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In Silico Analysis of *Piper cubeba* as a Potential Antidyspeptic Agent via Histamine H_2 Receptor (3UZE) Inhibition

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ABSTRACT

Dyspepsia is a common upper gastrointestinal disorder associated with excessive gastric acid secretion mediated by histamine H_2 receptor activation. This study aimed to evaluate the inhibitory potential of ten major bioactive compounds from *Piper cubeba*, namely cubebin, piperine, sabinene, beta elemene, terpine 4 ol, alpha thujene, alpha copaene, alpha phellandrene, Z isoeugenol, and dihydroeugenol, against the histamine H_2 receptor using an in silico approach. Molecular docking was conducted on the histamine H_2 receptor structure (PDB ID 3UZE), with ranitidine employed as a positive control, following protein and ligand preparation and docking protocol validation through redocking with RMSD values below 2 Å. All tested compounds successfully bound within the receptor active site, exhibiting binding affinity values ranging from approximately -6.6 to -9.2 kcal/mol. Several compounds, particularly cubebin and piperine, demonstrated interaction patterns and binding energies comparable to ranitidine, involving key hydrogen bonding and hydrophobic interactions with critical receptor residues. Drug likeness assessment using Lipinski's rule of five and ADMET prediction indicated that most compounds possessed favorable physicochemical and pharmacokinetic properties. Overall, these findings provide computational evidence supporting *Piper cubeba* as a promising natural source of histamine H_2 receptor inhibitor candidates for dyspepsia management, warranting further experimental validation.

Keywords: Piper cubeba, Phytoconstituents, Dyspepsia, Histamine H_2 Receptor, Molecular Docking.

INTRODUCTION

Dyspepsia is one of the most common upper gastrointestinal disorders encountered in clinical practice and is characterized by symptoms such as epigastric discomfort, heartburn, bloating, early satiety, nausea, and excessive belching. This condition is associated with several pathophysiological factors, including excessive gastric acid secretion, impaired gastrointestinal motility, Helicobacter pylori infection, and lifestyle-related factors such as irregular eating habits, caffeine consumption, psychological stress, and the use of nonsteroidal anti-inflammatory drugs [1]. Due to its high prevalence and recurrent nature, dyspepsia represents a significant burden on healthcare systems worldwide.

Current pharmacological management of dyspepsia mainly relies on acid-suppressive agents, particularly histamine H_2 receptor antagonists and proton pump inhibitors. Although these drugs are effective in reducing gastric acid secretion and relieving symptoms, their long-term use has been associated with adverse

† Footnotes relating to the title and/or authors should appear here.
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effects, drug interactions, and safety concerns. These limitations have encouraged the search for safer and more sustainable therapeutic alternatives, including bioactive compounds derived from medicinal plants [2].

Histamine plays a central role in the regulation of gastric acid secretion by activating histamine H_2 receptors located on gastric parietal cells. Activation of these receptors stimulates adenylate cyclase, leading to increased cyclic AMP levels and enhanced secretion of hydrochloric acid [3]. Ranitidine, a well-known histamine H_2 receptor antagonist, acts by competitively and reversibly inhibiting histamine binding to the H_2 receptor, resulting in a reduction of both the volume and acidity of gastric acid secretion. For this reason, ranitidine has long been used in the treatment of peptic ulcer disease, gastroesophageal reflux disease, and other acid-related disorders. Its established mechanism of action makes ranitidine a relevant standard ligand and positive control in structure-based studies aimed at discovering new histamine H_2 receptor inhibitors [4].

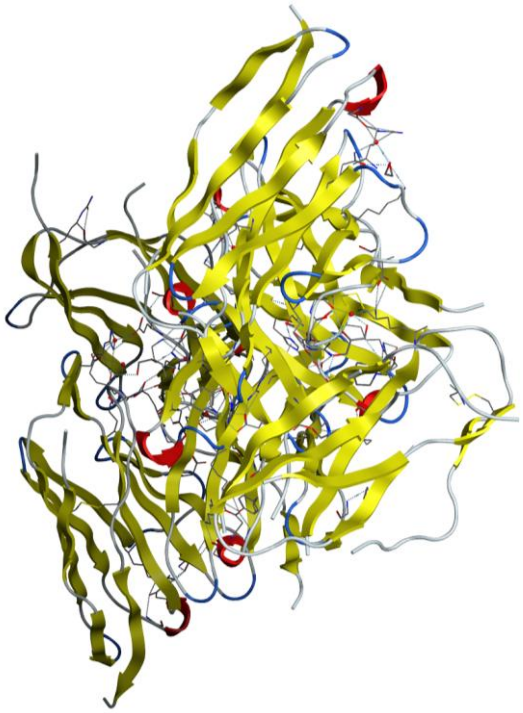
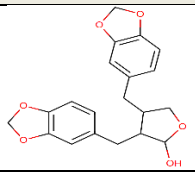
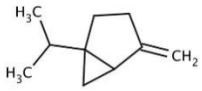
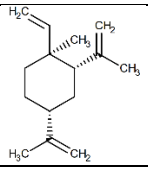
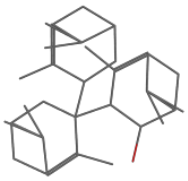
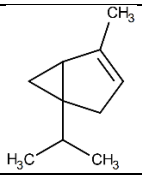
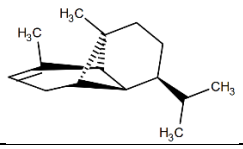
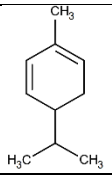
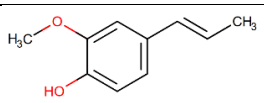
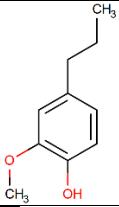
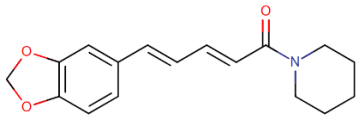


Figure 1. Structure of histamine H_2 receptor protein (PDB ID: 3UZE)

The use of traditional herbal medicines continues to increase, particularly in developing countries, due to their perceived safety, affordability, and broad pharmacological activity. One medicinal plant traditionally used in several Asian regions for gastrointestinal complaints is cubeb (*Piper cubeba* L.f.). The dried fruits of this plant have been used to treat mild abdominal pain, digestive disturbances, and various inflammatory conditions [5]. Recent pharmacological studies have reported that Piper cubeba possesses anti-inflammatory, antimicrobial, antioxidant, and organ-protective activities, supporting its potential as a phytopharmaceutical candidate for the management of digestive disorders, including dyspepsia [6].

