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Molecular docking simulation of Bioactive Compounds from *Curcuma longa* against *Helicobacter pylori*

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Abstract

Peptic ulcers are open sores that form on the lining of the stomach and upper small intestine and the primary causative pathogen is *Helicobacter pylori*. In this research, the inhibitory activities of bioactive compounds from *Curcuma longa*, against H. *pylori* (8H52) were studied. Eighty-three significant bioactive compounds were selected from the Zinc database and were initially screened using absorption, distribution, metabolism, excretion, and toxicity properties based on compliance with the Pfizer rule. Molecular docking studies were carried out with specific docking site dimensions of values x: -37.3658, y: -4.1028, and z: -22.8563, to identify the binding affinities and interactions. Ten phytoconstituents scored binding affinities between -7.8 and -10.1 kcal/mol. When compared to the control drug omeprazole (-8.8 kcal/mol), the compounds curcumin pyrazole (-10 kcal/mol), 4'-*O*-methylcatechin (-9.5 kcal/mol), and curcumin (-9.3 kcal/mol) displayed significant binding affinities and good interactions with alanine, valine, aspartic acid and glutamic acid amino acids respectively forming H-bonds with the phytochemicals. These results indicate that curcumin pyrazole, 4'-*O*-methylcatechin, and curcumin from *C. longa* can be used as potential inhibitors for *H. pylori* against peptic ulcers with no adverse effects.

Keywords: *Helicobacter pylori;* Peptic ulcers; Bioactive compounds; Molecular docking; Curcumin pyrazole

Introduction

The gram-negative helical-shaped bacterium *Helicobacter pylori* colonizes the human gastrointestinal tract and is particularly prone to infecting the gastric epithelium (Rothenbacher and Brenner 2003). The epithelium of the stomach is effectively shielded from pathogenic bacteria. The gastric mucosa has excellent resistance to bacterial infections. With a variety of special characteristics that allow *H. pylori*'s access into the mucus, swimming as well as attachment to epithelium makes *H. pylori* exceptionally well adapted to this particular habitat, leading to persistent colonization and transmission (Suerbaum and Michetti 2002). A variety of serious upper gastrointestinal (GI) disorders, including peptic ulcer disease, and gastric cancer, are related to *H. pylori* and therefore remain one of the most prevalent human infections in the world (Chey and Wong 2007).

In complex with nicotinamidine adenine dinucleotide phosphate (NADP), the carboxyspermidine dehydrogenase (CASDH) from *H. pylori* has the crystal structure 8H52; this protein includes spermidine, a positive polyamine crucial for a number of biological processes, including bacterial development and cell viability (Ko et al. 2022). Since spermidine is required for bacterial growth, *H. pylori* uses the enzymes carboxyspermidine dehydrogenase (CASDH) and carboxyspermidine decarboxylase

(CASDC) to biosynthesize it (Ko et al. 2022). Once inside the host's stomach, *H. pylori* uses its enzymatic activity (urease) to avoid the unfavorable acidic environment that are secreted in the stomach. Following this, *H. pylori* must advance toward the host's stomach epithelial cells using its bacterial flagellum. Next, precise connections between the bacteria's adhesions and the receptors on the host cell provide an efficient invasion and long-lasting infection, which then causes the destruction of tissue by releasing toxins (Kao et al. 2016).

A suitable treatment for gastropathy using the non-steroidal antiflamatory drugs (NSAID)-induced is still debatable despite recent advancements. Herbal medicines use for treating diseases is an ancient practice in many parts of the world with no adverse effects. Previously, the main treatment strategy aimed at lessening the production of gastric acids were thought to be the only factor in the development of ulcers. The current therapeutic strategy involves increasing mucosal protection while decreasing acid secretion (Wallace 2005). Numerous substances with natural origins have evidenced pharmacological properties against *H. pylori*, making them promising candidates as future drugs for treating gastric ulcers. Due to their safety, accessibility, and lack of negative side effects as compared to synthetic counterparts, these medications made from plants are likely to represent alternative but excellent options among other widely used peptic ulcers treatment options (Iwu et al. 1999).

Drug design is a significant field of research in which computational biophysics, biochemistry, and data science have recently gained prominence, and the use of computational techniques can aid in the prioritization and the creation of novel small molecules from large databases. There are two main categories of computer-aided drug design (CADD) methods: ligand-based drug design (LBDD) and structure-based drug design (SBDD). The goal of SBDD approaches is to discover critical locations and interactions that are crucial for each macromolecular target's specific biological functions. These macromolecular targets are often proteins or ribonucleic acid (RNA). To establish a connection between the physiochemical characteristics of a target and its ligands, LBDD techniques are used (Yu and MacKerell 2017). These techniques commonly employ the well-known Lipinski rule of five which covers the following calculations: Molecular weight (MW) $\leq$ 500, octanol/water partition coefficient (log P) $\leq$ 5, the number of hydrogen bond donors (HBDs) $\leq$ 5, and the number of hydrogen bond acceptors (HBAs) $\leq$ 10 (Lipinski et al. 1997). By utilizing bioinformatics approaches, the current study intended to find the potential phytochemicals from *Curcuma longa* against spermidine for inhibition of bacterial growth, and interruption of biological pathways necessary for the microorganism's existence through virtual screening, molecular docking and Adsorption, Distribution, Metabolism, Excretion and Toxicity (ADMET) prediction methods.

