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In Silico Study of Moringa Leaf (*Moringa oleifera* L.) Compounds as an Antiproliferative in Hepatocellular Carcinoma against TGF-β Receptor

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ABSTRACT. Liver cancer is a condition in which liver cells grow uncontrollably. Liver cancer, also known as hepatoma, occurs when cells proliferate and acquire malignant properties. Liver cancer is among the types of cancer with a high contribution to global mortality rates each year. This study aims to predict and identify the activity of compounds isolated from Moringa leaves (*Moringa oleifera* L.) against liver cancer by targeting the TGF-β receptor using molecular docking. The research was conducted using software tools including LigandScout, ADMETlab 2.0, BIOVIA Discovery Studio Visualizer, and AutoDock Tools. The results showed that ten out of eleven test compounds from *Moringa oleifera* L. leaves met Lipinski's Rule of Five, indicating their potential as good oral drug candidates. Pharmacophore screening yielded an AUC100 value of 0.94 with three hit compounds: rutin, kaempferol, and isorhamnetin. In the molecular docking stage, the compound with the lowest binding energy was Isorhamnetin, with a binding energy of -8.18 kcal/mol against the TGF-β receptor, and it also demonstrated a favorable ADMET profile.

INTRODUCTION

Liver cancer is divided into two types, namely primary liver cancer originating from liver parenchyma cells, while secondary liver cancer is caused by metastasis of organs around the intestines, breasts, lungs, pancreas, kidneys, and skin. Hepatocellular carcinoma is included in the primary liver cancer. Hepatocellular carcinoma is the most common primary tumor of the liver, accounting for 75% of all cancers of the liver (Watson *et al*., 2016; São Paulo *et al*., 2017). The malignancy of hepatocellular carcinoma arises from hepatocytes, which are large, polyhedral, or cuboidal epithelial cells that constitute a major component of the liver (Mescher, 2016; Abbas *et al*., 2024). Hepatocarcinoma has several risk factors, including prolonged alcohol consumption, hepatitis B, hepatitis C, and non-alcoholic fatty liver disease. In addition, it can be caused by Wilson's disease, hereditary hemochromatosis, alpha-1-antitrypsin deficiency, primary biliary cirrhosis, and autoimmune hepatitis (Ghouri *et al*., 2017).

Treatment of liver cancer usually depends heavily on the stage of the tumor (the size and spread of the tumor) and the severity of the underlying liver disease. Treatment of liver cancer includes chemotherapy, surgery, and liver transplantation. Chemotherapy treatment is given with antitumor drugs, such as fluorouracil and adriamycin, to extend life expectancy. Chemotherapy drugs will be given into the hepatic artery so that the drug goes directly into the cancer cells in the liver. In addition to being given antitumor drugs, liver surgery can be done when the liver cancer stage is still early (in one lobe only, and there are no signs of liver cirrhosis). The last treatment method, if liver cirrhosis has been found and there is ongoing liver damage (cancer cells have entered the portal vein), liver transplantation can be done (Peckenpaugh, 2009).

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Therefore, efforts to reduce the death rate of liver cancer are necessary to find safe and effective alternative therapies. Moringa (*Moringa oleifera* L.) is known as a nutritious plant, and almost all parts of the plant have benefits for human life; from the leaves, bark, stems, and flowers to the roots, it has long been known as a medicinal plant. Moringa leaves have a complete nutritional content, including iron, calcium, and vitamin A (Ulfa *et al*., 2023). Traditionally, this plant has been used to treat conditions such as hyperglycemia, inflammation, bacterial or viral infections, and cancer (Mthiyane *et al*., 2022; El-Hack *et al*., 2022). The high antioxidant content makes moringa leaves one of the sources of external antioxidants that promise to support cancer treatment (Kusmardika, 2020). Various parts of the moringa plant, such as its leaves, stems, flowers, and seeds, are known to contain significant antioxidant compounds, including α-, β-, and γ-tocopherol, stigmasterol, campesterol, quercetin, kaempferol, vitamin A, and vitamin C (Ulfa *et al*., 2023). The anticancer effect of moringa leaves comes from the abundant content of phenolic compounds, including phenol compounds and their derivatives, such as gallic acid, chlorogenic acid, luteolin, rutin, quercetin, kaempferol, isorhamnetin, and apigenin (Qanitah *et al*., 2023).

