Bioinformatic Study of the Active Compound of Morusin in Mulberry (*Morus alba*) against Breast Cancer

Sarmoko[1,2*], Afif Hariawan Pratama[2], Nur Amalia Choironi[2], Muhammad Salman Fareza[2]

[1]Department of Pharmacy, Sumatera Institute of Technology, South Lampung, Lampung, Indonesia
[2]Department of Pharmacy, Faculty of Health Sciences, Universitas Jenderal Soedirman, Purwokerto, Central Java, Indonesia

Abstract

Morusin, an active constituent of the mulberry plant (*Morus alba*), exhibits inhibitory effects on several types of cancer cells *in vitro*, including breast cancer. This study aimed to identify potential target proteins of morusin, investigate the binding energy, and explore type of interactions between morusin and the target protein. Morusin target was searched using the PubMed, STITCH, STRING, and Cytoscape databases. Subsequently, the obtained morusin target protein data underwent processing using Autodock Tools and DS BIOVIA to facilate the simulation of molecular docking between morusin and the target protein. The study identified EGFR, SRC, and MAPK1 as potential targets for morusin. Docking simulations revealed that both EGFR and SRC represent viable targets for morusin, as their binding energies were lower than those of the native ligand and lapatinib. Specifically, the bond energies at EGFR were -9.6, -7.5, and -9.2 kcal/mol for morusin, the native ligand, and lapatinib, respectively. Similarly, at SRC, the corresponding bond energies were -8.2, -6.4, and -5.3 kcal/mol. Morusin demonstrated binding interactions with Leu694, Val702, Leu820, Ala719, Leu768, and Lys721 at the active site of EGFR, and with Lys295 and Gly344 at the binding active sites of SRC. Consequently, morusin has the potential to suppress cancer cell growth by targeting EGFR and SRC.

Keywords: *cancer cells, EGFR and SRC as targets, molecular docking, morusin, mulberry plant*.

INTRODUCTION

Breast cancer exhibits a high prevalence of 19.2% among of all cancers in Indonesia (Gautama, 2022). Current treatment efforts use chemotherapy, radiation, and surgery. However, these approaches still have problems, such as drug resistance and recurrence, so developing new drugs is required. New drug development can be done in several stages, including the *in silico* step, leveraging the field of bioinformatics. Bioinformatics encompasses the integration of systematic and computational methodologies with the concept of "disease - gene - target – drug." This analytical

Submitted: April 6, 2023
Revised: May 17, 2023
Accepted: May 19, 2023
Published online: May 25, 2023

*Corresponding author: sarmoko@fa.itera.ac.id

approach incorporates various aspects including systems biology, network analysis, connectivity, redundancy, and pleiotropy. Through the utilization of databases and the formulation of mathematical models, bioinformatics enables the identification of potential target genes and the elucidation of complex drug mechanisms within the human body (Sun and Yang, 2019; Zhang, *et al.*, 2020).

Bioinformatic analysis methods have been utilized to investigate natural product and its potential pharmacological activity. For instance, Zhang, *et al*. (2020) conducted a bioinformatic analysis of *Prunella vulgaris* plants to identify the molecular targets of active compounds with the potential for anti-breast cancer. The study identified 19 active compounds and 31 potential genes, and then investigated the relationship between the active compounds and potential genes. The results showed that *Prunella vulgaris* has a promising preventive effect on breast cancer through the modulation of AKT1, EGFR, MYC, and VEGFA signaling pathways (Zhang, *et al*., 2020). Apart from *Prunella vulgaris*, mulberry plant (*Morus alba*) is also a promising herbal plant for further research. A network pharmacology analysis was also performed on *Morus alba*, specifically focusing on its potential effects on type 2 diabetes. The study identified AKT1 as the most significant among the 37 target proteins, considering its various functions within different pathways and its interactions with other target proteins (Tang, *et al*., 2021).

Mulberry (*Morus alba*) has traditionally been used to treat a wide range of conditions, including hypertension, diabetes, anemia, and malaria (Lallo, *et al*., 2020). Numerous studies have demonstrated the anticancer properties of mulberry extract, which can suppress the growth of breast cancer (Chen, *et al*., 2022; Wani, *et al*., 2023). *Morus alba* extract is reported to contain several active compounds including morusin (Panek-Krzyśko and Stompor-Gorący, 2021).

Morusin (Figure 1) is one of the many active chemicals found in mulberry. Bax, a pro-apoptotic protein, was reported to be upregulated by morusin in MCF-7, MDA-MB-231, MDA-MB-157, and MDA-MB-453 breast cancer cells (Kang, *et al*., 2017). Morusin's potential to suppress breast cancer growth requires further investigation. Bioinformatics is one of the ways for exploring the possibilities of morusin. The objective of this study to analyze the potential target proteins of morusin in inhibiting breast cancer, as well as to analyze its interaction with target receptors through molecular docking.

