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In-Silico Investigation of the Anti-Ulcer Potentials of Ethanolic Extract of *Chromolaena Odorata*

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A B S T R A C T
Chromolaena odorata, often known as devil weed (depending on the leaves), is a subtropical flowering shrub belonging to the Asteraceae family. It has been traditionally used as a herbal remedy for burns, wounds, skin infections, and unpleasant stomach ulcers. Its antibacterial, wound-healing, hemostatic, antioxidant, anti-inflammatory, platelet-protective, hypoglycemic, hypolipidemic, insecticidal, and anti-anemic qualities have been documented in several scholarly publications. Thirty (30) retentions with fifty-one (51) library/ID-suggested compounds were found in the GC-MS data of this study. When the identified compounds were docked against the stomach proton pump in order to cure ulcers, it was discovered that some of the ligands that were docked with The H+/K+-ATPase enzyme, 3-(Azepan-1-yl)-1,2-benzothiazole 1,1-dioxide, had a higher binding energy value (high binding energy value) of -8.4 kcal/mol in comparison to omeprazole, the conventional anti-ulcer medication (−8.0 kcal/mol). Strong binding of 3-(Azepan-1-yl)-1,2 benzothiazole 1,1-dioxide to the receptor implies that the molecule may have a higher potential for inhibiting the stomach proton pump than omeprazole. The plant's traditional usage for treating stomach ulcers may also be supported by this finding.

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INTRODUCTION

The herbaceous perennial Chromolaena odorata grows 1.5–2.0 meters tall, forming dense, tangled bushes of herbs with long, meandering branches that do not twine. C. odorata is a tropical and subtropical shrub species that belongs to the Asteraceae family that blooms . In Africa, a number of plant components are frequently used to heal burns, wounds, and skin infections. For example, internal bleeding and malaria are treated with an infusion made from fresh Chromolaena odorata leaves in Ghana and Nigeria (Benin). Similar reports of this plant's efficacious use in herbal medicine have come from other parts of the world. Examples include the plant's widespread usage in Vietnamese traditional medicine to heal stomach ulcers , and the use of the leaves to satisfy thirst in Thailand and Guatemala. external bleeding and, correspondingly, as an antibacterial agent . According to reports, the plant's leaf extract has very high nutritional content and is a rich source of mineral elements . It also has anti-inflammatory, antibacterial, anti-cancer, antidiabetic, and antioxidant qualities.

The stomach is the organ in the digestive system that moves food from the esophagus to the small intestine, where it undergoes additional processing. To reduce food into simpler chemicals, it generates acid and several other enzymes . A mucous layer shields the stomach's inner wall from acids and enzymes. Ulcers are sores caused by an imbalance between the stomach's digestive juices and the several components that support the lining of the stomach . The hallmark of peptic ulcer disease (PUD) is the breakdown of the gastrointestinal (GI) tract's inner lining due to stomach acid . The use of non-steroidal anti-inflammatory medicines (NSAIDs) and Helicobacter pylori (H. pyroli) are the primary risk factors for peptic ulcer disease . Phage Helicobacter It also one of the main ways to avoid stomach cancer. However, due to the extensive use of antibiotics, H. pylori's antibiotic resistance has progressively grown in recent years , which is now the primary cause of the infection's failure to be eradicated .

NSAIDs, which include low-dose aspirin, are among the most widely prescribed anti-inflammatory medications. Although NSAIDs have a long history of clinical usage and strong efficacy, such as their analgesic and anti-inflammatory effects , they can also cause mucosal harm through a variety of pathways. These medications may cause deadly complications from peptic ulcers. Most NSAIDs are weak acids that readily cross lipid membranes to enter epithelial cells when exposed to acidic gastric juice and become protonated. This can cause erosions, fast death of epithelial cells, superficial bleeding, and topical damage . The suppression of cyclooxygenase-1 (COX-1) is another important mechanism by which NSAIDs cause mucosal damage. This inhibits prostaglandin synthesis, which lowers the formation of gastric mucus and bicarbonate and results in a reduction in blood supply to the mucosa .