Phytochemical investigations have shown that Piper cubeba contains a wide range of bioactive compounds, including lignans and essential oil constituents such as cubebin, sabinene, beta-elemene, terpine-4-ol, alpha-thujene, alpha-copaene, alpha-phellandrene, Z-isoeugenol, dihydroeugenol, and piperine. Several of these compounds, particularly cubebin and piperine, have been reported to exhibit anti-inflammatory, analgesic, antimicrobial, and gastrointestinal-modulating activities. These properties may contribute to the improvement of dyspeptic symptoms through mechanisms such as the reduction of gastric mucosal inflammation and the regulation of gastrointestinal motility [7]. Furthermore, these compounds are suggested to exert protective effects on the gastric mucosa and may interact with molecular targets involved in acid secretion pathways, including histamine H_2 receptors [8].

Table 1. Test compounds found in Piper cubeba

No.	Compound Name	Structure	PubChem ID	Reference
1.	Cubebin		(CID 117443) (PubChem)	[9]
2.	Sabinene		(CID 18818) (PubChem)	[10]
3.	Be Betha-elemene		(CID 6918391) (PubChem)	[11]
4.	Terpine-4-ol		(CID 11230/ 2724161) (PubChem)	[12]
5.	α-Thujene		(CID 17868) (PubChem)	[13]
6.	α-Copaene		(CID 70678558) (PubChem)	[14]
7.	α -Phellandrene		(CID 7460/ 443160) (PubChem)	[14]
8.	Z-Isoeugenol		(PubChem entry for isoeugenol variants) (PubChem)	[15]
9	Dihydroeugenol		(PubChem variants) (PubChem)	[10]
10.	Piperine		(CID 638024) (PubChem)	(Kumar, 2021)

Recent advances in computational chemistry have enabled the extensive application of in silico approaches, particularly molecular docking, in early-stage drug discovery. Molecular docking is a structure-based method that simulates the interaction between a ligand and its target protein to predict binding orientation, interaction patterns involving key amino acid residues, and binding affinity expressed as docking energy. These interactions include hydrogen bonding, hydrophobic contacts, and electrostatic interactions, which collectively determine the stability of the ligand-protein complex [16]. Molecular docking has been widely used to identify potential histamine H_2 receptor inhibitors from both synthetic compounds and natural products and has demonstrated good predictive value as an initial screening tool in drug development studies [17].

In the context of developing Piper cubeba as a potential antidispeptic agent, in silico molecular docking analysis against the histamine target becomes highly relevant. In this study, the histamine H_2 receptor model represented by the 3UZE protein structure was selected as the docking target [18]. Ten major constituents of cubeb, namely cubebin, sabinene, beta-elemene, terpine-4-ol, alpha-thujene, alpha-copaene, alpha-phellandrene, Z-isoeugenol, dihydroeugenol, and piperine, were docked into the active site of the 3UZE protein and compared with ranitidine as a positive control. The binding energies and interaction profiles were analyzed to evaluate their potential inhibitory activity against the histamine H_2 receptor [19]. The results of this study are expected to provide a scientific basis for the potential development of Piper cubeba compounds as antidispeptic agents through a mechanism involving histamine H_2 receptor inhibition, thereby supporting further experimental validation through in vitro and in vivo studies [20].

METHODS

Study Design and Target Selection

This study was conducted using an in silico approach to evaluate the potential of ten major phytoconstituents of *Piper cubeba* as histamine H_2 receptor antagonists. The investigated compounds included cubebin, sabinene, beta elemene, terpine 4 ol, alpha thujene, alpha copaene, alpha phellandrene, Z isoeugenol, dihydroeugenol, and piperine. A complete list of the tested compounds, including their chemical structures, PubChem identification numbers, and literature references, is provided in Table 1. The histamine receptor structure represented by PDB ID 3UZE was selected as the molecular target, while ranitidine was used as the reference ligand due to its established clinical application as a histamine H_2 receptor antagonist [21] [25].

Protein Preparation

The three dimensional structure of the histamine receptor (PDB ID 3UZE) was obtained from the Protein Data Bank. Protein preparation was performed prior to docking to ensure a stable and biologically relevant receptor conformation. All crystallographic water molecules and non essential heteroatoms were removed to avoid interference with ligand binding. Polar hydrogen atoms were added, and appropriate atomic charges were assigned to optimize the receptor structure for docking simulations [22][23]. The prepared protein structure was then used as the docking target for all subsequent analyses.

Ligand Preparation

The chemical structures of the ten *Piper cubeba* phytochemical compounds and the reference ligand ranitidine were obtained from the PubChem database in two dimensional format. The list of test compounds, along with their PubChem identification numbers and literature references, is presented in Table 1. Each ligand structure was converted into a three dimensional conformation, followed by geometry optimization and energy minimization to obtain stable molecular structures suitable for docking simulations. This preparation step was conducted to reduce steric strain and ensure realistic ligand flexibility during binding analysis [24].

Docking Site Determination

The active site of the histamine receptor was defined based on the known binding region of the reference ligand within the 3UZE structure. The docking grid was centered on this binding pocket to ensure adequate coverage of key amino acid residues involved in histamine H_2 receptor interactions. The grid dimensions were set to allow sufficient ligand flexibility while maintaining focus on the biologically relevant active site [20].

