

Jurnal Info Kesehatan

Vol. 21, No. 1, March 2023, pp. 174-183

P-ISSN 0216-504X, E-ISSN 2620-536X

DOI: [10.31965/infokes.Vol21Iss1.1016](https://doi.org/10.31965/infokes.Vol21Iss1.1016)Journal homepage: <http://jurnal.poltekkeskupang.ac.id/index.php/infokes>**RESEARCH****Open Access****Bioactive Compounds of the Ethanol Extract of Butterfly Pea Petals (*Clitoria ternatea* L.) on Gastric Proton Pump: In-Silico Analysis****Atik Kurniawati^{1a*}, Sri Rahayu Lestari^{1b}, Fatchur Rohman^{1c}**¹ Department of Biology, State University of Malang, Malang, East Java, Indonesia.^a Email address: atik_kurniawati.2003428@students.um.ac.id^b Email address: sriahayulestari@um.ac.id^c Email address: fatchur.rohman.fmipa@um.ac.id

Received: 31 December 2022

Revised: 30 March 2023

Accepted: 31 March 2023

Abstract

Biodiversity of medicinal plants in Indonesia reflects the potential to be used to treat non-communicable diseases such as cancer. Gastritis is a kind of symptom felt in the stomach which may trigger severe abnormalities leading to a state of cancer. This study aims to determine the potential of bioactive compounds derived from the ethanol extract of butterfly pea petals (*Clitoria ternatea* L.) as an in-silico anti gastritis drug candidate. This was a descriptive study with a qualitative approach. The molecular docking method applied specific docking using PLANTS software. The results of molecular docking indicated that there might be similar potential as the control drug in inhibiting the gastric proton pump. Based on the analysis of the LCHRMS results, it was found flavonoid compounds in the extract of butterfly pea petals used for docking analysis. Each flavonoid compound and the docking score from highest to lowest were Rutin (-87.05), Quercetin-3 β -D-glucoside (-79.30), Quercetin (-79.28), Kaempferol (-74.80), Trifolin (-74.22), Genistein (-69.70), Kaempferol-3-glucoside-3''rhamnoside (-67.79), Biochanin A(1-) (-67.64), and Mauritianin (-58.26). The flavonoid compound named rutin had the highest docking score above the two control drugs of Omeprazole (-66.27) and Vonoprazan (-84.45). It can be concluded that based on in-silico study, the flavonoid compound of Rutin in the ethanol extract of butterfly pea petals (*Clitoria ternatea* L.) had the potential to inhibit the gastric proton pump to prevent gastritis. The chemical structure of Rutin differs from the two control drugs because it has a more complex structure consisting of five benzene rings. It is recommended to carry out further dynamic molecular test to find out which flavonoid compounds are the most stable affinity for the target protein. Based on the in-silico test, in vivo and in vitro study should be performed to find out more information about the potential of the flavonoid compounds in butterfly pea extract in inhibiting the action of the gastric proton pump.

Keywords: Anti-gastritis, Butterfly pea, in-silico.***Corresponding Author:**

Atik Kurniawati

Department of Biology, State University of Malang, Malang, East Java, Indonesia.

Email: atik_kurniawati.2003428@students.um.ac.id

©The Author(s) 2023. This article is distributed under the terms of the Creative Commons Attribution 4.0 International License (<http://creativecommons.org/licenses/by/4.0/>), which permits unrestricted use, distribution, and reproduction in any medium, provided you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons license, and indicate if changes were made. The Creative Commons Public Domain Dedication waiver (<http://creativecommons.org/publicdomain/zero/1.0/>) applies to the data made available in this article, unless otherwise stated.

1. INTRODUCTION

Indonesia is currently facing a triple burden regarding various disease problems. The existence of new emerging and re-emerging infectious diseases such as Covid-19, infectious diseases still become major health problems in Indonesia that have not been properly resolved. In addition, the incidence of non-communicable diseases tend to increase every year (Kementerian Kesehatan Republik Indonesia, 2020). Non-communicable diseases (NCDs) refer to chronic diseases classified as non-communicable from human to human, which last a long time and usually develop slowly. Unhealthy lifestyle behavior is a driving force for the development of several NCDs. According to previous studies, the evidence showed a relationship between lifestyle with oxidative and inflammatory processes as the main drivers of cell and tissue damage that underlied the development of NCDs (Seyedsadjadi & Grant, 2021).

Inflammation as the primary driver of cell and tissue damage due to lifestyle and unhealthy behavior can affect all parts of the body. Inflammation that occurs in the stomach is known as gastritis. The gastric mucosa is lined with a mucous membrane consisting of cells that are prone to inflammation. In addition to lifestyle and behavior, bacterial infections can also cause changes in the gastric mucosa. Combination of factors can lead to severe inflammation that develops into peptic ulcers and eventually gastric cancer (Rawla & Barsouk, 2019; Rugge et al., 2020; Rugge et al., 2021).