Many drugs, such as H2 receptor antagonists and proton pump inhibitors, are available to treat gastric ulcers; however, clinical evaluation of these drugs has shown side effects, relapse rates, and drug interactions . As a result, it is necessary to find an effective and safe anti-ulcer agent. The rapidly expanding body of research in this area indicates that, with improvements in nutritional and remedial therapies, gastric ulcers may become preventable within the next ten years. This can be achieved by fortifying the gastric mucosa's defense mechanisms while simultaneously reducing the factors that lead to gastric ulceration. Plants have been reported to be a more effective treatment for ulcers because they have little to no side effects in comparison to contemporary medications . Planning the most often researched and found to have potential benefits on wound healing, cytoprotection, antioxidants, anti-inflammatory agents, inhibition of gastric secretion, enhancement of mucus formation, up-regulation of HSP70, down-regulation of Bax protein, anti-secretory, and anti-H. pylori actions . Worldwide, C. odorata has been widely utilized in traditional treatments as a herbal cure for PUD. The plant's methanol/chloride extract [26] and crude ethanolic extract have both been shown by some researchers to have anti-ulcer properties in vivo in mice and rats, respectively. Since H+/K+ ATPase has been identified as the main gastric proton pump, there has been a lot of interest in the use of H+/K+ ATPase inhibition to regulate gastric pH. Therefore, the goal of the current investigation was to determine how C. odorata's anti-ulcer activity involves inhibiting H+/K+ ATP. In order to determine the phytochemicals' mode of action, the ethanolic crude extract's phytochemical content was first identified using GCMS. This was done by docking the phytochemicals against the gastric proton pump's crystal structure.

METHODOLOGY

Plant material collection

In May 2021, leaves of Chromolaena odorata were gathered from the area behind Imo State University's New Science Laboratory in Imo state, Nigeria. Professor Mbagwu of Imo State University's Department of Plant Science and Biotechnology verified the authenticity of the plant. Before being analyzed, the leaves were shade-dried at room temperature and then ground into a powder using a mortar and pestle stored in an amber-colored jar.

Preparation of the crude extract

By percolating 500 g of the sample with 750 ml of redistilled ethanol (92%) for 72 hours while stirring occasionally, the Chromolaena odorata powder was extracted. The extract was dried at 45°C in a Genlab oven after being filtered and concentrated using a rotary evaporator (Stuart, SO1, UK) .

Gas chromatography-mass spectrometry (GC–MS) analysis;

The sample, weighing one gram, was dissolved in ethanol and then automatically injected into an Agilent GC-MS (Agilent 19091-433HP, USA) connected to an Agilent Technologies mass spectrophotometer MS at the Multi-User Science Research Laboratory, Ahmadu Bello University, Zaria, Kaduna State, Nigeria. The GC-MS analysis was conducted under the following operating conditions: The oven's temperature was 50°C for two minutes, 100°C at a rate of 10°C per minute, 200°C, and it remained isothermal for ten minutes. The carrier gas used was helium, injected at a rate of 1 mL per minute, with a sample injection volume of 2µliters. A voltage of 70 eV was used to ionize the components of the sample. The duration of the GC was 24.50 minutes. Next, the structures of the discovered compounds were contrasted with those found in the NIST. use the NIST14.Library (2018) database. The compounds were compared to known compounds in the NIST library (C:\Database\NIST14.L) for retention durations and mass spectra . The component, name, retention period, and concentration are all included in the provided data. The PubChem database was used to determine the structures, molecular weight, and pubchem ID .

Molecular docking studies;

Protein-ligand docking Using Auto Dock Vina virtual screening software and Discovery studio software, a research of chemicals found in Chromolaena odorata was carried out to examine the interaction between the ligands and the active site of the H+/K+-ATPase enzyme.

Ligands preparation for docking;

The chemicals' three-dimensional structure was obtained from the PubChem service. For those compounds lacking 3D structures, Open Babel software was used to download 2D structures and then transform them into 3D structures in SDF format. within a command-line setting. In the same command line environment, hydrogen bonds were formed, charges were added by converting the compounds to MOL2 format and then back to PDBQT format, and energies were reduced by utilizing the MMFF94.

Preparation of receptor;

You could get the crystal structure of the tegoprazan-complexed gastric proton pump (PDB code: 7w47) from the Protein Databank (PDB). With the use of Discovery Studio software , the 3D structure receptor was created and stored as Pdb after water molecules and cofactors were eliminated. The receptor's active site was determined to be the binding location of tegoprazan.

