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Research article

In-silico exploration of piperine for invent proton pump and protein phosphatase non-receptor Inhibitors in gastric and peptic ulcer

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ABSTRACT

Anti-ulcer medicines that inhibit the H/K-ATPase enzyme by covalently binding to a cysteine residue of proton pump inhibitors. Through the aforementioned processes, tyrosine-protein phosphatase non-receptor type 11 (PTPN11) causes aberrant mitogenic signals and elongated morphological alterations, as well as the growth and progression of peptic ulcer and gastric cancer.Piperine is an antioxidant derived from the Piper Longum herb. Molecular docking studies and virtual screening were used to investigate it as an H/K ATPase and PTPN11 inhibitor. The Molecular Docking examination was conducted using the Pyrx 0.8 version free database, while virtual screening was conducted using Biovia Discovery Studio software.H/K-ATPase and PTPN11 have substantial binding affinity of 7.5 and 8.6 kcal/mol, respectively, according to molecular docking investigations. Piperine's anti-ulcer efficacy appears to be aided by H/K-ATPase and PTPN11 binding.

Keywords: Proton Pump inhibitors, H/K-ATPase, PTPN11, Molecular Docking, Virtual Screening, Ulcer, Piperine

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INTRODUCTION

An ulcer is a surface or region in the digestive tract where tissue has been destroyed or damaged by gastric juice or other digestive enzymes produced by the stomach [1,2]. Peptic ulcer disease, which arises in the stomach or small intestine and is caused by the released gastric acid by the stomach compartment, is the most prevalent primary kind of ulcer that primarily affects the global population [3]. Peptic ulcer illness is defined as a defect in the protective covering of the gastrointestinal tissue, with detectable deep or submucosa involvement [4]. Pain is frequently relieved at night when the pH of gastric juice in the stomach has raised (due to circadian variations), and the pain is localized to an empty stomach for 2 to 5 hours [5].

The gastric proton/potassium pump (H/K-ATPase) is a phosphoenzyme found in the parietal cells that is responsible for excessive gastric acid secretion into the stomach lumen, resulting in acid-related diseases [6]. As a result of its uniqueness to the parietal cells, this enzyme is seen as a good validated hit for anti-ulcer agents [6]. Because proton pump inhibitors impede the enzyme's action, they reduce amount of acidreleasedby the stomach.

Chronic infections are caused by Helicobacter pylori cagA-positive strains, which can progress to illnesses like pepsitic ulcers and stomach cancer [7]. Peptic ulcers are a common occurrence of lesioning in the stomach's corpus to antrum mucosae zone. The antral mucosa is colonized by H. pylori, which causes chronic inflammation.[8].