Physiologically, the secretion of hydrochloric acid in the stomach is carried out by parietal cells. Stimulation of the parietal cells drives the H⁺/K⁺ ATPase proton pump in the cell to move towards the secretory canaliculi which further pumps acid into the gastric lumen (Engevik et al., 2020; Sachs et al., 2007). Under normal physiological conditions, gastric acid production is controlled by a negative feedback mechanism. The hydrochloric acid produced will lead to a decrease in pH in the stomach. When the pH in the stomach is already acidic, these physiological changes provide feedback to D cells to release somatostatin in the gastric antrum which ultimately inhibits gastric acid secretion and restores homeostasis. In the event of gastritis, somatostatin cannot inhibit the stimulus resulting in continuous stimulation of the parietal cells (Metz et al., 2002).

There is a tremendous increase regarding the use of herbal medicines to cure ailments over the last three decades 80% of people worldwide rely on herbal medicine as the primary health care. The advantages that many people expect such as minimum side effects and low cost, maybe the reasons among patients to try complementary and alternative treatments such as herbal medicine (Bordbar et al., 2020). The study on herbal medicine regarding its therapeutic potential is based on the content of phenolic compounds, especially flavonoids. Flavonoids are the most common natural compounds of the polyphenol group found in plants (Ardalani et al., 2019). Several in vivo and in vitro researches revealed a gastro-protective effect of flavonoids on stomach ulcers (Zhang et al., 2020). Flavonoids-rich foods include fruits, vegetables, tea and cocoa plants (Egert & Rimbach, 2011). Many studies regarding the potential of flavonoids as anti-gastritis have been conducted related to their role as antioxidants. Besides that, flavonoid compounds have antiulcer activity which prevents gastric mucosal lesions due to several ulcerogenic (Elseweidy, 2011). Previous studies have shown the potential for flavonoids as anti-gastric ulcers predicted through molecular docking with gastric H₂ receptors (Zahran et al., 2021) and their interactions with gastric proton pump protein of H⁺/K⁺ ATPase which are as strong as anti-gastritis drugs (Sofi et al., 2020).

The butterfly pea petals (*Clitoria ternatea* L.) is a source of phenolic and flavonoid compounds (Jaafar et al., 2020). This plant often grows wild or cultivated in Southeast Asia Region (Ulimaz et al., 2020). In India, this plant is often used for Ayurvedic medicine due to its various benefits, including as an antioxidant (Muhammad Ezzudin & Rabeta, 2018). The

active compounds in butterfly pea petals include anthocyanins, flavonoids, tannins and terpenoids (Deorankar et al., 2020; Ma'ruf et al., 2021; Thuy et al., 2021). In Indonesia, the content of flavonoids in butterfly pea petals has yet to be extensively explored for anti-gastritis agents. However, such potentials need to be explored further to be used widely for the development of the local drug industry in Indonesia. The development of the traditional medicine industry in Indonesia has promising opportunities because Indonesia is included in the top five countries with mega biodiversity in the world. Based on literature studies or genetic heritage, most of plants in Indonesia have benefits as medicinal plants even though they have not been scientifically proven. The development of traditional medicines is also one of the focuses in the action plan of the Ministry of Health of the Republic of Indonesia which is oriented towards increasing the production capacity of imported herbal ingredients until 2024 (Kementerian Kesehatan Republik Indonesia, 2020).

Discovery of drugs from natural ingredients can be accelerated through in-silico study. In-silico study is considered the first step in discovering new drug candidates while reducing the need for analysis in wet laboratories and expensive clinical trials. Based on such nature, in-silico study is categorized as dry lab because it does not involve significant risks (Parikesit et al., 2017). Computational method works in drug discovery by predicting the binding of a drug candidate molecule to a target protein, predicting the affinity and activity of a molecule and observing three dimensions of compound bound to the active site of the protein or better known as molecular docking (Sarkar & Kellogg, 2009).

In-silico study to determine the activity of flavonoids in herbal plants to inhibit gastric proton pumps has not been widely carried out, even though in-silico is one of the basic studies useful in assisting study on gastritis which is difficult to do because it requires a lot of resources. Several in-silico studies revealed phytochemical compounds in herbal plants used to inhibit gastric proton pumps namely ferulic acid (Umre et al., 2018), epicatechin isolated from *Potentilla fulgens* (Rosaceae) (Laloo et al., 2021), xanthenes and coumarins isolated from *Calophyllum brasiliense* (Reyes-Chilpa et al., 2006), as well as amentoflavone and quercitrin isolated from *Hypericum perforatum* (Sofi et al., 2020). However, no studies reported the phytochemical compounds in the butterfly pea petals to inhibit the gastric proton pump. Based on this background, researchers are interested in determining the bioactive compounds in the ethanol extract of butterfly pea petals (*C. ternatea* L.) which have potential as anti-gastritis candidate by inhibiting gastric proton pump protein of H⁺/K⁺ ATPase in-silico.