Docking of the ligands with the receptor;

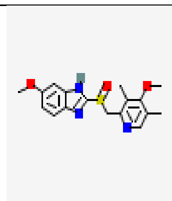
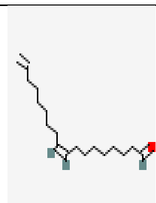
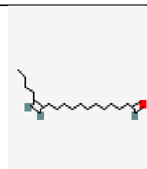
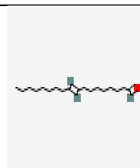
Since the receptor and ligand separate after autodock docking, Autodock vina was used to execute the docking of the ligands and receptors . Discovery studio software was used to visualize the interactions between the complexes.

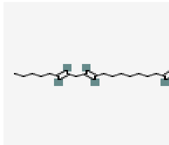
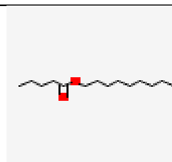
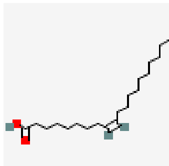
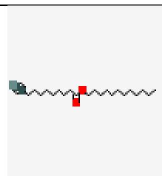
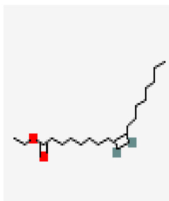
RESULTS AND DISCUSSION

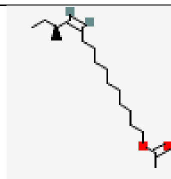
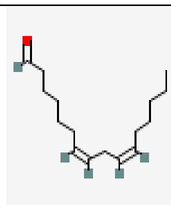
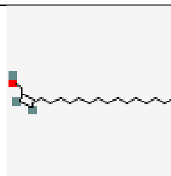
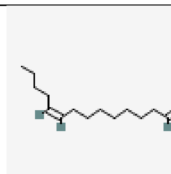
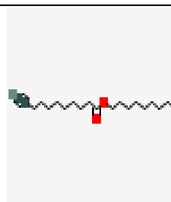
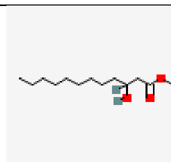
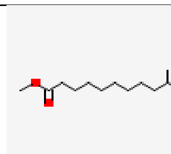
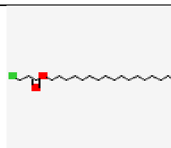
Gas chromatography-mass spectrometry (GC–MS) result:

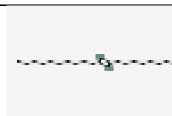
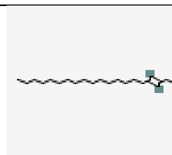
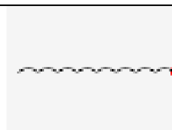
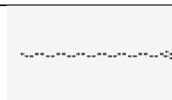
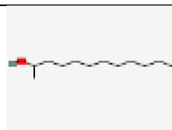
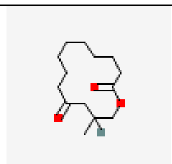
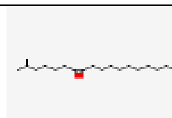
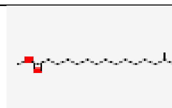
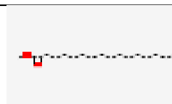
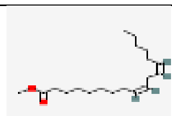
On GC-MS analysis, the gummy, dark green ethanolic extract of Chromolaena odorata leaves produced thirty (30) retentions with fifty-one (51) chemicals suggested by library/ID. The final product consists of forty-nine (49) aliphatic compounds, one aromatic heterocyclic molecule, 3-(Azepan-1-yl)-1,2-benzothiazole 1,1-dioxide, and one alicyclic compound, Oxacyclotetradecane-2,11-dione, -methyl. The outcome is displayed in Table 1 below, along with the structures, molecular weight, molecular formula, retention time, name of the compounds, PubChem ID, and percentage composition.