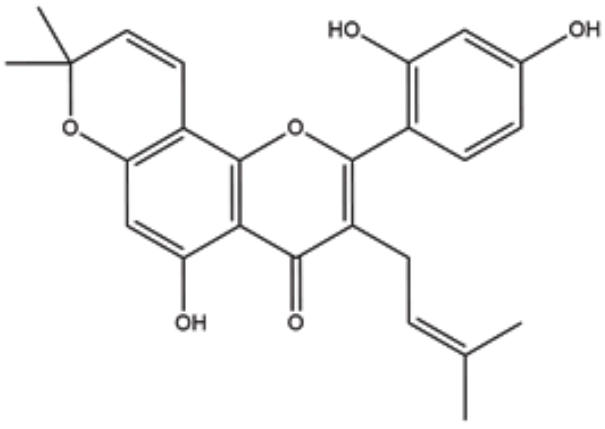

Figure 1. Chemical structure of morusin.

MATERIALS AND METHODS

Gene Target Identification

NCBI (https://ncbi.nlm.nih.gov/) was used to search for genes that regulate breast cancer. The search is done by entering the keyword "breast cancer cell" in Homo sapiens, and changing the search settings to genes. STITCH (http://stitch.embl.de/) was used to search for direct target protein (DTP). The keyword "morusin" was used to search for DTP from morusins by using the "item by name" option set to search for Homo sapiens organisms. STRING DB (https://string-db.org) was used to search for indirect target protein (ITP). The DTP of morusin was inserted into the protein by name column and changes the search to the organism Homo sapiens. The results of the data obtained were changed to a minimum interaction score of 0.7 and a maximum interactor of 20 (Hermawan, *et al*., 2021).

Potential Target Therapeutic Genes (PTTGs) Identification

Potential Target Therapeutic Genes (PTTGs) were obtained by comparing morusin's DTP and ITP with breast cancer regulatory genes. The intersection obtained were expressed as PTTGs from morusin. The tool used was Venny 2.1(https://bioinfogp.cnb.csic.es/tools/venny/).

Gene Ontology, KEGG Pathway, and Drug Assocation Analysis

WebGestalt (http://www.webgestalt.org/) was used to search for Gene Ontology analysis, KEGG Pathway, and Drug Association Analysis. Morusin PTTGs were entered into the Webgestalt Overrepresentation Enrichment Analysis (ORA) search option. Gene ontology consists of biological processes, cellular components, and molecular functions. Drug association analysis was done by changing the choice to drug and the functional database was changed to GLAD4U.

Protein-protein Interaction

The PTTGs obtained were analyzed for the relationship between each protein using STRING DB (https://string-db.org). The results obtained are a network of interactions between proteins.

Top 10 Hub Gene

The protein network results obtained from STRING DB were reprocessed using Cytoscape with the Cytohubba plugin to find the most interacting protein influenced by morusin using the degree parameter.

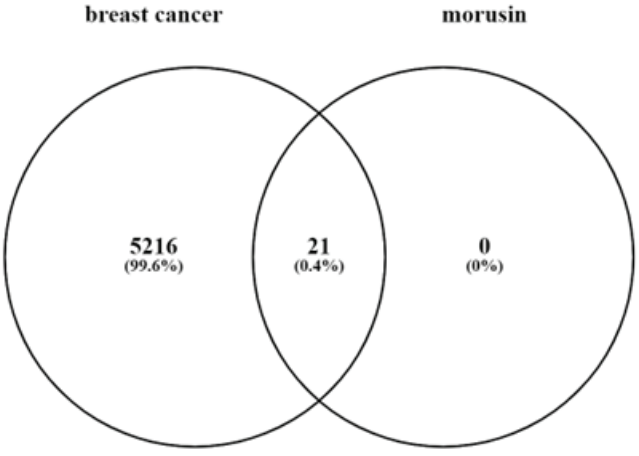

Figure 2. PTTGs of morusin from Venny 2.1.

Table 1. Potential anti-breast cancer target genes of morusin.

Gene name	Protein name
STAT3	Signal transducer and activator of transcription 3
EP300	E1A binding protein p300
FOS	Fos Proto-Oncogene, AP-1 Transcription Factor Subunit
JAK2	Janus kinase 2
FOXP3	Forkhead Box P3
EGFR	Epidermal Growth Factor Receptor
JAK3	Janus kinase 3
PIAS3	Protein Inhibitor Of Activated STAT 3
CCND1	Cyclin D1
HSP90AA1	Heat Shock Protein 90 Alpha Family Class A Member 1
RELA	RELA Proto-Oncogene, NF-KB Subunit
HIF1A	Hypoxia Inducible Factor 1 Subunit Alphanano
CREBBP	CREB Binding Protein
JAK1	Janus kinase 1
MAPK1	Mitogen-Activated Protein Kinase 1
IL10RA	Interleukin 10 Receptor Subunit Alpha
PTPN2	Protein tyrosine phosphatase, non-receptor type 2
SRC	SRC Proto-Oncogene, Non-Receptor Tyrosine Kinase
LEPR	Leptin Receptor
NANOG	Nanog Homeobox
AR	Androgen Receptor

Molecular Docking

The proteins EGFR (PDB ID: 4HJO) (Park, *et al*., 2012), SRC (PDB ID: 2BDF) (Dalgarno, *et al*., 2006), and MAPK1 (PDB ID: 2OJI) (Aronov, *et al*., 2007) were obtained from the Protein Data Bank (https://www.rcsb.org/). Prior to docking, the structures were prepared by removing water molecules and separating the native ligands using Chemdraw and Autodock tools. Validation was performed using Pymol software to assess the root mean square deviation (RMSD) value, where a good RMSD value is considered to be <2 Armstrong. The validated proteins were subsequently subjected to docking with morusin to evaluate the binding energy.