Oxidative stress, triggered by free radicals and reactive oxygen species, plays a crucial role in the development of degenerative diseases, including cancer, diabetes, atherosclerosis, and stroke. Preventing and resisting oxidative stress can involve using antioxidants; hence, antioxidants are very important for the body. Antioxidants neutralize free radicals generated by the body's metabolic processes or by external factors, such as air pollution, sun exposure, and environmental contamination. The mechanism of action of antioxidants is to donate hydrogen atoms or protons to free radicals, making them more stable. One potential natural source of antioxidants is moringa leaves (*Moringa oleifera* L.). This plant has long been used in traditional medicine due to its high nutrient and bioactive compound content. Antioxidants play an important role in inhibiting cancer cell growth, while potassium helps destroy cancer cells. In addition, the amino acid content in moringa leaves can enhance immune function (Kusmardika, 2020).

Transforming growth factor beta (TGF-β) is a multifunctional cytokine that is expressed by almost all tissues and cell types. Signal transduction from TGF-β can stimulate a wide range of cellular responses and is essential for embryonic development, wound healing, tissue homeostasis, and immune homeostasis in health. TGF-β dysfunction can play a key role in many diseases, and many targeted therapies have been developed to improve its pathogenic activity. In recent decades, extensive research on TGF-β signaling has been conducted, spanning a broad range of topics in health, disease, and therapy. Thus, a comprehensive overview of TGF-β signaling is necessary to provide a framework for studies in this area (Deng *et al*., 2024).

Members of the Transforming Growth Factor-beta (TGF-β) superfamily are essential for tissue homeostasis, and consequently, dysregulation of its signaling pathways contributes to the development of human diseases. In the liver, TGF-β signaling participates in all stages of disease progression from early liver injury to hepatocellular carcinoma (HCC). During liver carcinogenesis, TGF-β plays a dual role in cancer cells. It acts as a suppressor in the early stages but contributes to tumor development later in life after the cells have escaped its cytostatic effects. In addition, TGF-β can modulate the responses of cells in the tumor microenvironment, contributing to the development of HCC and promoting immune evasion of cancer cells. Thus, targeting the TGF-β pathway can be an effective therapeutic option for HCC treatment. However, it is crucial to identify biomarkers that predict tumor response and precisely select patients who can benefit from TGF-β inhibition therapy (Gonzalez-Sanchez *et al*., 2021).

Moringa leaves (*Moringa oleifera* L.) are known to have affinity with TGF-β receptors (TGFBR) through antioxidant properties that can ward off free radicals and may reduce the production of pro-inflammatory cytokines, thereby improving and protecting the potential for thioacetamide-induced liver damage (TAA) (Susanto *et al*., 2021). Based on research by Susanto *et al*. (2021), Moringa leaf extract used in male rats showed hepatoprotective effects by decreasing TGF-β expression and improving liver histological structure. In mice treated with moringa leaf extract, fewer immune cells were observed, and the tissue structure resembled that of placebo-treated mice. In addition, antioxidant compounds in moringa leaves can reduce the expression of TGF-β1 and the pro-inflammatory cytokines IL-6 and TNF-α, thereby suppressing hepatic stellate cell activity and inhibiting excess fibrogenesis.

The rapid reproduction or growth of cells to produce new tissues, cell parts, and offspring is known as proliferation. Antiproliferative compounds are substances that can inhibit growth via various mechanisms (Hidayah, 2023). Moringa leaves contain beta-carotene, vitamin C, vitamin E, flavonoids including quercetin, kaempferol, vicenin-2, and natural antioxidants. The flavonoids in it increase the levels of growth factors needed for wound healing, such as epidermal growth factor (EGF), transforming growth factor α (TGF-α), TGF-β, platelet-derived growth factor (PDGF), VEGF, and fibroblast growth factor (FGF), thereby accelerating healing. This benefit

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accelerates the inflammatory phase, leading to the proliferative phase starting earlier and wound healing occurring faster (Jaya *et al*., 2023).