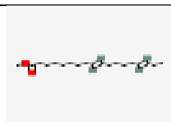
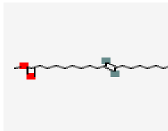
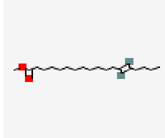
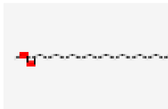
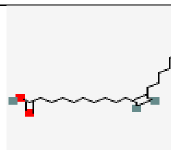
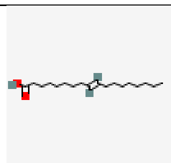
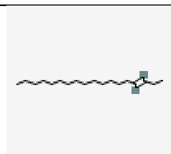
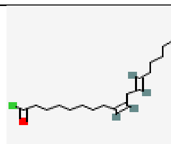
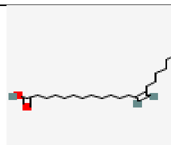
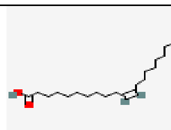
Table 1: GC-MS result of ethanolic extract of *chromolaena odorata* leaves extrac

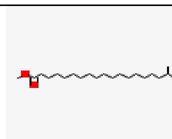
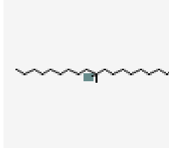
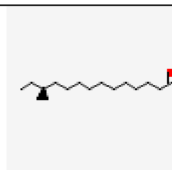
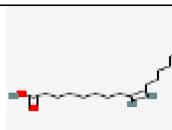
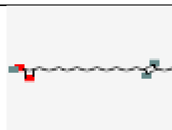
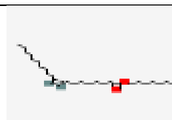
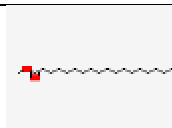
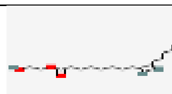
s/n	PK	Compounds Name	RT	% AREA	MW g/mol	MF	Pubchem id	COMPDS STRUCTURE
Cnt	-	**Omeprazole**	-	-	345.4	$C_{17}H_{19}N_3O_3S$	4594	
1	1a	9,17-Octadecadienal, (Z)-	8.987	0.35	264.4	$C_{18}H_{32}O$	5365667	
2	1b	13-Octadecenal, (Z)-	8.987	0.35	266.5	• $C_{18}H_{34}O$	5364497	
3	1c	9-Octadecenal	8.987	0.35	266.5	• $C_{18}H_{34}O$	5283381	

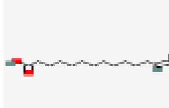
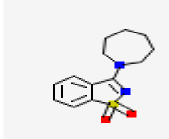
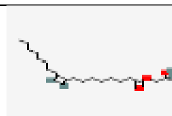
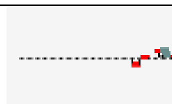
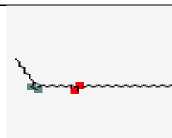
4	2a	9,12-Octadecadienal	10.329	2.21	264.4	• $C_{18}H_{32}O$	5283383	
5	2b	Pentanoic acid, 10-undecenyl ester	10.329	2.21	254.41	• $C_{16}H_{30}O_2$	543363	
6	3a	9-Eicosenoic acid, (Z)-	10.676	0.60	310.5	• $C_{20}H_{38}O_2$	5282767	
7	3b	Undec-10-ynoic acid, dodecyl ester	10.676	0.60	350.6	• $C_{23}H_{42}O_2$	91692432	
8	3c	Behenic alcohol	10.676	0.60	326.6	• $C_{22}H_{46}O$	12620	
9	4a	Ethyl Oleate	10.895	0.53	310.5	• $C_{20}H_{38}O_2$	5363269	

10	4b	(S)(+)-Z-13-Methyl-11-pentadecen-1-ol acetate	10.895	0.53	282.5	• $C_{18}H_{34}O_2$	91691416	
11	5b	cis,cis-7,10,-Hexadecadienal	11.158	0.61	236.39	$C_{16}H_{28}O$	5365665	
12	6a	Z-2-Octadecen-1-ol	11.284	0.35	268.5	$C_{18}H_{36}O$	5365011	
13	7a	9-Tetradecenal, (Z)-	11.413	0.43	210.36	$C_{14}H_{26}O$	5364471	
14	7b	Undec-10-ynoic acid, nonyl ester	11.413	0.43	308.5	$C_{20}H_{36}O_2$	91692547	
15	8a	Dodecanoic acid, methyl ester	11.581	1.27	230.34	$C_{13}H_{26}O_3$	155752	
16	8a	Undecanoic acid, 10-methyl-, methyl ester	11.581	1.27	214.34	$C_{13}H_{26}O_2$	554144	
17	9a	3-Chloropropionic acid, heptadecyl ester	13.367	0.10	347.0	$C_{20}H_{39}ClO_2$	545757	