Data Analysis

The data obtained from the molecular docking of the test compounds were compared to the positive control score, and the interactions between the ligand and the protein were analyzed. Suppose each test compound produces a bond energy value lower than the bond energy value created by the positive control. In that case, the test compound may potential to have favorable binding affinity.

RESULTS

Molecular Target of Morusin

To identify potential targets for breast anticancer, a search for molecular targets of morusin was conducted. Direct, indirect, and potential target genes were explored using STITCH, STRING DB, and Venny 2.0, respectively. The results showed that STAT3 was the direct target protein (DTP) of morusin, while 20 other proteins were identified as indirect target proteins (ITPs). The DTPs and ITPs were combined and then compared to 5237 breast cancer regulatory genes obtained from NCBI, and the analysis yielded 21 PTTGs of morusin (Figure 2, Table 1).

Table 2 Gene ontology of morusin.

Gene ontology	Description
Biological process	Response to cytokines
	Cytokine-mediated signaling pathways
	Upregulation of protein kinase
	Downregulation of growth receptors
	Cell proliferation regulation
Celullar component	Transcription factor complex
	Caveola
Molecular function	STAT protein binding
	NF-κB binding
	SH2 domain binding
	Protein kinase binding
	Growth hormone receptor binding

Gene Ontology and KEGG Pathway Analysis

Gene ontology is categorized into main classes: biological processes, cellular components, and molecular functions. Biological processes affected by morusin was associated with responses to cytokines and their signaling pathways, regulation of apoptosis and its signaling pathways, and regulation of cell proliferation. The cellular components where morusin acted were transcription factor complexes and caveolae. The molecular functions affected by morusin include binding to various proteins such as STAT, NF-κB, SH2 domains, protein kinases, and growth hormone receptors (Table 2). Furthermore, results of KEGG pathway enrichment PTTGs morusin was involved in 87 signaling pathways. The 10 cancer-related signaling pathways is shown in Table 3.

Drug Association Analysis

Ninety-five drugs have similar targets with morusin after drug association analysis. The list of anticancer drugs is shown in Table 4.

Protein-protein Interactions and Top 10 Hub Genes

Of the 21 morusin's PTTGs, the interactions between proteins were analyzed, obtaining 21 nodes, 133 edges, 12.7 avg node degree, 0.792 avg local clustering coeficient and PPI enrichment p-value <1.0e-16. Cytohubba plugin was used to find the most interactions of each protein. The top 10 gene morusin hubs with the highest score degree are STAT3, EGFR, FOS, HIF1A, EP300, SRC, CCND1, MAPK1, HSP90AA, and RELA (Figure 3).

Table 3 KEGG pathway of morusin.

No	Description	Enrichment ratio	Genes
1	JAK-STAT signaling pathway	25.647	CCND1, CREBBP, EGFR, EP300, IL10RA, JAK1, JAK2, JAK3, LEPR, PIAS3, PTPN2, STAT3
2	Signaling pathway HIF-1	24.237	CREBBP, EGFR, EP300, HIF1A, MAPK1, RELA, STAT3
3	Signaling pathway Il-17	14.892	FOS, HSP90AA1, MAPK1, RELA
4	Signaling pathway estrogen	12.636	EGFR, FOS, HSP90AA1, MAPK1, SRC
5	Signaling pathway ErbB	12.220	EGFR, MAPK1, SRC
6	Signaling pathway VEGF	11.737	MAPK1, SRC
7	Signaling pathway Toll-like receptor	9.9876	FOS, MAPK1, RELA
8	Signaling pathway TNF	9.4429	FOS, MAPK1, RELA
9	Signaling pathway PI3K-Akt	7.8246	CCND1, EGFR, HSP90AA1, JAK1, JAK2, JAK3, MAPK1, RELA
10	Apoptosis	7.6376	CCND1, EGFR, HSP90AA1, JAK1, JAK2, JAK3, MAPK1, RELA

