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In Silico Evaluation of Gossypium Hirsutum Phytoconstituents against Gastric H+/K+-ATPASE

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ABSTRACT

Peptic ulcer disease results from an imbalance between gastric acid and the defence mechanisms of the mucosa. The gastric H^+/K^+-ATPase is involved in the secretion of acid and has therefore been established as a therapeutic target. Phytoconstituents from plants may offer potential lead structures for the development of gastroprotective agents. The aim is to examine the predicted binding interactions between the phytoconstituents of Gossypium hirsutum and gastric H^+/K^+-ATPase and to assess their physicochemical properties and drug-likeness. Of the seventeen phytoconstituents identified from G. hirsutum, those were chosen for molecular docking studies with gastric H^+/K^+-ATPase (PDB ID: 5YLU). The structures of the protein and of the ligand were prepared by means of molecular modelling software. The docking was carried out using AutoDock Vina via PyRx, and the protein–ligand interactions were analyzed with the help of BIOVIA Discovery Studio Visualizer, while the physicochemical properties and drug-likeness were evaluated using SwissADME. The purpose of the docking analysis was to compare the predicted binding scores and interaction profiles of the selected phytoconstituents. The SwissADME analysis was carried out in order to assess their physicochemical properties and adherence to the usual drug-likeness criteria. Those compounds which show favourable predicted binding scores, pertinent interactions, and an appropriate physicochemical profile will be given priority for further study. The actual docking scores and the specific drug-likeness results for each compound have still to be included. This study offers an initial evaluation of the phytoconstituents of G. hirsutum as possible ligands of gastric H^+/K^+-ATPase. Those showing promise should undergo further biochemical and biological testing. Experimental verification is necessary in order to determine target inhibition, antiulcer effectiveness, bioavailability, and safety.

Keywords: gastric proton pump; molecular docking; phytoconstituents; Gossypium hirsutum; AutoDock Vina; drug-likeness

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INTRODUCTION

Peptic ulcer disease (PUD) is a disorder of the gastrointestinal tract which is marked by the development of ulcers in the mucosa of either the stomach or the duodenum due to a discrepancy between aggressive factors and the defence mechanisms of the mucous membrane. The main factors that contribute to it are infection with Helicobacter pylori, the use of non-steroidal anti-inflammatory drugs (NSAIDs), gastric acid, pepsin, and a failure of mucosal protection. The way in which PUD is managed is based on its underlying cause and can include acid suppression, the use of mucosal protective agents, and suitable antimicrobial treatment for infection with H. pylori [1,2].

The secretion of gastric acid is the result of several regulatory mechanisms, gastric H^+/K^+-ATPase being of central importance in the last stage of hydrochloric acid secretion by the parietal cells of the stomach. This enzyme, which is bound to the cell membrane, swaps the hydrogen ions inside the cell for potassium ions outside the cell, thus helping to acidify the stomach. Proton pump inhibitors reduce acid secretion by blocking this enzyme and are therefore still important as treatments for disorders related to acid. As a result, gastric H^+/K^+-ATPase is a relevant molecular target for the study of compounds that might have acid-suppressive activity [1,3].

Medicinal plants are a significant source of naturally occurring compounds with diverse chemical structures that can serve as starting points for drug discovery. The secondary metabolites found in them such as flavonoids, phenolic compounds, terpenoids, and glycosides—have been studied for a variety of biological activities. Yet the pharmacological effects of individual phytoconstituents are determined by their chemical structures, the biological targets they interact with, the extent of their exposure, and their safety profiles. It is therefore essential to carry out a systematic evaluation before any traditional or initial biological observations can be turned into therapeutic uses.