Moringa leaves (*Moringa oleifera* L.) may work as an antiproliferative against TGF-β receptors. The TGF-β signaling pathway is associated with proliferation. TGF-β signaling is involved in all stages of liver disease development, from primary liver injury, inflammation, and fibrosis to cirrhosis and cancer. TGF-β has cytostatic and apoptosis effects on hepatocytes, as well as supporting liver differentiation during embryonic development and liver physiological regeneration. Therefore, TGF-β signaling pathway tracking is being studied to prevent the progression of liver disease (Aly *et al*., 2020).

The results of the research conducted by Aly *et al*. (2020) showed a significant improvement after treatment with *Moringa oleifera* extract, and in the prophylactic group, a significant decrease in TNF-α and TGF-β levels to levels below normal. This is due to the hepatoprotective effect of *Moringa oleifera* against liver inflammation, as evidenced by decreased TNF-α levels in the liver, consistent with the findings of Mahajan *et al*. (2017) Tumor necrosis factor alpha (TNF-α) plays an important role in inflammation and fibrosis of the liver; it activates NF-κB, which is a major driver of inflammation, activates the main fibrogenic molecule TGF-β, and stimulates survival and production of active myofibroblasts through differentiation of hepatic stellate cells (HSCs)

Metformin was chosen as the standard compound because, in addition to being an antidiabetic drug, it has been shown to have anticancer effects, particularly in preventing the development of hepatocellular carcinoma (HCC). The mechanism involves both AMPK-dependent and AMPK-independent pathways that inhibit cancer cell growth and lower the risk of HCC (Kholili *et al*., 2023). Therefore, metformin is a relevant comparison in this study.

This study aims to find more affordable and effective antiproliferative candidates against hepatocellular carcinoma derived from moringa leaves. This study was carried out *in silico*, with compounds selected based on several parameters to ensure they have potential as drug candidates. Based on research Chang *et al*. (2022), it is explained that the compound is selected based on the variation of structure, the fulfillment of the parameters *drug-likeness*, *Screening* initial physicochemical properties and ADME/toxicity predictions to prioritize compounds with better pharmacokinetic character, and also based on compatibility with target receptor characteristics as can be seen from their pharmacophoric features and Fit score which can provide an estimate of the bond affinity strength. This is followed by molecular docking to estimate the orientation of drug candidate bonds to their protein targets, thereby identifying the complex with the highest affinity and stability.

RESEARCH METHODS

The tool used in this study is hardware, namely a laptop with Asus Vivobook 14 A1404ZA specifications, featuring an 11th Gen Intel(R) Core(TM) i5-1135G7 processor and 8 GB of RAM. The software used is PubChem, Pre-ADMET, Chem3D Pro 12.0, and DUD. E A Database of Useful Decoys: Enhanced, LigandScout, Research Collaboratory for Structural Bioinformatics (RCSB) Protein Data Bank, BIOVIA Discovery Studio 2021, and AutoDock Tools-1.5.6.

The ingredients used in this study include Transforming Growth Factor (TGF)-β, natural ligand structure PDB ID: 3HMM, standard drug Metformin, 11 moringa leaf compounds, namely rutin, kaempferol, quercetin, o-coumaric acid, myricetin, ellagic acid, ferulic acid, sinapic acid, gallic acid, syringic acid, and isorhamnetin.

Lipinski's Rule of Five Prediction

The active compounds contained in candidate plants from various sources were obtained through the https://pubchem.ncbi.nlm.nih.gov/page. Then, it was stored as 2D and 3D structures of each active compound identified. The physicochemical properties of each active compound were predicted using the SMILES code, which was copied into ADMETIab 2.0 and Mcule. The analysis of the prediction results for the candidate active compound in the drug must meet 5 Lipinski rules: molecular weight <500 Da, hydrogen bond donor count <5, hydrogen bond acceptor count <10, and log P <5 (Lipinski, 2000).

