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Proceeding Paper

Anti-Helicobacter Pylori Activity of Phytochemicals from *Artocarpus* spp.: In-Silico Analysis †

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Abstract: Peptic ulcer disease, affecting up to 20% of the global population, poses a significant health challenge with limited treatment options due to side effects and inefficiency of existing drugs. This study explores the potential of penicillin-binding proteins (PBPs) as targets for peptic ulcer treatment. PBPs, critical for bacterial cell wall integrity, are inhibited by beta-lactam antibiotics, leading to bacterial vulnerability. Flavonoids, prominent in plants, exhibit antimicrobial and gastroprotective properties against peptic ulcers. Docking analysis of 35 phytochemicals from the Artocarpus plant against PBP (PDB code: 1QMF) revealed **Artocarpin** as a promising candidate (docking score: −148.24 Kcal/mol). Artocarpin exhibited interactions with key amino acids and demonstrated favorable in-silico pharmacokinetics, including high absorption and good drug-likeness. Additionally, **Engeletin 5** and **Rutin** showed significant docking scores (−134.89 and −148.07 kcal/mol, respectively). Artocarpin, identified as a potential *H. pylori* inhibitor, presents a promising avenue for peptic ulcer treatment, warranting further exploration of its therapeutic application. This study contributes valuable insights into the molecular interactions of phytochemicals with PBPs, paving the way for novel and effective approaches in peptic ulcer therapy.

Keywords: Flavonoids; *Helicobacter pylori*; *Artocarpus* spp.; docking

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1. Introduction

The World Health Organisation classifies *Helicobacter pylori*, a spiral-shaped, Gram-negative bacillus that affects 50% of people worldwide, as a class 1 carcinogen [1]. *Helicobacter pylori* is one of the primary causative agents of chronic gastritis, which in turn causes the development of peptic ulcers [1]. By interacting with gastric epithelial cells, *H. pylori* directly colonises the gastric mucosa. It is commonly known that *H. pylori* causes intestinal metaplasia, severe atrophy, increased levels of mononuclear and neutrophilic infiltrates, apoptosis, and changes in the gastric epithelial cell cycle.

Antimicrobial resistance has been shown to reduce the global rates of *H. pylori* infection eradication, according to evidence from clinical practice [2]. Furthermore, there may be toxicity concerns with the main medications used to treat *H. pylori*.

As an alternative to triple therapy, a number of plant-based treatment approaches, including as plant extracts and isolated phytochemicals, have been explored recently to address drug resistance and side effects [3]. The importance of recent research on natural goods, particularly plant extracts high in flavonoids. These substances have demonstrated encouraging outcomes in addressing several modes of action of the anti-*H. pylori*. Flavonoids also strengthen the mucosal defences against peptic ulcers by enhancing their cytoprotective, antioxidative, anti-inflammatory, and antibacterial properties (Figures 1 and 2) [3]. Typically, a single kind of flavonoid can function as an anti-ulcer through a variety of ways. Numerous studies have shown how flavonoids protect the intestinal epithelium

[3]. These effects include preserving the integrity of the intestinal barrier, absorbing fats and carbohydrates, modifying the activities of enzymes, controlling secretions from the stomach, regulating the immune system, and interacting with pathogenic microorganisms. PBPs, or penicillin-binding proteins, have a critical role in the bacterial cell wall's maintenance. The penicillin-binding proteins that have an allosteric site binding mechanism cause the active site to slightly open during binding, increasing the accessibility of the site for substrate binding. Finding inhibitors that are able to bind to both the active and allosteric sites shows promise as a clinical approach [4]. Both the active and allosteric binding mechanisms had to be examined in order to accurately assess flavonoids' from Artocarpus spp. affinity for PBPs, as doing so would produce a different and extra inhibitory pattern. In present study, we have evaluated the set of Phytomolecules reported from Artocarpus against the PBP (Figure 1). This study puts forward the usefulness of flavonoids to assist the conventional drug therapy [4]. We further also evaluated in-silico pharmacokinetics to gain more insights of absorption, distribution, metabolism, excretion (ADME) characteristics.