The upland cotton plant, whose scientific name is Gossypium hirsutum L., is a member of the Malvaceae family and is mainly grown for its natural fibre. Besides its significance in agriculture, it also contains a wide variety of phytochemicals. A review of the flavonoids reported for this plant found 52 flavonoids belonging to several structural groups, such as flavonols, flavan-3-ols, flavanones, and their derivatives. The compounds mentioned include quercetin, kaempferol, myricetin, catechin, and various glycosides [4]. This chemical variety offers a basis for examining certain phytoconstituents as possible ligands of pharmacologically

important proteins. Yet the fact that these compounds are present in the plant does not in itself prove that they have gastroprotective efficacy or that they are suitable as therapeutic agents.

Molecular docking is a computational method which is based on structure and which is used to predict the possible way in which a ligand may bind within a protein's binding site as well as to estimate the relative binding affinity by means of a scoring function. It is often used in the early stages of virtual screening in order to prioritize the compounds for further study. AutoDock Vina is a docking program that is frequently used and which helps to assess the predicted interactions between a protein and a ligand [5]. A complementary evaluation of the physicochemical properties and drug-likeness can assist in spotting potential difficulties in the development of the candidate molecules. SwissADME offers computational tools for carrying out such an evaluation, even though its predictions do not cover pharmacological efficacy, clinical bioavailability or safety [6].

In this study, the 17 phytoconstituents identified from G. hirsutum were examined for their interaction with gastric H^+/K^+-ATPase by means of molecular docking performed with AutoDock Vina via the PyRx platform. The predicted interactions between the protein and the ligand were analysed using BIOVIA Discovery Studio Visualizer, and the physicochemical properties as well as the drug-likeness of the compounds were assessed with SwissADME. The objective of the study was to compare the predicted binding profiles of the selected compounds and to identify those most suitable for further experimental investigation. The results are meant to offer initial computational evidence and not to prove any enzyme inhibition or antiulcer activity.

MATERIALS AND METHOD

Study Design

The study was designed as a computational structure-based molecular docking investigation. Selected phytoconstituents reported from G. hirsutum were evaluated against gastric H+/K+-ATPase. (7,8)

Selection of Phytoconstituents (9)

Seventeen phytoconstituents were selected on the basis of their reported occurrence in G. hirsutum and their structural diversity. The selected compounds were:

1. Rutin
2. Quercetin
3. Kaempferol
4. Luteolin

5. Myricetin
6. Apigenin
7. Naringenin
8. Catechin
9. Epicatechin
10. Isorhamnetin
11. Kaempferol-3-O-beta-D-glucoside (Astragalin)
12. Quercetin-3-O-beta-D-glucoside
13. Ellagic acid
14. Betulinic acid
15. Campesterol
16. Daidzein
17. Chlorogenic acid

The occurrence of several of these flavonoids and their glycosides in G. hirsutum has been documented in the literature.

Protein Target Selection

The three-dimensional structure of gastric H+/K+-ATPase was obtained from the Research Collaboratory for Structural Bioinformatics Protein Data Bank (RCSB PDB). PDB ID 5YLU was selected as the receptor structure. (10)

PDB 5YLU represents the gastric proton pump in complex with vonoprazan and was determined by X-ray crystallography at a resolution of 2.80 Å. The structure provides an experimentally determined structural model of gastric H+/K+-ATPase suitable for structure-based analysis.

Protein Preparation

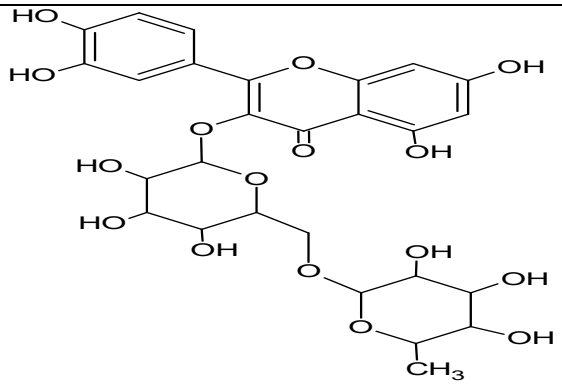
The receptor structure was prepared for molecular docking using an appropriate protein-preparation workflow. The co-crystallized ligand and unnecessary water molecules were removed where appropriate. Hydrogen atoms and charges were assigned, and the prepared receptor was converted into the required docking format with the help of discovery studio (11).

