Bioinformatic Test and Pharmacokinetic Profile Prediction of Gnetin-C Compound in Melinjo (*Gnetum gnemon* L.) Seeds Toward Colorectal Cancer

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Abstract

Cancer is one of the unresolved health problems in the world, including Indonesia. One of the most common types of cancer is colorectal cancer. Melinjo (*Gnetum gnemon* L.) is one of Indonesian local commodities which has many benefits including its potential to be developed as an anticancer agent. Through bioinformatics and molecular docking technology, the aim of this study was to investigate the functions of gnetin-C from melinjo against colorectal cancer. PkCSM database were used to search the ADMET (absorption, distribution, metabolism, elimination and toxicity) properties and stitch-string database were used to identify common genes related to colon cancer. During identification of colon cancer related genes, STAT3 protein showed the highest degree score. Furthermore, molecular docking was carried out to find out the interaction between the STAT3 protein and gnetin c compound found in melinjo seeds. From the docking stage, the pose with the best affinity energy was obtained with a docking score of 1,966 kcal/mol. this shows that the compound gnetin c has the potential to be used as a new anticancer agent from natural ingredients

Keywords: *Melinjo, Gnetum gnemon, colon cancer, bioinformatics, molecular docking.*

INTRODUCTION

Colorectal cancer is one of the major health problems in the world including Indonesia, which ranks second in the incidence of cancer-related deaths in the world (Gan, *et al*., 2023). According to data published by GLOBOCAN, in 2020 the incidence of colorectal cancer in Indonesia has reached 396.914 new cases and causes 234.511 deaths. Furthermore, colorectal cancer ranks fourth in the list of all cancer types cases in Indonesia.

Curative therapy that often used in treating colorectal cancer is surgery. However, surgery often results in cancer recurrence (Sari, *et al*., 2019). Among the 158 colorectal cancer patients who underwent surgery, as much as 71.2% had recurrences in the first 2 years, 17.6% within 2-3 years after surgery, 11.3% after more than 3 years, and only 0.01% do not recurrence within 5 years (Ryuk, *et al*., 2014). Besides surgery, there are other methods to treat colorectal cancer, namely

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chemotherapy and radiotherapy (Sari, *et al*., 2019). Chemotherapy is a method of treatment used for cancer which aims to inhibit cell proliferation and multiplication, as well as prevent invasion and metastasis (Amjad, *et al*., 2023). However, the side effects of chemotherapy also become a clinical obstacle in therapy because it has several negative effect on the patients. The most common side effects in cancer patients receiving chemotherapy are nausea, vomiting and fainting. Other frequent side effects are decreased appetite, hair loss, dry mouth and constipation (Altun and Sonkaya, 2018). Therefore, it is necessary to discover a new anticancer agents that has a good efficacy and minimal side effects.

As one of the mega-biodiversity countries, Indonesia is blessed with many natural resources that can be utilized as new medicines. A plant that has the potential to be used as a new anticancer agent is melinjo (*Gnetum gnemon* L.). Melinjo is one of Indonesian local commodities which has many benefits. Traditionally, melinjo is processed into vegetables or emping, and is even used to prevent several diseases (Prajnaparamita and Susanti, 2021). Melinjo seeds contain 9-11% protein, 16% fat, and 58% starch. In Addition, melinjo seeds also contain a class of alkaloids, flavonoids, saponins, tannins and stilbenoids (Kardela, *et al*., 2018). Gnetin C, one of the stilbenoids found in melinjo plants (*Gnetum gnemon*), has a stronger biological effect compared to other types of stilbenoids. Based on research conducted by Parupathi *et al* (2022), the gnetin-C compound was found to inhibit tumor progression activity in high-risk premalignant prostate cancer. In addition, melinjo seed ethanol extract is known to reduce viability and induce apoptosis in HSC-3 cancer cells. Apart from that, the ethyl acetate fraction of melinjo seeds is also known to have a cytotoxic effect on HeLa cells with an IC_{50} value of 21.69 g/ml (Savitri, *et al*., 2023).