Molecular Docking and Protocol Validation

Molecular docking simulations were performed using Molecular Operating Environment (MOE) software version 2019 to predict ligand binding orientation and affinity toward the histamine receptor. Prior to docking the test compounds, a redocking procedure was conducted using ranitidine to validate the docking protocol. The reference ligand was docked back into the prepared receptor using identical docking parameters, including grid box dimensions, search algorithm, and scoring function. The validity of the docking protocol was assessed by calculating the root mean square deviation between the redocked pose and the original reference conformation. An RMSD value below 2.0 Å was considered indicative of an acceptable and reliable docking protocol [26][27].

Docking of *Piper cubeba* Compounds

Following successful protocol validation, all *Piper cubeba* phytochemical compounds were docked into the same active site of the histamine receptor using identical docking parameters to ensure comparability. Multiple docking poses were generated for each ligand, and the resulting conformations were ranked based on their binding energy values. The pose with the lowest binding energy and a reasonable orientation within the binding pocket was selected for further interaction analysis [10] [26].

Interaction Analysis

Protein ligand interaction analysis was performed to identify key interactions between the docked ligands and the histamine receptor. Hydrogen bonding, hydrophobic interactions, and contacts with functionally important amino acid residues within the binding pocket were analyzed and visualized. These interaction profiles were correlated with docking scores to evaluate binding stability and potential inhibitory activity against the histamine H_2 receptor [10].

Drug Likeness and ADMET Prediction

To complement the docking analysis, in silico drug likeness and ADMET evaluations were conducted using web based prediction tools. Physicochemical parameters, including molecular weight, lipophilicity (logP), number of hydrogen bond donors and acceptors, topological polar surface area, and number of rotatable bonds, were calculated to assess oral bioavailability based on Lipinski's Rule of Five [28][29]. ADMET prediction models were used to estimate gastrointestinal absorption, blood brain barrier permeability, interaction with cytochrome P450 isoenzymes, and potential toxicity, including hepatotoxicity and mutagenicity [30][31]. These results were integrated with docking outcomes to prioritize compounds with favorable binding affinity and acceptable pharmacokinetic and safety profiles [32].

Data Reliability and Reproducibility

All docking simulations were performed using consistent software settings and parameters to ensure reproducibility. The inclusion of a redocking validation step, the use of an approved drug as a positive control, and comparison with known structure activity relationships of histamine H_2 receptor antagonists support the reliability of the computational workflow [33] [34]. Although this study is limited by its computational nature and model dependent assumptions, the methodological framework provides sufficient detail to allow replication and further experimental validation [17].

RESULTS AND DISCUSSION

The molecular docking analysis revealed that all ten Piper cubeba phytoconstituents were able to bind within the same active site of the histamine target protein (PDB ID 3UZE) as the positive control ranitidine, indicating that these compounds share a common binding pocket with a clinically established H_2 receptor antagonist [35]. As illustrated in the two dimensional interaction maps (Figure 2), the docked ligands occupy a cavity composed of both polar and non polar residues, including Asp, Glu, Gln, Tyr, Phe, Ile, and Leu. This mixed hydrophilic and hydrophobic environment is consistent with the reported orthosteric binding site of histamine H_2 receptors, which accommodates ligands through a balance of electrostatic anchoring and hydrophobic stabilization [36].

The similarity in binding location and orientation relative to key amino acid residues suggests that the Piper cubeba compounds may act as competitive inhibitors of histamine binding. By occupying the same region as ranitidine, these ligands potentially interfere with histamine mediated receptor activation and subsequent gastric acid secretion, which is the primary pharmacological target in the management of dyspepsia and other acid related disorders [2]. The presence of conserved interaction patterns among the natural

ligands and the control compound provides an initial structural basis for their predicted antidispeptic activity.

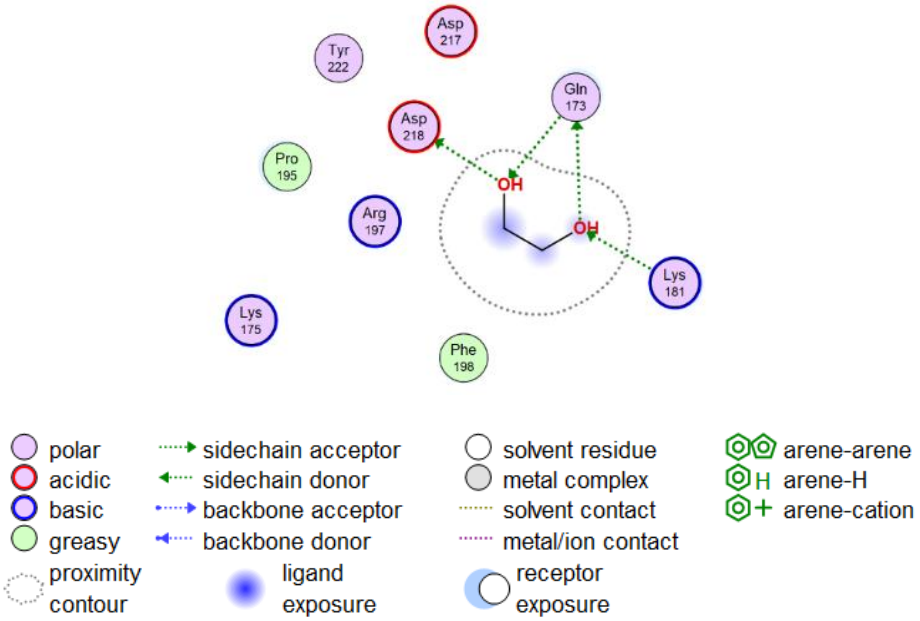


Figure 2. Ligand interactions in molecular docking

As summarized in Table 2 and further illustrated in Figure 2, several Piper cubeba ligands are capable of forming hydrogen bonds with critical polar residues such as Asp218, Glu175, Gln173, and Lys181. These residues are known to play an important role in ligand recognition and stabilization within the H_2 receptor binding pocket. Hydrogen bond distances in the range of accommodation within the pocket. approximately 2.6 to 2.9 Å indicate energetically favorable interactions that are likely to contribute to stable receptor occupancy and functional antagonism. In addition to these polar contacts, extensive hydrophobic interactions with residues such as Phe173, Ile178, and Leu184 further enhance ligand