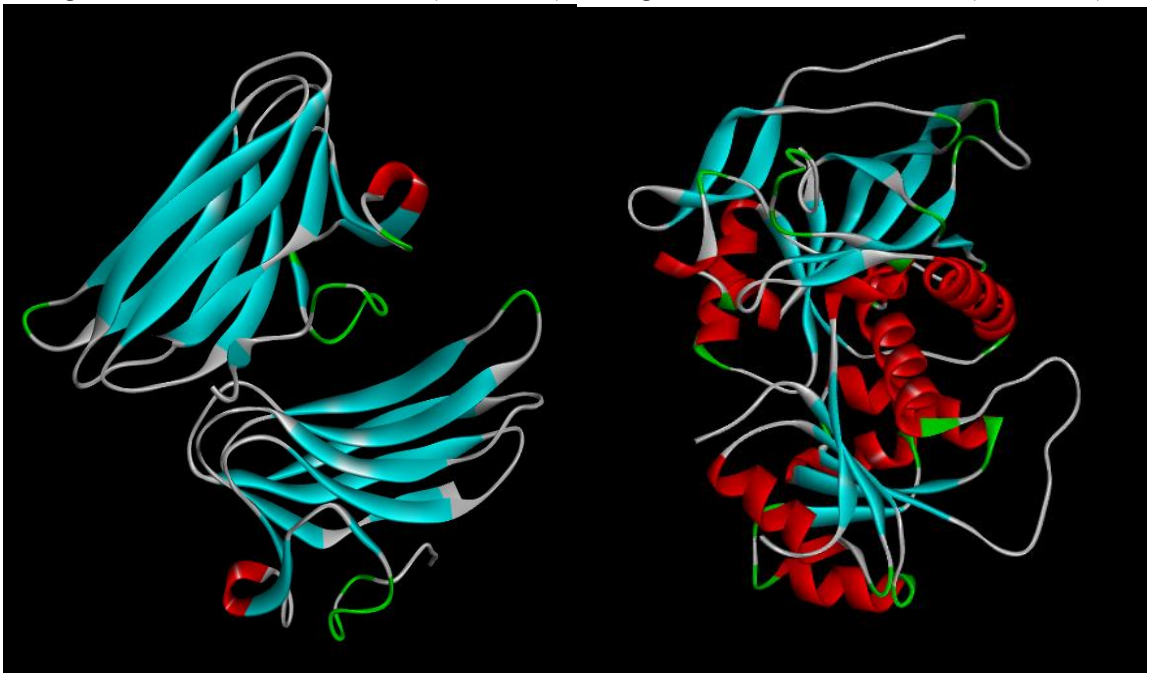
H. pylori injects the virulence factor CagA into the gastric epithelial layer via type IV secretion [9], and after tyrosine phosphorylation by the Src family protein tyrosine kinase [10,11], allosterically stimulates the phosphate activity of SHP2, also known as Tyrosine-protein phosphatase non-receptor type 11 (PTPN11) [12]. This causes aberrant mitogenic signals to be produced, as well as elon-gated morphological alterations. The host cell apoptosis is caused by the continuation of the subsequent processes [13]. Furthermore, epidemiological research has shown that cagA-positive H. pylori has a role in the cause, progression, and growth of peptic ulcer and gastric cancer via mentioned pathways [7,13,14].

Piper Longum Linn., sometimes known as 'Long pepper,' is one of the most important and oldest spices in the world. It belongs to the Piperaceae family. This plant comes from India and thrives in hot, humid regions. Some of the activities of the fruits include CNS

depressants, antipyretics, analgesics, hepatoprotective [15], bioavailability enhancer [16], antioxidant [17], anti-inflammatory. This paper explains Piperine, the plant's main therapeutically active component, which has antioxidant qualities and can be utilized to treat gastric and peptic ulcers.

Figure 1: Protein Structure of H/K-ATPase (PDB ID 2Zex)

Figure 2: Protein Structure of PTPN11 (PDB ID 3B70)