2. RESEARCH METHOD

The current study was conducted in January-August 2022 at the Department of Biology, State University of Malang, Integrated Laboratory of the Polytechnic of the Ministry of Health of Malang and Central Laboratory of Life Sciences, University of Brawijaya, Malang. This was a descriptive study with a qualitative approach through relevant literature studies. The descriptive study design aims to describe various findings, including the facts regarding the potential of the bioactive compounds of butterfly pea petals (*C. ternatea* L.) as an anti-gastritis agent.

Plant material and extraction process. The petals of the butterfly pea harvested freshly from the garden were dried in the sun for two days. The dried butterfly pea petals were milled using a grinder to produce powder of butterfly pea petals. The powder of the butterfly pea petals was filtered through a mesh to obtain a fine powder. 5 grams of butterfly pea petals powder was added with 100 ml of 70% ethanol and heated on a magnetic hotplate stirrer at 70°C for 8 hours. The extract was then filtered using filter paper and concentrated by evaporation. Furthermore, the liquid extract of the butterfly pea petals is heated in an oven to evaporate the remaining solvent (Aditiyarini & Iswuryani, 2021; Jeyaraj et al., 2020; Ludin et al., 2018). The butterfly pea petals extract was then screened for bioactive compounds using

the Liquid Chromatography – High Resolution Mass Spectrometry (LC-HRMS) with the brand Thermo Scientific Dionex Ultimate 3000 RSLCnano using microflow meter tool at the Central Laboratory of Life Sciences, Brawijaya University.

In-silico analysis using computer/laptop devices (hardware) and software was performed to predict the bioactive compounds of butterfly pea petals (*C. ternatea* L.) based on LC-HRMS data. The results of the compounds screening were further performed by selecting the flavonoid group compounds and downloading the metadata needed. Analysis was performed with the in-silico approach through the molecular docking method using the PLANTS software. The initial stage in the search for in-silico prediction of the potential of the active compound in butterfly pea petals was searching for information on the predicted compound using the PubChem webserver <https://pubchem.ncbi.nlm.nih.gov/>. In the molecular docking protocol using the PLANTS software, the required data from PubChem was a "canonical smile". After copying the canonical smile from PubChem, the chemical structure was prepared using MarvinSketch version 5.2.5.1 downloaded from <http://www.chemaxon.com>. Structural preparation using MarvinSketch included adjustment of the body's pH and conformation of the compound to 10 conformations (default). The results of compound preparation in MarvinSketch were saved under the name of "ligand.mol2" with file type of "Tripos Mol2 (*.mol2)" (Purnomo, 2019).

The target protein was downloaded from the RCSB Protein Data Bank web server on <https://www.rcsb.org/> and protein preparation was further performed using the YASARA software by removing water molecules, adding hydrogen and separating the native ligand from the protein. The protein file was saved in the "mol2" format under the name of "protein.mol2", while the native ligand was saved in the "mol2-sybyl mol2" format under the name of "ref_ligand.mol2" (Purnomo, 2019).

The native ligand file that had been prepared with YASARA was opened with MarvinSketch and the preparation was performed by adjusting the human pH and setting the compound conformation as much as 10 conformations (default). The results of the native ligand preparation through MarvinSketch were saved under the name of "ligand.mol2" with file type of "Tripos Mol2 (*.mol2)" (Purnomo, 2019).

The docking application applied here was PLANTS by referring to the method of a drug designer made by UGM Yogyakarta which successfully docked with PLANTS using 64-bit Windows via CMD (previously had to go through Co-PendriveLinux) (Purnomo, 2019). Before docking with PLANTS, it should be noted that PLANTS does not recognize the input "S.O2", so it is necessary to edit it to "S.o2" with the Notepad++ program (Purnomo, 2019).

Docking validation was performed to determine the value of Root mean square distances (RMSD). A docking protocol was acceptable if the docked RMSD heavy atoms compared to a reference were below 2.0 angstroms. Thus, if the value met the requirement of the docking protocol, further screening could be conducted virtually to find new inhibitor compounds for a target protein (Purnomo, 2019).

The docking of the predicted compound was performed after the docking protocol was accepted with the RMSD value of below 2.0 Angstrom. Steps for docking the predicted compound were made according to a valid docking protocol. The results of running docking can be observed in the work folder called "result" which contained docking files by selecting the excel file to see the docking score. The docking score described the conformation of the ligand that provided the lowest energy at the protein binding site (Purnomo, 2019)

Visualization aims to find the bond side equations between the predictive compound and the control compound. Docking results were further visualized using Ligplus and Pymol software. Before performing the visualization, there should be a treatment to make a theoretical PDB, namely the protein structure with the ligand resulting from the docking performed with

the YASARA software. At this stage an analysis of the interactions/bonds formed between the amino acid residues and the predicted compounds was performed (Purnomo, 2019).

