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Research Paper

Molecular Docking and ADMET Analysis of Bauhinia Acuminata Phytoconstituents Against Gastric H+/K+ Atpase

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ABSTRACT

Peptic ulcer is a long-term disease, that mainly occur due to imbalance between aggressive factor like acid secretion and protective mechanism of stomach lining. One of the key enzymes in acid secretion is H^+/K^+-ATPase. Current antiulcer drug is associated with side effects and recurrence. Therefore, there is a need to develop safer alternatives from natural sources. In the present study phytochemicals from bauhinia acuminata were assessed for their potential antiulcer property using molecular docking and ADMET analysis. Nine compounds were chosen based on literature and subjected to in-silico studies against H^+/K^+-ATPase using three protein structures. Among the tested compounds, Phlorizin, Quercetin, and Baicalein showed strong binding affinities, with Phlorizin exhibiting the highest docking score. These compounds exhibited interactions effectively through important key amino acid residues in the active site, indicating good inhibitory potential. Further ADMET analysis revealed that most compounds possessed acceptable pharmacokinetic properties and followed Lipinski's rule of five. Notably, Quercetin demonstrated a good balance between binding efficiency and drug-likeness, making it a promising candidate. Overall, the findings suggest that phytochemicals from Bauhinia acuminata, especially Quercetin, may serve as potential natural inhibitors of H^+/K^+-ATPase. However, further experimental studies are required to confirm their antiulcer activity and therapeutic applicability.

INTRODUCTION

Peptic ulcers are a chronic and recurrent illness caused by damage to the duodenal or stomach mucosa due to an imbalance between the mucosal defensive factors and the gastric aggressive factor [1]. Exogenous aggressive factors include stress, alcohol, smoking, use of anti-inflammatory drugs, consuming fatty foods, and infection caused by Helicobacter pylori. HCl together with pepsin,

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pancreatic enzymes, and bile, weakens the protective barrier of the gastrointestinal mucosa [2]. Symptoms often appear several hours after eating, when the food has exited the stomach, but acid production is high, and include bleeding and other symptoms. Pain in the upper abdomen is a common symptom of ulcers. Therefore, the importance of active phytoconstituents in the treatment of peptic ulcers has been explored.

Ulcers cause pain in the upper abdomen, and bleeding and other symptoms are often not felt until several hours after a meal, once the food has left the stomach, but the acid production remains high. Therefore, there has been an attempt to examine the role of active phytoconstituents in the treatment of peptic ulcers [3]. Gastric proton pump is the main enzyme in charge of making stomach contents more acidic. The proton pump is located in the very specialized stomach epithelial cell known as parietal cells [4]. Gastric proton pump is a key part of making acid because it moves H+ into the lumen in exchange for K+ [5]. The most commonly used acid-suppressive drugs in the world are proton pump inhibitors, including omeprazole, esomeprazole, pantoprazole, lansoprazole, rabeprazole, and dexlansoprazole [6]. However, these compounds function in an acidic canalicular pH in parietal cells, and their half-life in plasma is very short [4].

Recently, the use of natural products and alternative therapies has become more popular [1]. While there are numerous synthetic antiulcer medications, the severe long-term side effects have led to more research into plant-based alternatives [7]. Dwarf white bauhinia (*Bauhinia acuminata*) belongs to the Fabaceae family and contains phytochemicals including palmitic acid, phallic acid, esterified acid, gallic acid ursolic acid, carbohydrate, alkaloids, phenols, flavonoids, and glycosides [8]. It contains anti-inflammatory, antioxidant, and antidiabetic properties [9, 10] and its leaf shows antimicrobial, antidiarrheal, and anticancer properties [11, 12]. Molecular modelling is a computational technique employed in drug development and discovery that predicts the best way for small molecules (ligands) to bind to a target receptor or protein's active site [13].

