

In Silico Screening and Evaluation of Some Metabolites from *Momordica charantia* in the Treatment of Peptic Ulcers

D.S.V.G.K. Kaladhar^{1,*}, Akhilesh Tiwari², Shristi Sharma²

Abstract

Peptic ulcers are also called as or duodenal ulcers or gastric ulcers that are open sores generally develop in the lining of the stomach due to food and climatic factors. *H. pylori* infections are potentially the most dangerous and are linked to several diseases like diabetes, cancer, cardiovascular diseases, etc. In the present study, in silico screening and evaluation of some metabolites from *Momordica charantia* like Momorcharin, Momordicin, Metformin, Pioglitazone, Glipizide, Gliclazide and Glibenclamide in the treatment of peptic ulcers has been conducted. Vacuolating cytotoxin autotransporter (VacA) causes ulceration and gastric lesions is interacting with Urease subunit alpha (ure a), Outer membrane protein-adhesin (babA), Acid-activated urea channel (ureI; rapidly enhances the production of ammonia) and Cytotoxicity-associated immunodominant antigen (CagA). CagA is directly interacting with Serine/threonine-protein kinase CtkA and Cag island protein (virD4). Glibenclamide, Glipizide and Momorcharin has shown good results with Vac A and CagA involved in peptic ulcer. The present study has shown that Glibenclamide is found as effective molecule in the control of peptic ulcer.

Keywords: Peptic ulcers, Cag A, Vac A, in silico screening, *Momordica charantia*

INTRODUCTION

Since ancient times, wide varieties of medicinal plants have been used as vegetable and medicine sources, all around the world. One of the plants with combination of vegetable and medicine usage by humans is *Momordica charantia* (*Momordica* species), using as valuable plant for thousands of years. *Momordica charantia* (Figure 1) belongs to the Cucurbitaceae family, commonly known as bitter melon, karela, balsam pear, bitter gourd or kugua [1, 2]. It grows in sub-tropical and tropical regions of the world especially in countries like India, China, Malaya, Thailand, Singapore, Japan, East Africa, Vietnam, Amazon, Brazil, Colombia, Cuba, Ghana, Haiti, Nicaragua, New Zealand, Panama, Middle East, Central and South America [3, 4].

*Author for Correspondence

D.S.V.G.K. Kaladhar

¹Associate Professor and Head, Department of Microbiology and Bioinformatics, UTD, Atal Bihari Vajpayee University, Bilaspur, Chhattisgarh, India

²Research Student, Department of Microbiology and Bioinformatics, UTD, Atal Bihari Vajpayee University, Bilaspur, Chhattisgarh, India

Received Date: March 25, 2021

Accepted Date: March 27, 2021

Published Date: April 30, 2021

Citation: D.S.V.G.K. Kaladhar, Akhilesh Tiwari, Shristi Sharma. In Silico Screening and Evaluation of Some Metabolites from *Momordica Charantia* in the Treatment of Peptic Ulcers. Research & Reviews: Journal of Computational Biology. 2021; 10(1): 5–13p.



Figure 1. *Momordica charantia* fruit.

The leaves, fruit and seeds of *Momordica* species are wealthy, having more number of phytochemicals and may have many health-enhancing effects by having good nutraceutical components [5, 6]. *M. charantia* has been used in many traditional and folk medicines for a long period of time [7]. There are two varieties of *M. charantia* which are being cultivated in India. The first one is *M. charantia* var., *charantia* showing large fruits that are fusiform in shape and second one is *M. charantia* var., *muricata* that shows small round fruits [8]. Fruits of *Momordica charantia* are normally consumed as vegetable in some parts of sub-continental diet since several centuries. The fruits and seeds of *M. charantia* (Figure 2) are traditionally used across India that is showing good medicinal properties like anticancerous, antimicrobial, anti-inflammatory, antioxidant, antimutagenic, antihelminthic, abortifacient, antitumorous, antifertility and antidiabetic [9].



Figure 2. Morphological characteristics of *Momordica charantia*: (A) Unripe Fruits & Seeds; (B) Ripe Seeds

Figure 3 shows the compounds present in *Momordica charantia* like Momorcharin, Momordicin, Glibenclamide, Gliclazide, Glipizide, Metformin and Pioglitazone [10].