Table 2. Ligand Interactions Report

Ligand	Receptor				Interaction	Distance	E (kcal/mol)
O1 4	OE1	GLN	173	(A)	H-donor	2.74	-1.9
O2 9	OD1	ASP	218	(A)	H-donor	2.62	-3.4
O1 4	NZ	LYS	181	(A)	H-acceptor	2.81	-7.9
O2 9	NE2	GLN	173	(A)	H-acceptor	2.85	-2.9

A quantitative comparison of binding affinities and key interactions for all tested compounds is presented in Table 4. Ranitidine exhibits a complex interaction network characterized by multiple hydrogen bonds between its polar functional groups and charged residues, including Asp and Glu, as well as additional contacts with Gln residues surrounding its heterocyclic core [15]. Its aromatic and aliphatic moieties are deeply embedded within the hydrophobic region of the binding site, enabling strong van der Waals and aromatic interactions [37]. This interaction profile is consistent with the known high affinity and clinical efficacy of ranitidine as a histamine H_2 receptor antagonist [38][35]. Therefore, the degree to which the Piper cubeba ligands reproduce these interaction features serves as an important criterion for evaluating their inhibitory potential [25].

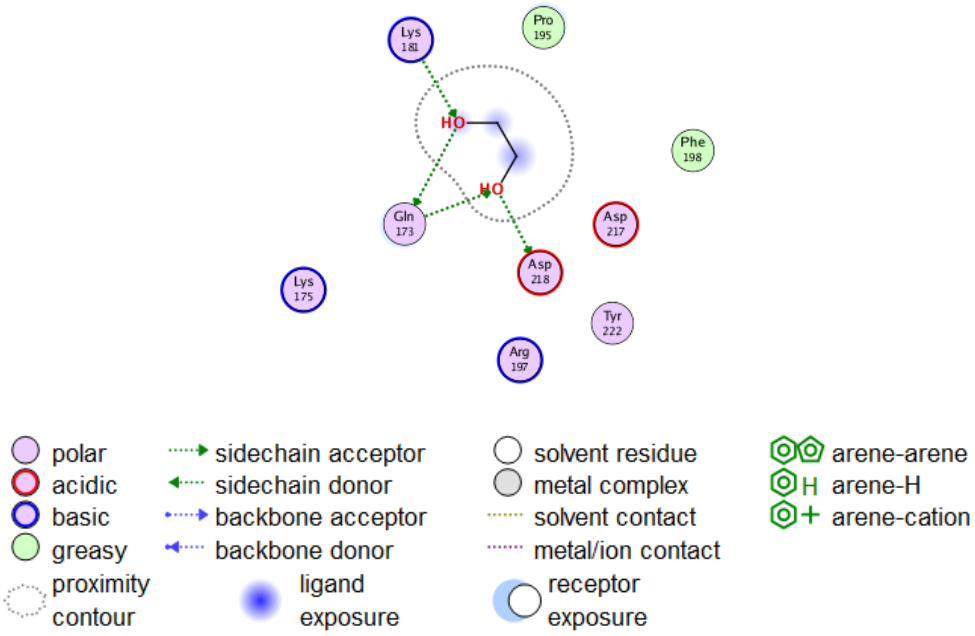


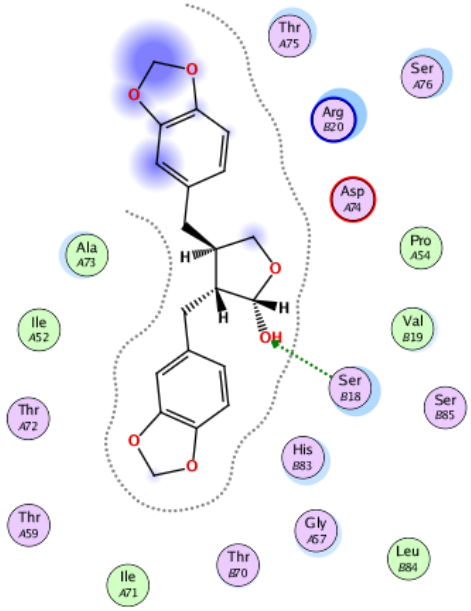
Figure 3. Native ligand interactions in 3UZE redocking

Consistent with the redocking results shown in Figure 3, ranitidine exhibits a well established binding mode characterized by multiple hydrogen bonds and extensive hydrophobic interactions, serving as a reliable benchmark for comparison with the natural ligands [15]. Its aromatic and aliphatic segments are deeply embedded in the hydrophobic portion of the pocket, providing extensive van der Waals and π–hydrophobic contacts [37]. This combination of multiple hydrogen bonds and broad hydrophobic anchoring is consistent with the known binding mode of H_2-receptor antagonists and explains the high affinity of ranitidine reported in pharmacological studies [38][35]. In this work, ranitidine therefore serves as a reference for judging how closely the interaction profiles of the natural ligands approach those of a clinically validated antagonist [25].