MATERIALS AND METHODS

Ligand selection and preparation:

Several phytochemicals from Bauhinia acuminata were collected from published literature and a library of compounds was used to prepare ligands using Schrodinger's lig prep interface, which was downloaded from the PubChem database [14].

Protein selection and preparation:

Refining the protein and generating a grid are important for proper docking. The protein data bank will provide the spatial structure of the target, H+K+ ATPase [15], using Pdb IDs 5YLU [16], 6JXI [18], and 7W47 [17]. All bound water molecules, unneeded atoms, and all bound ligands were removed from the protein during refinement. Structures were prepared by adding hydrogen atoms, removing alternate conformations, and adding missing atoms to incomplete residues. [15].

Figure 1: ***Bauhinia acuminata* L**

Molecular docking:

We used the Glide tool on Maestro 12.8 to do docking analysis. The library of ligands, or phytochemicals, was made and placed in the target

protein's active site with standard precision (SP) and extra precision (XP) replacing the flexible ligand sampling and only used for refinement.[13]
To check the docking process, the co-crystallized ligands (HKT, PCW, and 8BN) were re-introduced into the active sites of H+/K+-ATPase (PDB IDs: 5YLU, 6JXI, and 7W47). We compared the docking scores and binding orientations we got with the native ligand conformations to make sure that the docking process was reliable and accurate.[19]

Table 1: Docking score of co-crystallized ligands

SL NO	COMPOUND NAME	DOCKING SCORE (kcal/mol)			Amino acids at protein active site
		Pdb id: -			
		5ylu	6jxi	7w47	
1	Apigenin	-7.09	-2.52	-8.21	LEU811, ASP137, TYR799, VAL341, GLN884, GLH795, ASN138
2	Baicalein	-7.43	-4.04	-9.81	ASP137, ASN138, GLN884, LEU811, GLH795
3	Kaempferol	-7.15	-3.28	-8.83	ASP137, GLH795, GLN884, LEU811
4	Lupeol	No interaction	-1.703	-4.42	Not detected
5	Pentahydroxy Flavone	-7.92	No interaction	-8.90	GLH795, ASN138, ALA335, ASP132
6	Phlorizin	-8.87	-5.515	-10.90	GLN127, ARG328, TYR799, GLH795, GLN884, THR880, LEU811, ASP137, ASP132, VAL331
7	Pterosin	-5.74	-1.66	-5.69	ASN138, GLN127
8	Quercetin	-8.17	-4.85	-10.60	ASP137, GLH795, GLU343, GLN884, VAL1000, LEU811, VAL331
9	Berberine	-5.17	-0.66	-4.17	ASP137, GLN924, GLU900, ASP132, TYR799

Table 2: Docking scores of the investigated compounds with H^+/K^+-ATPase (using PDBstructures 5YLU, 6JXI, and 7W47)

PDB ID	Co-crystal Ligand	Docking score	Key interactions
5YLU	HKT	-8.871	GLU343, ALA339
6JXI	PCW	-2.663	GLN996, ARG994, GLU885
7W47	8BN	-7.827	LEU811, ASP137, ASP132, TYR799, VAL331

ADMET analysis:

The Qikprop tool was then used to test the hit compounds. The tool was used to predict the absorption, distribution, metabolism, excretion, and toxicity (ADMET) properties of the compounds including physicochemical parameters such as QPlogPC16, hydrogen bond donors/acceptors, Lipinski's rule of five, bioavailability score, P-glycoprotein substrate specificity, gastrointestinal absorption, blood–brain barrier permeability, and hepatotoxicity.[13]

Table 3: ADMET prediction of the identified phytoconstituents using SwissADME

S/N	Compound name	Mol. Weight (g/mol)	H-bond acceptors	H-bond donors	QPlogPC16	Lipinski violations
1.	Apigenin	270.241	3.75	2	9.706	0
2.	Baicalein	270.241	3.75	2	9.66	0
3.	Kaempferol	286.24	4.5	3	10.242	0
4.	Lupeol	426.724	1.7	1	11.612	1
5.	Pentahydroxy Flavone	392.318	7.5	4	11.38	0
6.	Phlorizin	436.415	12.5	6	15.00	1
7.	Pterosin	218.295	3.7	1	6.9	0
8.	quercetin	302.24	5.25	4	10.742	0