3. RESULTS AND DISCUSSION

Based on the results of bioactive compounds screening using the LC-HRMS method, nine flavonoid compounds were identified from the ethanol extract of butterfly pea petals identified, namely rutin, quercetin-3 β -D-glucoside, quercetin, kaempferol, trifolin, genistein, kaempferol-3-glucoside-3" rhamnoside, biochanin A(1), and mauritianin. Based on the results of docking using the PLANTS software (Table 1), it was revealed the docking scores of flavonoid compounds with the order from the highest to lowest: rutin (-87.05), quercetin-3 β -D-glucoside (-79.30), quercetin (-79.28), kaempferol (-74.80), trifolin (-74.22), genistein (-69.70), kaempferol-3-glucoside-3" rhamnoside (-67.79), biochanin A(1-) (-67.64), and mauritianin (-58.26). In comparison, the comparator drugs used in this study had a score of -84.45 for Vonoprazan and -66.27 for Omeprazole.

Table 1. Docking Scores for Flavonoids and Control Drugs (Omeprazole and Vonoprazan) on Target Protein of H⁺/K⁺ ATPase

Compound name	<i>Docking Score</i>
Mauritianin	-58.26
Biochanin A(1-)	-67.64
Kaempferol-3-glucoside-3" rhamnoside	-67.79
Genistein	-69.70
Trifolin	-74.22
Kaempferol	-74.80
Quercetin	-79.28
Quercetin-3 β -D-glucoside	-79.30
Rutin	-87.05
Omeprazole	-66.27
Vonoprazan	-84.45

The molecular docking results showed that the majority of compounds had a higher docking score than the control drug of omeprazole. There was one compound namely mauritianin, which had a docking score below all control drugs and only one flavonoid compound namely rutin, which had a higher docking score from the two control drugs. Thus, a statistical test was performed to compare the docking scores between rutin and vonoprazan by taking the docking score from ten conformations using the PLANTS software. The docking score describes the conformation of the ligand that provides the lowest energy for binding to the H⁺/K⁺ ATPase target protein. The docking score reflects an idea of how well the drug candidate molecule can bind to its target similar to experimental studies. Scoring was applied to evaluate and rank the ligand and target protein complexes predicted by the docking algorithm. A docking algorithm is a set of rules or parameters implemented in a docking tool to predict the conformation of target proteins and ligands (Dias & de Azevedo Jr., 2008). The docking algorithm applied in the PLANTS software is the Ant Colony Optimization (ACO) algorithm. ACO in PLANTS is known to perform well compared to other docking tools and is equivalent to the GOLD software used as a paid docking tool to search for drug compounds. ACO represents ant colonies that find food in real life by finding binding sites on target proteins (Korb et al., 2009; Spyraakis et al., 2021). The docking score used in the PLANTS software does not have a direct physical/chemical meaning, wherein lower scores represent the best docking produced by the docking tool. A lower docking value indicates that the predicted

compound can bind to the target protein by requiring little energy. Furthermore, the docking value can also mean positive if the predicted compound binds to the protein when energy is present, which is less favorable for the discovery of drug compounds.

Table 2. Protein-Ligand Interactions of Flavonoid Compounds of Butterfly Pea Petals Extract (*C. ternatea* L.) with Target Protein of H⁺/K⁺ ATPase.

Name of Compound	Protein-Ligand Interaction	
	Hydrogen bond	Hydrophobic bond
Rutin	-	Leu759, Thr724, Ile739, Ala755, Val373, Phe764, Leu376, Ala372
Omeprazole	Met757 (2.51)	Leu759, Phe764, Thr724, Asp756, Ala755, Ile739, Leu376, Ala372, Val373, Val367, Ile767
Vonoprazan	-	Val373, Val367, Ala372, Leu759, Phe764, Thr724, Ala755, Ile767, Asp756, Ile739, Leu376

Based on the docking results compared between the flavonoid compounds of the ethanol extract of butterfly pea petals and the PPI drug, it was found that most of the flavonoid compounds had a lower docking score compared to the omeprazole drug. There was only one flavonoid compound namely rutin with a higher docking score compared to the two PPI drugs (omeprazole and vonoprazan). Omeprazole was the first and most widely prescribed proton pump inhibitor drug to treat gastric disorders among adults (Lindberg et al., 1990; Olbe et al., 2003). Omeprazole works to stop gastric acid secretion by selectively inhibiting protein H⁺/K⁺ ATPase. Omeprazole binds covalently to cysteine residues via disulfide bridges on the alpha subunit of the H⁺/K⁺ ATPase protein. Such effect may inhibit gastric acid secretion for up to 36 hours (Sachs et al., 2006).