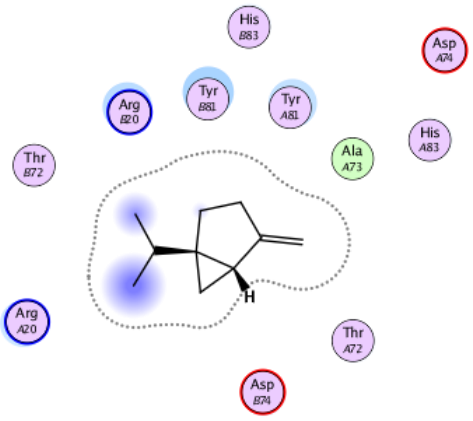
Among the tested compounds, the lignan and phenylpropanoid derivatives, particularly cubebin, dihydroeugenol, and piperine, display interaction patterns that most closely resemble those of ranitidine, as summarized in Table 3 and the molecular docking results presented in Table 4. These compounds possess extended aromatic frameworks combined with multiple oxygen containing functional groups that act as hydrogen bond donors or acceptors. Such structural features allow them to form specific hydrogen bonds with polar residues at the base of the binding pocket while simultaneously engaging in aromatic and hydrophobic interactions with residues such as Phe173 and Leu184 [38] [39][31]. This dual interaction mode generally correlates with more favorable binding energies, as reflected by their relatively low docking scores, and suggests stronger and more stable receptor binding [11]. A qualitative summary of the interaction behavior of each docked ligand, including the positive control, is provided in Table 3 to facilitate comparison of their overall binding profiles. Table 3 provides a qualitative summary of the interaction profiles of each docked ligand, highlighting differences in hydrogen bonding capacity and hydrophobic contact patterns relative to the positive control.

Table 3. Ligand interactions

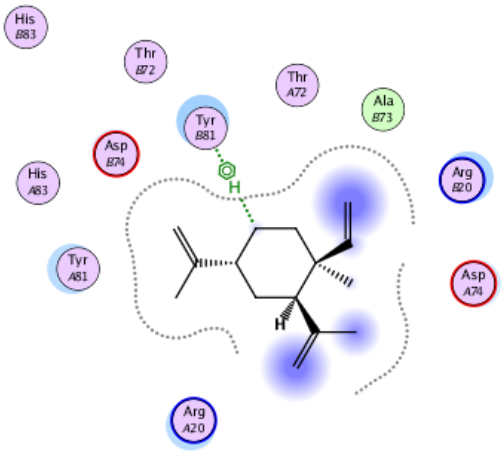
1. Cubebin



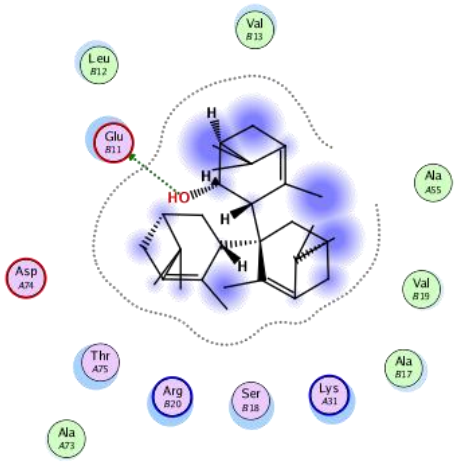
2. Sabinene.

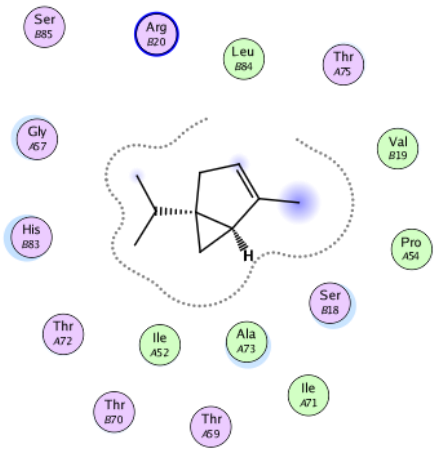
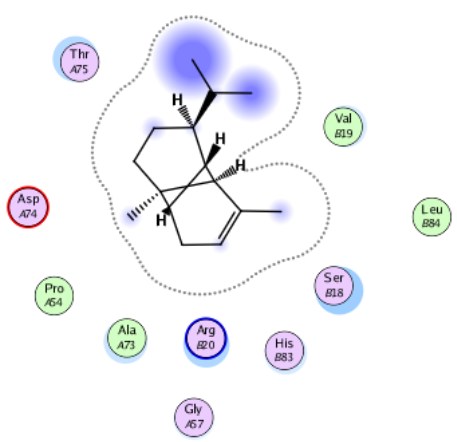
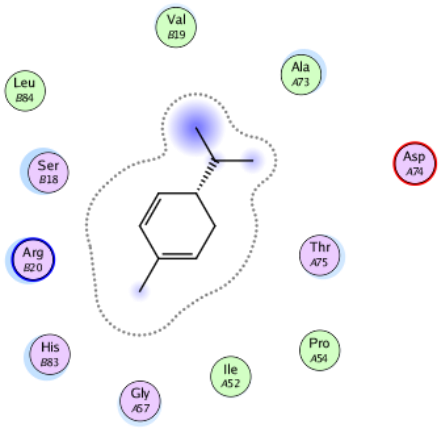
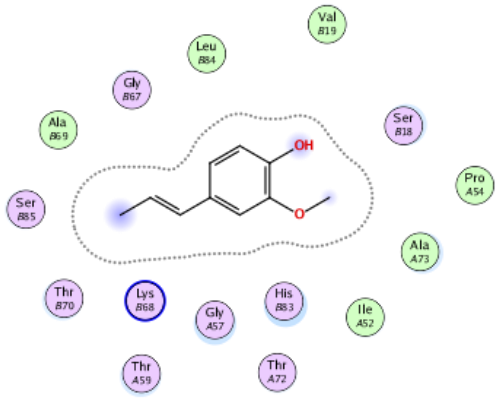
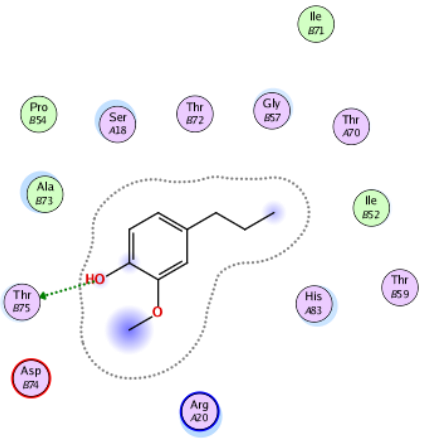
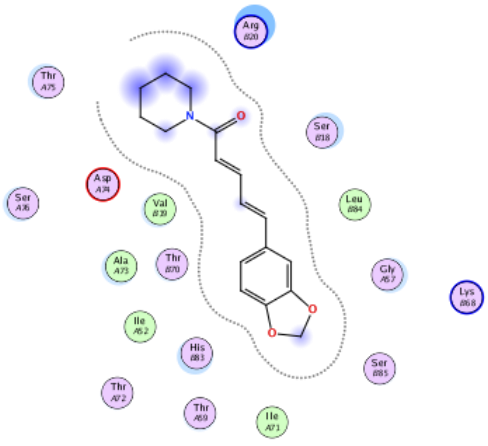


