-throughput virtual screening (HTVS) to filter the enormous dataset and ending with typical precision Docking to refine accuracy. The SP Docking data revealed 17 compounds with high binding affinity for the dopamine (D2) and serotonin (5-HT) receptors.

To assess their potential antipsychotic activity, the Docking scores of *Piper guineense* phytochemicals were compared to standard antipsychotics such as risperidone (-6.372 for dopamine, -8.802 for serotonin), olanzapine (-5.655 for dopamine, -9.389 for serotonin), and aripiprazole (-5.531 for dopamine, -8.194 for serotonin).

Three of the discovered compounds (6987, 17100, and 11463) had dopamine receptor binding scores of -5.704, -5.525, and -5.514, respectively, showing affinities comparable to or above aripiprazole (-5.531) and like olanzapine (-5.655). However, for serotonin receptor binding, just one drug, 44287 (-8.334), had an affinity comparable to risperidone but a lower dopamine receptor score (-4.91), indicating poor dual receptor action. These data indicate that compound 6987 is the most promising dopaminergic drug, with a higher Docking score than aripiprazole and a close resemblance to olanzapine. Furthermore, compound 44287 had a substantial serotonin receptor interaction but failed to satisfy the dopamine binding threshold for consideration as a dual-target drug.

4.3 ADME and Drug-Likeness Prediction and toxicity

Lipinski's Rule of Five (Ro5) serves as a guideline for evaluating the oral bioavailability of drug candidates, including antipsychotics. The rule suggests that a compound is more likely to exhibit poor absorption or permeation if it violates two or more of the following criteria: molecular weight above 500 Da, LogP above 5, more than 5 hydrogen bond donors, or more than 10 hydrogen bond acceptors. While many clinically approved antipsychotics adhere to these rules, several exceptions exist due to factors such as active transport mechanisms or prodrug strategies [22]. Lipophilicity, as assessed by LogP, is an important predictor of blood-brain barrier (BBB) penetration, which influences antipsychotic effectiveness. An optimum LogP (2-5) maintains a balance of membrane permeability and solubility. Molecular weight also influences CNS penetration, with most atypical antipsychotics falling inside the Rule of 5 (Ro5) range, however some bigger molecules use active transport. .

P-glycoprotein (Pgp), an efflux transporter, regulates antipsychotic brain penetration, altering efficacy and drug resistance. Perospirone inhibits Pgp, which increases brain accumulation, whereas genetic polymorphisms can improve olanzapine penetration [23-24]. Some antipsychotics also block Pgp, which may change drug transport and interactions [25]. Antipsychotics are extensively metabolized by the cytochrome P450 (CYP) system. Clozapine and olanzapine are metabolized by CYP1A2, whereas risperidone and aripiprazole are processed by CYP2D6 [26-27]. CYP3A4 contributes to the metabolism of quetiapine and ziprasidone, while aldehyde oxidase is involved in the breakdown of ziprasidone [28]. CYP inhibitors, such as fluvoxamine, can drastically modify medication levels, influencing treatment outcomes [28]. Understanding these metabolic and transport pathways is critical for increasing antipsychotic efficacy while reducing medication interactions.

4.4 Pharmacokinetic Assessment of Selected Compounds from *Aframomum melegueta*

The pharmacokinetic parameters of seven chosen compounds (PubChem CIDs: 6989, 163183900, 615800, 73174, 10582, 60795, and 17100) were assessed to identify their medicinal potential. The examination included critical issues such as gastrointestinal (GI) absorption, blood-brain barrier (BBB) permeability, interactions with P-glycoprotein (Pgp), metabolism via cytochrome P450 enzymes, and potential toxicity concerns. GI absorption is

