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IDENTIFICATION OF ANTIULCER ACTIVITY BY INSILICO METHOD IN SELECTED MEDICINAL PLANTS

R. SHARMILA[1*], S. P. RAJA RAJESHWARI[1], T. I. REVATHY[1], R. SARONA[1], M. SAPPANA SHREE[1], A. PREETHI[1], N. PRASANTH[1] AND K. AKILA[2]

[1]Biotechnology Department, Bishop Heber College, Bharathidasan University, Trichirappalli, Tamilnadu, India.
[2]Biotechnology Department, Bishop Heber College, India.

AUTHORS' CONTRIBUTIONS

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

Ulcer occurs when stomach acid damages the lining of the digestive tract caused by the bacteria Helicobacter pylori. Many pharmacological activities such as antiulcer activity can act against ulcer. Medicinal plants like Mimosa pudica and Vachellia nilotica has the antiulcer activity in a wide range. To study the antiulcer activity in medicinal plants using insilco studies by comparing the phytocompounds of plants with histamine 2 receptor as a binding protein, which is present in the stomach lining of homosapiens. Histamine 2 receptor was modelled using Swiss model and the ligand structures are obtained from PUB-CHEM, viewed easily via PYMOL. All the phytocompounds showed good binding energy with modelled protein on the docking methodology. Specifically ascorbic acid exhibited the lower binding energy of value -3.24 kcal/mol, indole and catechin shows highest binding energy of value -4.99 kcal/mol and -4.98 kacl/mol respectively. The results can be useful for the design and development of phytocompounds having better inhibitory activity against several types of ulcer.

Keywords: Histamine 2 receptor; homology modeling; docking; mimosins; binding interactions.

1. INTRODUCTION

Histamine plays a vital role in maintaining the secretion of gastric acid [1]. Histamine can control the restorative effect on smooth muscles from various organs such as respiratory tract, gut and shock like symptoms when injected into animals [2]. Histamine is one of the members of G-protein coupled receptor (GPCR)'s because it shows physiologic action by binding to the super family of seven transmembrane GPCR's [3]. H1, H2, H3 Histamine receptors, where histamine can bind and it can be distinguish by then selective antagonist drugs [4]. Histamine 2 receptors controls the diverse cellular functions, inclusive of innate and adaptive immune responses [5]. Ranitidine is an antagonist of H2 receptor-mediated responses to histamine and it can inhibits the gastric acid secretion in racks [6]. Drugs like ranitidine, nizatidine; famotidine shows great importance for gastric acid regulation [7]. The main function of H2R is to antagonise block H+secretion in the parental cells present in stomach [8]. Among the different types of Histamine receptors (H1R, H2R, H3R and H4R) the H2R is the G protein coupled receptors (GPCR) that can be mostly used in study of human cells [9]. Ulcer occurs when stomach acid damages the lining of the digestive tract. There are many types of ulcer such as mouth ulcer, oesophagus ulcer, peptic ulcer and genital ulcer. Among these types of ulcer, peptic ulcer is very common and it was seen among many people [10]. There are very important types of peptic ulcer are "gastric ulcer" and "duodenal ulcer". Gastric

**Corresponding author: Email: sharmilabiotech81@gmail.com;*

ulcers are open sores that develop on the inside lining of your stomach and the upper portion of your small intestine. The most common symptom of a gastric ulcer is stomach pain aand other symptoms such as nausea, vomiting and weight loss [11]. Duodenal ulcers are occurs at the beginning of small intestine. It may cause severe burning sensation in upper abdomen. Duodenal ulcers may found in children and especially it affects males [12]. Mimosa pudica is used to have the activity of antibacterial, antivenom, antifertility, anticonvulsant, antidepressant and aphrodisiac and also for other pharmacological activities. The common name of Mimosa pudica is touch-me-not plant. This plant may also for other used for the treatment of urogenital disorders. The leaves and stems of this plant contains an alkaloid mimosine. The leaves also contain mucilage and the root contains tannins [13]. This plant found to have many phytochemical componds like tannins, flavonoids, Saponins, gums, mucilage, Quercitin, glycosides, which have been selected to investigate antiulcer activity. It is highly used for its hepatoprotective activity [14]. Out of several species, Vachellia nilotica is one of the species that has been effectively utilized in folk medicine [15]. It is naturally widespread in the drier areas of Africa, from Sengal to Egypt and down to South Africa, and in Asia from Arabia eastward to India, Burma and Sri Lanka. The largest tracts are found in Sind. Tender leaves should be used for (after crushing) gargle and application to mouth ulcer, throat pain, cleaning mouth, prevent gum bleeding and tighten teeth [16]. Juices of tender leaves or paste applied for redness of eye and eye swelling. It is estimated that there are roughly 1380 species of Acacia worldwide.2 Acacia species— commonly known as Baboo [17]. The phytochemicals contribute chemically to a number of groups among which are alkaloids, volatile essential oils, phenols and phenolic glycosides, resins, oleosins, steroids, tannins and terpenes [18]. The bark, root, gum, leaves and flowers have found use for skin diseases, diarrhoea, dysentery, cough, diabetes, eczema, wound healing, burning sensation [19]. It has been recognized worldwide as a multipurpose tree National Academy of Sciences [20].