The preparation procedure was applied consistently to the receptor used for docking of all selected ligands.

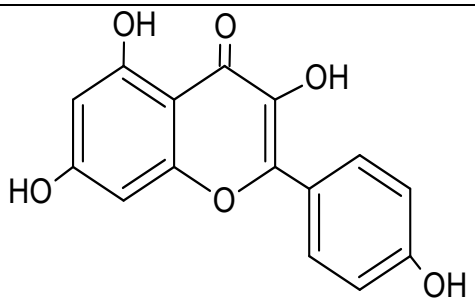
Ligand Preparation (12)

The structures of the selected phytoconstituents and reference drug were obtained from appropriate chemical databases or drawn using Chemsketch a chemical structure drawing software. The structures were converted into suitable three-dimensional representations and

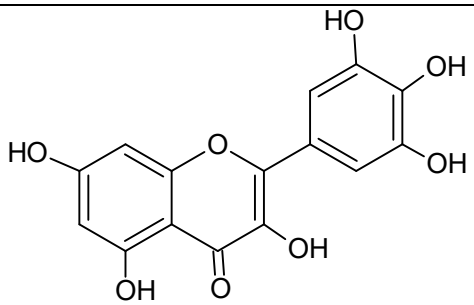
prepared for docking. Appropriate protonation, hydrogen addition and conversion to the docking-compatible format were performed before docking.



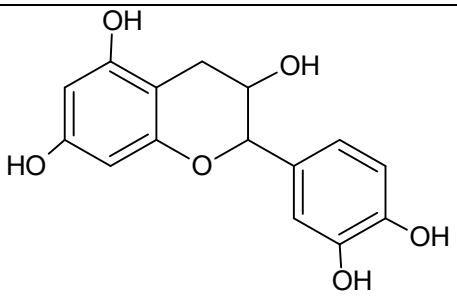
Rutin



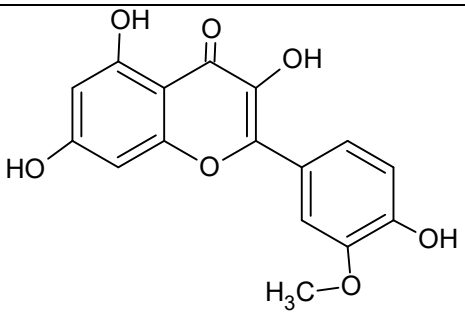
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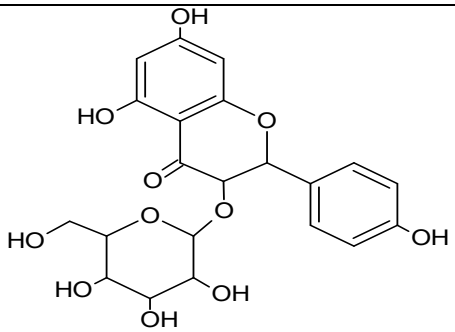
Myricetin