It is evident from ancient literature that diabetes is a killer disease that is linked to peptic ulcer especially in age above 30 years that affects humans and is present lifelong. The diabetic patients are mostly prone to develop *H. pylori* infection causing peptic ulcers [9, 11]. Some of the phytochemicals present in *M. charantia* is shown in Table 1.

Table 1. Phytochemicals present in *Momordica charantia*.

Source	Phytochemicals	Properties	Reference
Plant body	Momordenol, momordicine, momorcharins, charine, momordicilin, momordin, gentisic acid, diosgenin, momordinin, charatin, galacturonic acid, momordolol, cryptoxanthin, erythrodil, cucurbitines, elaeostearic, multiflorinol, goyasaponins, cucurbitecins, goyaglycosides, cycloartenols, cucurbitanes, Saponins, fixed oils, glycosides, alkaloids, steroids and proteins, triterpenes	anti-HIV, anti-ulcer, anti-inflammatory, anti-leukemic,	[12]
Seeds	Gultamic acid, leucine, urease, valine, threonine, isoleucine, methionine, phenylalanine	antimicrobial, antitumor and antidiabetic	
Fruit	Charantin, momordicine, polypeptide-p insulin, ascorbigen, palmitic, oleic, stearic, lauric, palmitic, myristic, palmitoleic, linolenic acid, threonine, alanine, aspartic acid, glutamic acid, serine, luteolin, pipelicolic acid, g-amino buteric acid,		

Mechanism of Epithelial Cell Signaling in *Helicobacter pylori*

Two major virulence factors of *H. pylori* are the vacuolating cytotoxin (VacA) and cytotoxin-associated antigen A (CagA) [13, 14]. VacA cleavage product binds to the tyrosine phosphatase receptor zeta (Ptpz) on the outer epithelial cells and the induced signaling leads to the phosphorylation of the G protein-coupled receptor kinase-interactor 1 (Git1) and finally induces

ulcerogenesis (Figure 4). The other virulence factor CagA as effector protein that is mediated through cag T4SS in translocation interacts with the protein tyrosine phosphatase SHP-2 induce MAPK signalling through Ras/Raf-dependent and -independent mechanisms. Deregulation of this pathway by CagA and Vac A may lead to apoptosis.