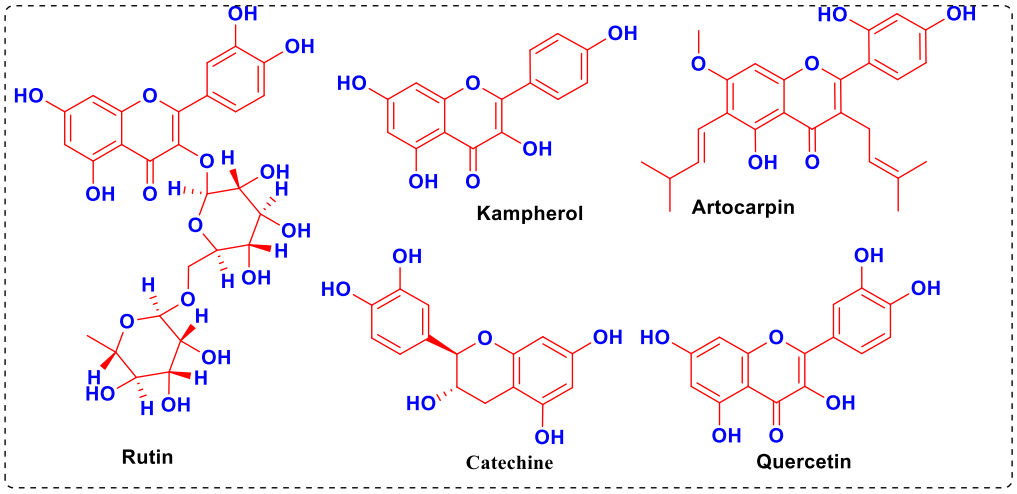

Figure 1. Isolated phytomolecules from *Artocarpus* spp.

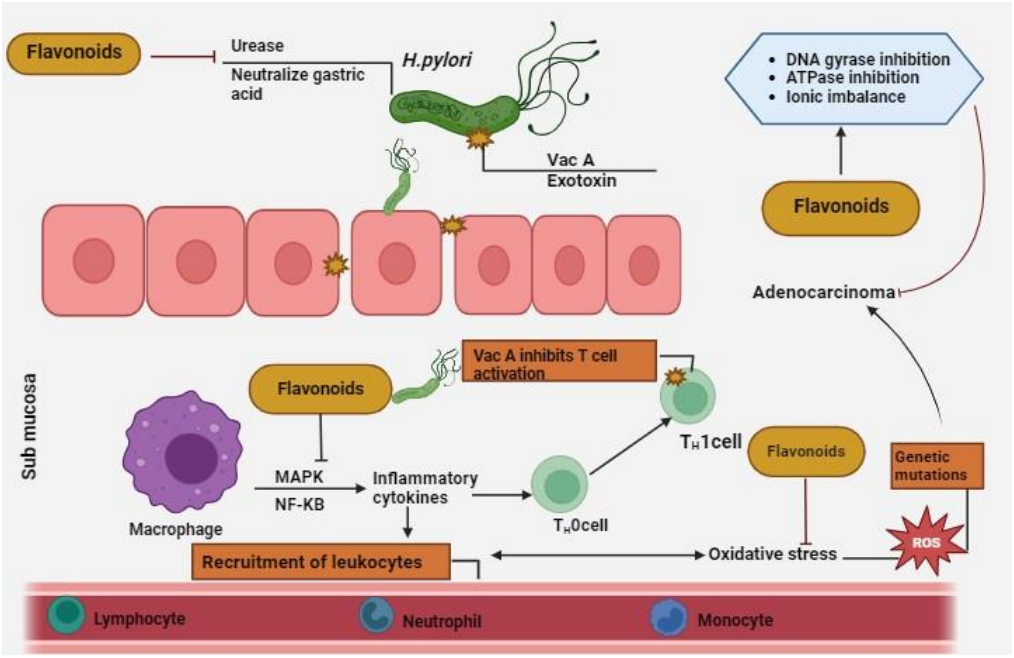

Figure 2. The potential mechanistic pathway for flavonoids actinbg as anti-*H. pylori* agents.