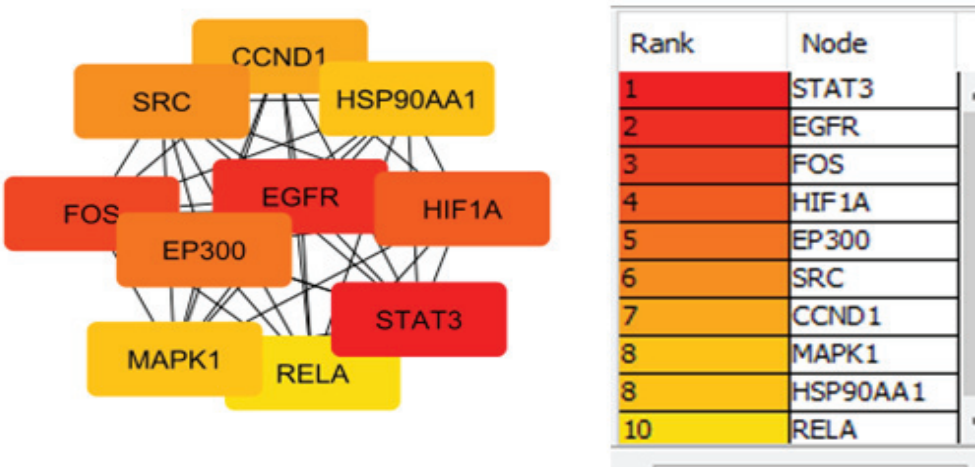

Figure 3. Top 10 hub gene of morusin.

Molecular Docking

The morusin was docked to EGFR, SRC, and MAPK1 proteins. The native ligand and lapatinib were docked as well as positive controls. The process was validated, results as shown in Table 5. Molecular docking of morusin showed that EGFR and SRC were potential targets of morusin. The bond energy of morusin was lower than that of the native and lapatinib ligands, with a bond energy of -9.6; -7.5; and -9.2 kcal/mol at EGFR and -8.2; -6.4; and -5.3 kcal/mol at SRC (Table 6). Morusin binds to EGFR with the key amino acid residues: Leu694, Val702, Leu820, Ala719, Leu768, and Lys721, while to SRC, the key amino acid residu was Lys295 and Gly344 (Figure 4). The interaction of morusin and amino acid residues are shown in Table 7.

DISCUSSION

We found 10 potential target of protein that can be targeted by morusin in breast cancer, including STAT3, EGFR, FOS, HIF1A, EP300, SRC, CCND1, MAPK1, HSP90AA, and RELA. Of the 10 genes, however, EP300, STAT3, FOS, HIF1A, RELA, HSP90AA1, and CCND1 are not well-established target as target of cancer drug. For example, EP300 is involved in increasing the apoptotic process so targeting EP300 can interfere with the apoptotic process. STAT3 can cause the cell growth process to become increasingly uncontrolled (Lee, *et al*., 2019). STAT3 has been identified as one of the top 10 gene targets of morusin. To validate this finding, we conducted a search for protein crystals and performed docking experiments using

Table 4. Drug association analysis.

Drug	Genes
Nilutamide	AR, HSP90AA1
Saracatinib	EGFR, SRC
Ruxolitinib	JAK1, JAK2, STAT3
Selumetinib	EGFR, MAPK1
Sunitinib	HIF1A, MAPK1
Gefitinib	EGFR, SRC, STAT3
Lapatinib	EGFR, SRC
Cetuximab	EGFR, SRC
Flutamide	AR, MAPK1
Erlotinib	EGFR, HSP90AA1, STAT3

Table 5. Protein validation result of EGFR, SRC, and MAPK1.

Protein	PDB ID	Native ligands	Validation score (RMSD)
EGFR	4HJO	aq4	1.346
SRC	2BDF	24a	1.101
MAPK1	2OJI	33a	0.736

PDB ID 6NUQ and 6NJS. However, the docking validation results for both proteins showed RMSD values exceeding 2, specifically 2.757 and 27.081, respectively. As a result, we did not to pursue further docking studies with this protein.

The targeting of FOS is currently not feasible due to the lack of a clear understanding regarding the molecular mechanism of c-fos and its effects in breast cancer (Muhammad, *et al*., 2017). Not all functions of HIF-1A are understood and do not always provide anti-tumor activity in clinical and pre-clinical studies (Shirai, *et al*., 2021). RELA cannot be targeted directly because RELA can be activated by itself even though it has been targeted to inhibit its activation (Giridharan and Srinivasan, 2018). Previous studies have not known the molecular mechanism of HSP90AA1 (Rong and Yang, 2018). Until now, there is no drug that targeted CCND1 directly, because CCND1 can only be affected through CDK4 and CDK6 (Goel, *et al*., 2017). So that the targets can be SRC, EGFR, and MAPK1.

EGFR is one of the receptor tyrosine kinases mediated by PI3 Kinase, Ras-Raf-MAPK, and JAK-STAT. These signaling pathways regulate various processes of cell proliferation and survival (Subramaniyan, *et al*., 2022). SRC regulates

Table 6. Binding energy value to protein target.

Protein	Morusin (kcal/mol)	Native ligand (kcal/mol)	Lapatinib (kcal/mol)
EGFR	-9,6	-7.5	-9.2
SRC	-8.2	-6.4	-5.3
MAPK1	-8.7	-8.7	-8.1

signaling from receptor tyrosine kinase through the SH2 domain, that regulate cell proliferation and survival (Ortiz, *et al*., 2021). MAPK1 is a protein present in the MAPK signaling pathway that activates several transcription factors CREB, c-Myc, and NF-κB (Braicu, *et al*., 2019). Therefore, morusin may affect cell growth through several signaling pathways like MAPK and JAK-STAT.