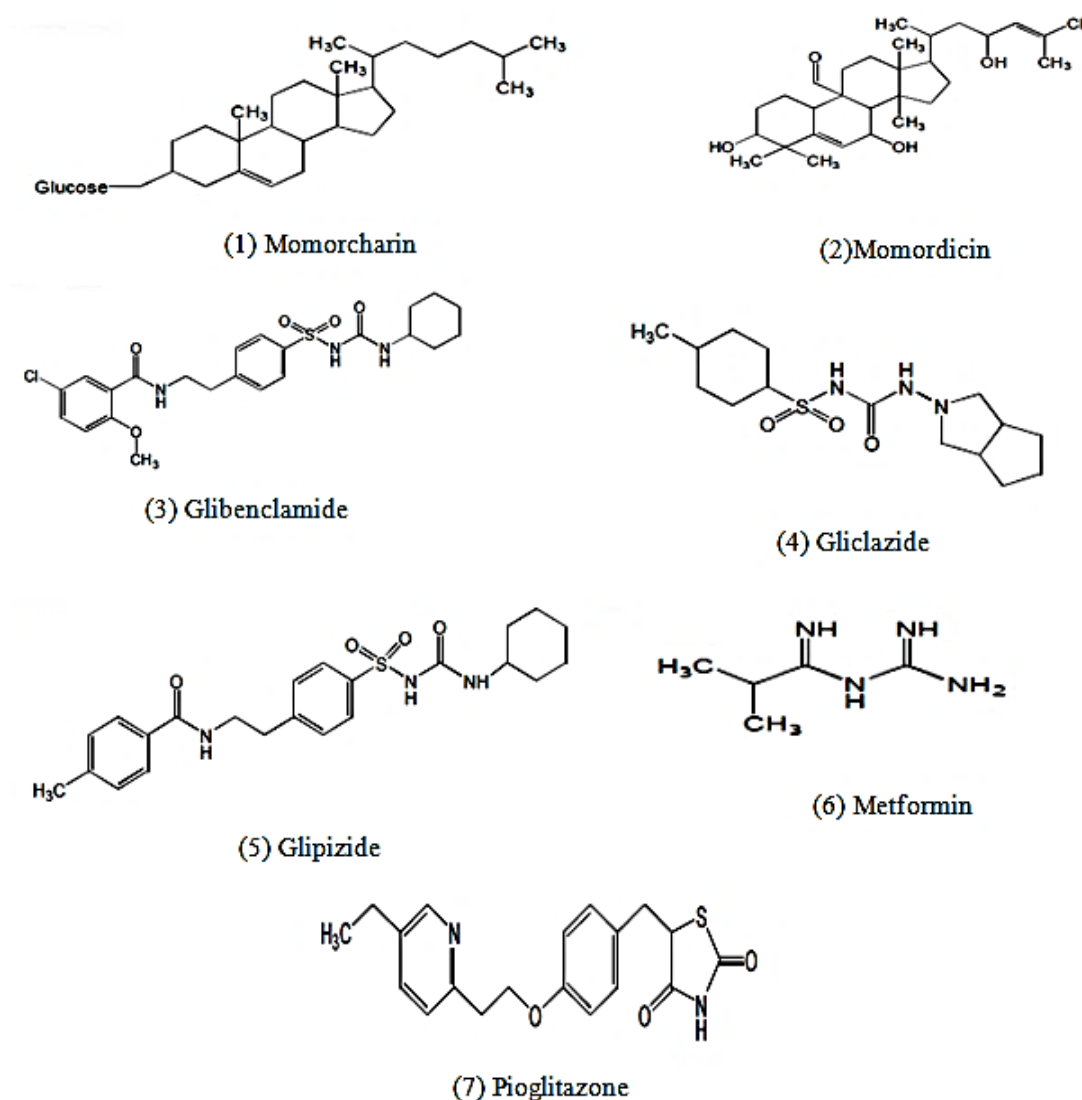


Figure 3. Chemical Structures of compounds present in *Momordica charantia*.

MATERIALS AND METHODS

The following system specifications are used for *in silico* study for screening of molecules:

Processor—Intel(R) Core(TM) i5-7200U CPU@2.50GHz 2.71GHz

Installed RAM—8.00 GB (7.90 GB usable)

System type—64-bit operating system, x64-based processor

Designing and Optimization of Ligands

ACD/ChemSketch v10.02 Freeware software is used for designing and optimization of chemical structures. The Freeware is a drawing package that allows drawing chemical structures including organics, organometallics and polymers. Some selected ligands designed using ACD/ChemSketch v10.02 in the present study is shown in Figure 5. It also includes features such as calculation of molecular properties like molecular weight, density, molar refractivity, etc.