Methodology

Computational tools

The key drug candidate's in silico investigation was carried out using bioinformatics tools including Zinc Database, RCSB PDB, PyRx 0.9x (Dallakyan & Olson, 2015), BIOVIA discovery studio , and Open Babel GUI (O'Boyle et al. 2011).

Protein Preparation

The crystal structure Carboxyspermidine dehydrogenase from *H. pylori* (PDB ID: 8H52) in conjunction with NADP was retrieved from Protein Data Bank obtained using X-ray diffraction method with a resolution of 3.10A°, R-value free 0.251, R-value work, and R-value observed 0.204 (Figure 1).

Protein was loaded using BIOVIA discovery studio visualization. Protein structure was prepared in to receptor by deletion of heavy atoms including co-crystallized ligands, water molecules, heteroatoms, actosite, and co-factors followed by the addition of charges and polar hydrogen. The protein structure was saved in PDBQT for further study utilized in PyRx

0.9x and BIOVIA discovery studio Visualization 2021 (Preman et al. 2022).

Figure 1: Helicobacter pylori carboxyspermidine dehydrogenase crystal structure in complex with NADP (PDB ID: 8H52) (Ko et al. 2022).

Aspects of Phytoconstituent's Physiochemistry, Drug kinetics, and Likeness

During the drug development process, standard computerized pharmacokinetics parameters and drug-likeness were established for the evaluation of physicochemical, pharmacological, and drug-like properties (Daina et al. 2017). Swiss ADME was used to screen phytoconstituents obtained from *C. longa* zinc database for ADMET predictions (Bakchi et al. 2022).

Ligand Preparation

Curcuma longa's collection of eighty-three natural substances in structure-data file (.sdf) format was mined and downloaded from Zinc Database. After initial screening utilized in SwissADME, ligands in .sdf format were converted to PDB format, energies of ligands were also minimized, these steps were done in PyRx 0.9x software to find the ligands that bind with carboxyspermidine dehydrogenase from *H. pylori* in combination with NADP to acquire a variety of binding sequences and Binding Affinities (BA).

Molecular Docking

Virtual screening of natural substances from *C. longa* against the target protein was done using Auto dock Vina in PyRx on the active site setting a grid box with dimensions of values x: -37.3658, y: -4.1028, and z: -22.8563. Following the docking results, the conformations with the lowest binding affinities than the control drug were chosen to investigate interacting residues extensively.

Results and Discussion

The current research examined 83 natural compounds from *C. longa* with the purpose of inhibiting spermidine, which is produced by *H. pylori* using enzyme carboxyspermidine dehydrogenase (CASDH). Curcumin Pyrazole (ZINC19816066), 4'-*O*-methylcatechin (ZINC14642912), and curcumin (ZINC100067274) were discovered to have substantial anti-spermidine properties. Spermidine synthesized by carboxyspermidine dehydrogenase (CASDH) is essential for bacteria growth and differentiation, so *H. pylori* bond on the surface and facilitate stickiness to stomach epithelium cells. Curcumin pyrazole, 4'-*O*-methylcatechin, and curcumin have been identified to be critical for the suppression of spermidine to block the protein's formation.

ADMET Analysis

Binding affinities of the ligands are not the only factor to describe them as best therapeutic candidates, therefore ADMET parameters become more prevalent in the drug development process (Daina et al. 2017). Approximately 95% of the initially chosen phytochemicals from *C. longa* met the

requirements of the Lipinski rule of five. The most well-known rule for assessing drug likeness and identifying whether a molecule is effectively absorbed orally or not, which was proposed by Lipinski (Lipinski et al. 1997). In this study ADMET properties were predicted using SwissADME, three bioactive phytochemicals with the top scores had ADMET properties as indicated in Table 1.

Based on the ADMET data retrieved from swissADME server, after analyzing several attributes like solubility class, gastrointestinal (GI) absorption, blood-brain barrier (BBB) permeability, P-glycoprotein (P-gp) substrate interaction, cytochrome inhibition and log $K_{p,}$ showed good results. Also according to the Lipinski rule of five curcumin pyrazole, 4'-O-methylcatechin and curcumin have zero violation (Lipinski et al. 1997).