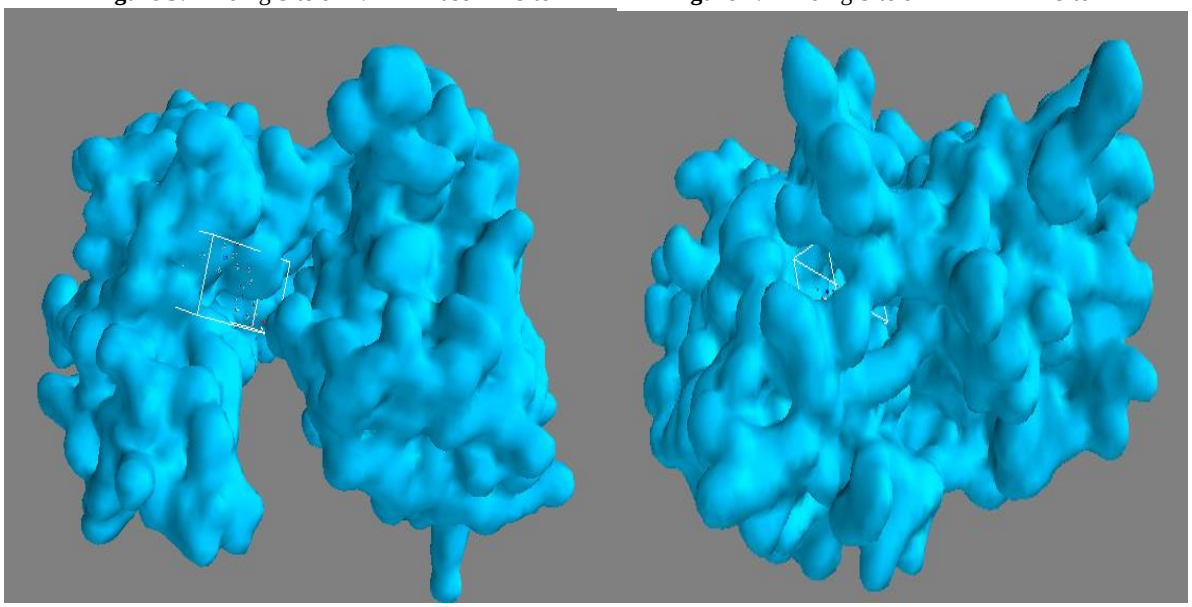
EXPERIMENTAL

Molecular Docking-

Proton Pump Inhibitor with H/K-ATPase (PDB ID 2Zex) and Tyrosine Protein Phosphatase non-receptor with PTPN11 (PDB ID 3B70) protein structures were rectified from the free protein database www.rcsb.org using the selection criteria of good resolution indicated in Fig.1 and Fig.2 Biovia Discovery Studio Visualizer was used to dye the Proton Pump Inhibitor and Protein Phosphatase non-receptor structurally. Fig.3 and Fig.4 illustrate the Ligand Binding Sites of Proton Pump Inhibitors with H/K-ATPase and Protein Phosphatase Non-Receptor with PTPN11.

Figure 3: Binding Site of H/K-ATPase inhibitor

Figure 4: Binding Site of PTPN11 inhibitor



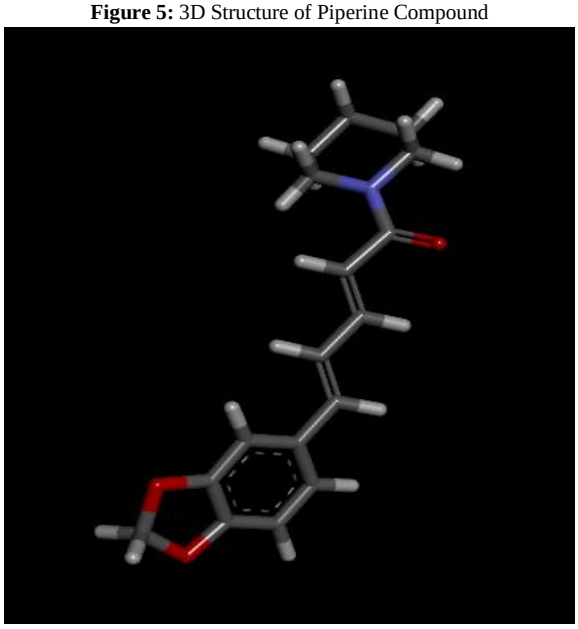
The natural ligand was removed because it could interfere with docking induction. Fig.5 shows the Ligand Structures of Piperine Compounds.

By shifting water molecules and adding polar hydrogen atoms, protein clarity is required to secure the native shape of H/K-ATPase and PTPN11native ligand. Native ligands were removed since they could interfere with docking induction.

Piperine structure was sketched, converted to mol2format, and optimized using Biovia Discovery Studio Visualizer and molecular mechanics calculations with MMFF. A root means square

deviation (RMSD) of less than 1.0 was regarded acceptable for replicating docking activations [18,19].

Figure 5: 3D Structure of Piperine Compound



Docking is used to activate GRIP docking, which is a versatile protein-ligand docking approach. The rotation angle between two conformations was preserved at 10°during docking activation, and the total number of rotations was set to 30.The best docking position for each molecule was chosen based on its binding energy and the amount of connections it has, such as hydrogen bond contacts, aromatic interactions, charge interactions, and the complex's binding energy.

Prediction for ADME

Selected phytochemical structures are investigated further for in silico pharmacokinetic research in order to predict characteristics that may alter pharmacokinetics bearing [20]. The Swiss Institute of Bioinformatics established the ADME web portal, which is used to calculate physicochemical attributes as well as prognostic ADME parameters and drug like nature [21,22,23].

Pharmacophore Screening

Pharmacophores are a group of qualities that are required for biological activity. The Piperine pharmacophore was created using the Zinc Pharmer Free Database, which is important for binding to H/K-ATPase and PTPN11.The H/K-ATPase protein structure and PTPN11 protein structure were used as references for the Pharmacophore Screening. The lowest feature threshold in pharmacophore prognosis was preserved at 3 and the maximum at 5.