Along with the passage of time, technological advances are growing rapidly. Currently, the development of new drugs can utilize technology as a preliminary test. The method often used in the development of new drugs is bioinformatics using STITCH-STRING databases and molecular docking. STITCH-STRING is used to analyze the target protein, while molecular docking is used to analyze the interaction between the compound and the target protein on a molecular scale (Kenyori, *et al*., 2022). Based on this background, researchers examined the anticancer activity of melinjo seeds (*Gnetum gnemon* L.) against colorectal cancer by *in silico* method.

METHODS

Direct target proteins (DTPs) were obtained from STITCH database (http://stitch.embl.de/) based on gnetin-C compound and homo sapiens organism. Then, indirect target proteins (ITPs) from each DTPs were obtained from STRING database (https://string-db.org/). The DTPs and ITPs were then downloaded and synchronized with the colon cancer regulatory genes which were downloaded via the PubMed gene database (Keyword: Homo sapiens colorectal cancer associated 1) with the considerations of the absence in mutation. The selected target proteins were then visualized using Cytoscape to determine the top 10 protein based on the degree score. The protein with the highest degree score was then analyzed for its interaction with the test compound using molecular docking.

Molecular docking begins with downloading the 6NJS protein (PDB ID : 6NJS) structure via Protein Data Bank (www.rscb.org) and downloading the gnetin-C ligand via PubChem (http://pubchem.ncbi.nlm.nih.gov) by copying the Simplified Molecular Input line Entry System (SMILES) code and sketched using Marvin Sketch. Before docking the ligand, the protein and ligand are prepared with AutoDock V4.2 with the addition of charges and polar hydrogen atoms and then saved with .pdbqt format.

To ensure the validity of the docking method, validation is carried out. This process

conducted using AutoDock by re-linking the original ligand on the target protein. Next, determine the Root Mean Square Deviation (RMSD) value using the Windows Command Prompt (CMD). The conformation chosen is a conformation that has an RMSD value of <2 Å.

If the docking method valid, molecular docking can be started. This process was carried out using AutoDock Vina application by attaching the gnetin-C molecule to the target protein that obtained from STITCH-STRING process. In the AutoDock Tools application, the gridbox of ligand attachment site is adjusted to the position in the center of the ligand. Then, the values contained in the gridbox are copied to the conf.txt which contains docking information. Then, affinity energy values and RMSD were determined using the CMD with the code vina.exe –config conf.txt –log log.txt. The conformation chosen is the one that has and RMSD value of <2 Å.

Furthermore, the prediction of the pharmacokinetic profile of the gnetin-C compound was carried out by copying the gnetin-C compound SMILES code obtained from PubChem (http://pubchem.ncbi.nlm.nih.gov) to PkCSM website (https://biosig.lab.uq.edu.au/pkcsm/prediction). Then, the data about molecular weight, Log*P*, rotatable bonds, hydrogen donors, hydrogen acceptors, surface area, intestinal absorbtion, VDss, clearance and toxicity of the gnetin-C compound will appear on the website. This data then analyzed using the Lipinski rule of five.

RESULTS

Top 10 colon cancer target proteins obtained from bioinformatics STITCH-STRING for the gnetin-C compound can be seen in Table 1. Based on the result of the analysis, target protein with the highest degree score is STAT3 protein. Top target proteins are visualized using Cytoscape to form nodes that connected by edges as shown in Figure 1. Nodes describe an interacting target protein, while edges are lines connecting nodes that indicate the presence of interaction.

Table 1. Top 10 target protein based on degree score.