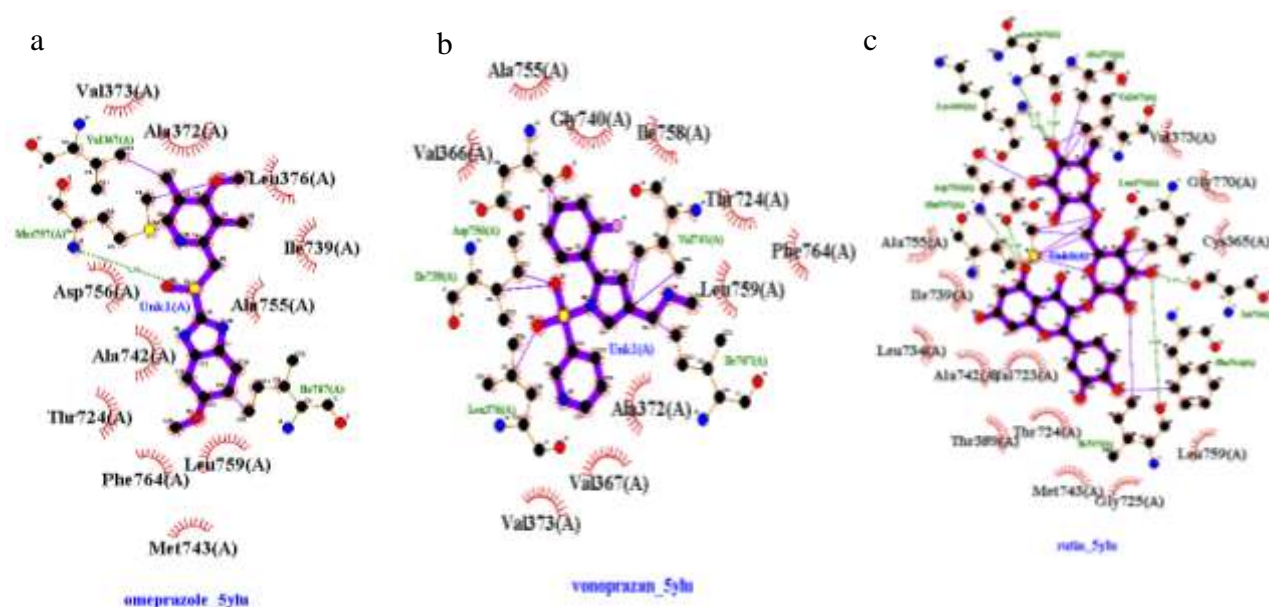


Figure 1. Visualization of Interactions of Omeprazole (a), Vonoprazan (b) and Rutin (c) Compounds on the Binding Site of Target Protein of H⁺/K⁺ ATPase Using LigPlot⁺ Software.

The docking visualization (Figure 1) in the LIGPLOT⁺ diagram presents the interaction patterns of hydrogen bonds and hydrophobic bond contacts of each ligand (omeprazole, vonoprazan and rutin). In Figure 1, the bond between the ligands is shown in purple, which

connects the atoms in the ligand. Hydrogen bonds are shown as green dotted lines that form between the two atoms. Hydrophobic contact is indicated by the appearance of an arc with fingers or eyelashes. Contacting atoms are shown with the fingers pointing backward. Plot titles and ligand residues are shown in blue. Figure 1 revealed differences in the chemical structure of the flavonoids between rutin and the two control drugs, wherein the form of the flavonoids in rutin was more complex with five benzene rings and the two control drugs had three benzene rings.

Based on the protein-ligand interaction table, it was known that the compounds that bound the most to the target protein were rutin and kaempferol-3-glucoside-3''rhamnoside by forming hydrogen bonds and hydrophobic bonds. Based on literature, it is known that the interaction between proteins and ligands is mediated by chemical bonds such as hydrogen, hydrophobic, ionic, and so on. However, based on the same literature, hydrogen bonding has the greatest effect in protein and ligand interactions. In addition, there are hydrophobic bonds that affect protein-ligand interactions. Hydrophobic bonds can increase the affinity of most ligand compounds with their receptors. This is indicated by the relatively more significant number of hydrophobic groups compared to hydrogen bonds (Davis & Teague, 2010; Wang et al., 2020).

Rutin is flavonoid compound in plants with the potential as drug candidate due to its pharmacological properties such as antioxidants, cytoprotective, anti-carcinogenic, anti-ulcer and so on (Ganeshpurkar & Saluja, 2017). The results showed that rutin compound extracted from butterfly pea petals had the lowest score in the docking score for the H⁺/K⁺ ATPase target protein. Although the statistical test results showed no significant difference between rutin and natural ligands that inhibited the target protein of H⁺/K⁺ ATPase (vonoprazan), the docking results found that rutin might have potential as an anti-gastritis candidate by inhibiting H⁺/K⁺ ATPase protein in the stomach. Such finding is in line with previous molecular docking studies which showed rutin activity as an inhibitor of H⁺/K⁺ ATPase protein in the stomach (Dubey et al., 2013a; Dubey et al., 2013b).