Ghose filter establishes the following conditions on drug-likeness: computed log P should be within the range of -0.4 and 5.6; molecular weight should be within the range of 160 and 480; molar refractivity within the range of 40 and 130; and the total number of atoms within the range of 20 and 70 (Ghose et al. 1999), which were all having good results.

Veber's rule for the three ligands had good results since a medicine may have acceptable oral bioavailability if it has 10 rotatable bonds (RTB) or less and a topological polar surface area (TPSA) of no more than 130*A*° (Kowalska et al. 2018).

Egan rule deems a candidate medication to have adequate oral bioavailability with $-1.0 \leq \log P \leq 5.8$ and TPSA ≤ 130 Å^2, thus curcumin pyrazole, 4'-O-methylcatechin and curcumin had better results (Halder and Elma 2020). The compounds have 0 pain alerts, therefore revealed to be therapeutic candidate for the treatment of peptic ulcers.

Zone Bioavailability

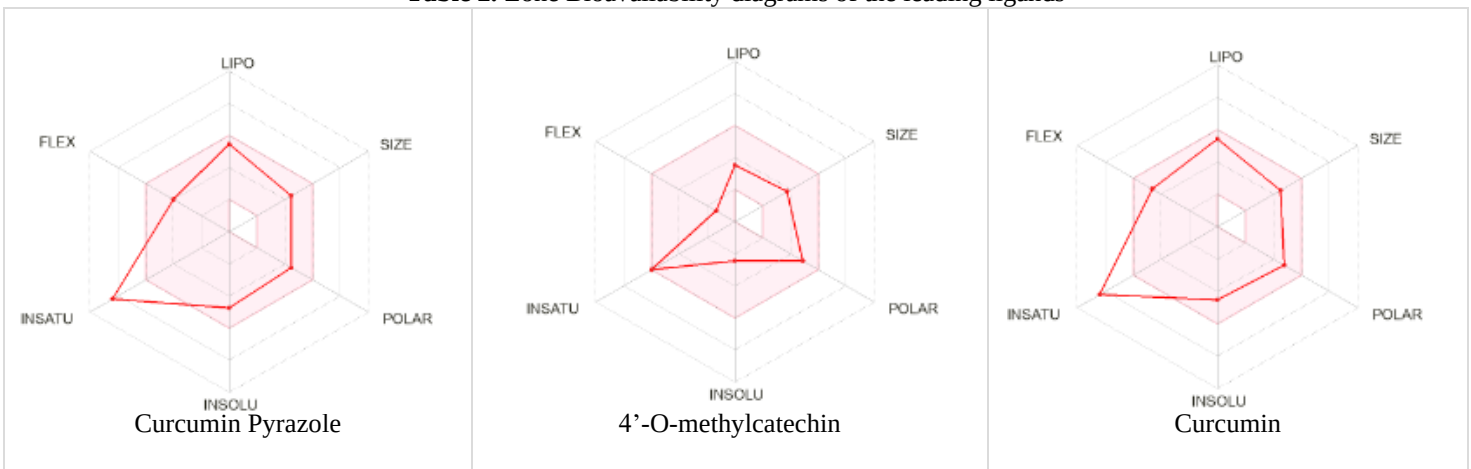
The chosen phytochemicals matched the requirements of Lipinski's law, indicating that they possess drug-like properties. More extensive and trustworthy tests, we performed by considering the bioavailability radar using swissADME (Daina et al. 2017). The variables comprise saturation, lipophilicity, size, polarity, solubility, and flexibility. For a molecule to be classified as drug-like, its radar plot must at least lie within the colored zone. For each attribute, the pink zone indicates the proper range such as lipophilicity: XLOGP3 between -0.7 and +5.0, size: molecular weight (MW) between 150 and 500 g/mol, polarity: TPSA between 20 and 1302, solubility: log S between – 6 and 0, saturation: sp3 hybridization fraction >0.25, and flexibility: < 9 rotatable bonds, therefore curcumin pyrazole, 4'-O-methylcatechin, and curcumin have oral bioavailability as enlisted in Table 2.