Morusin was successfully docked to EGFR, SRC, and MAPK1. In EGFR, morusin showed a better score than the native ligand and lapatinib, with the bond energy values were -9.6; -7.5, and -9.2 kcal/mol. Morusin binds to Leu694, Val702, Leu820, Ala719, Leu768, and Lys721. These amino acids are the active site of EGFR (Hajalsiddig, *et al*., 2020). In SRC, morusin showed a better score than the native and lapatinib ligands, where the bond energy values were -8.2; -6.4; and -5.3 kcal/mol. Morusin binds to Lys295 and Gly344, in which these amino acids are active sites in SRC (Hurtado, *et al*., 2020; Kufareva and Abagyan, 2008). The native ligands and lapatinib bind to Leu273, Leu293, Val281, and Ala293 which are important sites in the binding of compounds and proteins. In MAPK1 morusin has equal energy as the native ligand. The bond energies of morusin, native ligand, and lapatinib were -8.7; -8.7; and -8.1 kcal/mol. Morusin and native ligands have different binding bonds, morusin binds to Met106 and the native ligand binds to Gln103. Although the

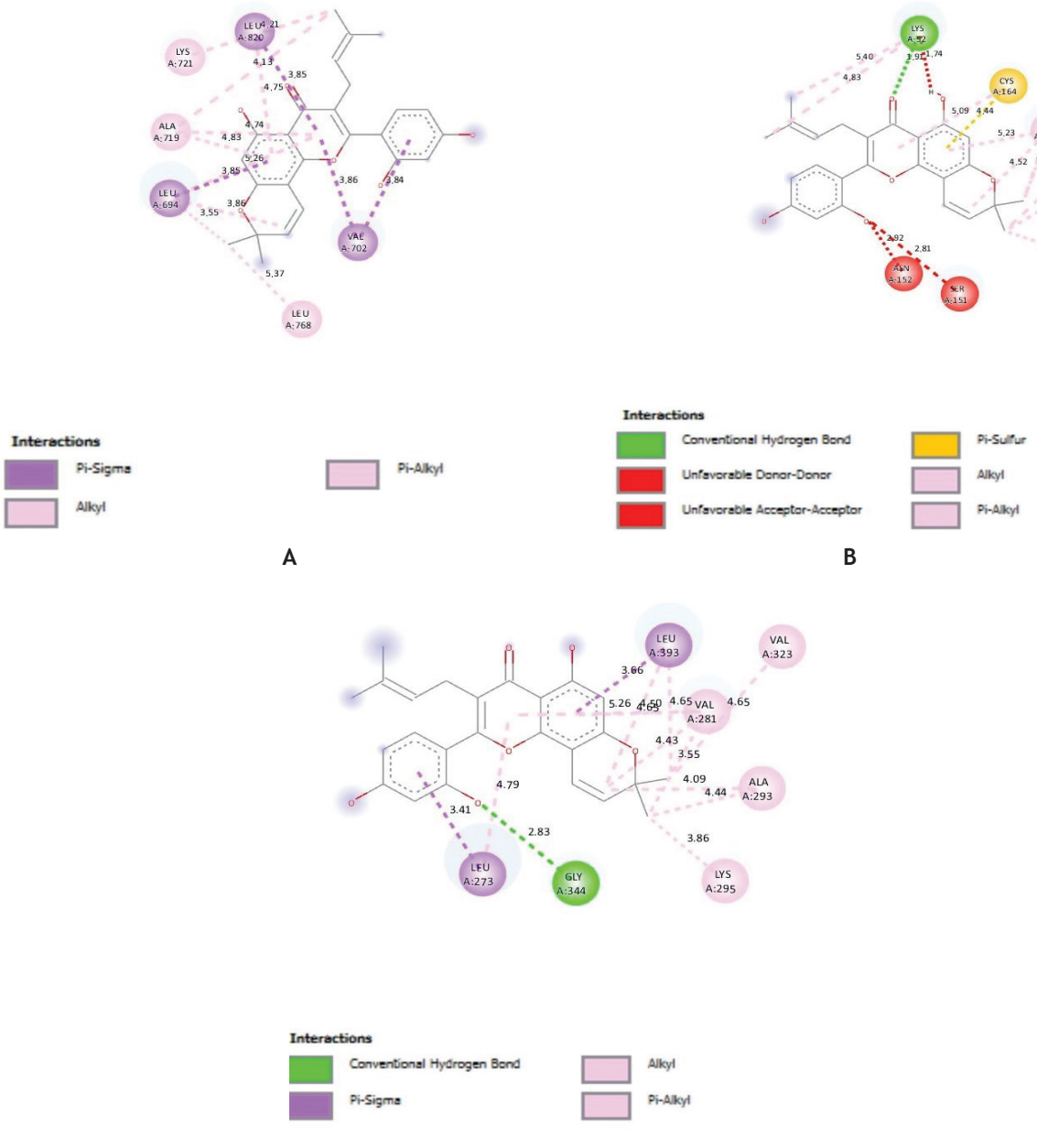

Figure 4. Interaction of morusin to protein targets. (A) EGFR, (B) MAPK1, (C) SRC.

binding was difference, the energy value was same, suggesting the binding provide the same affinity by targeting EGFR and SRC.