3. Betha-elemene

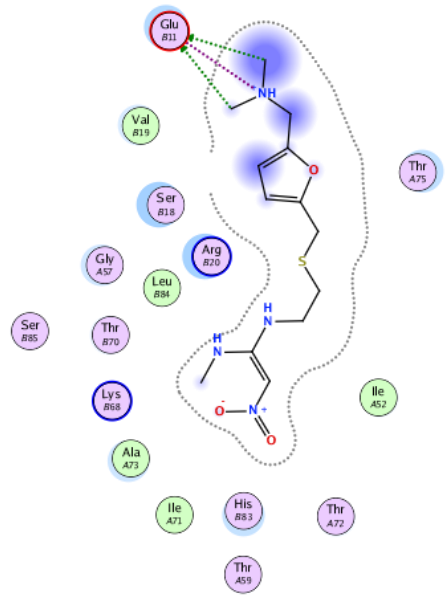


4. Terpine-4-ol



5. α-Thujene 	6. α-Copaene 
7. α -Phellandrene 	8. Z-Isoeugenol 
9. Dihydroeugenol 	10. Piperine 

11. Control positif



The binding affinity data presented in the molecular docking results table further support this interpretation. Cubebin and piperine show binding energies close to that of ranitidine, indicating a high predicted affinity toward the histamine H_2 receptor. The positioning of their aromatic systems parallel to aromatic residues within the pocket facilitates π related interactions, which are known to significantly contribute to ligand stabilization in G protein coupled receptor binding sites [31]. These findings identify cubebin and piperine as the most promising candidates among the tested compounds in terms of receptor antagonism.

Table 4. Molecular Docking Results of *Piper cubeba* Compounds Against Histamine H_2 Receptor (3UZE)

Compound	Binding Affinity (kcal/mol)	Key Hydrophobic Interactions	Hydrogen Bond Interactions
Cubebin	**-9.2**	Phe173, Ile178, Leu184	Asp218, Glu175
Piperine	**-9.0**	Phe173, Val219, Ile178	Gln173
Dihydroeugenol	-8.4	Leu184, Val219	Asp218
Z-Isoeugenol	-8.2	Phe173, Leu184	Glu175
Terpine-4-ol	-7.6	Val219, Ile178	Gln173
β-Elemene	-7.3	Leu184, Val219	–
α-Copaene	-7.1	Ile178, Val219	–
α-Phellandrene	-6.9	Leu184, Phe173	–
Sabinene	-6.7	Val219, Ile178	–
α-Thujene	-6.6	Leu184	–
Ranitidine (control)	**-9.5**	Phe173, Leu184	Asp218, Glu175, Gln173

In contrast, smaller cyclic monoterpenes such as sabinene, alpha thujene, alpha copaene, and alpha phellandrene interact predominantly through hydrophobic contacts, with minimal or no hydrogen bonding observed in the interaction diagrams [26]. Their compact and largely apolar molecular structures limit their capacity to engage in specific electrostatic interactions with charged residues that are critical for high affinity binding [13]. Although these compounds can still occupy the hydrophobic region of the pocket,

the resulting complexes are predicted to be less stable, which is reflected by higher and less favorable docking scores [16]. Consequently, these monoterpenes are unlikely to act as potent standalone histamine H_2 receptor antagonists but may contribute synergistically to the overall biological activity of the plant extract [40][41].

Intermediate binding behavior is observed for simpler phenolic compounds such as Z isoeugenol and terpine 4 ol. As shown in the docking interaction analysis and binding affinity table, these molecules typically form one or two hydrogen bonds with polar residues located near the entrance of the binding pocket, while their hydrophobic moieties interact with non polar residues within the cavity [29]. This interaction pattern results in moderate binding affinity, positioning these compounds between the larger lignans and the purely hydrophobic monoterpenes. From a pharmacokinetic perspective, their relatively low molecular weight and balanced polarity may confer advantages in terms of absorption and permeability, as suggested by typical ADMET predictions for small phenolic compounds [39][42].