ADME-Tox Prediction

The structures of the compounds in the test plant, in SMILES format, were copied from https://pubchem.ncbi.nlm.nih.gov/. ADME-Tox prediction was performed using the ADMET Screening feature on https://preadmet.webservice.bmdrc.org/. Next, choose one of the prediction features from Pre-ADMET: Drug-likeness Prediction, ADME Prediction, and Toxicity Prediction. Predictions were produced for each compound in

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the form of Human Intestinal Absorption (HIA), Caco-2, Plasma Protein Binding (PPB), Brain-blood Barrier (BBB), mutagens, and carcinogens (Dewayani *et al*., 2023; Lestyawan *et al*., 2024).

Pharmacophore Validation and Screening

Pharmacophore model validation was carried out by preparing active databases, decoys, and test compounds. A total of 100 active compounds and 400 decoy compounds were compiled in an MDL MOL/SD file format and analyzed using BIOVIA Discovery Studio software. All test compound types were converted to tests using LigandScout and stored in .ldb format. The minimized database was then reopened in LigandScout. Next, compound clustering was performed by clicking the cluster to create clusters for all compounds. Then, the compounds were sorted by selecting the cluster ID column and changing the type from training to ignored until only one training type remained. After obtaining 1 type of training in each cluster, pharmacophores were generated, yielding up to 10 models. The ten models were stored in .pmz format and moved with the "copy to the other perspective" feature into the "screening perspective". After completion, the ROC curve screening results were displayed by pressing the ROC curve plot button for ten pharmacophoretic models, and the best ROC result was selected. After pharmacophore validation, pharmacophore screening was performed. In the "screening perspective", the test compound database was inserted by pressing the database "load screening". After that, the test compound database was marked by applying a green color and removing the color mark from the other databases (active and decoy). In the "ligand-based perspective", the best model was transferred to the "screening perspective", and "performance screening" was carried out until the process was completed and the "hit" compound was obtained (Fernanda *et al*., 2023).

***Molecular Docking* and Test Result Visualization**

Before docking the molecules, ligands, and receptors were prepared. The ligand structure was downloaded from the PubChem website and prepared in AutoDock Tools by adding Hydrogen atoms, assigning Gasteiger charges, and applying torsion. The 3D structure of the TGF-β receptor (PDB ID: 3HMM) and its natural ligands were obtained from the Protein Data Bank and prepared in BIOVIA Discovery Studio by removing the original water, hydrogen, and ligand molecules. The selection of the protein structure (GDP ID: 3HMM) was based on its resolution of lower than 2.0 Å, *i.e.*, 1.7 Å, which provides high-accuracy atomic positions and yields a more accurate representation of the structure, making it more suitable for computational modeling. The selection of proteins was also based on the availability of the DUD-E database, ensuring that the protein structures used for docking and pharmacophore screening come from the same source. The consistent use of PDB code at both stages of analysis ensures that the built model remains aligned and standardized. This is important for producing more specific, representative, and coherent observations, thereby enabling more accurate interpretation of the results. The receptors and ligands of the preparation were stored in .pdbqt format. Validation was done through redocking the receptor with its natural ligands using AutoDock Tools. Validation is considered good if the RMSD value is < 2 Å. The observed parameters included RMSD values, hydrogen bonds, and amino acid residues. Furthermore, the determination of the grip was carried out based on the position of the natural ligand. The test ligand docking simulation on the receptor was run 100 times using the genetic algorithm, and the results were stored in .dpf format. The visualization of test results in 2D and 3D was performed using the AutoDock Tools application and the BIOVIA Discovery Studio Visualizer software, which displays interaction data between ligands and amino acids. The visualization results were saved in JPG format (Lestyawan *et al*., 2024).