The limitation in this study was regarding molecular docking without applying molecular dynamics to know clearly which predictive compound is maturely bound to the target protein so as to predict whether the protein-compound complex can change the configuration of the gastric proton pump and cause a reaction.

4. CONCLUSION

Based on the results of data analysis and the discussion described, it can be concluded that: The ethanol extract of butterfly pea petals (*C. ternatea* L.) contained flavonoid compounds that have potential as anti-gastritis in inhibition of gastric proton pump protein of H⁺/K⁺ ATPase through molecular docking using the PLANTS software. Flavonoid compound predicted to have the most potential as anti-gastritis by in-silico inhibition of gastric proton pump protein of H⁺/K⁺ ATPase was rutin. The chemical structure of Rutin differs from the two control drugs because it has a more complex structure consisting of five benzene rings.

It is recommended to determine the content of extracts derived from solvents other than ethanol so as to identify bioactive compounds other than ethanol extract. Molecular docking prediction can be followed up with molecular dynamic simulation to comprehensively understand molecular dynamics using an in-silico approach.

REFERENCES

- Aditiyarini, D., & Iswuryani, E. O. (2021). Effect of various factors on anthocyanins extraction from butterfly pea flower (*Clitoria ternatea* l.). *Nova Biotechnologica et Chimica*, 20(1), e817. <https://doi.org/10.36547/nbc.817>
- Ardalani, H., Hadipanah, A., & Sahebkar, A. (2019). Medicinal Plants in the Treatment of

- Peptic Ulcer Disease: A Review. *Mini-Reviews in Medicinal Chemistry*, 20(8), 662-702. <https://doi.org/10.2174/1389557520666191227151939>
- Bordbar, G., Miri, M. B., Omidi, M., Shoja, S., & Akhavan, M. (2020). Comparison of a Novel Herbal Medicine and Omeprazole in the Treatment of Functional Dyspepsia: A Randomized Double-Blinded Clinical Trial. *Gastroenterology Research and Practice*, 2020 (5152736). <https://doi.org/10.1155/2020/5152736>
- Davis, A. M., & Teague, S. J. (2010). ChemInform Abstract: Hydrogen Bonding, Hydrophobic Interactions, and Failure of the Rigid Receptor Hypothesis. *ChemInform*, 30(24). <https://doi.org/10.1002/chin.199924325>
- Deorankar, P., Gangiwale, R., Chintamani, R., & Singh, R. P. (2020). Evaluation of ethanolic and aqueous extract of clitoria ternatea for antimicrobial activity. *Indian Journal of Natural Products and Resources (IJNPR)[Formerly Natural Product Radiance (NPR)]*, 11(3), 194-198. <http://doi.org/10.56042/ijnpr.v11i3.29958>
- Dias, R., & de Azevedo Jr., W. (2008). Molecular Docking Algorithms. *Current Drug Targets*, 9(12), 1040-1047. <https://doi.org/10.2174/138945008786949432>
- Dubey, S., Ganeshpurkar, A., Shrivastava, A., Bansal, D., & Dubey, N. (2013a). Rutin exerts antiulcer effect by inhibiting the gastric proton pump. *Indian Journal of Pharmacology*, 45(4), 415-417. <https://doi.org/10.4103/0253-7613.115011>
- Dubey, S., Ganeshpurkar, A., Bansal, D., & Dubey, N. (2013b). Experimental studies on bioactive potential of rutin. *Chronicles of Young scientists*, 4(2), 153-157. <https://doi.org/10.4103/2229-5186.115556>
- Egert, S., & Rimbach, G. (2011). Which sources of flavonoids: Complex diets or dietary supplements?. *Advances in Nutrition*, 2(1), 8-14. <https://doi.org/10.3945/an.110.000026>
- Elseweidy, M. (2011). Role of Natural Antioxidants in Gastritis. *Gastritis and Gastric Cancer - New Insights in Gastroprotection, Diagnosis and Treatments*. <https://doi.org/10.5772/24336>
- Engevik, A. C., Kaji, I., & Goldenring, J. R. (2020). The physiology of the gastric parietal cell. *Physiological Reviews*, 100(2), 573-602. <https://doi.org/10.1152/physrev.00016.2019>
- Ganeshpurkar, A., & Saluja, A. K. (2017). The Pharmacological Potential of Rutin. *Saudi Pharmaceutical Journal*, 25(2), 149-164. <https://doi.org/10.1016/j.jsps.2016.04.025>
- Jaafar, N. F., Ramli, M. E., & Salleh, R. M. (2020). Optimum extraction condition of clitoria ternatea flower on antioxidant activities, total phenolic, total flavonoid and total anthocyanin contents. *Tropical Life Sciences Research*, 31(2), 1-17. <https://doi.org/10.21315/tlsr2020.31.2.1>
- Jeyaraj, E. J., Lim, Y. Y., & Choo, W. S. (2020). Extraction methods of butterfly pea (*Clitoria ternatea*) flower and biological activities of its phytochemicals. *Journal of Food Science and Technology*, 58, 2054-2067. <https://doi.org/10.1007/s13197-020-04745-3>
- Kementerian Kesehatan Republik Indonesia. (2020). *Peraturan Menteri Kesehatan Republik Indonesia Nomor 21 Tahun 2020 Tentang Rencana Strategis Kementerian Kesehatan Tahun 2020-2024*. Jakarta: Kementerian Kesehatan Republik Indonesia.
- Korb, O., Stützle, T., & Exner, T. E. (2009). Empirical scoring functions for advanced Protein-Ligand docking with PLANTS. *Journal of Chemical Information and Modeling*, 49(1), 84-96. <https://doi.org/10.1021/ci800298z>
- Laloo, D., Sinha, S. K., Prasad, S. K., & Hemalatha, S. (2021). Gastric H⁺, K⁺-ATPase inhibitory effects of the active constituent isolated from *Potentilla fulgens* roots: An in vivo and in silico molecular docking studies. *Phytomedicine Plus*, 1(3), 100037. <https://doi.org/10.1016/j.phyplu.2021.100037>
- Lindberg, P., Brndstrm, A., Wallmark, B., Mattsson, H., Rikner, L., & Hoffmann, K. J. (1990). Omeprazole: The first proton pump inhibitor. *Medicinal Research Reviews*, 10(1), 1-54.