RESULT AND DISCUSSION

Virtual Screening & Molecular Docking studies

Protein structures of Proton Pump Inhibitor and Tyrosine Protein Phosphatase non-receptor complex with H/K-ATPase and PTPN11, respectively, were retrieved from the free protein database www.rcsb.org for molecular docking vitalization. To demonstrate the value of docking conventions, H/K-ATPase and PTPN11 were redocked and the RMSD was calculated. The RMSD between co-crystallized H/K-ATPase and PTPN11 and docked posture was 0.60 and 0.75, indicating that the docking convention was capable of producing binding conformations that were close to empirically discovered interactions [24].

Figure 6: Binding interaction of Piperine with/K-ATPase (Generated using Free Version of Discovery Studio Visualizer)

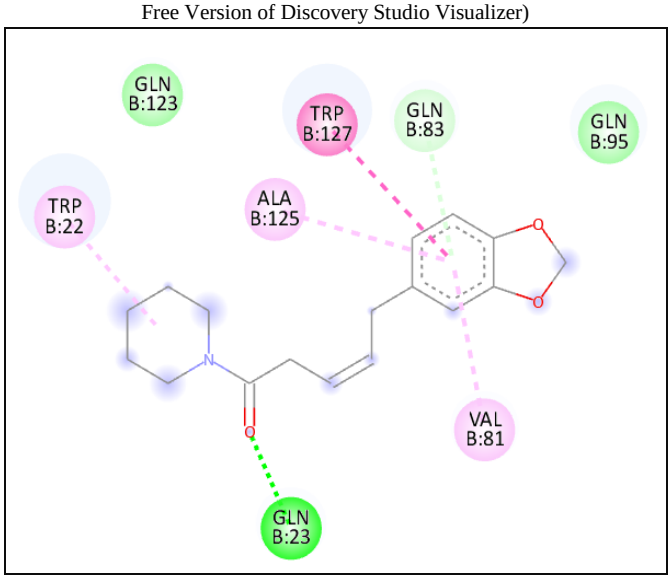
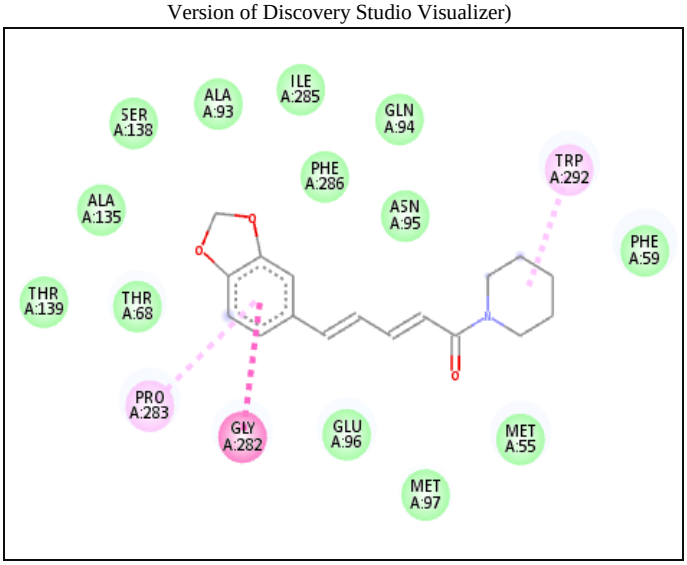


Figure 7: Binding interaction of Piperine with PTPN11 (Generated using Free Version of Discovery Studio Visualizer)



Piperine was discovered to be interacting with Proton Pump inhibitor and Tyrosine Protein Phosphatase non-receptor in stable conformation after a thorough examination of its binding energy. With H/K-ATPase, piperine had a docking score of -7.5.TRP B:22, ALA B:125, VAL B:81 by formation of Pi-Alkyl interaction, and TRP B:127 by formation of Pi-Pi Stacked interaction were discovered to interact with GLN B:23 by formation of Conventional Hydrogen bond. As illustrated in Fig.6, Vander Wal interaction with GLN B:23, GLN B:83, and GLN B:95.