This indicates that morusin could be a potential compound in inhibiting cancer (Figure 4). However, this study has limitations in that it only shows potential targets and the active site of the target protein. Some experiment that have clarified protein target, such as bax and survivin (Kang, *et al*., 2017), did not included in the screening of bioinformatic approach, suggesting the limitation of the study. Further research is needed to examine the movement of each atom in a moving protein using molecular dynamics.

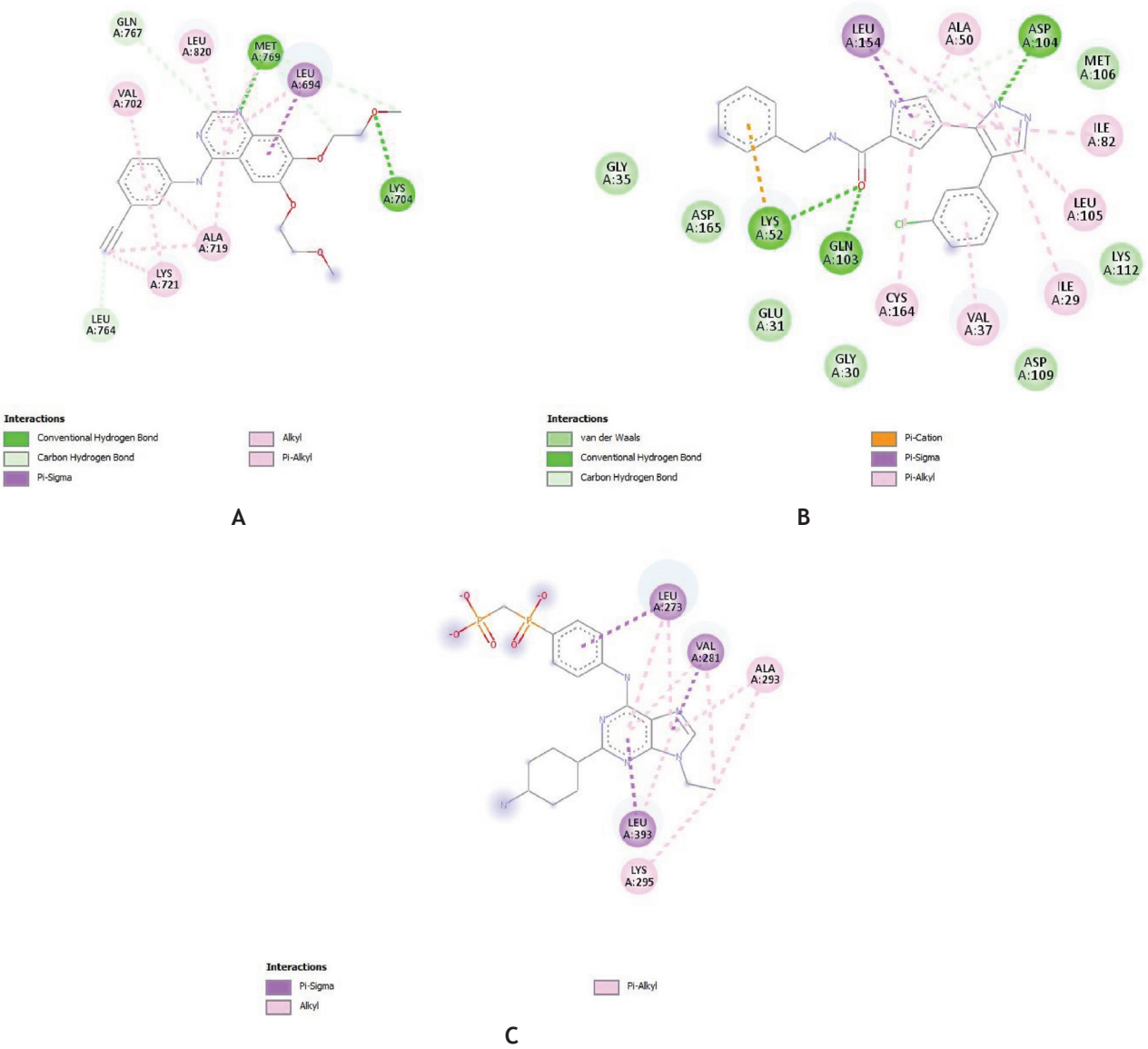

Figure 5. Interaction of native ligand to protein targets. (A) EGFR, (B) MAPK1, (C) SRC.