No	Protein	Degree score
1	STAT3	15
2	STAT5B	15
3	STAT5A	13
4	STAT1	11
5	SOCS3	11
6	PTPN11	10
7	SOCS1	8
8	JAK2	7
9	SH2B1	6
10	GRB2	5

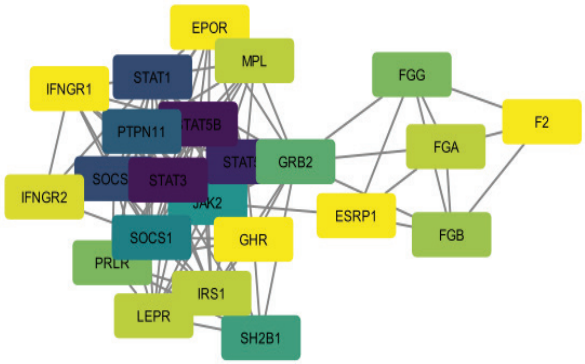

Figure 1. Top protein based on degree score.

The STAT3 protein are used for further analysis using the molecular docking test. In this study, the 6NJS protein (PDB ID: 6NJS) was used as the main target protein to analyze the activity of the gnetin-c compound. Based on the result of docking method validation, this docking method can be considered valid and reliable because from the re-docking activity, the RMSD value obtained was 1.702.

In this study, 9 structural conformations were obtained with different RMSD and affinity energy results. The lowest affinity and RMSD

Table 2. Molecular docking result.

Ligand	Conformation	Affinity (kcal/mol)
Gnetin-C 2	-	8.9
5-FU 2	-	3.3

values were obtained from the 2nd conformation with values of -8.2 kcal/mol and 1.945 respectively. In addition, the affinity and RMSD values of 5-fluorouracil (5-FU) that commonly used in cancer treatment in the community were -3.3 kcal/mol and 1.626 respectively. The result of docking visualization can be seen in Table 3 and Figure 2.

Table 3. Interaction between ligand and amino acid.

Amino Acid	Interaction
TYR A: 657	Hydrogen bond
GLN A : 644	Hydrogen bond
PRO A : 639	Hydrogen bond
GLU A : 638	Hydrogen bond
VAL A : 637	Pi-Alkyl
SER A : 636	Hydrogen bond
SER A : 613	Hydrogen bond
GLU A : 612	Hydrogen bond
SER A : 611	Hydrogen bond
ARG A : 609	Attractive charge

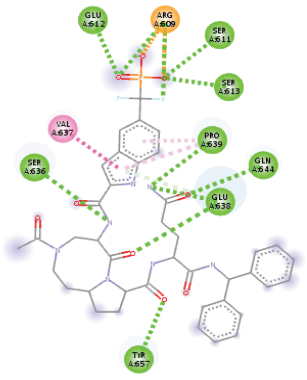

Figure 2. Interaction between gnetin-C and STAT-3.

Based on the 2D visualization, gnetin-C compounds and the receptor have hydrogen bonds with amino acids such as TYR A:657, GLN A:644, PRO A:639, GLU A:638, SER A:636, SER A:613, GLU A: 612 and SER A:611. Prediction results of physicochemical propertied of gnetin-C can be seen in Table 4.

Table 4. Physicochemical properties of gnetin-C.

Description	Value	Lipinski Rule of Five Criteria
Molecular weight	454.478 Da	≤500 Da
LogP	5.6506	≤5
Rotatable bonds	4	≤10
Acceptors	6	≤10
Donors	5	≤5
Surface Area	195.452	-

From Table 4, it can be analyzed that gnetin-C compound has a molecular weight less than 500, Log*P* value more than 5, acceptor and donor are less than 10. Based on the obtained data, the compound gnetin-C is predicted to be easily absorbed and orally active because it meets the Lipinski's Rule of Five criteria for molecular weight, rotatable bonds, hydrogen donors, hydrogen acceptors, and only violating one criterion, which is Log*P*.

Table 5. Pharmacokinetic profile prediction of gnetin-C.