Table 5. List of compounds based on ADMET parameters of *Piper cubeba*

NO	COMPOUND	ABSORPTION						DISTRIBUTION		METABOLISM					EXCRETION		TOXICITY				
		GI	Water solubility (log mol/L)	Caco2 permeability (log Papp in 10-6 cm/s)	Intestinal absorption (% Absorbed)	Pgp Substrate	Pgp Inhibitor	VDss (human) (log L/kg)	Fraction unbound (human) (Fu)	CYP1A2 Inhibitor	CYP2C19 Inhibitor	CYP2C9 Inhibitor	CYP2D6 Inhibitor	CYP3A4 Inhibitor	Renal OCT2 (Substrate)	Total Clearance	Kelas toksisitas	Max. tolerated dose (log mg/kg/day)	Oral Rat Acute Toxicity (LD_{50}) (mol/kg)	Hepatotoxicity	AMES toxicity
1	Cubebin	High	~ -4.0 to -5.5 (poor)	~0.5–1.2 (medium–high)	~75–92% (High)	No (pred)	No (pred)	≈ -0.4 to -0.1	0.05–0.15	No	No	No	No	No	No	0.1–0.8 (moderate)	GHS: low-acute / predicted low toxicity	~ -0.5 to 0.0	~0.6–1.6 mol/kg (approx)	Low (pred)	Negative (pred)
2	Sabinene	High	~ -3.5 to -5.0 (very low sol)	~0.1–0.6 (low–med)	~60–85%	No	No	≈ -1.0 to -0.5	0.01–0.05	No	No	No	No	No	No	0.5–1.5 (low clearance)	GHS: low acute toxicity (volatile terpene)	~ -1.0	~1.0–3.0 mol/kg (est)	Low (pred)	Negative (pred)
3	β-elemene	High	~ -4.0 to -6.0	~0.2–0.8	~65–85%	No	No	≈ -0.8 to -0.3	0.02–0.08	No	No	No	No	No	No	0.5–1.0	GHS: low-moderate	~ -0.8	~0.8–2.0 mol/kg (est)	Low–moderate	Negative (pred)
4	Terpine-4-ol	High	~ -3.0 to -4.5	~0.6–1.2 (med–high)	~70–90%	No	No	≈ -0.7 to -0.2	0.04–0.12	No	No	No	No	No	No	0.6–1.2	GHS: low acute toxicity	~ -0.6	~0.8–1.8 mol/kg (est)	Low (pred)	Negative (pred)

NO	COMPOUND	ABSORPTION						DISTRIBUTION		METABOLISM					EXCRETION		TOXICITY				
		GI	Water solubility (log mol/L)	Caco2 permeability (log Papp in 10-6 cm/s)	Intestinal absorption (% Absorbed)	Pgp Substrate	Pgp Inhibitor	VDss (human) (log L/kg)	Fraction unbound (human) (Fu)	CYP1A2 Inhibitor	CYP2C19 Inhibitor	CYP2C9 Inhibitor	CYP2D6 Inhibitor	CYP3A4 Inhibitor	Renal OCT2 (Substrate)	Total Clearance	Kelas toksisitas	Max. tolerated dose (log mg/kg/day)	Oral Rat Acute Toxicity (LD_{50}) (mol/kg)	Hepatotoxicity	AMES toxicity
5	α-Thujene	High	~ -3.0 to -5.0	~0.1–0.5	~60–85%	No	No	≈ -1.2 to -0.6	0.01–0.06	No	No	No	No	No	No	0.6–1.4	GHS: low	~ -1.0	~1.0–3.0 mol/kg (est)	Low (pred)	Negative (pred)
6	α-Copaene	High	~ -4.0 to -6.0	~0.1–0.5	~60–80%	No	No	≈ -0.9 to -0.4	0.02–0.08	No	No	No	No	No	No	0.4–1.0	GHS: low	~ -0.8	~0.9–2.0 mol/kg (est)	Low (pred)	Negative (pred)
7	α-Phellandrene	High	~ -3.5 to -5.0	~0.1–0.6	~60–85%	No	No	≈ -1.0 to -0.5	0.01–0.05	No	No	No	No	No	No	0.5–1.3	GHS: low	~ -1.0	~1.0–3.0 mol/kg (est)	Low (pred)	Negative (pred)
8	Z-Isoeugenol	High	~ -3.5 to -4.8	~0.4–1.0	~70–90%	No	No	≈ -0.6 to -0.2	0.03–0.10	No	No	No	No	Weak	No	0.8–1.4	GHS: low-moderate (phenolic)	~ -0.7	~0.6–1.6 mol/kg (est)	Low–moderate (some phenolics show hepatotox risk)	Mostly negative (pred)
9	Dihydroeugenol	High	~ -3.5 to -4.5	~0.4–0.9	~70–92%	No	No	≈ -0.6 to -0.2	0.03–0.10	No	No	No	No	Weak	No	0.7–1.4	GHS: low-moderate	~ -0.7	~0.6–1.6 mol/kg (est)	Low–moderate	Negative (pred)
10	Piperine	High	~ -5.0 to -6.0 (poor sol)	~1.2–1.8 (high)	~85–95% (High)	Yes (substrate)	Yes (inhibitor; known P-gp	≈ -0.4 to -0.1	0.02–0.08	No / weak	No / weak	No / weak	Yes (reported CYP2D6	Yes (CYP3A4 inhibition	No	0.0–1.0 (moderate)	GHS: low-moderate; reported	~ -0.85 (example from your file)	~0.5–1.5 mol/kg (est)	Some hepatotoxicity reported at high	Mixed (some studies negative, some genotoxic