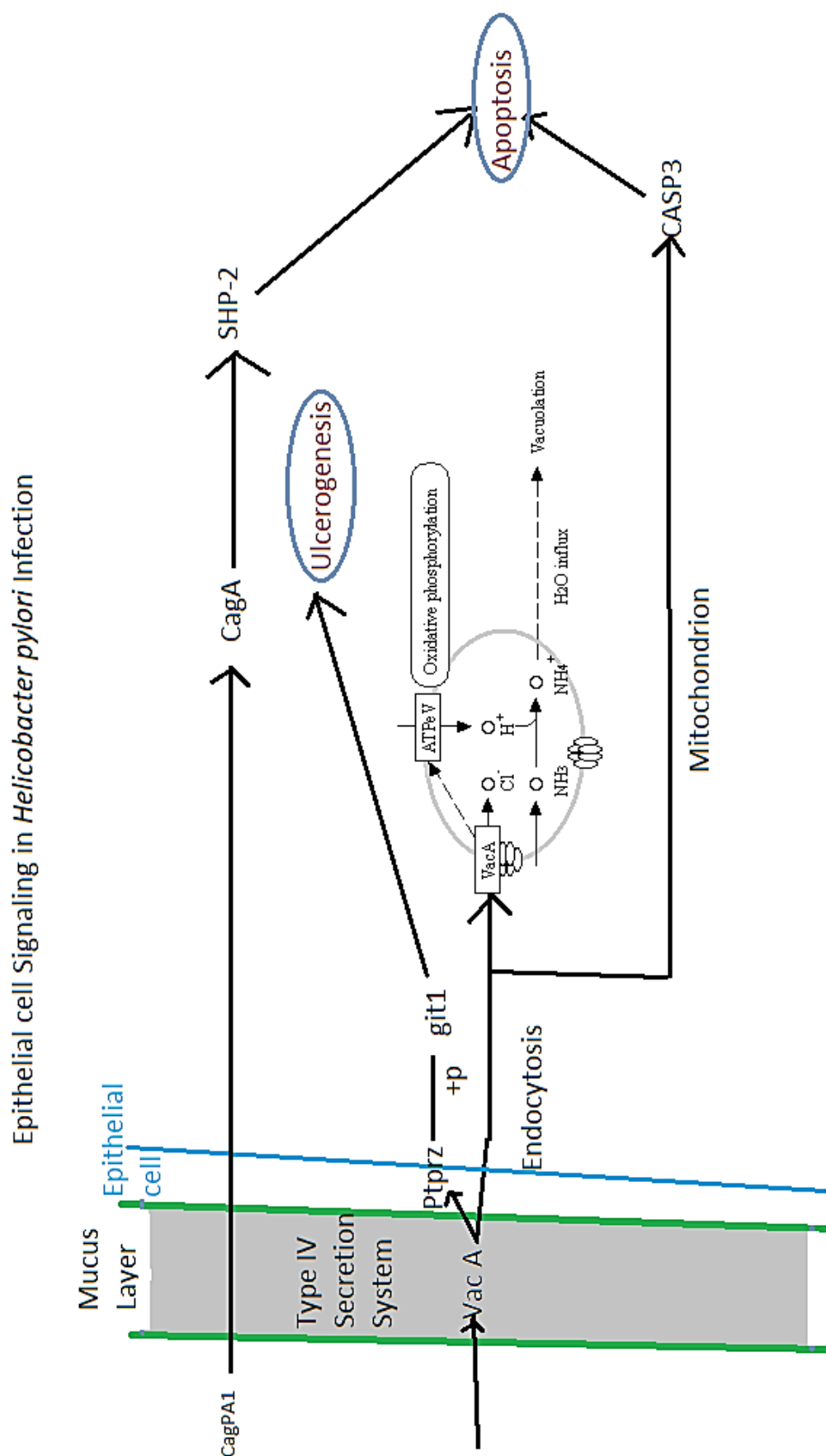


Figure 4. Mechanism of VacA and CagA in epithelial cell signaling in *Helicobacter pylori*.

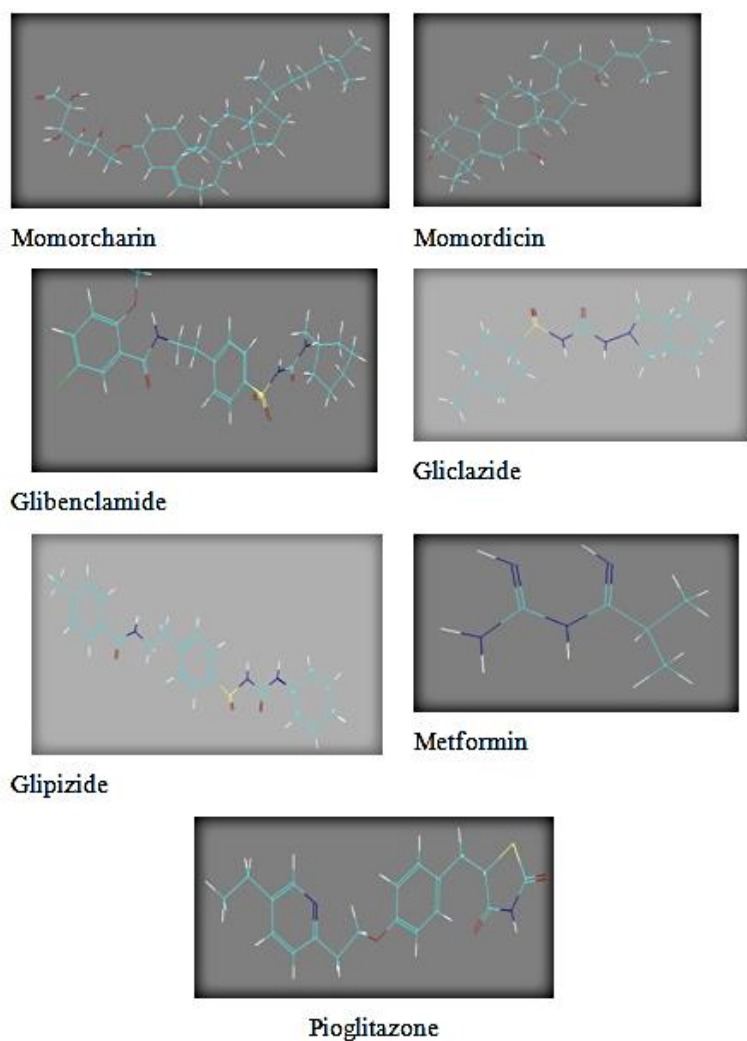


Figure 5. *In silico* designed structures using ACD/ChemSketch v10.02.