2. MATERIALS AND METHODS

2.1 Sequence Alignment and Structure Prediction

The amino acid sequence of histamine 2 receptor (HRH2) (UNIPORT ACCESSION NUMBER: P25021) from the species homosapiens was retrieved from the UniProtKB database [21]. A BLAST (BASIC LOCAL ALIGNMENT SEARCH TOOL) search was performed to select the template. The three-dimensional protein structure was generated using Swiss model, because of the absence of crystal structure of histamine 2 receptor. The respective template was retrieved from protein databank (PDB) [22]. When choosing the templates, it is important to consider the sequence identity. When these parameters are high the resulting model would be sufficiently good to allow structural and functional research. The amino acid sequence P25021 was obtained from Uniprot KB database are subjected to homology modelling using Swiss Modeller. Swiss modeller is an online tool, which would choose template automatically from PDB and generate 3-D protein based on template structure. PubChem is a public chemical information archive developed and maintained by the U.S. National Institutes of Health (NIH). PubChem collects chemical substance descriptions and their biological activities from hundreds of data sources and provides them to the public free of charge. With receiving millions of requests from tens of thousands users per day, PubChem serves as a key resource for biomedical

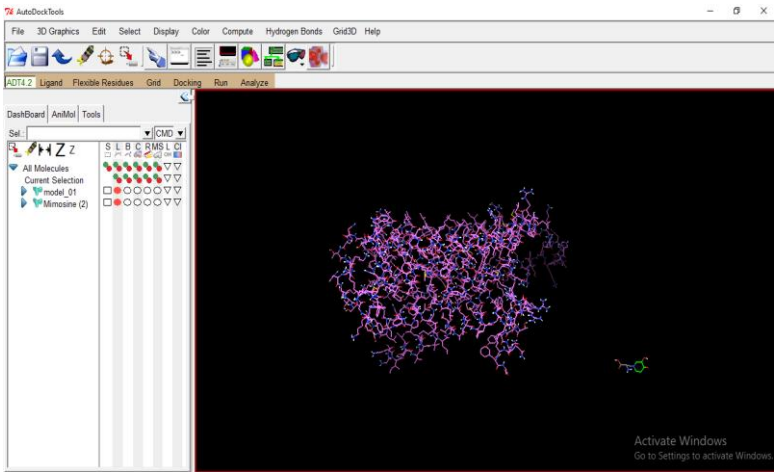


Fig. 1. Selection of ligand to interact with target for docking

science communities in many areas, including cheminformatics, chemical biology, medicinal chemistry, and drug discovery. Detailed information on PubChem is given elsewhere [23,24,25]. The structure of protein and ligand can be viewed easily through PYMOL.

2.1 Docking Methodology

The active sites prediction was carried out using Castp. Ten different phytochemicals and Histamine 2 receptor were selected form molecular docking. Molecular docking studies were performed on all the natural compounds separately by using Autodock4.2. Using the Lamarckian genetic algorithm (LGA) , the gdf file was generated. Initially, the modelled Histamine 2 receptor protein was loaded and hydrogens were added before saving it in PDBQT format. Later the ligand was loaded to interact with target. The grid parameters were selected and calculated using Autogrid. Run the autodocks to gain word file, which provides the binding energy of protein–ligand docking.