Model Name	Predicted value	Ideal value
Intestinal absorption (human)	95.62%	>80%
VDss	-2.046	Low if <-0.15 High if >0.45
CYP3A4 substrate	Yes	-
CYP2C9 inhibitor	Yes	-
Total clearance	-0.129	Higher is better
Hepatotoxicity	No	-

From Table 5, it can be seen that the gnetin-C intestinal absorption value in human is more than 80%, From the total clearance value, the rate of compound excretion can be predicted through pharmacokinetic calculations (Krihariyani, *et al*., 2020). In the term of its toxicity, gnetin-C doesn't cause hepatotoxicity so it's safe to use.

DISCUSSION

Top 10 colon cancer target protein obtained from bioinformatics STITCH-STRING for the gnetin-C compound can be seen in Table 1 and visualized by Cytoscape. Based on the result of the analysis, target protein with the highest degree score was obtained, namely STAT3 protein with degree score 15.

Signal transducer and activator of transcription 3 (STAT3) is a crucial transcription factor that associated with colorectal cancer initiation and development. STAT3 mediates major inflammatory mechanisms in cancer-associated collitis, becomes overactive in colorectal cancer and promotes cancer cell proliferation, tumor growth, angiogenesis, invasion and migration. STAT3, when continually activated, moves to the nucleus and amplifies gene expression. This amplification supports various cellular processes such as increased cell growth, angiogenesis, resilience against apoptosis, prolonged survival, fostering inflammation that aids tumor growth, evading the immune system response and ultimately metastasis. Recent findings reveal that STAT3 also has contribution to tumour development through other mechanism, such as promoting inflammation that leads to cancer, influencing obesity and metabolic disorders, supporting cancer stem cells and facilitating the creation of environments conducive to cancer spread before metastasis. Therefore, STAT3 is considered as a promising therapeutic target (Gargalionis, *et al*., 2021).

The STAT3 protein then used for further analysis using the molecular docking test. In this study, 6NJS (PDB ID: 6NJS) protein which is the core of STAT3 was used. This protein was chosen because it exists in the human body and no mutations were found. This protein is linked to its original ligand in the form of SD36 compound which will later be used to validate the docking method. Docking validation needs to carried out to confirm the reliability of the docking method. In the validation process, the parameter observed is RMSD value. RMSD is the deviation distance between the position of the ligand after docking stage and the actual position of the original ligand (Rustini, *et al*., 2019). The docking method can be said valid if the RMSD value is <2Å (Mylanda, *et al*., 2021). The greater the RMSD value, the further away (deviated) docked ligand position from the original ligand is (Suherlan, *et al*., 2021). Based on the result of validation, this docking method can be considered valid and reliable because the RMSD value obtained was 1,702.

The potential of a compound as a drug can be seen from the results of molecular docking (Kenyori, *et al*., 2022). In molecular docking, it is necessary to determine the gridbox size. Gridbox forms lika a cube which will determine the binding site on the receptor based on coordinates in the form of x, y and z. This aims to determine the ligand conformation with the lowest energy (Sari, *et al*., 2020). Therefore, good docking results can be seen from the affinity energy parameters. Binding affinity can indicate the activity of the ligand and receptor molecules. The smaller the binding affinity, the stronger bond formed between the ligand and the receptor (Hanif, *et al*., 2020). Furthermore, the binding energy also affects the conformational stability. The strong interaction between the ligand and receptor tend to be at the lowest energy state. In that state, molecule will be more stable, so the smaller the binding energy, the more stable the interaction is (Ambarsari & Sumaryada, 2014). In this study, 9 structural conformations were obtained with different RMSD and affinity energy results. The lowest affinity value were obtained from the 2nd conformation with values of -8.2 kcal/mol. In addition,the affinity value of 5-fluorouracil (5-FU) that commonly used in cancer treatment in the community were -3.3 kcal/mol. If the result of the affinity values between gnetin-C and 5-FU were compared, gnetin-C produces a lower affinity energy value than 5-FU. As stated by Jin, *et al*., the threshold for binding energy values is -5.0 kcal/

mol. Therefore, any values below -5.0 kcal/mol are regarded as having strong binding energy to receptor targets (Jin, *et al*., 2021). Therefore, it can be said that gnetin-C can bind more strongly and stable to the receptor than 5-FU.