RESULTS AND DISCUSSION

Lipinski's Rule of Five Prediction

Lipinski's Rule of Five was used to predict a compound's ability to cross the cell membrane and assess its potential as an oral drug (Cahyaningrum *et al*., 2024). Prediction results for Lipinski's Rule of Five are shown in Table 1. Lipinski's Rule of Five plays a major role in the discovery of new drug compounds. This rule is specifically used to predict drug similarity, especially the physicochemical properties of a compound and its rate of oral absorption in the human body (Dewayani *et al*., 2023). Orally administered drug compounds must meet these rules. In addition, this rule allows the permeability of a drug during passive diffusion to be observed (Arief and Hairunnisa, 2022). Lipinski's Rule of Five states that a compound is considered to have drug-like properties if it meets the criteria, i.e., it has a molecular weight of 500 Daltons, has a hydrogen bond donor number of 5, a log partition coefficient value of P 5, and a hydrogen bond acceptor number of 10 (Lipinski, 2000).

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Each parameter of Lipinski's Rule of Five relates to a compound's pharmacokinetic properties and bioavailability during an organism's metabolic processes. If a compound meets these five rules, then the properties in the compound will increase as well. The partition coefficient parameter (log P) is related to the lipophilicity of the drug, which affects the ability of a compound to penetrate the cell membrane composed of lipids. The greater the log value of P, the greater the hydrophobicity properties and the stronger the ability to penetrate the cell membrane. However, if the partition coefficient is greater than 5, it will lead to higher toxicity because the compound will be retained longer on the membrane, reducing the selectivity of the drug-target interaction. The molecular weight parameter should be less than 500 Daltons, as drugs with molecular weights exceeding this value have reduced ability to penetrate biological membranes. The hydrogen bond parameter has a rule that the number of acceptor hydrogen bonds is no more than 10 and the number of donor hydrogen bonds is no more than 5. If the number of hydrogen bonds increases, the energy required to drive the absorption process will also increase (Kilo *et al*., 2019).

Table 1. Lipinski's Rule of Five (RO5) prediction result.

No.	Compound Name	Pubchem ID	Molecular weight (< 500 Da) 1 Da = 1 g/mol	Log P (<5)	Hydrogen Bonding		Compliance
					Donor (<5)	Acceptor (< 10)	
1.	Metformin	4091	129.100	0.062	5	5	Yes
2.	Rutin	5280805	610.150	-1.687	10	16	No
3.	Kaempferol	5280863	286.050	2.656	4	6	Yes
4.	Quercetin	5280343	302.040	2.155	5	7	Yes
5.	o-Coumaric acid	637540	164.050	2.182	2	3	Yes
6.	Myricetin	5281672	194.060	1.803	2	4	Yes
7.	Ellagic acid	5281855	302.010	1.117	4	8	Yes
8.	Ferulic acid	445858	194.1834	1.4986	2	4	Yes
9.	Sinapic acid	10743	224.070	1.572	2	5	Yes
10.	Gallic acid	370	170.020	0.645	2	5	Yes
11.	Syringic acid	10742	198.050	1.212	2	5	Yes
12.	Isorhamnetin	5281654	316.060	2.541	4	7	Yes

Based on Lipinski's Rule of Five (RO5), of the eleven compounds in moringa leaves (*Moringa oleifera* L.), only one, rutin, does not meet the rule. This implies that rutin has poor membrane permeability, so the likelihood of oral absorption is very low, whereas the other 10 compounds meet Lipinski's Rule of Five. Therefore, there are only ten compounds that can be administered orally, namely kaempferol, quercetin, o-coumaric acid, myricetin, elagatic acid, ferulic acid, sinapic acid, gallic acid, siringic acid, and isorhamnetin. Rutin compounds cannot be administered orally, but they can still be developed into drugs via other routes of administration, such as intraperitoneal injection (Prasad and Prasad, 2019). In addition, Lipinski's Rule of Five also relates to the pharmacokinetic properties and bioavailability of compounds, as well as the permeability of a drug in passive diffusion. Based on the analysis, the rutin compound showed lower pharmacokinetic properties and bioavailability than the other 10 compounds.

Determination of ADME-Tox

ADME-Tox is determined to assess the pharmacokinetic properties of the drug candidate compound. The parameters observed include the absorption process, distribution, and potential toxicity, which can cause genetic mutations and are carcinogenic (Dewayani *et al*., 2023). The results of the determination of ADME-Tox are shown in Table 2.