3. RESULTS

3.1 Homology Modelling and Model Evaluation

The present study reports that the template protein (PDB ID: 7bts) having high degree of homology with P25021 protein was used as a template with good atomic resolution of its crystal structure. The target sequence of Histamine 2 receptor (UNIPROT accession number: P25021-Human) bearing 289 aminoacid residues was retrived from the uniprot protein sequence database with Accession No.P25021. Using BLAST , PDB ID 7bts was identified and selected as template to predict the model. The structure was modelled using Swiss Modeller. The modelled target has a single chain A on it.

3.2 Molecular Docking Results

In the context of molecular modelling, docking is an important method can predict the preferred orientation of one molecule to another when bound to each other to form a stable complex. Knowledge of the preferred orientation, in turn, may be used to predict the strength of association or binding affinity between two molecules. All docking were performed as blind dockings (blind docking refers to the use of a grid box that is large enough to encompass any possible ligand – receptor complex) using Autodock. In order to obtain more information concerning the energetically favourable docked images and the binding sites, the binding posses of the ligands with a target were shown visually in fig respectively.

All the phytocompounds showed good binding energy with modelled protein. Specifically ascorbic acid exhibited the lower binding energy of value -3.24 kcal/mol indole and catechin shows highest binding energy of value -4.99 kcal/mol and -4.98 kacl/mol respectively. The phytochemicals with their corresponding interactions and binding energies are shown in the following Table 1.