Table 1. ADME Analysis of the bioactive compounds

Property	Descriptor	Value			Unit
		(Curcumin Pyrazole) ZINC19816066	**(4'-O-methylcatechin) ZINC14642912**	**(Curcumin) ZINC100067274**	
Physiochemical	Molecular weight	364.39	304.29	368.38	g/mol
	Number of heavy atoms	27	22	27	
	Number of aromatic heavy atom	17	12	12	
	Number of rotatable bonds	6	2	7	
	Number of H-bond acceptors	5	6	6	
	Number of H-bond donors	3	4	3	
	Molar Refractivity	87.60	99.38.77	103.70	
Lipophilicity	*Log* $P_{o/w}$	3.42	2.02	3.17	
Water solubility	*Log S*	-4.73	-2.43	-3.61	
	Solubility	9.07e-04; 2.49e-06	1.12e+00; 3.69e-03	2.09e+00; 7.19e-03	mg/ml; mol/l
	Class	Moderate Soluble	Soluble	Soluble	
Pharmacokinetics	GI absorption	High	High	High	
	BBB permeant	No	No	No	
	P-gp substrate	No	Yes	Yes	
	CYP1A2	No	No	No	
	CYP2C19	No	No	No	
	CYP2C9	Yes	No	Yes	
	CYP2D6	No	No	No	
	CYP3A4	No	Yes	Yes	
	Log K_p	-5.64	-7.67	-5.72	cm/s
Druglikeness	Lipinski	Yes: 0 violation	Yes: 0 violation	Yes: 0 violation	
	Ghose	Yes	Yes	Yes	
	Veber	Yes	Yes	Yes	

	Egan Muegge Bioavailability score	Yes Yes 0.55	Yes Yes 0.55	Yes Yes 0.55	
Pharmaceutical Chemistry	PAINS Brenk Lead likeness Synthetic accessibility	0 Alert 0 Alert MW >350 3.14	0 Alert 0 Alert Yes 3.61	0 Alert 3 Alert MW >350 3.42	

Table 2. Zone Bioavailability diagrams of the leading ligands



Ethnomedicinal use, Binding Affinities and Interactions of bioactive compounds

Curcumin pyrazole possesses potent antioxidant and hypoglycemic properties (Puneeth and Sharada 2015). Curcumin pyrazole in *C. longa* has inhibition of spermidine with a binding affinity of -10 kcal/mol (Table 3) against the target.

4'-O-Methylcatechin is a derivative of catechins, catechins have been reported to be useful in avoiding carcinoma of the liver, malignancies of the prostate, throat cancer, intestinal cancer, and lung cancer (Isemura 2019). It has also demonstrated to possesses inhibition properties against *H. Pylori* with binding affinity of -9.5 kcal/mol (Table 3).

Curcumin is beneficial in the treatment of oxidative and inflammatory disorders, as well as metabolic syndrome, arthritis, anxiety, and high cholesterol levels (Hewlings and Kalman 2017). Therefore, curcumin possesses inhibition properties against spermidine with binding affinity of -9.3 kcal/mol (Table 3). It is clearly seen from Table 3 that curcumin pyrazole, 4'-O-methylcatechin and curcumin possesses high binding affinity compare to omeprazole, hence they are proposed to effectively for treatment of peptic ulcers.

Ligand interacts with membrane cell surface receptors as soon as it reaches the human body, as a result these receptor interactions with different molecules or surfaces are influenced by van der Waals (dispersion) forces, hydrogen bonds, Pi-Pi stacked bonds, Pi-Alkyl bond and Alkyl interactions.

In defining the selectivity of ligand binding, hydrogen-bonds are absolutely essential and has been critical in influencing the binding of ligands (Karimi and Sanchooli 2020). In order for protein-ligand complexes to develop and remain stable, van der Waals forces must be present and therefore promoting the affinity (Bitencourt-Ferreira et al. 2019). The folding of proteins depends on hydrophobic interactions (pi-alkyl, alkyl, pi-sigma, pi–pi). Therefore, hydrophobic interaction between biomolecules and phytochemicals is essential to binding affinity and specificity, and it helps keep proteins stable by allowing them to lose surface area and eliminate unintentional interactions with water (Vinod et al. 2023).

Table 3. Structures, binding affinities, and bonds formed by the ligands

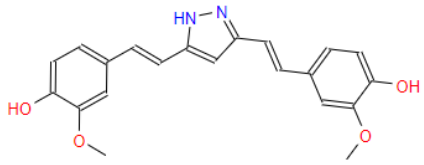
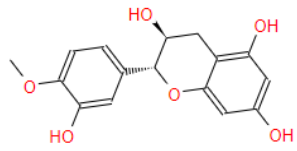
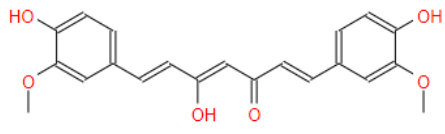
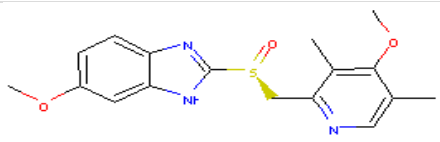
S/No	Substances	Structures	Binding Affinity (Kcal/mol)	Bond formed
1.	Curcumin Pyrazole ($C_{21}H_{20}N_2O_4$)		-10	Van der waals, Convectional Hydrogen Bond, Carbon Hydrogen Bond, Pi-Sigma, Pi-Pi Stacked, Amide-Pi Stacked and Alkyl
2.	4'-O-methylcatechin ($C_{16}H_{16}O_6$)		-9.5	Van der waals, Convectional Hydrogen Bond, Pi-Pi Stacked, Alkyl and Pi-Alkyl
3.	Curcumin ($C_{21}H_{20}O_6$)		-9.3	Van der waals, Convectional Hydrogen Bond, Carbon Hydrogen Bond, Pi-Pi Stacked and Alkyl
4.	OMEPRAZOLE ($C_{17}H_{19}N_3O_3S$)		-8.8	Convectional Hydrogen Bond, Pi-Pi Stacked, Pi-Alkyl