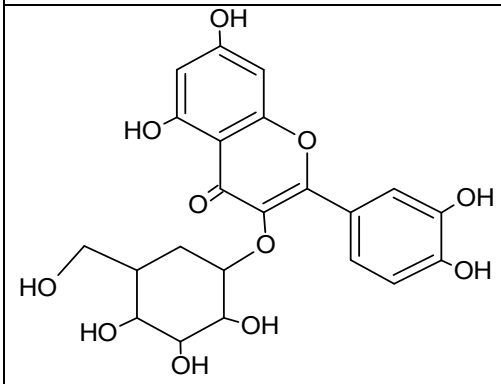
Catechin



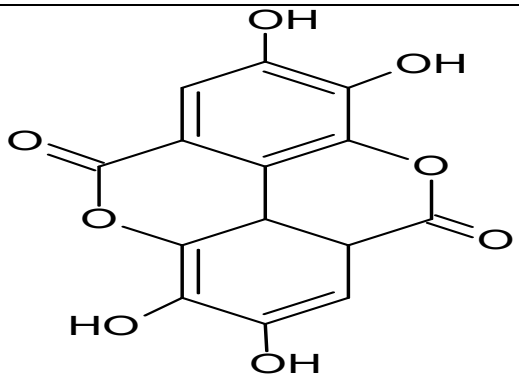
Isorhamnetin



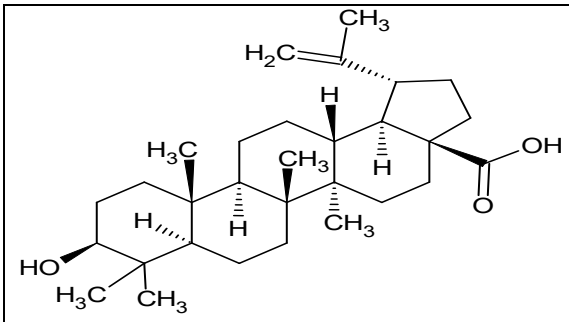
Kaempferol-3-O-B-D



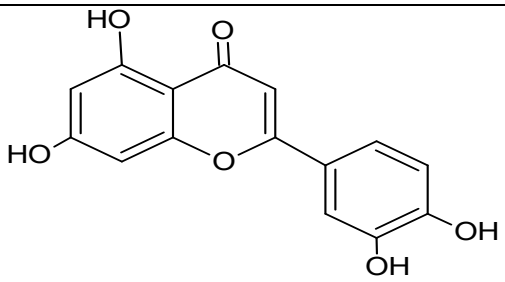
Quercetin-3-O-B-glucoside



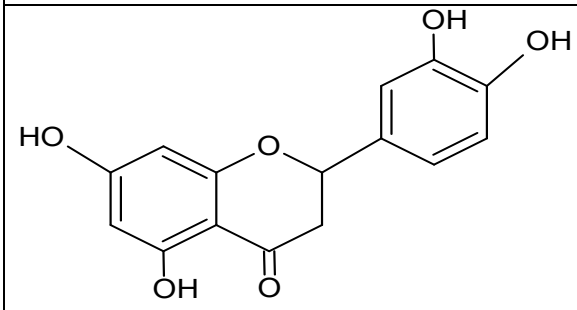
Ellagic acid



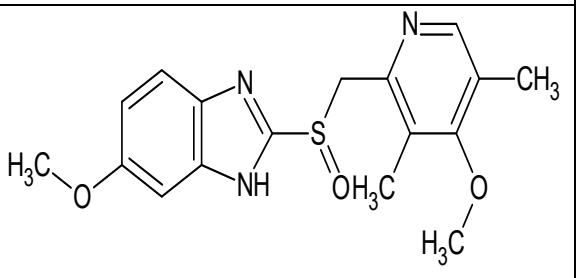
Betulinic acid



Luteolin



Quercetin



Omeprazole

Reference Drug

Omeprazole was selected as the reference antiulcer drug for comparative computational analysis. The same protein preparation and docking protocol should be applied to omeprazole and all phytoconstituents to allow a consistent comparison.

Molecular Docking (13)

Molecular docking was performed using AutoDock Vina through the PyRx platform. A defined docking search space encompassing the selected binding region of gastric H+/K+-ATPase was used. The same docking parameters were maintained for all ligands and the reference drug.

Docking scores were expressed in kcal/mol. More negative predicted binding-affinity values indicate more favorable scoring according to the AutoDock Vina scoring function; however, docking scores are computational predictions and should not be interpreted as direct measurements of experimental binding affinity or biological activity.