important for oral bioavailability and affects systemic medication exposure. Except for CID 17100, which has lesser absorption, all of the tested compounds show high GI absorption. Antipsychotic medicines rely on effective BBB penetration to activate the central nervous system (CNS). All of the identified drugs have BBB permeability, indicating possible CNS action. This trait is consistent with typical antipsychotic medications, which require BBB penetration to provide therapeutic effects. Pgp, a major efflux transporter, controls medication distribution and impacts resistance. None of the chosen drugs were identified as Pgp substrates, implying a lower sensitivity to efflux-mediated drug resistance. In contrast, typical antipsychotics such as CID 135398745 and CID 5073 are Pgp substrates, implying that the chosen compounds may have an advantage in sustaining larger intracellular concentrations within the CNS. Metabolism assessment focused on CYP1A2, CYP2D6, and CYP3A4, major enzymes involved in drug biotransformation. CID 6989 and CID 615800 are CYP1A2 inhibitors, indicating potential interactions with drugs metabolized by this enzyme. CID 163183900 inhibits CYP2D6, while CID 60795 and CID 163183900 inhibit CYP3A4, suggesting possible interactions with other substrates of these enzymes. Standard antipsychotics also exhibit CYP450 inhibition, implying that metabolism-related drug interactions should be carefully considered when using these compounds in combination therapies. The selected substances, based on their enzyme inhibition characteristics, may pose drug-drug interactions. CYP1A2 inhibition (CID 6989, CID 615800) may extend the effects of medications processed by this enzyme, such as caffeine and theophylline. CYP2D6 inhibition (CID 163183900) may influence the metabolism of antidepressants and beta-blockers, whilst CYP3A4 inhibition (CID 163183900, CID 60795) may interfere with the metabolism of statins, immunosuppressants, and certain antipsychotics. These interactions merit further pharmacokinetic and clinical investigation. None of the chosen compounds violated Lipinski's criteria, showing good drug-likeness. The bioavailability ratings ranged from 0.55 to 0.85, indicating a reasonable systemic exposure following treatment. The toxicity profiles of the chosen chemicals from *Aframomum melegueta* raise several safety issues. Some compounds, like CID 73174, CID 10582, and CID 17100, have no toxicity across all indicators, making them the most attractive candidates for therapeutic development. These chemicals have no evidence of hepatotoxicity, neurotoxicity, nephrotoxicity, respiratory toxicity, cardiotoxicity, or carcinogenicity, showing a very positive safety profile. In contrast, CID 6989, CID 163183900, CID 615800, and CID 60795 exhibit active neurotoxicity, with some additionally exhibiting respiratory toxicity. While these chemicals still have therapeutic potential, their neurotoxic effects warrant additional exploration and possible changes to increase safety. Despite these concerns, their inactive profiles in other toxicity markers suggest they may still be viable candidates if their risks can be mitigated. Overall, *Aframomum melegueta* yields compounds with strong therapeutic potential, but further refinement is required to address identified toxicity risks.

4.5 Pharmacokinetic Assessment of Selected Compounds from *Piper guineense*

The pharmacokinetic analysis of the chosen compounds—CID 6987, CID 17100, and CID 11463—reveals important features related to their potential as CNS-active drugs in an *in silico* antipsychotic investigation. CID 6987 and CID 17100 have strong gastrointestinal (GI) absorption, indicating good oral bioavailability and the potential to reach therapeutic doses when taken orally. In contrast, CID 11463 has low GI absorption, implying potential limitations in oral administration and the necessity for alternate delivery techniques, such as prodrugs or parenteral formulations, to improve bioavailability. All three compounds are blood-brain barrier (BBB) permeant, which is required for medications that target the central nervous system (CNS), such as antipsychotics. This indicates that they can successfully enter the brain and exert their pharmacological actions. Additionally, none of the selected compounds are substrates for P-glycoprotein (Pgp), an efflux transporter that can limit CNS drug accumulation. The absence of Pgp-mediated efflux enhances their retention within the brain, making them more suiTable for neuropsychiatric applications. Regarding metabolic interactions, none of the compounds inhibit major cytochrome P450 enzymes (CYP1A2, CYP2D6, and CYP3A4), which are crucial for drug metabolism. This minimizes concerns about potential drug-drug interactions, particularly in polypharmacy scenarios common in psychiatric treatment. Furthermore, all three compounds comply with Lipinski's Rule of Five, having zero violations, which supports their drug-likeness and potential for oral bioavailability. Their bioavailability score of 0.55 further indicates moderate oral absorption and systemic exposure. Three chemicals (PubChem CIDs: 6987, 17100, and 11463) were tested for hepatotoxicity, neurotoxicity, nephrotoxicity, respiratory toxicity, cardiotoxicity, and carcinogenicity to determine their possible dangers in antipsychotic medication development. CID 6987 demonstrated active neurotoxicity, implying that it may have deleterious effects on the central nervous system, such as neuronal damage or cognitive impairment. While it may have pharmacological use, its neurotoxic profile raises safety concerns, demanding additional in vivo validation. However, it exhibited no toxicity in the other categories tested. In contrast, CID 17100 and CID 11463 demonstrated no toxicity across all criteria, indicating a favorable safety profile. These chemicals could be attractive antipsychotic candidates, but further testing is required to ensure their safety. Overall, while CID 6987 requires further scrutiny due to neurotoxicity,

CID 17100 and CID 11463 appear safer. Future studies should refine these findings through additional computational and experimental validation.