RESULT AND DISCUSSION

To verify the reliability of the docking protocol, the co-crystallized ligands of the target proteins (PDB IDs: 5YLU, 6JXI, and 7W47) were re-docked into their corresponding active binding sites. The docking scores were −8.871 kcal/mol for 5YLU, −2.663 kcal/mol for 6JXI, and −7.827 kcal/mol for 7W47. The re-docked ligand poses fit well with their original crystallographic shapes, which shows that the docking protocol worked. This validation step makes sure that the ligand–protein interactions are structurally reliable and reduces the number of false-positive predictions.

Docking against PDB ID: 5YLU

Phlorizin had the strongest binding affinity of the tested compounds (−8.87 kcal/mol), then Quercetin (−8.17 kcal/mol) and Pentahydroxy flavone (−7.92 kcal/mol). The docking score of Phlorizin (−8.871 kcal/mol) was comparable to that of the co-crystal ligand, which means that it binds strongly to the active site. These values were much better than those of the reference compound Berberine (−5.17 kcal/mol), which suggests that flavonoid derivatives may be better at stopping things.

Docking against PDB ID: 6JXI

The 6JXI conformation was more favourable for binding Phlorizin (−5.515 kcal/mol) and Quercetin (−4.85 kcal/mol) than Berberine (−0.66 kcal/mol). Lower docking scores for this protein structure suggest that the binding pocket could alter its shape, which could affect ligand fit. Even though the docking scores were lower for this protein conformation, the phytoconstituents still had a stronger binding affinity than the co-crystal ligand (−2.663 kcal/mol). This suggests that they may be able to adapt to changes in the binding site's structure.

Docking against PDB ID: 7W47

The most favourable interactions were distinctly noted with PDB ID: 7W47. Phlorizin had the strongest binding affinity (−10.90 kcal/mol), then closely by Quercetin (−10.60 kcal/mol) and Baicalein (−9.81 kcal/mol). These values were much better than the co-crystal ligand (−7.827 kcal/mol), which means that the phytoconstituents in the active site bind more strongly and stably. These findings suggest that this protein conformation may more accurately depict the active inhibitory site of H^+/K^+-ATPase.

Table 4: Predicted pharmacokinetic profiles of the selected phytoconstituents

Compound name	Drug likeness	Bioavailability Score (%)	p-g substrate specificity	Gi absorption rate	BBB permeability
Apigenin	yes	3	No	High	No
Baicalein	Yes	3	No	High	No
Kaempferol	Yes	3	No	High	Non
Lupeol	No	1	Yes	Low	No
Pentahydroxy Flavone	Yes	2	Yes	Moderate	No
Phlorizin	No	2	Yes	Moderate	No
Pterosin	Yes	3	No	High	No
Quercetin	yes	2	no	Moderate	No

Interaction of the active compounds with protein–ligand analysis revealed that the active compounds mainly bound to key amino acid residues in the H^+/K^+-ATPase binding pocket, such as ASP137, GLH795, GLN884, LEU811, ASN138, and TYR799. The two stabilizing factors were hydrophobic interactions and hydrogen bonds. The high docking score of phlorizin can be attributed to the several interactions with key residues, and quercetin showed stable binding with GLH795 and ASP137. ADMET profiling revealed that the majority of compounds followed Lipinski's criteria for drug likeness, except Lupeol & Phlorizin, which showed one infraction, while apigenin, baicalein, kaempferol, and pterosin were predicted to have good gastrointestinal absorption, and lupeol was predicted to have poor absorption. Some of the compounds found to be P-glycoprotein substrates may affect bioavailability. None of the phytochemicals were expected to penetrate the blood-brain barrier. Although phlorizin has the highest docking affinity, its therapeutic potential may be limited due to pharmacokinetic limitations. Quercetin, on the other hand, shows good ADMET properties and strong binding affinity, making it the most promising lead compound. Overall, the comparison with co-crystal ligands shows that many phytoconstituents have the same or better binding affinity, which shows that they could be good natural inhibitors of gastric proton pump.