Retrieval of Receptors

Crystal Structure of the *Helicobacter pylori* Vacuolating Toxin p55 Domain (2QV3.pdb) and crystal structure of the *Helicobacter pylori* CagA oncoprotein (4DVY.pdb) has been retrieved from protein databank (<https://www.rcsb.org/>) (Figure 6).

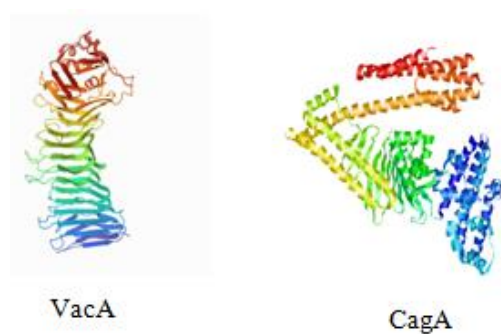


Figure 6. Selected receptors.

Protein-Protein Interactions

Protein-protein interactions for VacA, ctkA and CagA as inputs are submitted to string database and analyzed for the proteins responsible for peptic ulcers.

Receptor and Ligand Interaction

Interaction between Receptor (i.e. VacA protein of *Helicobacter pylori*) and Ligand molecules of *Momordica charantia* (i.e. Momorcharin, Momordicin, Metformin, Pioglitazone, Glipizide, Gliclazide and Glibenclamide) are done by using molecular docking software. The interactions are designed along with calculation of binding energy of molecules for evaluation of highly active molecule that are identified among the selected molecules.

RESULTS AND DISCUSSIONS

Protein-protein interaction of VacA, ctkA and CagA has been shown in Figure 7.