4.6 Molecular ligand interaction with receptors

Ligand interaction refers to the binding of a ligand, which can be a small molecule, ion, or protein, to a target protein or receptor, playing a crucial role in biological processes such as signal transduction, gene regulation, and drug efficacy [29-30]. Understanding these interactions is fundamental in drug discovery, as it helps elucidate mechanisms of biological regulation and optimize drug design. Various types of bonds contribute to ligand-protein interactions, including hydrogen bonds, salt bridges, hydrophobic interactions, dispersion forces, and coordination bonds. Hydrogen bonds are particularly important in stabilizing protein-ligand complexes, involving the sharing of a hydrogen atom between two electronegative atoms, such as oxygen or nitrogen, thereby enhancing specificity and binding strength [29-30]. The strength and accessibility of hydrogen bonding groups within a binding site significantly influence ligand-protein interaction representation [30]. Salt bridges, formed between oppositely charged residues, contribute to the stability of ligand-protein complexes [29]. Hydrophobic interactions occur between nonpolar regions of the ligand and the protein, leading to water exclusion from the binding site, which enhances binding affinity and specificity [32-33]. These interactions have important implications for drug activity, as hydrogen bonds and salt bridges enhance stability and specificity, while hydrophobic interactions and dispersion forces contribute to binding affinity and drug potency [29, 31]. A deeper understanding of these interactions enables the optimization of ligand structures to improve drug efficacy, making them fundamental in the design of antipsychotic agents [30, 34]. The Docking results reveal critical interactions between standard antipsychotic drugs and plant-derived compounds with dopamine (D2) and serotonin (5-HT2A) receptors. These interactions play a vital role in determining the binding affinity and potential antipsychotic activity of the compounds. The study highlights the importance of Asp114, Glu95, and other key residues in ligand binding and receptor modulation. The Docking analysis shows that typical antipsychotic medications have substantial interactions with both dopamine and serotonin receptors. Compound CID 5073 interacts to the dopamine receptor by a salt bridge with Asp114, which is a frequent stabilizing interaction in dopamine receptor ligands. Furthermore, it exhibits several interactions with the serotonin receptor, including a hydrogen bond with Leu229, a salt bridge with Asp155, and π-π stacking with Phe243, indicating substantial dual receptor affinity. Similarly, CID 60795 creates a salt bridge and hydrogen link with Asp114, as well as an extra halogen bond with Lys121, to connect to the dopamine receptor. For serotonin receptor contacts, it forms π-π stacking with Trp151 and Phe332, as well as a hydrogen bond with Cys337. These interactions reinforce the established pharmacological roles of these standard antipsychotics, characterized by their ability to modulate both receptors effectively.

4.7 *Aframomum melegueta*

Several plant-derived molecules shown potential interactions with dopamine receptors, particularly at Asp114, a key residue for ligand binding. CID 6869, CID 10582, and CID 17100 all established hydrogen bonds with Asp114 in *Aframomum melegueta*, indicating that they may have dopamine receptor function. However, CID 615800 and CID 73134 showed no interactions, indicating a low or no binding potential. The existence of persistent hydrogen bonding with Asp114 indicates that drugs from *Aframomum melegueta* may have selective dopamine receptor affinity rather than dual receptor interactions.

4.8 *Piper guineense*

For *Piper guineense*, CID 17100 formed a hydrogen bond with Asp114, similar to some compounds from *Aframomum melegueta*. However, CID 11463 and CID 6987 did not exhibit any binding interactions. This suggests that *Piper guineense* compounds may have limited dopamine receptor affinity, potentially requiring structural modifications to enhance binding efficiency. Among the plant-derived compounds, Compounds from *Aframomum melegueta* and *Piper guineense* primarily interact with dopamine receptors, suggesting they may have selective D2 receptor activity. Further *in silico* analysis, molecular dynamics simulations, and in-vitro validation are needed to confirm their potential as novel antipsychotic agents.

5.0 CONCLUSION

From the *in silico* experiments, *Piper guineense* 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 *Aframomum melegueta* showed selective dopaminergic activity, making them potential sources of dopamine-modulating antipsychotic agents with many of these compounds possessed favorable pharmacokinetic and ADMET properties

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