With PTPN11, Piperine was shown to have a docking score

of -8.6. Piperine was discovered to interact with PRO A:283, TRP A:292, and GLY A:282 by forming a Pi-Alkyl interaction and an Amide Pi-Stacked interaction. THR A:139, THR A:68, ALA A:135, SER A:18, ALA A:98, Vander Wal interaction as demonstrated in Fig.7, ILE A:285, GLN A:94, PHE A:286, ASN A:95, PHE A:59, GLU A:96, MET A:97, MET A:55.,

Piperine compound with favorable docking findings was examined for physicochemical property analysis utilizing Swiss ADME (http://www.swissadme.ch) to determine its pharmacokinetic profile. As indicated in Table No.1, recognized Piperine had favorable drug-like features such as high GI absorption and good BBB penetration.

Prediction for ADME Evaluation

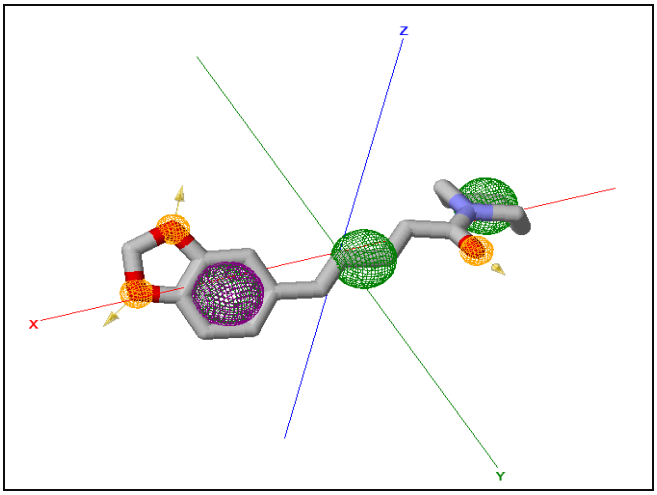
Table No 1: ADME Prediction of Piperine

Molecule	#Rotatable Bonds	#H Bond Acceptor	#H Bond Doner	TPSA	iLOGP	GI Absorption	BBB permeant
Piperine	4	3	0	38.77	3.38	High	yes

Pharmacophore Screening

Piperine, which is responsible for Proton Pump Inhibitornd Tyrosine Protein Phosphatase non-receptor inhibition, was discovered through pharmacophore screening, a category of qualities that are dominant for interactions with biological targets. The pharmacophore prognosis of Proton Pump Inhibitor and Tyrosine Protein was determined using the structure of H/K-ATPase and PTPN11.For interaction with Proton Pump Inhibitor (H/K-ATPase) and Tyrosine Protein Phosphatase non-receptor (PTPN11), the pharmacophore model revealed the importance of Hydrogen bond acceptor and donor, Aromatic center, and Aliphatic groups properties. Piperine's developed Pharmacophore Screening characteristics are depicted in Figure.8.

Figure 8: Developed Pharmacophore Screening of Piperine Compound



According to the results of Insilico exploration, if the binding energy between the protein and the ligand is greater than -7, the two have a high affinity for each other. Piperine derivatives bind to Proton Pump Inhibitor and Tyrosine Protein Phosphatase Non-Receptor with a binding affinity of -7.5 and -8.6 respectively. As a result, as an antioxidant, it can be utilized to treat gastric and peptic ulcers.

CONCLUSION

Proton Pump Inhibitor (H/K-ATPase) and Tyrosine Protein Phosphatase Non-receptor (PTPN11) will be used as a supplement to treat gastric and peptic ulcers. Piperine exhibited promising results in both gastric and peptic ulcers, according to the study, and it has a high binding affinity for H/K-ATPase and PTPN11 inhibitors. According to the Molecular docking study and Virtual Screening survey, Piperine molecule will have affinity to interact with Proton Pump Inhibitor (H/K-ATPase) and Tyrosine Protein Phosphatase non-receptor (PTPN11) without detrimental effects. And evidence showing H/K-ATPase and PTPN11 inhibitors are involved in the maintenance and development of gastric and peptic ulcers, as well as supplementary Neuropathic Pain treatments, will continue to be useful.

Future prospects of research work

While docking is commonly used, it is a rather complex technique. Setting up docking experiments requires prior knowledge of the target's structural biology. False-positives affect docking results, yet they nonetheless help to decrease the huge chemical space required for biological testing.

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