- <https://doi.org/10.1002/med.2610100102>
- Ludin, N. A., Al-Alwani, M. A., Mohamad, A. B., Kadhum, A. A. H., Hamid, N. H., Ibrahim, M. A., ... & Sopian, K. (2018). Utilization of natural dyes from zingiber officinale leaves and clitoria ternatea flowers to prepare new photosensitisers for dye-sensitised solar cells. *Int. J. Electrochem. Sci*, 13(8), 7451-7465. <https://doi.org/10.20964/2018.08.04>
- Ma'ruf, N. Q., Antasionasti, I., Fatimawali, F., & Tallei, T. (2021). Analisis GC-MS Ekstrak Metanol dan N-Heksan dari Bunga Telang (*Clitoria ternatea* L.). *Pharmakon*, 10(2), 857-862. <https://doi.org/10.35799/pha.10.2021.34035>
- Metz, D. C., Ferron, G. M., Paul, J., Turner, M. B., Soffer, E., Pisegna, J. R., & Bochenek, W. J. (2002). Proton pump activation in stimulated parietal cells is regulated by gastric acid secretory capacity: A human study. *Journal of Clinical Pharmacology*, 42(5), 512-519. <https://doi.org/10.1177/00912700222011562>
- Muhammad Ezzudin, R., & Rabeta, M. S. (2018). A potential of telang tree (*Clitoria ternatea*) in human health. *Food Research*, 2(5), 415-420. [https://doi.org/10.26656/fr.2017.2\(5\).073](https://doi.org/10.26656/fr.2017.2(5).073)
- Olbe, L., Carlsson, E., & Lindberg, P. (2003). A proton-pump inhibitor expedition: The case histories of omeprazole and esomeprazole. *Nature Reviews Drug Discovery*, 2, 132-139. <https://doi.org/10.1038/nrd1010>
- Parikesit, A. A., Anurogo, D., & Putranto, R. A. (2017). Pemanfaatan bioinformatika dalam bidang pertanian dan kesehatan (The utilization of bioinformatics in the field of agriculture and health). *E-Journal Menara Perkebunan*, 85(2), 105-115. <https://doi.org/10.22302/iribb.jur.mp.v85i2.237>
- Purnomo, H. (2019). *Molecular Docking Parasetamol dan Analognya Menggunakan PLANTS (Protein-Ligands ANT-System)*. Rapha Publishing.
- Rawla, P., & Barsouk, A. (2019). Epidemiology of gastric cancer: Global trends, risk factors and prevention. In *Przegląd Gastroenterologiczny*, 14(1), 26-38. <https://doi.org/10.5114/pg.2018.80001>
- Reyes-Chilpa, R., Baggio, C. H., Alavez-Solano, D., Estrada-Muñiz, E., Kauffman, F. C., Sanchez, R. I., & Mesia-Vela, S. (2006). Inhibition of gastric H⁺,K⁺-ATPase activity by flavonoids, coumarins and xanthenes isolated from Mexican medicinal plants. *Journal of Ethnopharmacology*, 105(1-2), 167-172. <https://doi.org/10.1016/j.jep.2005.10.014>
- Rugge, M., Savarino, E., Sbaraglia, M., Bricca, L., & Malfartheiner, P. (2021). Gastritis: The clinico-pathological spectrum. *Digestive and Liver Disease*, 53(10), 1237-1246. <https://doi.org/10.1016/j.dld.2021.03.007>
- Rugge, M., Sugano, K., Sacchi, D., Sbaraglia, M., & Malfartheiner, P. (2020). Gastritis: An Update in 2020. *Current Treatment Options in Gastroenterology*, 18, 488-503. <https://doi.org/10.1007/s11938-020-00298-8>
- Sachs, G., Shin, J. M., & Howden, C. W. (2006). Review article: The clinical pharmacology of proton pump inhibitors. *Alimentary Pharmacology and Therapeutics*, 23(SUPPL. 2), 2-8. <https://doi.org/10.1111/j.1365-2036.2006.02943.x>
- Sachs, George, Shin, J. M., Vagin, O., Lambrecht, N., Yakubov, I., & Munson, K. (2007). The gastric H,K ATPase as a drug target: Past, present, and future. *Journal of Clinical Gastroenterology*, 41(SUPPL.2), S226-S242. <https://doi.org/10.1097/MCG.0b013e31803233b7>
- Sarkar, A., & Kellogg, G. E. (2009). Book Review of Computational Drug Design. A Guide for Computational and Medicinal Chemists. *Journal of Medicinal Chemistry*, 52(15), 4977. <https://doi.org/10.1021/jm900605k>
- Seyedsadjadi, N., & Grant, R. (2021). The potential benefit of monitoring oxidative stress and inflammation in the prevention of non-communicable diseases (NCDs). In *Antioxidants*, 10(1), 15. <https://doi.org/10.3390/antiox10010015>