Docking visualization is a method to reveal the interaction between ligands and amino acid residues (Sari, *et al.*, 2020). The interactions can be in the form of non-covalent bonds such as electrostatics, van der waals, hydrogen and hydrophobic bonds. Hydrophobic bonds can occurs due to the attractive force of hydrogen atom with another atom that has a large electronegativity in a molecule. Hydrogen bonds is the strongest bonds among the other and have an important role in the stability of the ligand to the receptor. (Lins and Brasseur, 1995). Based on the prior research, both hydrogen and hydrophobic interactions can stabilize a compound at the protein's active site, alter the binding energy value, and enhance the efficacy of the compounds when they interact with the protein (Pantsar and Poso, 2018).

Based on the 2D visualization, gnetin-C compounds and the receptor have hydrogen bonds with amino acids such as TYR A:657, GLN A:644, PRO A:639, GLU A:638, SER A:636, SER A:613, GLU A: 612 and SER A:611. The number of bond/ interactions formed between gnetin-C and cancer cell proteins can be an indicator that gnetin-C has the ability and potential to be developed as a new anticancer agent (Lelita, *et al*., 2017).

Prediction results of physicochemical propertied of gnetin-C can be seen in Table 4. The hydrophobicity of compound can be assessed through its partition coefficient value (log*P*). A higher log*P* indicates greater hydrophobicity of the compound. Additionally, highly hydrophobic compound can increase the risk of toxicity. In this study, the log*P* of gnetin-C is exceeding 5, signifies its elevated hydrophobicity. Hydrophobic compounds tend to linger longer in lipid bilayers due to the bilayers inherent hydrophobic properties. Consequently, these compounds distribute more extensively troughout the body, thereby diminishing their selectivity in binding to target receptors. The distribution of a drug also can be influenced by the molecular weight of the compound, particularly in its ability to penetrate biological membranes via passive diffusion. Compounds with larger molecular sizes typically has lower penetration abilities through biological membranes. Based on the result. It is known that gnetin-C can penetrate through biological membranes easily because it has molecular weight of less than 500 (Ruswanto, *et al.*, 2022).

The parameters regarding hydrogen bond donor groups (<5) and hydrogen bond acceptor groups (<10) plays an important role in the biological activity of a compound. The presence of hydrogen bonds can significantly impact the physiochemical properties of a compound. The number of hydrogen bond donor groups in a compound tends to form hydrogen bonds with solvents. Similarly, hydrogen bond acceptor groups influence permeability by favorably interacting with strong hydrogen-bonding solvents. Consequently, compounds interacting with polar solvents may experience reduced permeation through the lipid bilayer.

According to Chander *et al.* (2017), the compound is said to have a good absorption if the absorption value is >80%. From Table 5, it can be seen that the gnetin-C intestinal absorption value in human is more than 80%, which means that gnetin-C has a good absorption. The volume of distribution (VDss) is the theoritical volume of the total dose of drug that needs to be distributed evenly to give the same concentration as in blood plasma. The higher the VDss, the more distributed drug in tissues rather than plasma (Krihariyani, *et al*., 2020). Predicting the excretion prosess of the compounds can be done by measuring the total clearance. Total clearance is a combination of hepatic clearance (metabolism in the liver and bile) and renal clearance. From the total clearance value, the rate of compound excretion can be predicted through pharmacokinetic calculations (Krihariyani, *et al*., 2020). In the term of its toxicity, gnetin-C doesn’t cause hepatotoxicity so it’s safe to use.

CONCLUSION

From the results of this study, it can be concluded that the target protein obtained from the bioinformatics test is STAT3. From the molecular docking stage, the lowest affinity energy value was -8.9 kcal/mol, lower than 5-FU. On the other hand, pharmacokinetic profile prediction shows that Gnetin-C can be easily abosorbed and active orally. This shows that the compound gnetin-C has good potential in inhibiting colorectal cancer proteins and has the potential to be developed into new anticancer agents from natural ingredients.