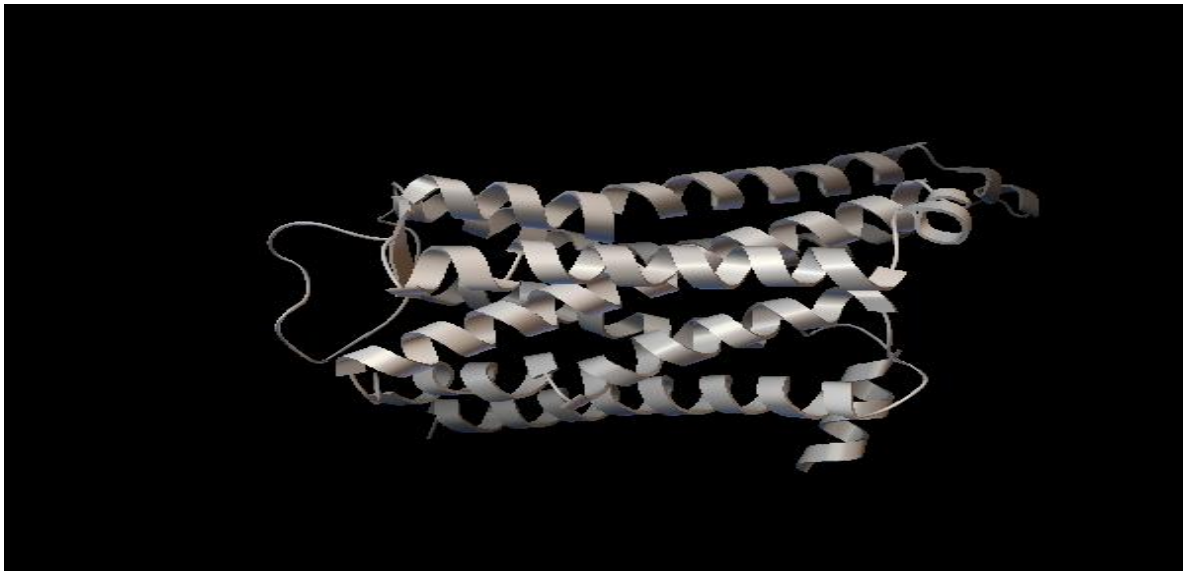


Fig. 2. Cartoon model of predicated Histamine 2 receptor

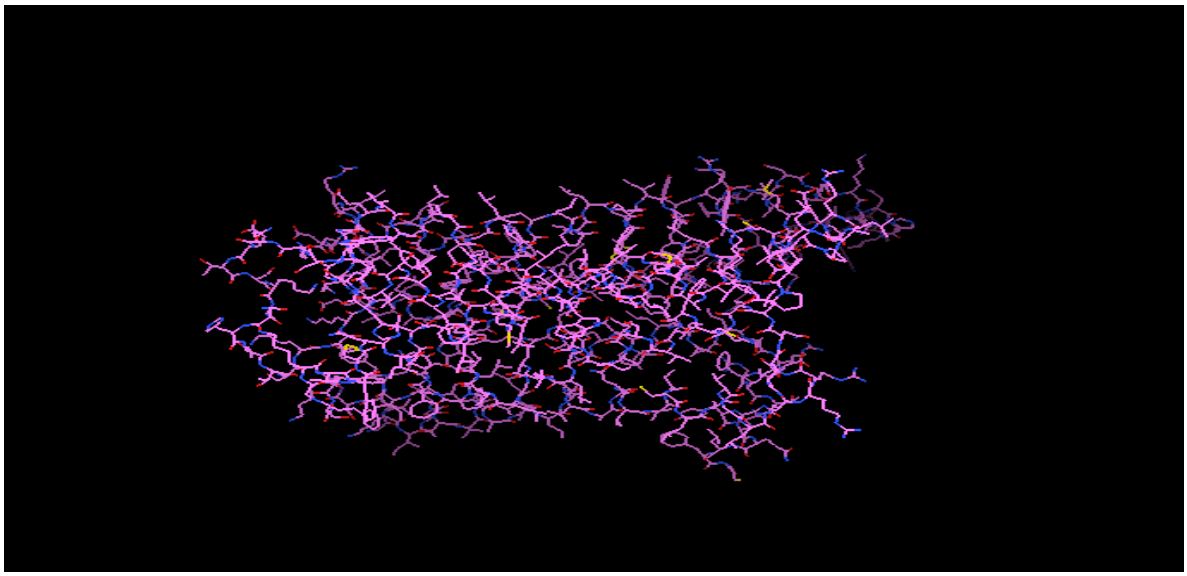


Fig. 3. Autodock structure of Histamine 2 receptor

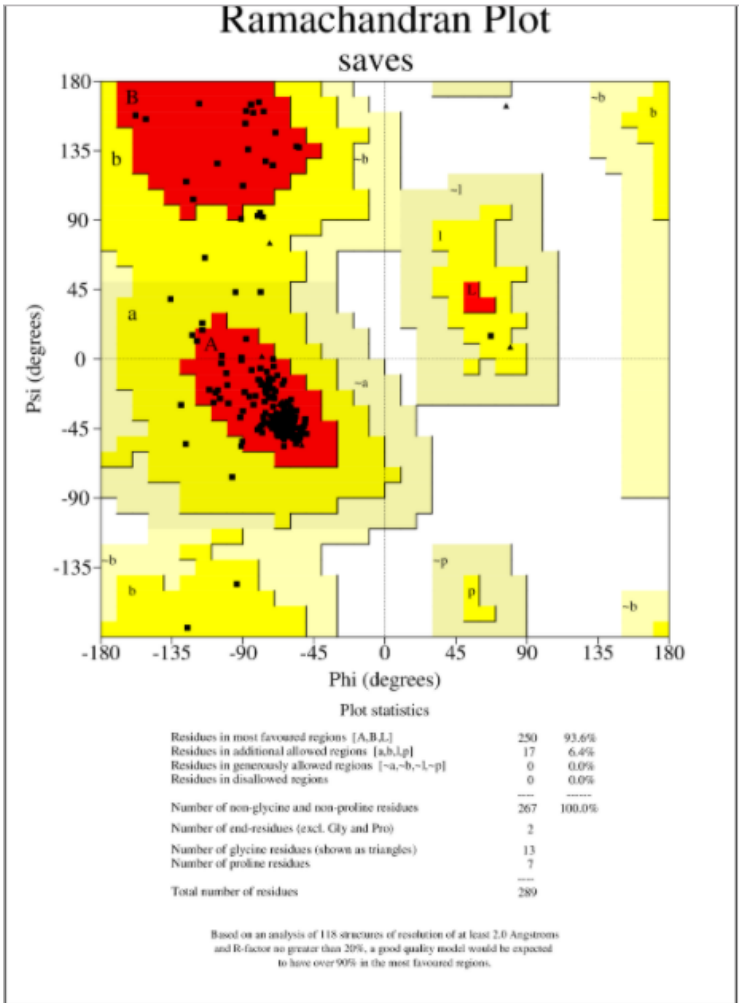
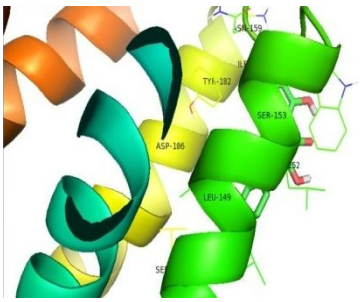