Analysis of Protein-Ligand Interactions

The docked complexes were analyzed using BIOVIA Discovery Studio Visualizer. The interaction profiles were examined for hydrogen bonds, hydrophobic interactions, electrostatic interactions and other relevant contacts. The interacting amino-acid residues were recorded for the best-ranked binding pose of each ligand.

Drug-Likeness and ADME Analysis

The physicochemical and drug-likeness properties of the selected compounds were evaluated using SwissADME. Parameters including molecular weight, lipophilicity, topological polar surface area, hydrogen-bond donors, hydrogen-bond acceptors, rotatable bonds and Lipinski rule-of-five characteristics were considered.

Drug-likeness predictions were used only as preliminary computational indicators and were not interpreted as experimental evidence of absorption, safety or therapeutic efficacy.

RESULTS

Molecular Docking Analysis

Table 1 should therefore contain the newly generated docking scores for all 17 phytoconstituents and omeprazole.

Table 1: Chemical constituents of Gossypium hirsutum and their docking score

Sr. No.	Compound	PubChem ID	Docking Score	Binding energies
1	Rutin	5280805	-9.4	1277.68
2	Quercetin	5280343	-9.3	196.47
3	Kaempferol	5280863	-9.1	177.71
4	Luteolin	5280445	-7.9	160.95
5	Myricetin	5281672	-7.9	181.11
6	Apigenin	5280443	-7.3	160.11
7	Naringenin	439246	-7.1	723.52
8	Catechin	9064	-7.6	260.03
9	Epicatechin	72276	-7.3	166.27
10	Isorhamnetin	5281654	-7.8	192.18
11	Kaempferol-3-O-β-D-Glucoside (Astragalin)	5282102	-8.4	291.51
12	Quercetin-3-O-β-D-Glucoside	5280804	-7.6	284.76
13	Ellagic acid	5281855	-7.8	249.59
14	Betulinic acid	64971	-8.8	585.89
15	Campesterol	173183	-6.9	445.65
16	Daidzein	5281708	-8.0	172.35
17	Chlorogenic acid	1794427	-6.3	57.70
Reference drug	Omeprazole	4594	-6.9	445.62

Protein-Ligand Interaction Analysis

The binding interactions of the highest-ranked compounds should be examined using the corrected 5YLU receptor. The interacting residues should be reported directly from the redocking output.

Table 2: Predicted interactions of selected phytoconstituents with gastric H+/K+-ATPase

Sr.no.	Ligand	Interacting amino acids	No. of amino acids
1	Rutin	Glutamine[B:109], Arginine[A:9], Phenylalanine[A:7], Histamine[B:112], Threonine[A:8], Aspartic acid[A:13]	6
2	Kaempferol	Serine[A:15], Glycine[A:51], Glutamine[A:109], Glutamine[A:111], Histamine[A:112], Aspartic acid[B:13], Cysteine[A:49], Alanine[A:48]	8
3	Myricetin	Histamine[A:10], Glutamic acid[B:111], Glycine[B:51], Aspartic acid[A:13], Alanine[B:48]	5
4	Catechin	Aspartic acid[A:13], Histamine[A:10]	2
5	Isorhamnetin	Alanine[B:48], Cysteine[A:49], Histamine[B:112], Glutamic acid[B:111], Glutamine[B:109]	5
6	Kaempferol-3-0-B-D-Glucoside	Glycine[B:51], Histamine[B:112], Glutamic acid[B:111], Alanine[B:48], Tyrosine [A:54]	5
7	Quercetin-3-O-B-D-Glucoside	Histamine[B:112], Histamine[A:10], Aspartic acid[A:13], Methionine[B:110], Cysteine[B:49], Glutamine[B:109]	6
8	Ellagic acid	Aspartic acid[A:13], Cysteine[B:49], Glycine[B:51], Glutamic acid[B:111], Histamine[B:112], Asparagine[A;17], Cysteine[B:49]	7
9	Betulinic acid	Tyrosine [A:54], Asparagine[A;17], Cysteine[B:49], Alanine[B:48], Aspartic acid[A:13], Histamine[A:10], Histamine[B:112], Glutamic acid[B:111], Glutamine[B:109], Glycine[B:51],Histidine[A:112], Methionine[A;110], Serine[A:50]	13
10	Chlorogenic acid	Tyrosine [A:54], Glycine[B:51], Cysteine[B:49], Histamine[B:112], Glutamic acid[B:111], Valine[B:113]	6
11	Quercetin	Histamine[A:10], Methionine[B:110], Histamine[B:112]	3
12	Luteolin	Methionine[B:110], Histamine[A:10], Asparagine[A;10]	3