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REFERENCES

Altun, I., and Sonkaya, A., 2018, The Most Common Side Effects Experienced by Patients Were Receiving First Cycle of Chemotherapy, *Iran Journal Public Health*, **47**(8), 1218-1219.

Amjad, M.T., Chidharla, A., and Kasi, A., 2023, In Cancer Chemotherapy. s.l.: StatPearls Publishing. https://www.ncbi.nlm.nih.gov/books/NBK564367/

Arwansyah, Ambarsari L., and Sumaryada, T.I., 2014, Simulasi Docking Senyawa Kurkumin dan Analognya Sebagai Inhibitor Reseptor Androgen Pada Kanker Prostat, *Current Biochemistry*, **1**(1), 11-19.

Boland, C.R., and Goel, A., 2010, Microsatellite instability in colorectal cancer, *Gastroenterology*, **138**(6), 2073-2087.

Dewi, C., Utami, R., and Riyadi, N.H., 2012, aktivitas antioksidan dan antimikroba ekstrak melinjo (*Gnetum gnemon* L.), *Jurnal Teknologi Hasil Pertanian*, **5**(2), 74-81.

Gan, Y., Li, X., Han, S., Zhou, L. and Li, W., 2023, Targeting Mcl-1 Degradation by Bergenin Inhibits Tumorigenesis of Colorectal Cancer Cells, *Pharmaceuticals*, **16**(2), 241.

Gargalionis, A.N., Papavassiliou, K.A., and Papavassiliou, A.G., 2021, Targeting STAT3 Signaling Pathway in Colorectal Cancer, *Biomedicines*, **9**(8), 1016.

Hanif, A.U, Lukis, P.A., and Fadlan, A., 2020, Pengaruh Minimisasi Energi MMFF94 dengan MarvinSketch dan Open Babel PyRx pada Penambatan Molekular Turunan Oksindola Tersubstitusi, *Alchemy Journal of Chemistry*, **8**(2), 33-40.

Kardela, W., Fauziah, F., and Mayesri, S., 2018, Biji Melinjo (*Gnetum gnemon* L.): Aktivitas Sebagai Antidiare, *Jurnal Farmasi Higea*, **10**(1), 49-57.

Kenyori, I.K., Alamsyah, M.S., and Nurjanah, C.I.A., 2022, Studi *In Silico* Senyawa Bioaktif Kuersetin kulit Jeruk Nipis (*Citrus aurantifolia*) Sebagai Agen Antikanker Payudara, *Berkala Ilmiah Mahasiswa Farmasi*, **9**(1), 1-10.

Krihariyani, D., Sasongkowati, R., and Haryanto, E., 2020, Studi *In Silico* Sifat Farmakokinetik, Toksisitas, dan Aktivitas Imunomodulator Brazilein Kayu Secang Terhadap Enzim 3-Chymotrypsin-Like Cysteine Protease Coronavirus, *Journal of Indonesian Medical Laboratory and Science*, **1**(1), 76-90.

Kuhn, M., von Mering, C., Campillos, M., Jensen, L.J., and Bork, P., 2008, STITCH : interaction networks of chemicals and proteins, *Nucleic Acids Research*, **36**(suppl 1), D684-D688.

Kusmiati, A., Haryani, T.S., and Triastinurmiatiningsih, 2019, Aktivitas Ekstrak Etanol 96% Kulit Biji Melinjo (*Gnetum gnemon*) Sebagai Antibakteri Salmonella enteritidis, *Ekologia*, **19**(1), 27-33.

Lelita, R., Gunawan, R., and Astuti, W., 2017, Studi Docking Molekular Senyawa Kuersetin, Kalkon dan Turunannya Sebagai Inhibitor Sel Kanker Payudara MCF-7 (MICHIGAN CANCER FOUNDATION-7), *Jurnal Atomik*, **2**(2), 190-196.