ADME-Tox predictions were generated for each compound that met Lipinski's rule using the PreADMET-Tox software. ADMET prediction was performed to obtain information on the pharmacokinetic properties of a compound, including ADME parameters (absorption, distribution, metabolism, and excretion), as well as the drug candidate's toxicity (Dewayani *et al*., 2023). Absorption parameters were reviewed through Human Intestinal Absorption (HIA) and Caco-2. HIA predicts the likelihood that a drug compound will be absorbed by the human gut after oral administration. The resulting HIA parameter (++) indicates that the drug compound is absorbed quite well, while (---) indicates that the absorption of the drug compound is low. Caco-2 predicts the ability of a drug

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compound to penetrate intestinal cells, specifically through the layers of Caco-2 cells that mimic the walls of the human intestine. A compound is considered to have good Caco-2 permeability if the predicted value is > (-5.15) log cm/s. After testing, it was found that there was 1 compound that had a HIA value (++), which indicated good absorption, namely only rutin compounds, and other compounds had a HIA value (--), namely kaempferol, quercetin, o-coumaric acid, myricetin, ellagic acid, ferulic acid, sinapic acid, gallic acid, syringic acid, and isorhamnetin. Meanwhile, in the Caco-2 test, several compounds showed good Caco-2 values, namely Kaempferol, o-Coumaric Acid, Ferulic Acid, Sinapic Acid, Syringic Acid, and Isorhamnetin, with values greater than -5.15 log cm/s (Wulandari *et al*., 2023).

Table 2. The results of the determination of ADME-Tox.

No	Compound Name	Absorption HIA (%)	PPB Distribution (%)	Mutagen Toxicity	Carcinogenic	
1.	Metformin	---	-5.745	5.598%	Non Mutagen	++
2.	Rutin	++	-6.740	87.111%	Mutagen	---
3.	Kaempferol	---	-4.974	97.861%	Mutagen	---
4.	Quercetin	---	-5.204	95.496%	Mutagen	---
5.	o-Coumaric acid	---	-4.903	90.365%	Non Mutagen	---
6.	Myrisetin	---	-5.653	92.766%	Non Mutagen	---
7.	Ellagic acid	--	-5.312	78.228%	Non Mutagen	-
8.	Ferulic acid	---	-4.902	89.754%	Non Mutagen	-
9.	Sinapic acid	--	-4.962	88.799%	Non Mutagen	--
10.	Gallic acid	---	-5.728	53.494%	Non Mutagen	---
11.	Syringic acid	---	-5.142	50.890%	Non Mutagen	---
12.	Isorhamnetin	---	-5.056	96.235%	Mutagen	---

Distribution predictions are reviewed through the Plasma Protein Binding (PPB) and Blood-Brain Barrier (BBB). PPB predicts the percentage of drug binding with blood plasma proteins. The United Nations is interpreted with a < value of 90% indicating poor results, while a > value of 90% indicates good results because the compound will bind strongly to the protein, and its therapeutic effects can be reduced. The BBB parameter predicts the likelihood that a drug compound can break through the physiological barrier between the circulatory system and the brain. BBB is indicated by (+), which means the drug passes through the brain membrane, or (-), which means the drug does not pass through the brain membrane. After testing, it can be concluded that the compounds kaempferol, quercetin, o-coumaric acid, myricetin, and isorhamnetin exhibit high PPB values, indicating nonspecific binding to plasma proteins. This suggests that they have a longer half-life and less excretion (Tahiroğlu *et al*., 2025). In the BBB test, all active compounds produced (-), indicating that none can penetrate the Blood-Brain Barrier, which is a parameter that indicates a lower likelihood of toxicity because the therapeutic target is not intended to reach the brain (Lestyawan *et al*., 2024).