Drug-Likeness and Physicochemical Properties (14)

The physicochemical properties of the selected compounds were evaluated using SwissADME. The analysis included molecular weight, lipophilicity, topological polar surface area, hydrogen-bond donors and acceptors, rotatable bonds and Lipinski rule-of-five compliance.

Table 3: Predicted physicochemical and drug-likeness properties of selected phytoconstituents

Sr. No.	Ligand	Physicochemical Properties						Lipinski's Rule	N viol
		MW	TPSA	LogP	HA	HD	N rotf		
1	Rutin	612.53 g/mol	265.52 Å²	1.4	16	10	6	No	3
2	Quercetin	288.25 g/mol	107.22 Å²	1.62	6	4	6	Yes	0
3	Kaempferol	286.24 g/mol	111.13 Å²	1.7	6	4	1	Yes	0
4	Luteolin	286.24 g/mol	111.13 Å²	1.86	6	4	1	Yes	0
5	Myricetin	318.24 g/mol	151.59 Å²	1.08	8	6	1	Yes	1
6	Apigenin	270.24 g/mol	90.90 Å²	1.89	5	3	1	Yes	0
7	Naringenin	272.25 g/mol	86.99 Å²	1.75	5	3	1	Yes	0
8	Catechin	290.27 g/mol	110.38 Å²	1.33	6	5	1	Yes	0
9	Epicatechin	290.27 g/mol	110.38 Å²	1.37	6	5	1	Yes	0
10	Isorhamnetin	316.26 g/mol	120.36 Å²	2.35	7	4	1	Yes	0
11	Kaempferol-3-O-β-D-Glucoside (Astragalin)	448.38 g/mol	190.28 Å²	1.29	11	7	2	No	2
12	Quercetin-3-O-β-D-Glucoside	452.37 g/mol	206.60 Å²	0.91	12	8	4	No	2
13	Ellagic acid	302.19 g/mol	141.34 Å²	0.79	8	4	3	Yes	0
14	Betulinic acid	456.70 g/mol	57.53 Å²	3.83	3	2	0	Yes	1
15	Campesterol	400.68 g/mol	20.23 Å²	4.97	1	1	2	Yes	1
16	Daidzein	256.25 g/mol	66.76 Å²	1.52	4	2	5	Yes	0
17	Chlorogenic acid	354.31 g/mol	164.75 Å²	0.96	9	6	1	Yes	1
	Omeprazole	345.42 g/mol	96.31 Å²	1.64	5	1	5	Yes	0

DISCUSSION

The present study was designed to investigate the potential interaction of phytoconstituents reported from G. hirsutum with gastric H+/K+-ATPase using molecular docking. The gastric proton pump is a clinically important target because it is responsible for the final step of gastric acid secretion. Experimentally determined structures of the gastric proton pump have provided structural information concerning its inhibitor-binding region and have facilitated structure-based investigations.

G. hirsutum contains a diverse range of flavonoids and related secondary metabolites. Published phytochemical literature has reported quercetin, kaempferol, myricetin, rutin, catechins and several glycosylated derivatives from different tissues of the plant. This chemical diversity provides a rational basis for preliminary computational screening of selected constituents.