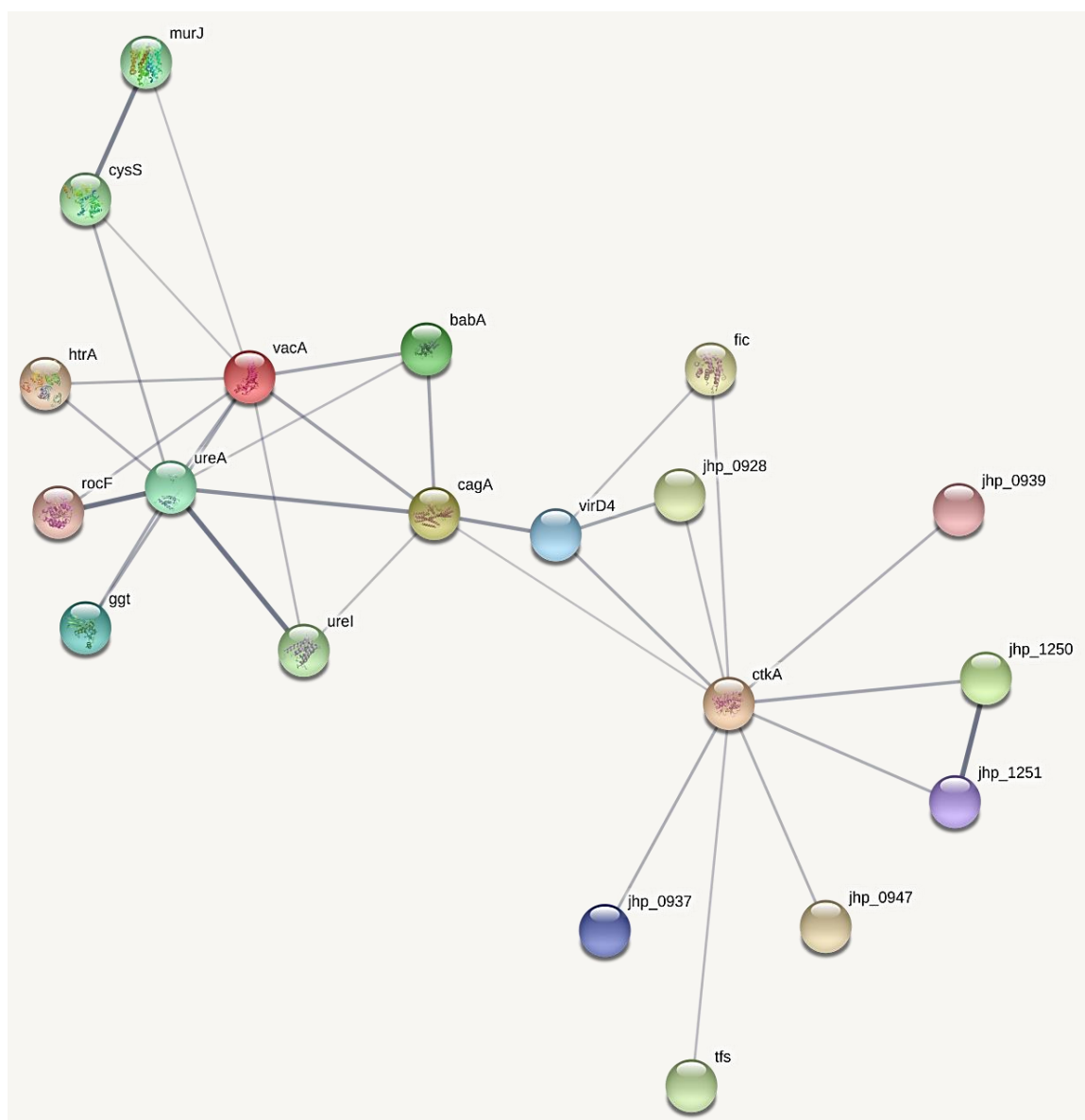


Figure 7. Protein-protein interaction in *Helicobacter pylori* J99.

Vacuolating cytotoxin autotransporter (VacA) causes ulceration and gastric lesions is interacting with Urease subunit alpha (ure a), Outer membrane protein-adhesin (babA), Acid-activated urea channel (ureI; rapidly enhances the production of ammonia) and Cytotoxicity-associated immunodominant antigen (CagA). CagA is directly interacting with Serine/threonine-protein kinase CtkA and Cag island protein (virD4).

Docking Results

Interaction result of binding energy between vacA and cagA receptors with selected Ligand molecules are as follow (Table 2).

Table 2. Docking results of protein and Ligand.

Ligand	VacA	CagA
Glibenclamide	-112.73	-127.82
Gliclazide	-85.17	-96.53
Metformin	-74.33	-72.58
Glipizide	-112.44	-109.97
Momordicin	-95.57	-99.66
Pioglitazone	-93.25	-105.85
Momorcharin	-103.22	-110.93

The active site of VacA with Glibenclamide is shown as H-S-ARG-546, H-S-GLU-548, H-M-SER-597, V-S-ARG-546, V-M-GLU-548, V-S-GLU-548, V-M-THR-549, V-S-THR-549, V-M-GLY-550, V-S-TYR-573 and V-M-SER-597 based on docking results (Figure 8).

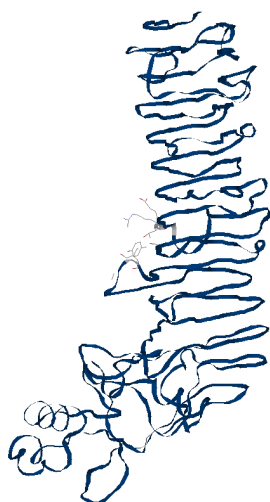


Figure 8. Docking of VacA with Glibenclamide.

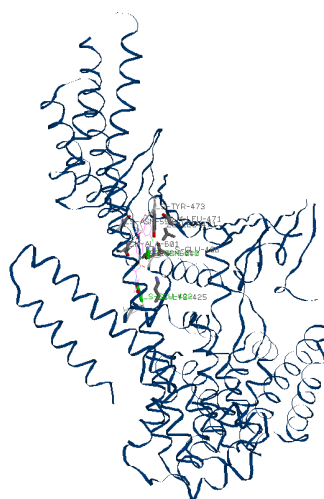


Figure 9. Docking of CagA with Glibenclamide.