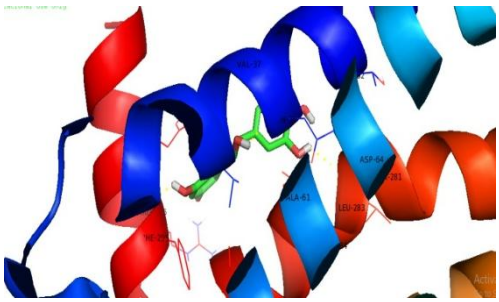
Fig. 4. Ramachandran Plot of modelled protein Histamine 2 Receptor showing ~93.6% residues in most favored region

Table 1. The phytochemicals with their corresponding interactions and binding energies are shown

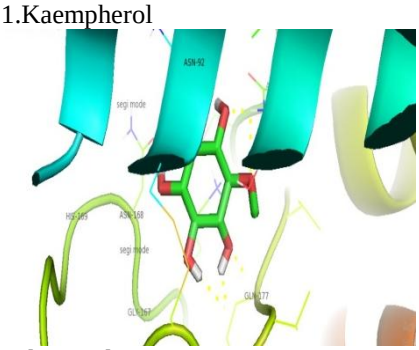
Si.no	Compounds name	Interacting amino acids	Binding energy (kcal/mol)
VACHELLIA NILOTICA			
1.	Kaempherol	ASN-179,ASN-159,LEU-152,TYR-182,ASP-186,ILE-145,ILE-154,SER-146, VAL-181,LEU-149,SER-153	-4.55
2.	Catechin	ASN-280,SER-281,LEU-283,ASN-284,THR-32,ASN-36	-4.98
3.	Ellagic acid	NO INTERACTIONS	NO BINDING ENERGY
4.	d-pinitol	GLY-167,ASN-168,HIS-169,ASN-159,LYS-175,GLN-177,LYS-166,ILE-154	-4.72
5.	Glucopyranoside	VAL-176,LYS-175,LYS-88	-3.40
MIMOSA PUDICA			
1.	Ascorbic acid	ASN-159,SER-160,VAL-178,LYS-166,GLN-177,GLY-167,ASN-92,PHE-90,LYS-175	-3.24
2.	Indole	ARG-296,THR-297	-4.99
3.	Mannosamine	VAL-176,LEU-274,ALA-76,LEU-72,GLN-79,CYS-174,TRP-84,TYR-94,TYR-94,TRP-84,GLN-79	-4.48
4.	Calcium oxalate	NO INTERACTIONS	NO BINDING ENERGY
5.	Mimosine	NO INTERACTIONS	NO BINDING ENERGY