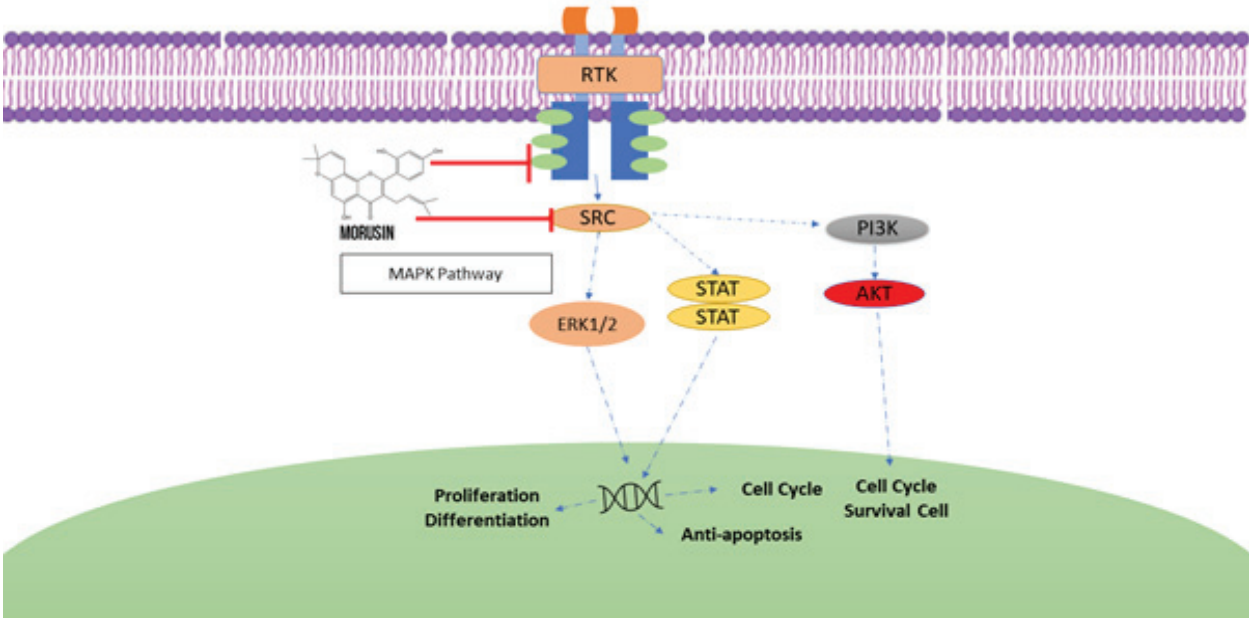

Figure 6. Possible mechanism of morusin to inhibit cancer.

CONCLUSIONS

Morusin can target EGFR, SRC, and MAPK1 proteins. The docking simulation resulted in morusin being able to be docked to EGFR and SRC which produced bond energies of -9.6 and -8.2 kcal/mol and bound to the amino acids Leu694, Val702, Leu820, Ala719, Leu768, and Lys721 on EGFR and bound to the amino acids Lys295 and Gly344 in SRC which are the active sites of these proteins.

ACKNOWLEDGMENT

This work was supported by the Jenderal Soedirman University under the International Research Collaboration (Project No. T/481/ UN23.18/PT.01.03/2022).

COMPETING INTERESTS

None.

REFERENCES

Aronov, A.M., Baker, C., Bemis, G.W., Cao, J., Chen, G., Ford, P.J., *et al.*, 2007, Flipped out: structure-guided design of selective pyrazolylpyrrole ERK inhibitors, *J. Med. Chem.*, **50**(6), 1280–1287.

Braicu, C., Buse, M., Busuioc, C., Drula, R., Gulei, D., Raduly, L., *et al.*, 2019, A comprehensive review on MAPK: A promising therapeutic target in cancer, *Cancers (Basel)*, **11**(10), 1618.

Chen, C.-P., Chan, K.-C., Ho, H.-H., Huang, H.-P., Hsu, L.-S., and Wang, C.-J., 2022, Mulberry polyphenol extracts attenuated senescence through inhibition of Ras/ERK via promoting Ras degradation in VSMC, *Int J Med Sci.*, **19**(1), 89–97.

Dalgarno, D., Stehle, T., Narula, S., Schelling, P., van Schravendijk, M.R., Adams, S., *et al.*, 2006. Structural basis of Src tyrosine kinase inhibition with a new class of potent and selective trisubstituted purine-based compounds, *Chem*

Biol Drug Des., **67**, 46–57.

Gautama, W., 2022, Breast cancer in indonesia in 2022: 30 years of marching in place, *Indonesian Journal of Cancer*, **16**(1), 1-2.

Giridharan, S., and Srinivasan, M., 2018, Mechanisms of NF-κB p65 and strategies for therapeutic manipulation, *J Inflamm Res.*, **11**, 407–419.

Goel, S., DeCristo, M.J., Watt, A.C., BrinJones, H., Sceneay, J., Li, B.B., *et al.*, 2017, CDK4/6 inhibition triggers anti-tumour immunity, *Nature*, **548**(7668), 471–475.