Figure 4a, 4b, 4c, and 4d represent potential amino acids (AA) that interact with ligands and contribute to their overall binding. Moreover, curcumin pyrazole forms convectional hydrogen bonds with VAL A: 83, ASP A: 143 amino acids, and creates carbon hydrogen bond with ALA A: 9. GLY A: 10 was also observed to interact through van der Waal force with the bioactive compound. VAL A: 12 formed Pi-sigma whereas PHE A: 183 formed Pi-Pi stacked bond. ILE A: 343 and ALA A: 84 form alkyl interaction with the ligand (Figure 4 a).

4'-O-methylcatechin showed formation of convectional hydrogen bonds with GLU A: 83 amino acids. PHE A: 183 formed Pi-Pi stacked bond. VAL A: 12 creates alkyl interaction with the ligand (Figure 4 b).

Curcumin formed convectional hydrogen bond with ALA A: 84, LYS A: 289 and ASP A: 143 amino acids also ASP A: 169 formed carbon hydrogen bond with ligand. Pi-Pi stacked bond was observed on ILE A: 343 and LEU A: 85 (Figure 4 c). While omeprazole formed convectional hydrogen bond with GLY A: 11. Pi-Pi stacked bond showed interaction with PHE A: 183, also HIST A: 231 and VAL A: 12 formed Pi-alkyl with the ligand (Figure 4 d).

It is clearly that turmeric has a variety of *H. Pylori*-inhibitory properties from the binding affinities and interaction it exhibited. Therefore, curcumin pyrazole, 4'-O-methylcatechin and curcumin are ideal inhibitors and therapeutic agents against a broad spectrum of peptic ulcer diseases due to their superior inhibitory activities and optimal pharmacokinetics compare to omeprazole.

Convectional hydrogen bond formed with VAL A: 83, ASP A: 143, and ALA A: 9 had bond distances of 2.58*A*°, 2.99*A*°, and 2.31*A*° respectively. Pi-Pi stacked formed with PHE A: 183 (4.08*A*°) and ALA (4.47*A*°). Pi-sigma formed with VAL A: 12 (3.59*A*°). Bond distances of alkyl interaction were ALA A: 84 (4.13*A*°) and ILE A: 343 (4.17*A*°) (Figure 5).

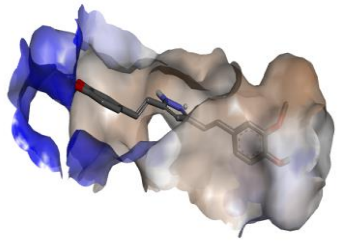
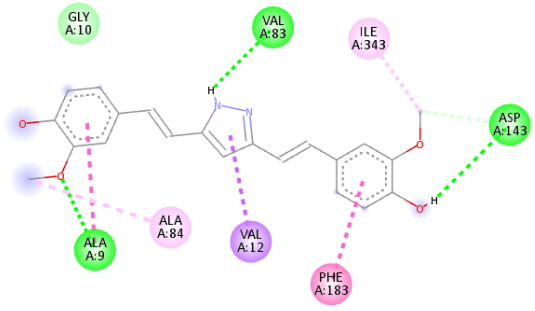
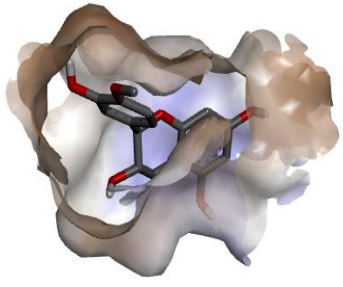
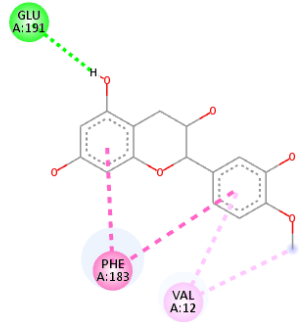
Convection hydrogen bond with GLU A: 191 had bond distance (2.25*A*°), Pi-Pi stacked with PHE A: 183 (4.54*A*° and 5.30*A*°). Alkyl interacted with VAL A: 12 (4.51*A*° and 4.13*A*°) (Figure 5).