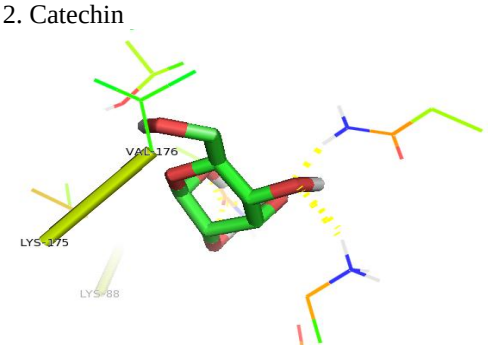
1.Kaempherol



2. Catechin

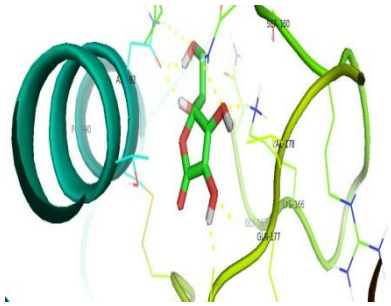


4.d-pinitol

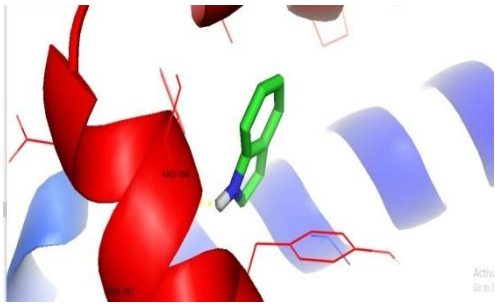


5.Glucopyranoside

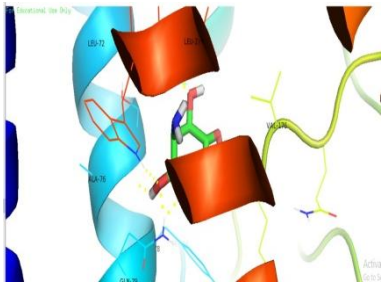
Plate 1. ***Vachellia nilotica***



1.Ascorbic acid



2. Indole



3.Mannosamine

Plate 2. Mimosa pudica

4. DISCUSSION

Peptic ulcer disease is a term applied for gastric and duodenal ulcers. It is one of the ubiquitous disorders of gastrointestinal tract. Peptic ulcers are the result of imbalance between 'offensive (acid, pepsin, and H. pylori) and defensive factors mucin, prostaglandin, bicarbonate, nitric oxide and growth factors)' [26]. Current prevalent strategy for combating peptic ulcers includes reducing gastric acid production and promoting gastric mucosal growth. Prevalent drug therapy for management of peptic ulcers includes use of histamine H2 receptor blockers, proton pump inhibitors, antacids, prostaglandin analogs and anti-H. pylori agents [27]. Results are revealed that among the ten phytochemicals chosen from selected medicinal plants, seven of those were showing protein- ligand molecular docking with interacting amino acid. Among the seven phytocompounds maximum binding energy is obtained on ascorbic acid (-3.24 kcal/mol) followed by glucopyranoside (-3.40 kcal/mol). But three of those compounds namely ellagic acid (Vachellia nilotica) and mimosine, calcium oxalate (Mimosa pudica) were not shown any binding interaction. The following graph shows the binding energies of seven compounds, in a linear format.

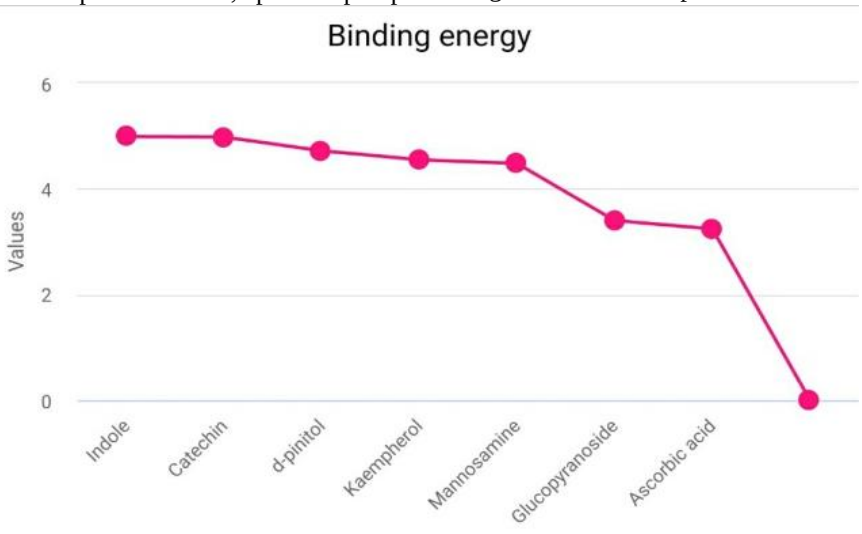


Fig. 5. Binding energies of phytochemicals

5. CONCLUSION

Molecular docking stimulation study was undertaken to investigate the binding mechanism of Histamine H2 receptor and ligands derived from phytocompounds of plants to enable the finding of potential antiulcer activity. The results indicate that the binding specificity of each ligand is varying in protein. This molecular docking has revealed good binding energy interactions. Our result shows lower binding energy to the phytochemicals such as glycopyranoside and ascorbic acid at the value of -3.4 and -3.24 respectively. The results of our present study can be useful for the design and development of phytocompounds having better inhibitory activity against several types of ulcer. It can be further validated in wet lab studies for its proper function. These predictions will essentially leads to effective treatments.

DISCLAIMER

The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

CONSENT AND ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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