Hajalsiddig, T.T.H., Osman, A.B.M., and Saeed, A.E.M., 2020, 2D-QSAR Modeling and Molecular Docking Studies on 1H-Pyrazole-1-carbothioamide Derivatives as EGFR Kinase Inhibitors, *ACS Omega*, **5**, 18662–18674.

Hermawan, A., Ikawati, M., Jenie, R.I., Khumaira, A., Putri, H., Nurhayati, I.P., *et al.*, 2021, Identification of potential therapeutic target of naringenin in breast cancer stem cells inhibition by bioinformatics and *in vitro* studies, *Saudi Pharm J.*, **29(1)**, 12–26.

Hurtado, D.X., Castellanos, F.A., Coy-Barrera, E., and Tello, E., 2020, Prostaglandins Isolated from the Octocoral *Plexaura homomalla*: *In Silico* and *In Vitro* Studies Against Different Enzymes of Cancer, *Mar Drugs* **18**(3), 141.

Kang, S., Kim, E.-O., Kim, S.-H., Lee, J.-H., Ahn, K.S., Yun, M., and Lee, S.-G., 2017, Morusin induces apoptosis by regulating expression of Bax and Survivin in human breast cancer cells, *Oncol. Lett.*, **13**(6), 4558–4562.

Kufareva, I., and Abagyan, R., 2008, Type-II kinase inhibitor docking, screening, and profiling using modified structures of active kinase states, *J. Med. Chem.*, **51**(24), 7921–7932.

Lallo, S., Hardianti, B., Umar, H., Trisurani, W., Wahyuni, A., and Latifah, M., 2020, Anti-inflammatory and Wound Healing Activities of Mulberry Barks (*Morus alba* L.) Extract, *Galenika Journal of Pharmacy*, **6**(1), 26–36.

Lee, H., Jeong, A.J., and Ye, S.-K., 2019, Highlighted STAT3 as a potential drug target for cancer therapy, *BMB Rep.*, **52**(7), 415–423.

Muhammad, N., Bhattacharya, S., Steele, R., Phillips, N., and Ray, R.B., 2017, Involvement of c-Fos in the Promotion of Cancer Stem-like Cell Properties in Head and Neck Squamous Cell Carcinoma, *Clin. Cancer Res.*, **23**(12), 3120–3128.

Ortiz, M.A., Mikhailova, T., Li, X., Porter, B.A., Bah, A., and Kotula, L., 2021, Src family kinases, adaptor proteins and the actin cytoskeleton in epithelial-to-mesenchymal transition, *Cell Commun. Signal.*, **19**(1), 67.

Panek-Krzyśko, A., and Stompor-Gorący, M., 2021, The Pro-Health Benefits of Morusin Administration-An Update Review, *Nutrients* **13**(9), 3043.

Park, J.H., Liu, Y., Lemmon, M.A., and Radhakrishnan, R., 2012, Erlotinib binds both inactive and active conformations of the EGFR tyrosine kinase domain, *Biochem. J.*, **448**(3), 417–423.

Rong, B., and Yang, S., 2018, Molecular mechanism and targeted therapy of Hsp90 involved in lung cancer: New discoveries and developments (Review), *Int. J. Oncol.*, **52**(2), 321–336.

Shirai, Y., Chow, C.C.T., Kambe, G., Suwa, T., Kobayashi, M., Takahashi, I., *et al.*, 2021, An Overview of the Recent Development of Anticancer Agents Targeting the HIF-1 Transcription Factor, *Cancers (Basel)*, **13**(11), 2813.

Subramaniyan, V., Fuloria, S., Gupta, G., Kumar, D.H., Sekar, M., Sathasivam, K.V., *et al.*, 2022, A review on epidermal growth factor receptor's role in breast and non-small cell lung cancer, *Chem. Biol. Interact.*, **351**, 109735.

Sun, Y., and Yang, J., 2019, A bioinformatics investigation into the pharmacological mechanisms of the effect of Fufang Danshen on pain based on methodologies of network pharmacology, *Sci. Rep.*, **9**, 5913.

Tang, J.-W., Xiong, X.-S., Qian, C.-L., Liu, Q.-H., Wen, P.-B., Shi, X.-Y., *et al.*, 2021, Network pharmacological analysis of ethanol extract of Morus alba linne in the treatment of type

2 diabetes mellitus, *Arabian Journal of Chemistry*, **14**(10), 103384.

Wani, M.Y., Ganie, N.A., Wani, D.M., Wani, A.W., Dar, S.Q., Khan, A.H., *et al.*, 2023, The phenolic components extracted from mulberry fruits as bioactive compounds against cancer: A review, *Phytother Res.*, **37**(3), 1136–1152.

Zhang, X., Shen, T., Zhou, X., Tang, X., Gao, R., Xu, L., *et al.*, 2020, Network pharmacology based virtual screening of active constituents of *Prunella vulgaris* L. and the molecular mechanism against breast cancer, *Sci. Rep.*, **10**, 15730.