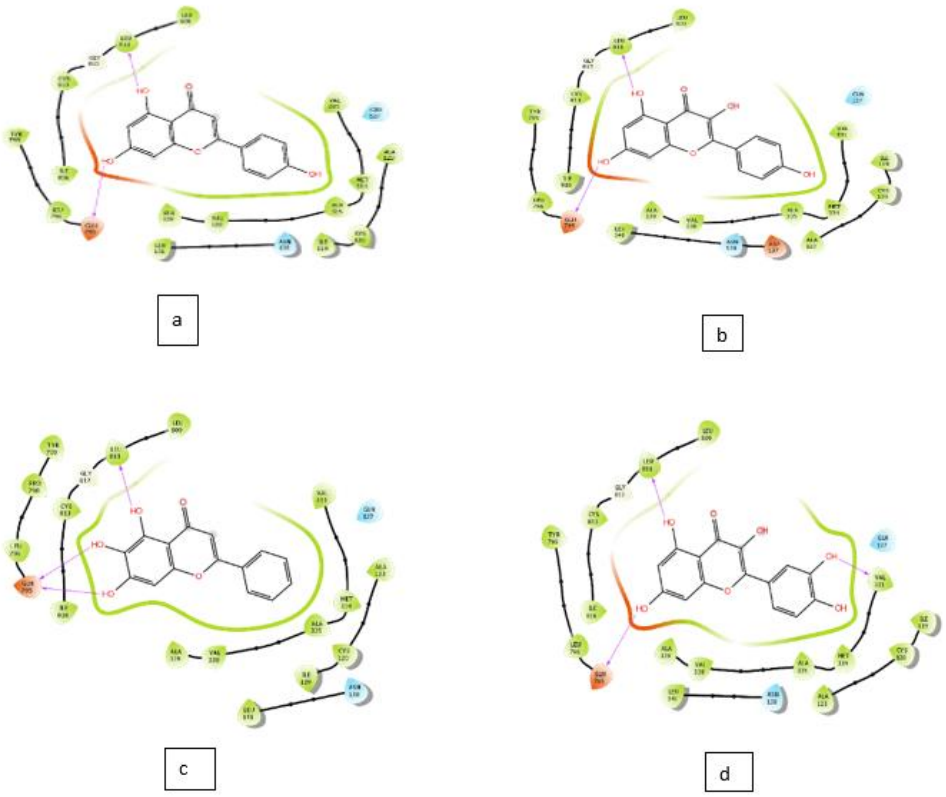

Figure2: Ligand Interaction diagram of phytochemicals (a) apigenin, (b) quercetin, (c) baicalein, (d) kaempferol

CONCLUSION

The *in- silico* analysis conducted in this study identified Quercetin, Baicalein, and Apigenin as promising inhibitors of H^+/K^+-ATPase. These phytoconstituents exhibited strong binding affinities and favourable ADMET profiles, outperforming the reference compound Berberine. The reliability and accuracy of the molecular docking protocol were successfully validated using co-crystallized ligands. Among the tested compounds, Quercetin stood out as the most promising lead candidate due to its well-balanced pharmacokinetic profile and significant binding affinity.

These results indicate that phytoconstituents derived from *Bauhinia acuminata* possess potential as natural antiulcer agents. Nevertheless, additional *in vitro* and *in vivo* studies are essential to prove their therapeutic efficacy and safety.

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