2. Materials and Methods

2.1. Molecular Docking Simulations

The 3D crystal structure of the Penicillin-binding protein (PDB code: 1QMF) was downloaded from protein database bank. The concerned 3D structure was then processed to add missing H-atoms, and missing amino acid residues. The binding site for this protein was referred from the earlier publication. The docking was then done with the software 'iGemDock'[5]. Finally, the visualization was done with the 'Discovery Studio 2020 Visualizer' [8–26].

2.2. In-Silico Drug-Likeness and ADMET Analysis

The top 3 hits were further analyzed for in-silico pharmacokinetics using 'SwissADME' (http://www.swissadme.ch, accessed on). The toxicity parameters were then assessed using toxicity assessments were conducted using 'admetSAR' (http://lmmd.ecust.edu.cn:8000/) [6].

2.3. Boiled Egg Model Analysis

At different phases of the drug development process, it is essential to estimate two pharmacokinetic behaviours: brain access and gastrointestinal absorption. For this reason, an accurate predictive model called the Brain Or IntestinaL EstimateD permeation method (BOILED-Egg) is developed. It computes the lipophilicity and polarity of tiny compounds. The same two physicochemical characteristics yield concurrent predictions for intestine and brain penetration, which may be easily translated into molecular design due to the model's quickness, precision, conceptual simplicity, and easily understandable graphical output. The BOILED-Egg can be used in many different contexts, such as evaluating drug candidates for development or filtering chemical libraries in the early stages of drug discovery.

3. Results and Discussion

3.1. Molecular Docking Simulations

The dataset of 35 molecules were analysed against Penicillin-binding proteins (PBPs). Out of 35 Phytomolecules, the Phytomolecule Artocarpin depicted strong interaction with PBP (PDB code: 1QMF) via THR 526, TRP 374, Ser 337, Ser 395, Thr 550, Met 527, and Tyr 595 (Tables 1 and 2, Figure 3). The docking interaction showed H-bonding, van der Waals and π-π types interactions. The standard Amoxicillin demonstrated major interactions with Trp 374, Ser 571, Gly 549, Thr 526, and Ser 395. The standard Amoxicillin (docking score: −109.20 kcal/mol) had lesser affinity as compared with Artocarpin (docking score: −148.24 kcal/mol) against the PBPs [7]. PBPs, or penicillin-binding proteins, have a critical role in the bacterial cell wall's maintenance. The penicillin-binding proteins that have an allosteric site binding mechanism cause the active site to slightly open during binding, increasing the accessibility of the site for substrate binding [7]. Finding inhibitors that are able to bind to both the active and allosteric sites shows promise as a clinical approach. It was vital to look into both the active and allosteric binding mechanisms in order to accurately assess Artocarpin's affinity for PBPs, as doing so may reveal a different and additional inhibitory pattern. Moreover, our re-docking validation protocol also resulted RMSD value below 1.4 Å, suggesting valid docking results.

Table 1. Docking interaction energies* of selected bio-active molecules and **3** FDA approved drugs for target protein 4P8C.

Molecules	**-iGemDock Interaction Energy**	**Molecules**	**-iGemDock Interaction Energy**
Quercetin	−111.11	Artonin A	−117.1
Ascorbates	−84.29	Artocarpanone	−98.62

Catechine	−94.99	Caffeic acid	−78.51
Lupeol acetate	−90.55	Cycloheterophyllin	−125.23
Bita -sitosterol	−97.62	Cyclocommunol	−106.54
Kaempferol	−107.95	Isobavachalcone	−121.11
Gallic acid	−90.35	Artonin E	−128.21
Engeletin 5	−134.89	Heterophyllin	−131.91
Oxyresveratrol	−72.08	Cyclomorusin	−120.05
Artocarpin	**−148.24**	Cryptoxanthin	−92.1799
Cycloartocarpin	−111.69	Myricetin	−82.5936
Cudraflavone	−111.35	Ascorbic acid	−85.54
Vanillic acid	−79.88	Cinnamic acid	−69.96
Isorhamnetin	−113.3	Ferulic acid	−79.6
Psoralenoside	-107.8	Betulinic acid	−95.9
Epigallocatechin Gallate	−140	Resorcinol	−59.9
Morin	−106.1	Norartocarpetin	−105
Ursolic acid	−99.6	Pyrogallol	−69.1
Artocarpesin	−112.9	**Rutin**	**−148.07**
Albanin A	−107.9	Arbutin	−98.2
Engeletin	−116.79	Diethyl phthalate	−83.86
α-amyrin acetate	−92.9	β-amyrin acetate	−95.27
Cycloartenol	−92.66		
		Amoxicillin *	**−109.20**

* Docking scores have been provided only for the higher affinity scored target protein.