18	9b	9-Eicosene, (E)-	13.367	0.10	280.5	$C_{20}H_{40}$	5365037	
19	9c	3-Eicosene, (E)-	13.367	0.10	280.5	$C_{20}H_{40}$	5365051	
20	10a	1-Hexadecanol	17.773	0.07	242.44	$C_{16}H_{34}O$	2682	
21	10b	Cetene	17.773	0.07	224.42	$C_{16}H_{32}$	12395	
22	10c	2-Dodecanol	17.773	0.07	186.33	$C_{12}H_{26}O$	25045	
23	11a	Oxacyclotetradecane-2,11-dione, -methyl-	19.762	0.13	240.34	$C_{14}H_{24}O_3$	543408	
24	11b	Disparlure	19.762	0.13	282.5	$C_{19}H_{38}O$	205983	
25	12a	Pentadecanoic acid, 14-methyl-, methyl ester	20.309	2.20	270.5	$C_{17}H_{34}O_2$	21205	
26	12b	Hexadecanoic acid, methyl ester	20.309	2.20	270.5	$C_{17}H_{34}O_2$	8181	
27	13a	9,12-Octadecadienoic acid (Z,Z)-, methyl ester	23.378	0.27	294.5	$C_{19}H_{34}O_2$	5284421	

28	13b	9,15-Octadecadienoic acid, methyl ester, (Z,Z)-	23.378	0.27	294.5	$C_{19}H_{34}O_2$	5362738	
29	14a	10-Octadecenoic acid, methyl ester	23.580	6.01	296.5	$C_{19}H_{36}O_2$	5364425	
30	14b	trans-13-Octadecenoic acid, methyl ester	23.580	6.01	296.5	$C_{19}H_{36}O_2$	5364506	
31	15a	Methyl stearate	24.159	1.15	298.5	$C_{19}H_{38}O_2$	8201	
32	16a	cis-Vaccenic acid	24.886	0.23	282.5	$C_{18}H_{34}O_2$	5282761	
33	16b	9-Octadecenoic acid	24.886	0.23	282.5	$C_{18}H_{34}O_2$	637517	
34	16c	3-Octadecene, (E)-	24.886	0.23	252.5	$C_{18}H_{36}$	5365984	
35	17a	9,12-Octadecadienoyl chloride, (Z, Z)-	25.152	0.13	298.9	$C_{18}H_{31}ClO$	86740353	
36	18a	cis-13-Eicosenoic acid	27.130	0.47	310.5	$C_{20}H_{38}O_2$	5312518	
37	18b	cis-11-Eicosenoic acid	27.130	0.47	310.5	• C_2 $_0H$	5282768	

						$_{38}O_2$		
38	19a	Methyl 18-methylnonadecanoate	27.693	0.53	326.6	$C_{21}H_{42}O_2$	530340	
39	19b	Nonadecanoic acid, 10-methyl-, methyl ester	27.693	0.53	326.6	$C_{21}H_{42}O_2$	554154	
40	19c	Tetradecanoic acid, 12-methyl-, methyl ester, (S)-	27.693	0.53	256.42	$C_{16}H_{32}O_2$	23618376	
41	20a	Oleic Acid	29.109	0.51	282.5	$C_{18}H_{34}O_2$	445639	
42	20c	trans-13-Octadecenoic acid	29.109	0.51	282.5	$C_{18}H_{34}O_2$	6161490	
43	21a	(Z)-Decyl icos-9-enoate	29.993	0.69	450.8	• $C_{30}H_{58}O_2$	76964864	
44	22a	Methyl 20-methyl-heneicosanoate	30.963	2.90	354.6	$C_{23}H_{46}O_2$	15089804	
45	23a	9-Octadecenoic acid (Z)-, 2-hydroxyethyl ester	32.061	2.86	326.5	$C_{20}H_{38}O_3$	5364420	

46	24a	cis-13-Octadecenoic acid	34.013	25.45	282.5	$C_{18}H_{34}O_2$	5312441	
47	25a	3-(Azepan-1-yl)-1,2-benzothiazole 1,1-dioxide	34.475	11.05	264.35	$C_{13}H_{16}N_2O_2S$	535203	
48	25b	Erucic acid	34.475	11.05	338.6	$C_{22}H_{42}O_2$	5281116	
49	27a	9-Octadecenoic acid (Z)-, 2,3-dihydroxypropyl ester	34.777	6.74	356.5	$C_{21}H_{40}O_4$	5283468	
50	30a	Glycerol 1-palmitate	38.298	1.00	330.5	$C_{19}H_{38}O_4$	14900	
51	30c	Oleic acid, eicosyl ester	38.298	1.00	563.0	$C_{38}H_{74}O_2$	6436542	

