ejpmr, 2023,10(9), 375-378

SJIF Impact Factor 6.222

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

Research Article

ISSN 2394-3211

EJPMR

MOLECULAR DOCKING STUDIES OF GASTROPROTECTIVE ACTIVITY OF GERMINATED FENUGREEK SEEDS

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Article Received on 22/06/2023 **Article Revised on 12/07/2023** **Article Accepted on 02/08/2023**

ABSTRACT

Gastric ulcer is a very common disorder which occurs due to imbalance between aggressive and protective factors. Today herbal medicines are in medical trend due to their low cost and fewer side effects. The current study was performed to evaluate the gastro-protective activity of fenugreek seeds and ranitidine by molecular docking. In this, study two constituents of Fenugreek i.e., quercetin, kaempferol and ranitidine were docked with protein PDB ID-6M9T.

KEYWORDS: Fenugreek, Chemical constituents, Ranitidine, Molecular docking.

INTRODUCTION

Gastric ulcers (GU) is a very common disease which is characterize by the open sores in the mucosal lining of the stomach and may occurs due to the imbalance of defensive and injurious factors of gastric mucosa such as Helicobacter pylori (H. pylori) infection, high consumption of nonsteroidal anti-inflammatory drugs such as such as ibuprofen, naproxen and indomethacin, drinking, smoking, and over stress The symptoms may range from mild abdominal discomfort to gastrointestinal perforation and bleeding [Mousa et al., 2019; Wannasarit et al., 2020].

The current treatment of peptic ulcers consists mainly of anti-secretory medications, such as histamine H_2 receptor antagonists and proton pump inhibitors (PPIs) and cytoprotectors such as sucralfate and bismuth salts. In cases of *H. pylori* infection some antimicrobials are prescribed for the treatment but these medications are costly and produce adverse effects such as bleeding and perforation (Serafim et al., 2020). From this perspective, the gastroprotective and antiulcerogenic potential of many medicinal plants and their isolated constituents has been investigated to develop complementary treatments to alleviate the severity of ulcerative diseases and prevent recurrence episodes.

Herbs are multi-ingredient and multi-target in treating diseases, and their pharmacodynamic ingredients and molecular mechanisms are often difficult to identify. With the advancement of network technology and bioinformatics, computer-aided identification methods of drug-target interactions represented by network pharmacology and molecular docking have been developed to provide support for the research of herbs with complex action mechanism. They greatly reduce the initial time and cost of experimental determination of drug-target interaction and improve the chances of finding ideal drug candidates (Zhou et al., 2022).

From many literatures it was found that quercetin is a known and very active constituent of plant which posses anti-ulcer, anti-cancer, antioxidant, and anti-inflammatory activities. It also cause apoptosis and inhibit the growth of various cancer cells. A study explains that quercetin produces anti-Cancer action in Xenograft Models with EBV-Associated Human Gastric Carcinoma (Lee et al., 2016). Another study explains that quercetin with melatonin act as an antiulcer agent against Indomethacin induced gastric ulcers due to their significant antioxidant, anti inflammatory and anti-apoptotic action (Abdel-Tawab et al., 2020).Rutin is also an important bioflavonoid which is found in tomato, orange, carrot, sweet potato, black tea and apple peels. Rutin is also known for their different pharmacological action such as neuroprotective, anti-allergic, anti-ischaemic, and anti-inflammatory activity due to its antioxidant action. A study showed that rutin is very effective for gastric ulcer lesions (Abdel-Raheem et al., 2010).

Molecular docking is one of the widely adapted methods to predict the binding affinities between the ligand and the target protein and further the lead optimization. Additionally, the molecular docking imparts knowledge on the interactions at the atomic level [Wang et al., 2016] and predicts the ideal binding mode [Rampogu et al., 2018]. Molecular docking, generally evaluates the

binding conformations, its orientation, and the accommodation of the small molecule at the active site of the proteins binding site and are read as scores [Meng et al., 2011]. The molecular dynamics simulation imparts knowledge on the nature of the small molecules at the proteins binding pocket thereby affirming the appropriate binding modes. The identified Hits that have demonstrated a higher dock score than the reference compounds or the known drugs, exhibiting the interactions with the key residues complemented by stable molecular dynamics simulation results, are considered the most promising candidate compounds (Rampogu et al., 2018).