Table 2. Energy contribution of the key residues computed by docking methodology.

Sr. No.	Molecules	Residues with Contribution Energy
1.	Amoxicillin	THR 526, TRP 374, Ser 337, Ser 395, Thr 550, Met 527, and Tyr 595
2.	Artocarpin (Best docked)	THR 526, TRP 374, Ser 337, Ser 395, Thr 550, Met 527, and Tyr 595

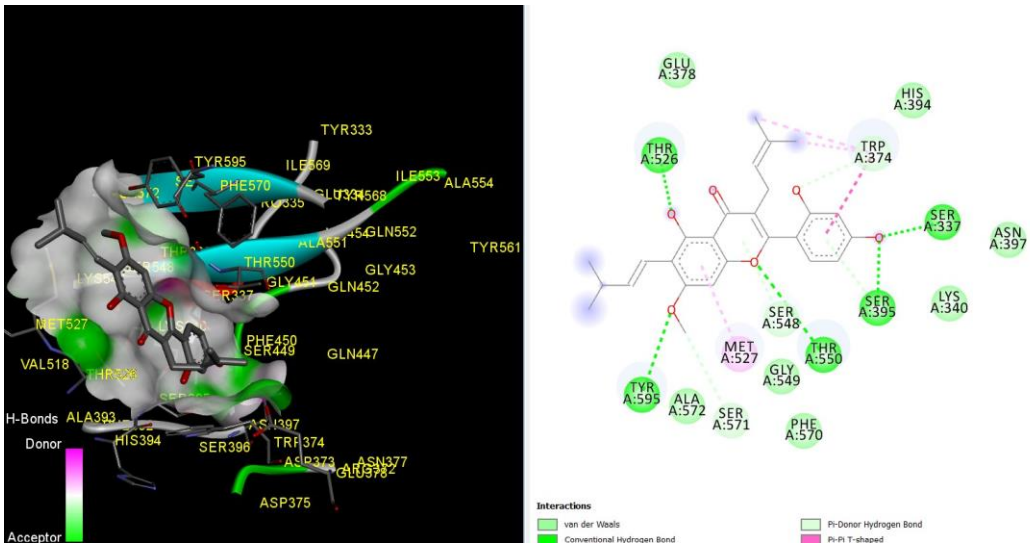

Figure 3. 2D and 3D-interaction profiles for best docked *Artocarpin* with **target PBP**.

Table 3. In-silico ADMET profiling for top **3** best docked hits against target **1QMF**.

Properties	Artocarpin *	Rutin	Engeletin 5

GI absorption	**High**	**High**	**High**
BBB permeant	**Low**	**Low**	**Low**
P-gp substrate	**NO**	**NO**	**NO**
CYP1A2 inhibitor	**NO**	**NO**	**NO**
CYP2C19 inhibitor	**Yes**	**Yes**	**Yes**
CYP2C9 inhibitor	**NO**	**NO**	**NO**
CYP2D6 inhibitor	**NO**	**NO**	**NO**
CYP3A4 inhibitor	**NO**	**NO**	**NO**
Lipinski	**Yes**	**Yes**	**Yes**
Ghose	**NO**	**NO**	**NO**
Veber	**Yes**	**Yes**	**Yes**
Egan	**Yes**	**Yes**	**Yes**
Blood Brain Barrier	**-**	**-**	**-**

* Best docked.