Sn=Serial number, cnt=Controle, PK=Peak number, RT= Retention time, MW=Molecular weight, MF=Molecular formula

Molecular docking result;

One of the most common and potentially fatal diseases to strike a major portion of the global population in the last 200 years is peptic ulcer disease, which has a high morbidity and death rate. Nigeria had 5,846 fatalities from Peptic Ulcer Disease in 2020, accounting for 0.39% of all deaths, according to the most recent WHO data. The excessive secretion of gastric acid into the stomach lumen, which results in acid-related illnesses, is caused by the gastric proton/potassium pump (H+/K+-ATPase), a phosphoenzyme that is resting and concentrated in the parietal cells. As a result, this enzyme is specific to parietal cells and is seen as a good validated hit for anti-ulcer drugs because proton pump inhibitors decrease stomach acid secretion by inhibiting the enzyme's activity. Research on the molecular docking of 51 after the compounds found in the ethanolic extract of Chromolaena odorata were processed, the compounds' docking scores were displayed in Table 1. According to the outcome, the docking scores are between -4.8 and -8.4 kcal/mol. By completely flooding the binding site in the target protein, all of the compounds were found to substantially block the H+/K+-ATPase enzyme. Furthermore, the images of the optimal low binding energy (high binding energy values) for the docked ligands are shown in Figures 2, 3, and 4. With the highest docked score of −7.1 kcal/mol, Oxacyclotetradecane-2,11-dione, -

methyl-, and ligand 3-(Azepan-1-yl)-1,2-benzothiazole 1,1-dioxide are the most powerful among the ligands that were docked with the enzyme H+/K+-ATPase. The docking analysis outcome Additionally, c shown that the energy value of 3-(Azepan-1-yl)-1,2-benzothiazole 1,1-dioxide is lower (high binding energy value) of -8.4 kcal/mol in contrast to the binding energy value of -8.0 kcal/mol for omeprazole, the anti-ulcer medication of choice.

In addition, four alkyl interactions and seven Van Der Waals interactions with the amino acid residues in the active site were observed. These hydrophobic interactions suggested that the compound binds deep within the active site. The compound 3-(Azepan-1-yl)-1,2-benzothiazole 1,1-dioxide exhibits hydrogen interactions with TYR799, ALA335 and pi-sigma interactions with ALA335 which it uses to stabilize its aromatic nucleus. The second greatest binder, oxacyclotetradecane-2,11-dione, -methyl-, was shown to exhibit hydrophobic interactions. At residues PHE 818 and ALA 144, pi-alkyl interactions have been found. Van der Waals interactions with seven residues of amino acids were the next type of interaction. Additionally, the interactions of Omeprazole, the control chemical, were discovered. interacted through hydrogen bonding with CYS813, ASN138, and it also possessed pi There were 16 van der Waals interactions with residues at the active site in addition to interactions with ASP132, TYR799, and ALA335 that were noted. The explanation for the high binding energies found in the results can be found in the compounds' visible interactions.