Many Studies exhibited that Endogenous PGs affects a number of gastric functions to help mucosal defense of the stomach. PGE2 modulate an important function that is secretion of mucus/HCO3 secretion via receptor such as EP4/EP1 receptors and that's how it inhibited acid secretion or motility via EP3 or EP1 receptors, respectively, according to previous studies s [Araki et al., 2000], [Takeuchi et al., 2001], [Yokotani et al. 1996], By inhibiting acid secretion at parietal cells directly and histamine release at enterochromaffin-like (ECL) cells indirectly, PGE2's acid-inhibitory effect was mediated in two different ways by EP3 receptors. In this Molecular docking study The Protein Data Bank (PDB) repository was used to obtain the prostaglandin E2 receptor's crystal structure (PDB ID: 6M9T). [Audet et al., 2019]

Molecular docking studies

Molecular docking was executed independently for ulcer. The ligands along with their Protein (PDB ID-6M9T) was obtained from the RCSB protein data bank were docked to assess their binding affinities. It was interesting to note that ranitidine has generated a lower dock score while quercetin produced a higher dock score as compared to their respective reference compound.

Molecular dockscore between the drug targets and the compound (table 2).

The interaction of the ligands with the proteins was evaluated with the key residues located at the active site. The reference compound ranitidine was seen to form a hydrogen bond with the NH atom of TYR A: 46 residue, an N7 atom with a bond length of 5.382 A (angstrom), PHE A:182 form the pie-pie bond with a ligand molecule. VET was found to interact with the protein by forming H-bonds. The O-atom of the ligand has interacted with the ASN-48 with a bond length of 7.194 A(). The H-atom of the ligand has also interacted with GLN-262.

Quercetin was also found to interact with the protein by forming hydrogen H-bonds with the OH-atom interact with various protein as ALA:27 and SER A:28, the another H-bond of the ligand show interaction with ARG-A:24 and CYSA:32 having a bond length of 3.262.

Kaempferol was also found to interact with the protein by forming an h-bond with the GLUA:6

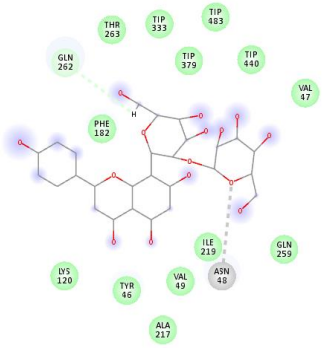

Figure 1: VET interaction with protein amino acids.

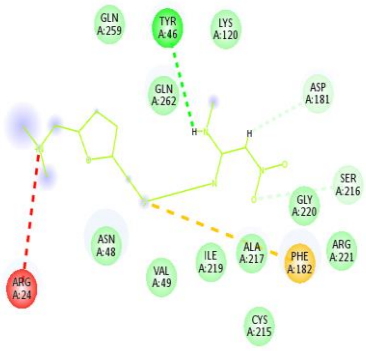

Figure 2: reference compound Ranitidine.

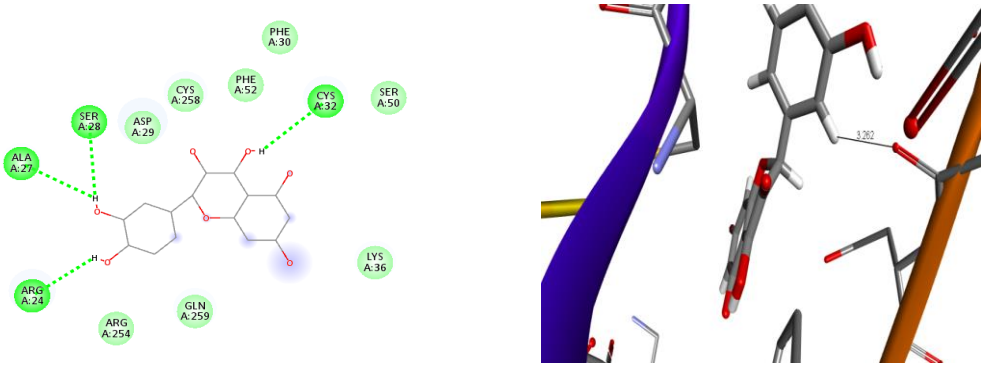

Figure 3: Quercetin interaction with amino Acids and Their bond length.