Molecular docking can be used to compare the predicted interaction of structurally diverse compounds with a selected protein target. In the present investigation, AutoDock Vina was

selected for docking because it provides a widely used computational approach for predicting ligand poses and estimating relative binding scores.

The corrected study uses PDB ID 5YLU rather than 4CP3. This correction is essential because 5YLU is an experimentally determined structure of gastric H+/K+-ATPase, whereas 4CP3 does not represent the gastric proton pump. The 5YLU structure was determined by X-ray diffraction at 2.80 Å resolution and contains the gastric proton pump in complex with vonoprazan.

The newly generated docking results should be interpreted comparatively within the same docking protocol. A compound exhibiting a more negative docking score than omeprazole may be described as having a more favorable predicted docking score under the applied computational conditions. It should not, however, be described as being clinically superior, pharmacologically more effective or safer than omeprazole solely on the basis of docking.

Particular attention should be given to the interaction pattern of the highest-ranked ligands. Hydrogen bonding, hydrophobic interactions and other contacts may contribute to ligand stabilization within the predicted binding region. However, docking poses are computational models and should be experimentally validated.

The drug-likeness analysis provides complementary information. Several flavonoids may comply with commonly applied physicochemical filters, whereas highly glycosylated compounds such as rutin and flavonoid glycosides may exhibit higher molecular weight and polar surface area. Such properties can influence permeability and oral pharmacokinetic behavior. SwissADME provides computational predictions and should therefore not be interpreted as direct evidence of human absorption or therapeutic suitability.

The present study has several limitations. First, molecular docking provides computational predictions rather than experimental measurements of enzyme inhibition. Second, docking scores depend on the receptor structure, ligand preparation, protonation state, search space and scoring function. Third, the selected compounds may differ substantially in solubility, membrane permeability, metabolism and systemic exposure. Finally, antiulcer activity is multifactorial and cannot be established solely by interaction with gastric H+/K+-ATPase.

Accordingly, the highest-ranked compounds should be considered candidates for subsequent experimental studies, including enzyme inhibition assays, gastric acid secretion models, antioxidant and cytoprotective assays, and appropriate in vivo antiulcer models.

Limitations of The Study

The study is entirely computational and does not provide experimental confirmation of antiulcer activity. Docking scores represent predicted binding affinity and are dependent on the

computational protocol. The predicted binding pose may not fully reproduce the dynamic environment of the membrane-associated gastric proton pump. Drug-likeness and ADME predictions do not establish clinical pharmacokinetics or safety. Experimental validation is required before therapeutic conclusions can be drawn.

CONCLUSION

The present in silico study was designed to evaluate selected phytoconstituents of Gossypium hirsutum against gastric H+/K+-ATPase. The corrected molecular target, PDB ID 5YLU, represents an experimentally determined gastric proton pump structure and is therefore appropriate for the proposed antiulcer-oriented docking investigation.

The final ranking of the phytoconstituents should be based on newly generated docking scores and interaction profiles obtained against 5YLU. Compounds demonstrating favorable predicted binding and acceptable physicochemical characteristics may be considered candidates for further investigation. Nevertheless, the computational findings should be regarded as preliminary and cannot by themselves establish antiulcer efficacy, clinical superiority, safety or therapeutic effectiveness. Appropriate biochemical, in vitro and in vivo studies are required to validate the computational predictions.

Future Perspectives

The compounds identified from the corrected docking study may be subjected to further experimental investigation. Future studies may include in vitro H+/K+-ATPase inhibition assays, gastric acid secretion studies, antioxidant and cytoprotective assays, molecular dynamics simulations and experimental antiulcer animal models. Pharmacokinetic and toxicity investigations should also be performed for promising candidates before consideration of further pharmaceutical development.

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