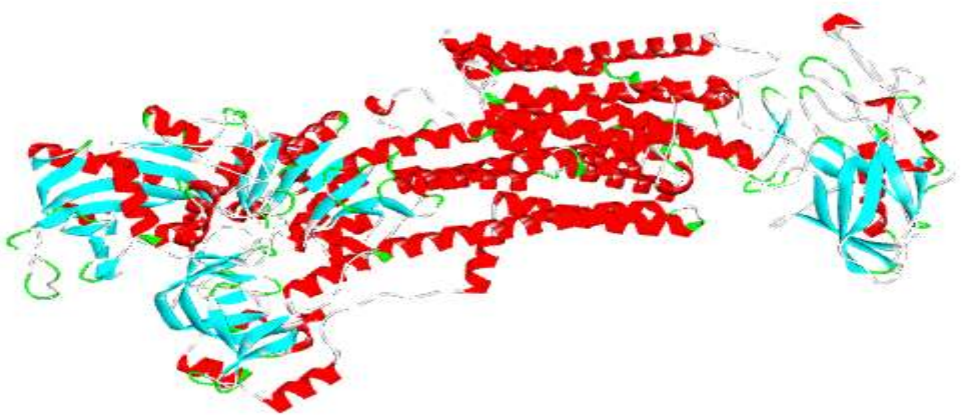


Figure 1: Crystal structure of the gastric proton pump. (PDB **ID: 7w47)**

Table 2: Binding energies of the compounds on the protein target

GC-MS s/n	PK#	Compounds	Pubchem id	Binding Energy kcal/mol
Cntr		Control (Omeprazole)	4594	-8.0
47	25a	3-(Azepan-1-yl)-1,2-benzothiazole 1,1-dioxide	535203	-8.4
23	11a	Oxacyclotetradecane-2,11-dione, -methyl-	543408	-7.1

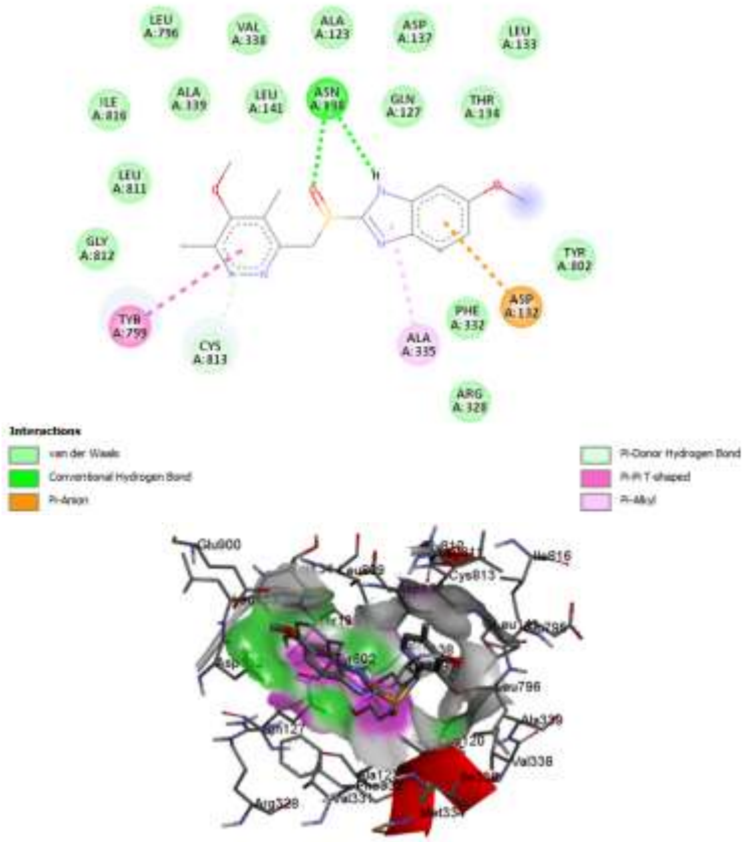


Figure 2: 2d and 3d interaction of the gastric proton pump with the control Omeprazole.