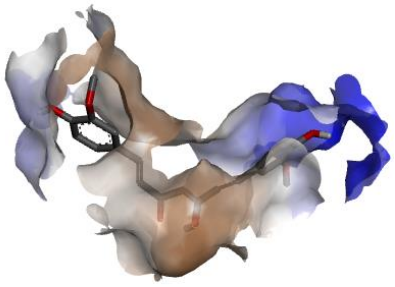
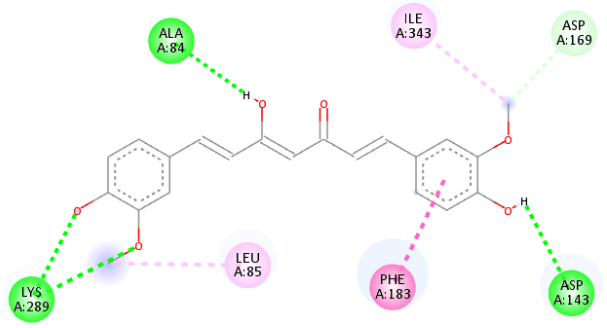
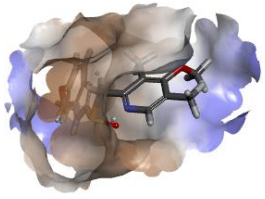
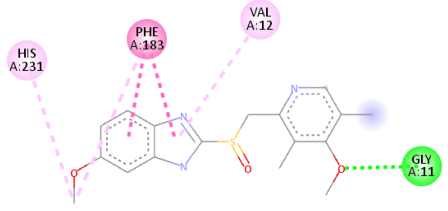
Curcumin formed convectional hydrogen bond with LYS A: 289 (2.38*A*° and 2.68*A*°), ALA A: 84 (2.32*A*°), and ASP A: 143 (2.55*A*°) bond distances. Pi-Pi stacked with PHE A:183 (4.12*A*°). Alkyl formed with ILE A: 343 (4.03*A*°) and LEU A: 85 (4.75*A*°) (Figure 5).

Omeprazole formed convectional hydrogen bond with GLY A: 11 of 2.14*A*° , Pi-Pi stacked with PHE A: 183 of 3.66*A*° and 4.26*A*°, Pi-alkyl with HIS A: 231, PHE A: 183, VAL A:12 of 4.53*A*°, 4.58*A*°, and 5.27 *A*° respectively (Figure 5).

Bond lengths associate with bond strengths, the higher value of bond lengths has lower value of bond strength between the two bonded molecules, bond lengths are crucial to energy calculations in the realm of molecules. Protein-ligand complexes can remain stable when the system's binding energy is low (Finn and Kavraki 1999).

Curcumin pyrazole formed three convectional hydrogen bonds, Pi-Pi stacked, Pi-sigma and alky interaction, complex structure is stable with good bond distances compare with omeprazole which has few bonds formed with the amino acids.

	3D interaction diagram	2D interaction diagram
a	 a) 3D interaction structure of Curcumin Pyrazole in pocket of 8H52	 b) 2D interaction structure of Curcumin Pyrazole docked with 8H52 visualized using Biovia Discovery studio
b	 a) 3D interaction structure of 4'-O-methylcatechin in pocket of 8H52	 b) 2D interaction structure of 4'-O-methylcatechin docked with 8H52 visualized using Biovia Discovery studio.

c	 a) 3D interaction structure of Curcumin in pocket of 8H52	 b) 2D interaction structure of Curcumin docked with 8H52 visualized using Biovia Discovery studio.
d	 a) 3D interaction structure of Omeprazole in pocket of 8H52	 b) 2D interaction sturcture of Omeprazole docked with 8H52 visualized using Biovia Discovery studio.