The active site of CagA with Glibenclamide is shown as H-S-GLN-410, H-S-GLU-422, V-S-GLU-406, V-S-GLN-410, V-S-GLU-422, V-S-LYS-425, V-M-LEU-471, V-S-LEU-471, V-S-TYR-473, V-S-ASN-597, V-M-ALA-601 and V-S-LYS-604 based on docking results (Figure 9).

Glibenclamide, Glipizide and Momorcharin has shown good results with Vac A and CagA involved in peptic ulcer. Glibenclamide is found as best molecule in the control of peptic ulcer.

Since ancient times, fruits and vegetables from plants have been used as natural medicine [9]. In Turkish folk medicine, Fruits and seeds of *Momordica charantia* L. is using frequently by the people in folk medicine for rapid healing of peptic ulcer and cutaneous lesions [15]. The ethanol extract of the *Momordica charantia* fruits has reported significant activity against HCl–EtOH induced ulcerogenesis in diethyldithiocarbamate-induced ulcer rats and indomethacin-pretreated rats and models [16].

The *cagA* and Vac A production in *Helicobacter pylori* have been reported as major virulence factors causing ulcerogenesis [17]. A useful marker that can be used to understand risk of peptic ulcer disease development is *cagPAI* genes or segments like *cagA* promoter, *cagA*, *cagM*, *cagE*, *tnpA*, *tnpB*, *cagT* and Left End of *Cag* II (LEC) region [18]. Hence, controlling of CagA or VacA proteins in *Helicobacter pylori* can able to cure peptic ulcers. The present in *in silico* analysis shown that the selected compounds from *Momordica charantia* like Glibenclamide have shown more effective in the control of peptic ulcer. Glibenclamide therapy involves up-regulation of hepatic PPAR α expression and is a new therapeutic strategy for diabetes [19], Wound Healing Enhancing Effects [20] and peptic ulcers.

CONCLUSION

In the present study, *in silico* screening and evaluation of some metabolites from *Momordica charantia* in the treatment of peptic ulcers has been conducted. Glibenclamide present in *Momordica charantia* is found effective in the control of peptic ulcer based on *in silico* analysis. Further *in vitro* and *in vivo* studies have to be conducted for better control of peptic ulcers.

Acknowledgement

The authors like to thank administration of Atal Bihari Vajpayee University for providing facilities to conduct the research work.

REFERENCES

1. Fan M, Kim EK, Choi YJ, Tang Y, Moon SH. The role of *Momordica charantia* in resisting obesity. *Int J Environ Res Public Health*. 2019;16(18):3251. doi: 10.3390/ijerph16183251, PMID 31487939.
2. Yan JK, Wu LX, Qiao ZR, Cai WD, Ma H. Effect of different drying methods on the product quality and bioactive polysaccharides of bitter gourd (*Momordica charantia* L.) slices. *Food Chem*. 2019;271:588–96. doi: 10.1016/j.foodchem.2018.08.012, PMID 30236720.
3. Behera TK, Singh AK, Staub JE. Comparative analysis of genetic diversity in Indian bitter gourd (*Momordica charantia* L.) using RAPD and ISSR markers for developing crop improvement strategies. *Sci Hortic*. 2008;115(3):209–17. doi: 10.1016/j.scienta.2007.08.013.
4. Thiagarajan SK, Rama Krishnan K, Ei T, Husna Shafie N, Arapoc DJ, Bahari H. Evaluation of the effect of aqueous *Momordica charantia* Linn. extract on zebrafish embryo model through acute toxicity assay assessment. *Evid Based Complement Alternat Med*. 2019;2019:9152757. doi: 10.1155/2019/9152757, PMID 31186668.
5. Jan B, Shams R, Dar AH, Singh A, Khan SA. Bitter gourd. In: Antioxidants in vegetables and nuts-properties and health benefits. Singapore: Springer; 2020. p. 175–89.
6. Singh V, Mahaur S, Kushwaha SK. Nutraceuticals: A new golden era in health and disease. *Asian J Res Chem*. 2018;11(3):652–8. doi: 10.5958/0974-4150.2018.00117.7.
7. Kumar KS, Bhowmik D. Traditional medicinal uses and therapeutic benefits of *Momordica charantia* Linn. *Int J Pharm Sci Rev Res*. 2010;4(3):23–8.
8. Poovitha S, Parani M. In vitro and in vivo α -amylase and α -glucosidase inhibiting activities of the protein extracts from two varieties of bitter gourd (*Momordica charantia* L.). *BMC Complement Altern Med*. 2016;16(1);Suppl 1:185. doi: 10.1186/s12906-016-1085-1, PMID 27454418.
9. Grover JK, Yadav SP. Pharmacological actions and potential uses of *Momordica charantia*: a review. *J Ethnopharmacol*. 2004;93(1):123–32. doi: 10.1016/j.jep.2004.03.035, PMID 15182917.
10. Singh J, Cumming E, Manoharan G, Kalasz H, Adeghate E. Medicinal chemistry of the anti-diabetic effects of *Momordica charantia*: active constituents and modes of actions. *Open Med Chem J*. 2011 [Suppl];5(Suppl 2):70–7. doi: 10.2174/1874104501105010070, PMID 21966327.
11. De Luis DA, De La Calle H, Roy G, De Argila CM, Valdezate S, Canton R, Boixeda D. *Helicobacter pylori* infection and insulin-dependent diabetes mellitus. *Diabetes Res Clin Pract*. 1998;39(2):143–6. doi: 10.1016/s0168-8227(97)00127-7, PMID 9597384.