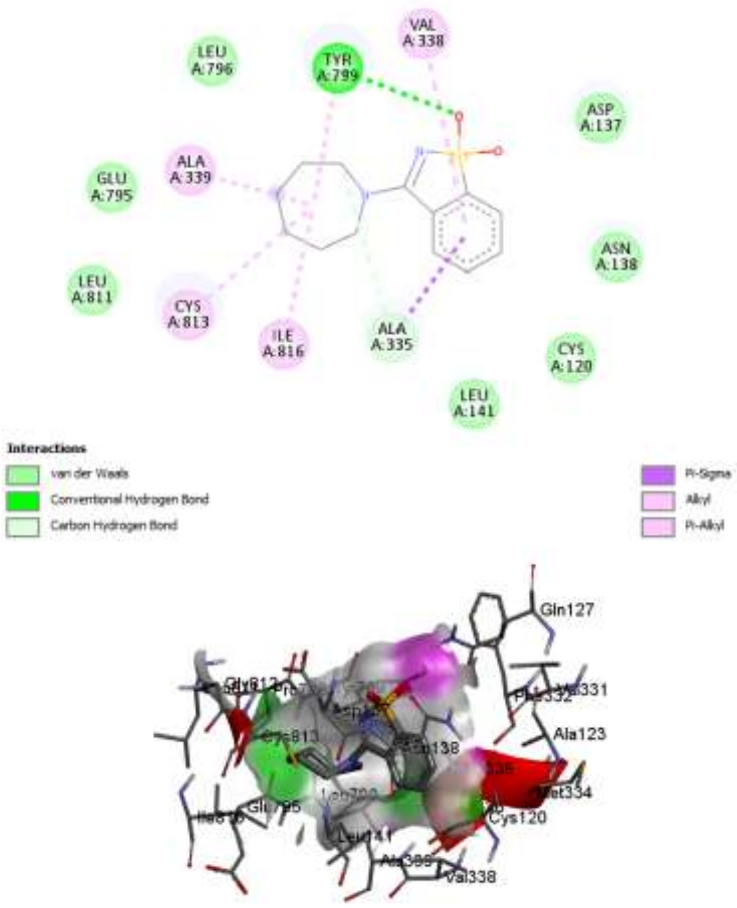


Figure 3: 2d and 3d interaction of the gastric proton pump with 3-(Azepan-1-yl)-1,2-benzothiazole 1,1-dioxide

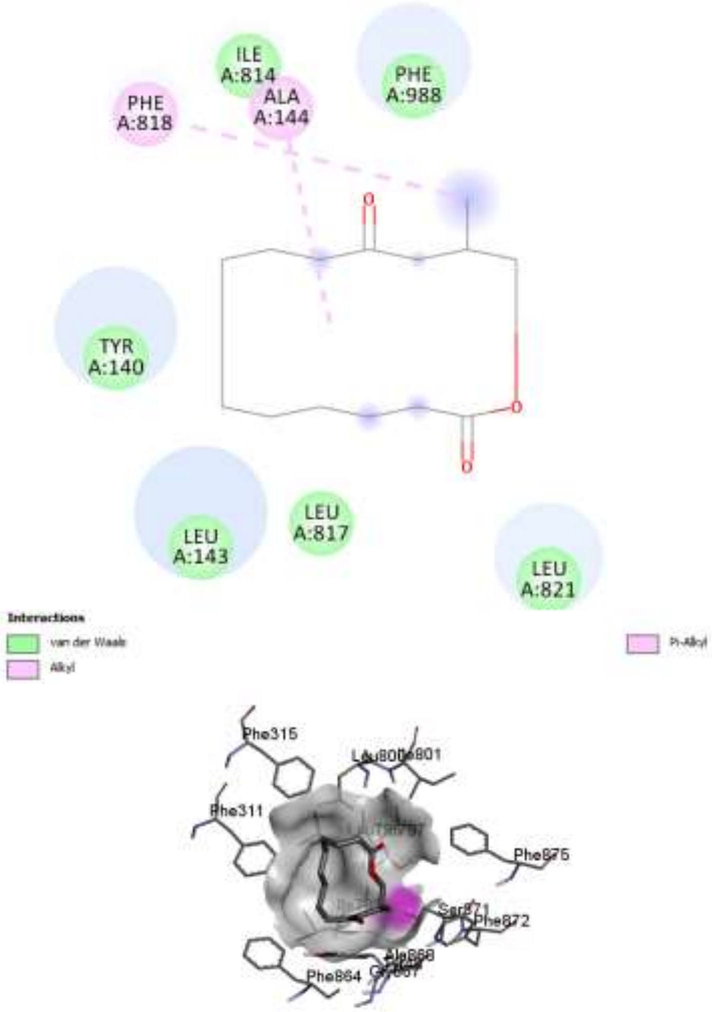


Figure 4: 2d and 3d interaction of the gastric proton pump with Oxacyclotetradecane-2,11-dione, -methyl-

CONCLUSION

The ethanolic extract of Chromolaena odorata has been shown to suppress the gastric proton pump, indicating that it is a particularly effective herbal supplement for the treatment of stomach ulcers. The ethanolic extract of the sample revealed the presence of fifty-one (51) chemicals according to the GCMS results. When the extracts were subjected to in-silico molecular docking, only the two cyclic compounds in the GC-MS result had inhibitory characteristics against the gastric proton/potassium pump (H+/K+-ATPase) that were similar to those of the widely used synthetic medication omeprazole. Given that 3-(Azepan-1-yl)-1,2-benzothiazole 1,1-dioxide has a better docking score (−8.4 kcal/mol) than omeprazole (-8.0 kcal/mol), it is likely that the plant has superior stomach proton pump inhibitory capabilities.

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