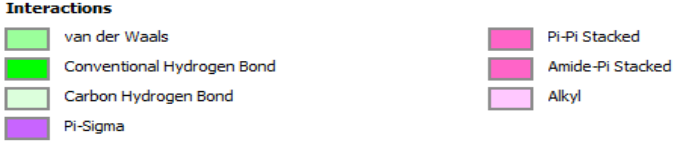
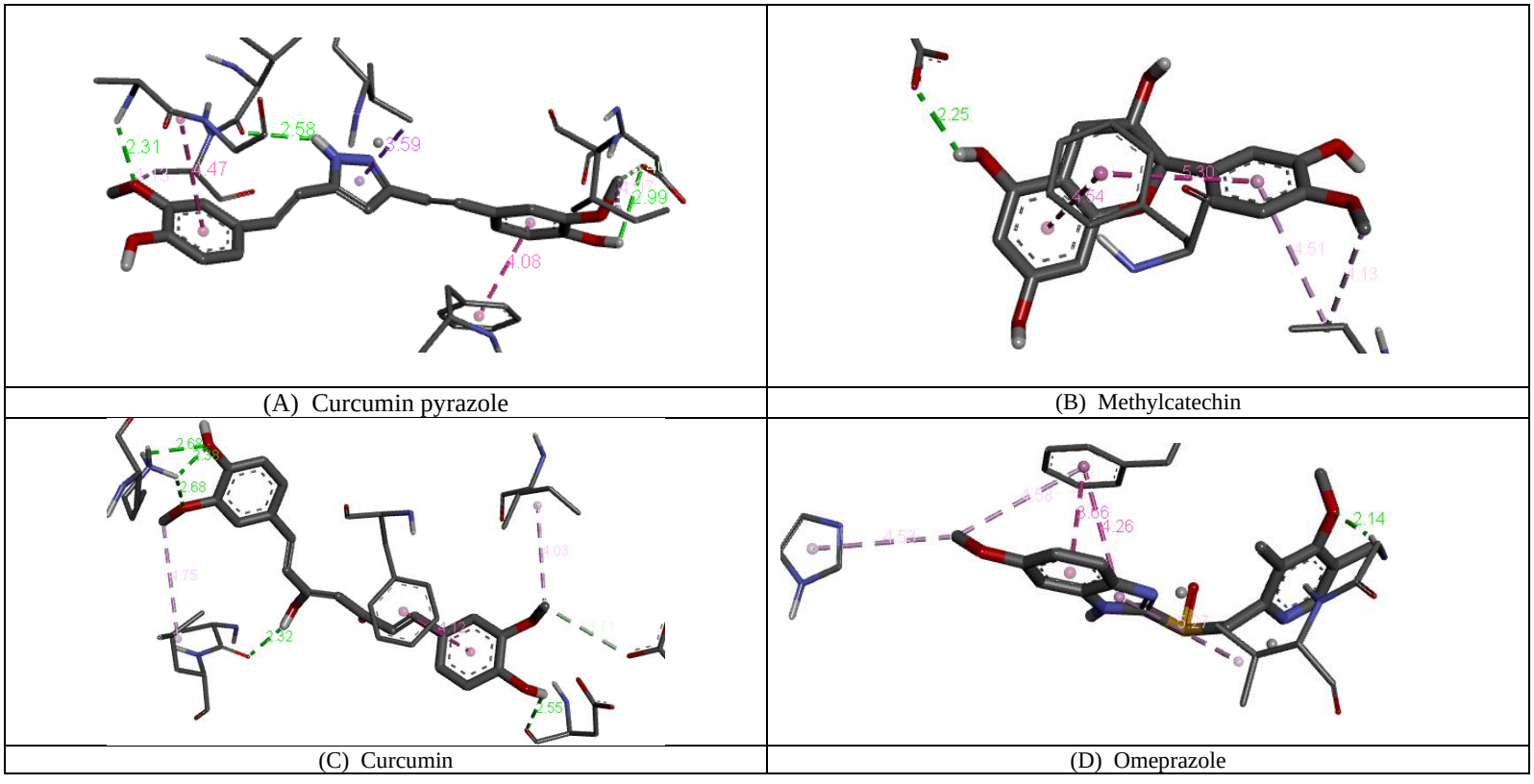


Figure 4



(A) Curcumin pyrazole | (B) Methylcatechin

(C) Curcumin | (D) Omeprazole

Figure 5. Bond distances of ligands receptor chain (A, B, C, and D)

Conclusion

In this study eighty-three significant bioactive compounds from *curcuma longa* were investigated as potential inhibitors for the treatment of peptic ulcers. By using computer assisted virtual screening tools for ADMET, these bioactive compounds from curcuma longa were subjected to virtual screening. The results show that Curcumin Pyrazole (-10 kcal/mol), 4-O-methylcatechin (-9.5 kcal/mol), and Curcumin (-9.3 kcal/mol) are potential compounds for treatment of peptic ulcers because the possess high binding affinity compare to omeprazole (-8.8 kcal/mol) which is the routinely synthetic drug. Moreover, the interactions of those compounds were observed to be more favourable than omeprazole. Thus, the bioactive compounds are proposed to be a possible candidate for medicines against 8H52 to inhibit bacterial growth and cell development so as to promote healthy and well-being for the peptic ulcers disorders.

Conflicts of interest

The authors declare that there are no conflicts of interest in this study.

Sample availability

Since this is an *in silico* approach, actual sample were not used in the analysis.

References

Bakchi B, Krishna AD, Sreecharan E, Ganesh VBJ, Niharika M, Maharshi S, Puttagunta SB, Sigalapalli DK, Bhandare R R and Shaik, AB 2022 An Overview on Applications of SwissADME Web Tool in the Design and Development of Anticancer, Antitubercular and Antimicrobial agents: A Medicinal Chemist's Perspective. *J. Mol. Struc*. 1259: 132712.