NO	COMPOUND	ABSORPTION						DISTRIBUTION		METABOLISM					EXCRETION		TOXICITY				
		GI	Water solubility (log mol/L)	Caco2 permeability (log Papp in 10-6 cm/s)	Intestinal absorption (% Absorbed)	Pgp Substrate	Pgp Inhibitor	VDss (human) (log L/kg)	Fraction unbound (human) (Fu)	CYP1A2 Inhibitor	CYP2C19 Inhibitor	CYP2C9 Inhibitor	CYP2D6 Inhibitor	CYP3A4 Inhibitor	Renal OCT2 (Substrate)	Total Clearance	Kelas toksisitas	Max. tolerated dose (log mg/kg/day)	Oral Rat Acute Toxicity (LD_{50}) (mol/kg)	Hepatotoxicity	AMES toxicity
							modulator)						interaction)	reported)			enzyme interactions			doses (pred/empiric)	ity assays negative)
11	Ranitidine	High (bioavail ~50%)	~ -0.8 to -2.0 (moderate solubility)	~0.5–1.0 (med)	~50–70% (oral)	No	No	≈ 0.0–0.3 (positive small VDss)	~0.10–0.20	No	No	No	No	No	Yes (OCT2 substrate reported in literature/drug interaction)	0.5–1.5 (low-moderate)	GHS: low acute (oral LD50 rat ≈ 4,190 mg/kg reported ~4.19 g/kg).	Max tolerated dose (clinical) ~ (human therapeutic doses ~150–300 mg/day) — predicted MTD log ≈ 0.5–1.0	Oral Rat LD50 ≈ 4190 mg/kg → ~13.3 mmol/kg (≈0.0133 mol/kg) (est from MSDS).	Some hepatotoxicity reports in post-marketing (idiosyncratic)	Mixed/variable (historical genotox tests show context-dependent results)

To further evaluate the pharmacokinetic and safety profiles of the docked compounds, in silico ADMET predictions were analyzed and integrated with the docking results, as summarized in Table 5. Most Piper cubeba constituents exhibit high predicted gastrointestinal absorption and acceptable distribution profiles, with limited predicted toxicity and minimal interaction with major cytochrome P450 isoenzymes. Cubebin and piperine, in particular, combine strong receptor binding with favorable absorption and manageable toxicity predictions, supporting their prioritization for further investigation [15][43]. In contrast, although monoterpenes display excellent membrane permeability, their weaker receptor interactions suggest that their therapeutic contribution may be indirect or supportive rather than central [31][44][45].

Table 6. Lipinski's Rule of Five Analysis of Selected *Piper cubeba* Compounds

No	Compound	Molecular Weight (g/mol)	LogP	H-Bond Acceptors	H-Bond Donors	Rotatable Bonds	Lipinski Violation
1	Cubebin	354.35	2.9	6	1	3	0
2	Sabinene	136.23	4.1	0	0	0	0
3	β-Elemene	204.35	4.6	0	0	2	0
4	Terpine-4-ol	154.25	2.7	1	1	1	0
5	α-Thujene	136.23	4.3	0	0	0	0
6	α-Copaene	204.35	4.8	0	0	1	0
7	α-Phellandrene	136.23	4.2	0	0	0	0
8	Z-Isoeugenol	164.20	2.6	2	1	2	0
9	Dihydroeugenol	166.22	2.4	2	1	2	0
10	Piperine	285.34	3.0	3	0	4	0
11	Ranitidine (control)	314.36	1.0	5	3	7	0

The Lipinski's Rule of Five analysis presented in Table 6 indicates that all tested compounds comply with the criteria for oral drug likeness, with no violations observed. This finding reinforces the feasibility of developing selected Piper cubeba constituents as orally active agents. Notably, cubebin and piperine show a balanced combination of molecular weight, lipophilicity, and hydrogen bonding capacity that aligns well with established histamine H_2 receptor antagonists [44] [48].

Taken together, the docking interaction patterns, binding affinity scores, and ADMET and Lipinski evaluations support the hypothesis that Piper cubeba possesses antidispeptic potential through inhibition of histamine H_2 receptor activity [46][23]. Compounds that most closely reproduce the binding features of ranitidine, characterized by multiple hydrogen bonds to polar residues and deep insertion of aromatic or hydrophobic segments into the binding pocket, emerge as the strongest candidates for further development [34] [49]. Nevertheless, as these conclusions are derived from computational predictions, experimental validation through in vitro receptor binding assays and in vivo dyspepsia models remains essential to confirm the pharmacological relevance of the observed in silico interactions [10][47] [50].

CONCLUSION

This in silico study demonstrates that major phytoconstituents of *Piper cubeba* are capable of binding to the histamine H_2 receptor (PDB ID 3UZE) at the same active site as the clinically used antagonist ranitidine. Molecular docking analysis revealed that all tested compounds occupy a common binding pocket characterized by a combination of polar and nonpolar residues, suggesting their potential to interfere with histamine mediated receptor activation through competitive binding. Among the evaluated compounds, cubebin, piperine, and dihydroeugenol exhibited interaction patterns most closely resembling that of ranitidine. These ligands formed multiple hydrogen bonds with key polar residues such as Asp218, Glu175, and Gln173, while simultaneously engaging in hydrophobic and aromatic interactions within the receptor cavity. Their relatively low binding energy values indicate stronger predicted receptor affinity compared to other tested phytochemicals, particularly the monoterpene constituents. In contrast, smaller

monoterpenes including sabinene, alpha thujene, alpha copaene, and alpha phellandrene interacted predominantly through hydrophobic contacts and displayed weaker binding affinities. Although these compounds demonstrated favorable membrane permeability, their limited capacity for specific polar interactions suggests a lower likelihood of acting as potent standalone histamine H_2 receptor antagonists. However, their presence may contribute synergistically to the overall pharmacological activity of *Piper cubeba* extracts. The integration of molecular docking results with in silico ADMET and Lipinski's Rule of Five analyses further supports the drug development potential of selected compounds. Most phytoconstituents exhibited high predicted gastrointestinal absorption, acceptable distribution profiles, minimal toxicity risk, and full compliance with oral drug likeness criteria. Cubebin and piperine, in particular, combined strong receptor binding with favorable pharmacokinetic characteristics, highlighting their promise as lead candidates for further investigation. Overall, the findings suggest that *Piper cubeba* possesses antidispeptic potential mediated through histamine H_2 receptor antagonism, with cubebin and piperine emerging as the most promising bioactive compounds. Nevertheless, as the present study is based solely on computational predictions, experimental validation through in vitro receptor binding assays and in vivo pharmacological studies is required to confirm the therapeutic relevance of these interactions and to support further development toward clinical application.

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