3.2. In-Silico ADMET Studies

Cytochrome P450 (CYPs) enzymes play a crucial role in diverse metabolic processes within the human body, serving as key catalysts for the transformation of various endogenous and exogenous compounds. These enzymes, predominantly located in the liver, contribute significantly to the biotransformation of drugs, xenobiotics, and endogenous substances, influencing their absorption, distribution, metabolism, and excretion. Our study focuses on understanding the implications of CYP-mediated metabolism on the pharmacokinetics of potential drug candidates. Through in-silico calculations, we evaluated the ADMET (absorption, distribution, metabolism, excretion, toxicity) properties of the top three docked hits, shedding light on their behaviour within the intricate landscape of human physiology. Notably, Artocarpin exhibited favourable characteristics, such as positive human intestinal absorption profiles, while also demonstrating a lack of carcinogenicity, absence of AMES toxicity, and a class IV acute oral toxicity profile (Figure 4). These findings provide valuable insights into the interplay between molecular docking and the intricate network of cytochrome enzymes, offering a comprehensive understanding of the potential therapeutic relevance of the studied compounds.

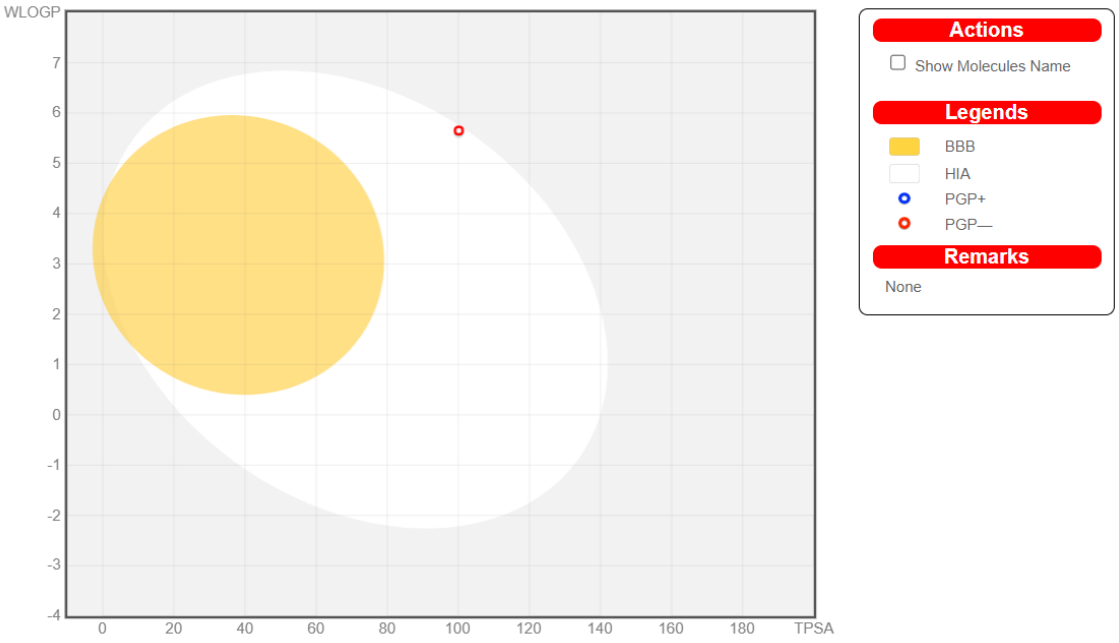

Figure 4. Boiled-Egg model analysis for the phytochemical Artocarpin.

4. Conclusions

In present study, we analyzed the potential of Artocarpus phytochemicals against the PBP as indicated by higher docking score of same. Moreover, among list of 35 known phytocompounds, it had low Human Ether-a-go-go-Related Gene Inhibition, No AMES Toxicity and No Carcinogens. This study may provide further directions to develop more potent anti-*H. pylori* compounds.

Author Contributions: For research articles with several authors, a short paragraph specifying their individual contributions must be provided. The following statements should be used "Conceptualization, S.Y. and A.P.; methodology S.Y. and A.P.; writing—original draft preparation, S.Y. and A.P.; writing—review and editing SY. and AP. All authors have read and agreed to the published version of the manuscript.

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Conflicts of Interest: The authors declare no conflicts of interest.

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