Bitencourt-Ferreira G, Veit-Acosta M and de Azevedo WF 2019 Van der Waals potential in protein complexes. *Methods Mol. Biol*. 79-91.

Chey WD and Wong BC 2007 American College of Gastroenterology guideline on the management of Helicobacter pylori infection. *Am. J. Gastroenterol*. 102(8): 1808-1825.

Daina A, Michielin O and Zoete V 2017 SwissADME a free web tool to evaluate pharmacokinetics, drug-likeness and medicinal chemistry friendliness of small molecules. *Sci Rep*. 7(1): 42717.

Dallakyan S and Olson AJ 2015 Small-molecule library screening by docking with PyRx. *Methods Mol. Biol*. 2015: 243-250.

Finn PW and Kavraki LE 1999 Computational approaches to drug design. *Algorithmica*, 25(2): 347-371.

Ghose AK, Viswanadhan VN and Wendoloski JJ 1999 A knowledge-based approach in designing combinatorial or medicinal chemistry libraries for drug discovery. 1. A qualitative and quantitative characterization of known drug databases. *J Comb Chem*. 1(1): 55-68.

Halder SK and Elma F 2020 In silico identification of novel chemical compounds with anti-TB potential for the inhibition of InhA and EthR from Mycobacterium tuberculosis. *J Clin Tuberc Other Mycobact*. 2020.2012. 2004.411967.

Hewlings SJ and Kalman, DS 2017 Curcumin: A review of its effects on human health. *Foods*. 6(10): 92. https://doi.org/10.3390/foods6100092

Isemura M 2019 Catechin in human health and disease. *Molecules*. In Vol. 24, pp. 528

Iwu MW, Duncan AR, and Okunji CO 1999 New antimicrobials of plant origin. *Perspectives on new crops and new uses*. ASHS Press, Alexandria, VA. 457: 462.

Kao CY, Sheu BS and Wu JJ 2016 Helicobacter pylori infection: An overview of bacterial virulence factors and pathogenesis. *Biomed. J*. 39(1): 14-23.

Karimi P and Sanchooli M 2020 Investigation of resonance assisted hydrogen bond (RAHB) in some pyridine-based complexes: Intramolecular and intermolecular interactions. *J. Mol. Struct*. 1204: 127546.

Ko KY, Park SC, Cho SY and Yoon SI 2022 Structural analysis of carboxyspermidine dehydrogenase from Helicobacter pylori. *Biochem Biophys Res Commun*. 635: 210-217.

Kowalska M, Fijałkowski Ł and Nowaczyk A 2018 The biological activity assessment of potential drugs acting on cardiovascular

system using Lipinski and Veber Rules. *J Educ Health Sport*. 8(12): 184-191.

Lipinski CA, Lombardo F, Dominy BW and Feeney P J 1997 Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings. *Adv Drug Deliv Rev*. 23(1-3): 3-25.

O'Boyle NM, Banck M, James CA, Morley C, Vandermeersch T and Hutchison GR 2011 Open Babel: An open chemical toolbox. *Jcheminform.* 3(1): 1-14.

Preman G, Mulani M, Bare A, Relan K, Sayyed L, Jha V and Pandey K 2022 Virtual Screening of Phytochemicals for Anti-Tubercular Potential Using Molecular Docking Approach. *J Tuberc*. 5(1), 1030.

Puneeth HR and Sharada A 2015 Antioxidant and hypoglycemic effects of curcumin pyrazole derivatives. *Int J Pharm Pharm Sci*. *7*(4): 244-249.

Rothenbacher D and Brenner H 2003 Burden of *Helicobacter pylori* and *H. pylor*i-related diseases in developed countries: recent developments and future implications. *Microbes Infect.* 5(8): 693-703.

Suerbaum S and Michetti P 2002 Helicobacter pylori infection. *N Engl J Med*. 347(15): 1175-1186.

Vinod SM, Murugan SS, Krishnan A, Ravichandran K, Karthikeyan P, Kotteswaran B and Rajendran K 2023 Complexity of the Role of Various Site-Specific and Selective Sudlow Binding Site Drugs in the Energetics and Stability of the Acridinedione Dye–Bovine Serum Albumin Complex: A Molecular Docking Approach. *ACS Omega*. 8(6): 5634-5654.

Wallace JL 2005 Recent advances in gastric ulcer therapeutics. *Curr. Opin. Pharmacol*. 5(6): 573-577.

Yu W and MacKerell AD 2017 Computer-aided drug design methods In Sars p(Ed.). *Antibiotics: Methods Protocols* 85-106. Springer Nature.