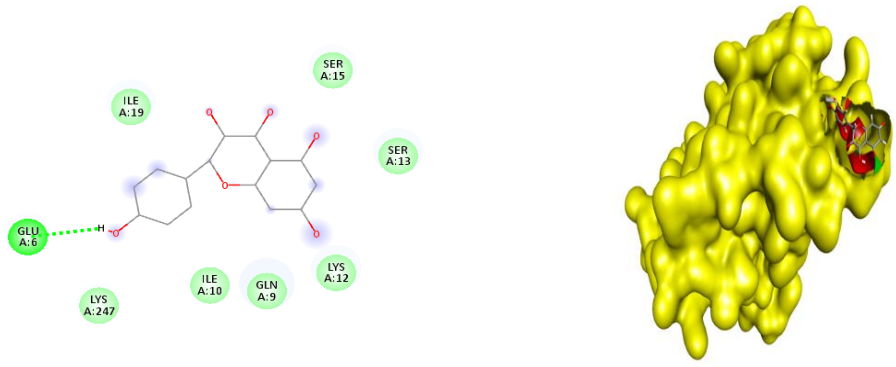

Figure 4: Kaempferol interaction with amino Acid and Their surface cluster structure in which ligand is docked.

Binding free energy analysis:

Binding free energies are computed that inspect the protein fluctuation and ligand conformations thereby ensuring a suitable positioning of the ligand within the binding site. The MM/PBSA calculations have produced a favorable delta G ranging between -10 to 100 KJ/mol for gastric ulcers. Furthermore, the average binding energy produced by reference was -7.80KJ/mol. The binding free energies were subsequently calculated for Quercetin, VET, and kaempferol protein systems for ulcers. 10 snapshots were evenly extracted and the binding free energies were computed accordingly. The binding energies ranged between -5 to 50KJ/mol, as in Table 2.

Table 1: The molecular interactions between the Compound and The protein.

S. No.	Compound	Bond length	Hydrophobic Interaction
01	Vet	7.194	Gln 262, thr 263, tip333, tip379, tip483, tip 440, val47, ASN48
02.	Ranitidine	5.382	ALA217, PHE 182, GLy 220, SER216, TYR 46, ASP 181, ARG 24
03.	Quercetin	3.62	ALA27, SER 28, CYS 32, ARG 24
04.	Kaempferol	3.72	GLUA:6

Table 2: Molecular dock scores between the drug Targets and The compound.

S. NO.	Name of compound	JDOCKER interaction energy
01	Ranitidine	-7.80
02	Quercetin	7.91
03	VET	8.20
04	Kaempferol	7.37

From the result, it is evident that VET, Quercetin has represented higher JDOCKER interaction energy values than their respective reference compound ranitidine. These results demonstrate that the VET, Quercetin and Kaempferol have stronger binding affinities than the reference inhibitor.

RESULT AND DISCUSSION

Gastric ulcer is a very common disorder that occurs due to an imbalance between aggressive and protective factors. Today herbal medicines are in medical trend due to their low cost and fewer side effects. The current study was performed to evaluate the gastro-protective activity of fenugreek seeds and ranitidine by molecular docking. In this, study two constituents of fenugreek i.e. quercetin and kaempferol and ranitidine were docked with EP3 receptor protein. The interaction of the ligands with the proteins was evaluated with the key residues located at the active site. Binding free energies are computed that inspect the protein fluctuation and ligand conformations thereby ensuring a suitable positioning of the ligand within the binding site. The MM/PBSA calculations have produced a favorable delta G ranging between -10 to 100 KJ/mol for gastric ulcers. The compounds VET, and Quercetin has represented higher JDOCKER interaction energy values than their respective reference compound ranitidine. These results demonstrate that the VET, Quercetin and Kaempferol have stronger binding affinities than the reference inhibitor.

ACKNOWLEDGEMENT

This research work was kindly supported by the faculty of the Department of Pharmacy, Integral university Lucknow & faculty of the Department of Pharmacy Barkatullah University, Bhopal. The author would like to thank their colleague for their support and give valuable time.

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