Lins, L., and Brasseur, 1995, The hydrophobic effect in protein folding, *The FASEB Journal*, 9(7), 535-540.

Marmol, I., Sanchez-de-Diego, C., Dieste, A.P., Cerrada, E., and Yoldi, M.J.R., 2017, Colorectal Carcinoma: A General Overview and Future Perspectives in Colorectal Cancer, *International Journal of Molecular Sciences*, **18**(1), 197.

Meng, X-Y., Zhang, H-X., Mezei, M., and Cui, M., 2011, Molecular Docking: A powerful approach for structure-based drug discovery, *Current Computer-Aided Drug Design*, **7**(2), 146-157.

Mylanda, V., Ramadhan, N.E., and Viviani, R.N., 2021, Studi Penambatan Molekuler Senyawa Bioaktif Biji Habbatussauda (*Nigella sativa*) Terhadap ERα Sebagai Alternatif Pengobatan Kanker Payudara Dalam Upaya Pemberian Data Ilmiah, *Berkala Ilmiah Mahasiswa Farmasi*, **8**(1), 13-25.

Narayanan, N.K., Kunimasa, K., Yamori, Y., Mori, M., Mori, H., Nakamura, K., Miller, G., *et al.*, 2015, Antitumor activity of melinjo (*Gnetum gnemon* L.) seed extract in human and murine tumor models *in vitro* and in colon-26 tumor-bearing mouse model *in vivo*, *Cancer Medicine*, **4**(11), 1767-1780.

Pino, M.S. and Chung, D.C., 2010, The chromosomal instability pathway in colon cancer, *Gastroenterology*, **138**(6), 2059-2072.

Prajnaparamita, K., and Susanti, S., 2021, Karakter Morfologis dan Perkembangan Anatomis Biji Melinjo (*Gnetum Gnemon* L.), *Jurnal Biogenesis*, **17**(2), 49-60.

Rastini, M.B.O., Giantari, N.K.M., Andyani, K.D., and Laksmiani, N.P.L., 2019, Molecular Docking Aktivitas Antikanker dari Kuersetin Terhadap Kanker Payudara Secara *In Silico, Jurnal kimia (Journal of Chemistry)*, **13**(02), 180-184.

Ryuk, J.P., Choi, G-S., Park, J.S., Kim, H.J., Park, S.Y., Yoon, G.S., *et al.*, 2014, Predictive factors and the prognosis of recurrence of colorectal cancer within 2 years after curative resection, *Annals of surgical treatment and research*, **86**(3), 143-51.

Sari, I.W, Junaidin and Pratiwi, D., 2020, Studi Molecular Docking Senyawa Flavonoid Herba Kumis Kucing (*Orthosiphon stamineus* B.) Pada Reseptor α-Glukosidase Sebagai Antidiabetes Tipe 2, *Jurnal Farmagazine*, **7**(2), 54-60.

Sari, M.I., Wahid, I., and Suchitra, A., 2019, Kemoterapi Adjuvan pada Kanker Kolorektal, *Jurnal kesehatan Andalas*, **8**(1), 51-58.

Simos, T., Georgopoulou, U., Thyphronitis, G., Koskinas, J., and Papaloukas, C., 2015, Analysis of protein interaction networks for the detection of candidate hepatitis B and C biomarkers, *IEEE J Biomed Health Inform*, **19**(1), 181-189.

Suherlan, S., Rohayah, R., and Fakih, T.M, 2021, Uji Aktivitas Antikanker Payudara Senyawa Andrografolida dari Tumbuhan Sambiloto (*Andrographis paniculata* (Burm F) Ness.) Terhadap Human Epidermal Growth Factor Receptor2 (HER-2) Secara *in silico*, *Jurnal Ilmiah Farmasyifa*, **4**(2), 39-50.