- Sofi, S. H., Nuraddin, S. M., Amin, Z. A., Al-Bustany, H. A., & Nadir, M. Q. (2020). Gastroprotective activity of *Hypericum perforatum* extract in ethanol-induced gastric mucosal injury in Wistar rats: A possible involvement of H⁺/K⁺ ATPase α inhibition. *Heliyon*, 6(10), E05249. <https://doi.org/10.1016/j.heliyon.2020.e05249>
- Spyrakakis, F., Sarkar, A., & Kellogg, G. E. (2021). Docking, Scoring, and Virtual Screening in Drug Discovery. *Burger's Medicinal Chemistry and Drug Discovery*. <https://doi.org/10.1002/0471266949.bmc301>
- Thuy, N. M., Minh, V. Q., Ben, T. C., Nguyen, M. T. T., Ha, H. T. N., & Van Tai, N. (2021). Identification of anthocyanin compounds in butterfly pea flowers (*Clitoria ternatea* L.) by ultra performance liquid chromatography/ultraviolet coupled to mass spectrometry. *Molecules*, 26(15), 4539. <https://doi.org/10.3390/molecules26154539>
- Ulimaz, T. A., Ustari, D., Aziza, V., Suganda, T., Concibido, V., Levita, J., & Karuniawan, A. (2020). Genetic Diversity of Butterfly Pea [*Clitoria ternatea*] from Indonesia Based on Flower and Yield Component Traits in Two Land Conditions. *Jurnal AgroBiogen*, 16(1). <https://doi.org/10.21082/jbio.v16n1.2020.p1-6>
- Umre, R., Ganeshpurkar, A., Ganeshpurkar, A., Pandey, S., Pandey, V., Shrivastava, A., & Dubey, N. (2018). In vitro, in vivo and in silico antiulcer activity of ferulic acid. *Future Journal of Pharmaceutical Sciences*, 4(2), 248-253. <https://doi.org/10.1016/j.fjps.2018.08.001>
- Wang, Y., Liu, M., & Gao, J. (2020). Enhanced receptor binding of SARS-CoV-2 through networks of hydrogen-bonding and hydrophobic interactions. *Proceedings of the National Academy of Sciences of the United States of America*, 117(25), 13967-13974. <https://doi.org/10.1073/pnas.2008209117>
- Zahran, E. M., Abdelmohsen, U. R., Hussein, A. S., Salem, M. A., Khalil, H. E., Yehia Desoukey, S., Fouad, M. A., & Kamel, M. S. (2021). Antiulcer potential and molecular docking of flavonoids from *Ocimum forskolei* Benth., family Lamiaceae. *Natural Product Research*, 35(11), 1933-1937. <https://doi.org/10.1080/14786419.2019.1645662>
- Zhang, W., Lian, Y., Li, Q., Sun, L., Chen, R., Lai, X., Lai, Z., Yuan, E., & Sun, S. (2020). Preventative and therapeutic potential of flavonoids in peptic ulcers. *Molecules*, 25(20), 4626. <https://doi.org/10.3390/molecules25204626>