12. Paul A, Raychaudhuri SS. Medicinal uses and molecular identification of two *Momordica charantia* varieties-a review. *Electron J Biol.* 2010;6(2):43–51.
13. Nejati S, Karkhah A, Darvish H, Validi M, Ebrahimpour S, Nouri HR. Influence of *Helicobacter pylori* virulence factors CagA and VacA on pathogenesis of gastrointestinal disorders. *Microb Pathog.* 2018;117:43–8. doi: 10.1016/j.micpath.2018.02.016, PMID 29432909.
14. Xiang Z, Censini S, Bayeli PF, Telford JL, Figura N, Rappuoli R, Covacci A. Analysis of expression of CagA and VacA virulence factors in 43 strains of *Helicobacter pylori* reveals that clinical isolates can be divided into two major types and that CagA is not necessary for expression of the vacuolating cytotoxin. *Infect Immun.* 1995;63(1):94–8. doi: 10.1128/iai.63.1.94–98.1995, PMID 7806390.
15. Ozbakiş Dengiz G, Gürsan N. Effects of *Momordica charantia* L. (Cucurbitaceae) on indomethacin-induced ulcer model in rats. *Turk J Gastroenterol.* 2005;16(2):85–8. PMID 16252198.
16. Gürbüz I, Akyüz C, Yeşilada E, Şener B. Anti-ulcerogenic effect of *Momordica charantia* L. fruits on various ulcer models in rats. *J Ethnopharmacol.* 2000;71(1–2):77–82. doi: 10.1016/s0378–8741(99)00178–6, PMID 10904148.
17. Kim JM, Kim JS, Jung HC, Song IS, Kim CY. Virulence factors of *Helicobacter pylori* in Korean isolates do not influence proinflammatory cytokine gene expression and apoptosis in human gastric epithelial cells, nor do these factors influence the clinical outcome. *J Gastroenterol.* 2000;35(12):898–906. doi: 10.1007/s005350070003, PMID 11573725.
18. Mattar R, Marques SB, Monteiro MDS, Dos Santos AF, Iriya K, Carrilho FJ. *Helicobacter pylori* cag pathogenicity island genes: clinical relevance for peptic ulcer disease development in Brazil. *J Med Microbiol.* 2007;56(1):9–14. doi: 10.1099/jmm.0.46824–0, PMID 17172510.
19. Abdel-Rahman RF, Soliman GA, Saeedan AS, Ogaly HA, Abd-Elsalam RM, Alqasoumi SI, Abdel-Kader MS. Molecular and biochemical monitoring of the possible herb-drug interaction between *Momordica charantia* extract and glibenclamide in diabetic rats. *Saudi Pharm J.* 2019;27(6):803–16. doi: 10.1016/j.jsps.2019.05.002, PMID 31516323.
20. Rezaeizadeh, ALIREZ A. 2013. Some mechanisms for wound healing enhancing effects of bitter gourd (*Momordica charantia* L.) extract in diabetic rats (Doctoral dissertation, Ph. D. Thesis, Universiti Putra Malaysia, Serdang, Malaysia).