Toxicity parameters are used to predict the possible presence of mutagens and carcinogens. The mutagenic properties of a compound can cause genetic changes or mutations in cells, while its carcinogenic properties can cause cancer. Both are interpreted as (+), indicating the probability of being a mutagen or carcinogen, and (-), indicating the probability of not being a mutagen or carcinogen. After testing, it was found that 4 compounds showed a potential to become mutagens: rutin, kaempferol, quercetin, and isorhamnetin. This can happen because, in general, flavonoid compounds exhibit mutagenic activity related to their basic molecular structure. It is known that mutagenicity is associated with the ability to increase oxidative stress and DNA damage (Alcaraz *et al*., 2021*)*. For the carcinogen parameter, the data showed that all compounds produced a (-), indicating a low probability of carcinogenicity (Lestyawan *et al*., 2024).

Based on the results, a pharmacokinetic profile for each compound was generated. The parameters reviewed for absorption are HIA is the extent to which a drug or compound can be absorbed by the human intestine, Caco-2 (Human Colon Adenocarcinoma) is a prediction of a drug in the permeability of drug transfer through the epithelial cells of the colon; for distribution is PPB to predict the distribution of drug compounds based on affinity to blood proteins; and for toxicity is a test against mutagens that show There is a potential to cause genetic mutations and carcinogens that can predict a compound that causes cancer (Wulandari *et al*., 2023). Metformin has an HIA value

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(---), which indicates that the absorption of this drug is quite low in the gastrointestinal tract. This is also supported by the low Caco-2 value, which indicates that intestinal cell penetration is difficult. The UN value of 5.598% indicates that the compound is not strongly bound to plasma proteins, which can reduce its therapeutic effect. Nonetheless, metformin is not mutagenic, but it has potentially carcinogenic properties.

The results of the pharmacokinetic profile prediction showed that the good results at the parameters of the HIA were rutin; at Caco-2 were kaempferol, o-coumaric acid, ferulic acid, synaptic acid, syringic acid, and isorhamnetin; at PPB were Kaempferol, Quersetin, o-Kumaric Acid, Myricetin, and Isorhamnetin; at BBB none showed (+); at Mutagens that produced mutagens that produced mutagens probabilities were rutin, kaempferol, quercetin, and isorhamnetin; and in the carcinogen the whole compound produces (-).

Pharmacophore Validation and Screening

In general, the area under the curve (AUC) is considered valid when it exceeds 0.7 (Sangande and Uneputty, 2021), indicating that selectivity is acceptable and that the model can effectively distinguish between two groups, such as active and inactive compounds. Based on the test, the ROC curve with an AUC of 0.94 showed valid results and could select well. In addition, 126 hit compounds were identified among 500 tested compounds (100 active and 400 decoys). Pharmacophores are structural elements of a drug compound that are needed to ensure optimal interaction with a specific biological target and to activate or inhibit the desired biological response (Riyaldi *et al*., 2022). On the ROC curve (Figure 1), the x-axis shows the percentage of decoys obtained (false positive rate), also commonly known as 1-Specificity. Lower x-axis values indicate a higher level of accuracy. Meanwhile, the y-axis indicates the percentage of active compounds that are successfully recognized as true positive rate or sensitivity, while the higher the value on the y-axis, the higher the accuracy rate.

Another parameter, the AUC value on the ROC curve, is in the range 0 to 1. AUC assesses the model's accuracy; the higher the value, the better the ability to select the active compound over decoys. When the AUC is 0.5, it indicates that the model cannot perform selection. Conversely, if the AUC value increases above 0.5 or approaches 1, the model's accuracy will be higher. Generally, the AUC value is considered valid when ≥ 0.7, as it already has acceptable selection criteria (Sangande and Uneputty, 2021). A ROC curve with an AUC of 0.94 was obtained, indicating that the model is valid. Known active compounds or true positives, as many as 91 out of 100 compounds, then for recognized decoy compounds or false positives, as many as 35 out of 400 decoys, so that the total hits obtained were 126 hits. The presence of 126 hit compounds indicates that they were selected as early candidates because they meet criteria that match pharmacophore features, suggesting they have the potential to be active as drugs (Sangande and Uneputty, 2021). The hit compound will then proceed to the next stage, which is molecular docking.

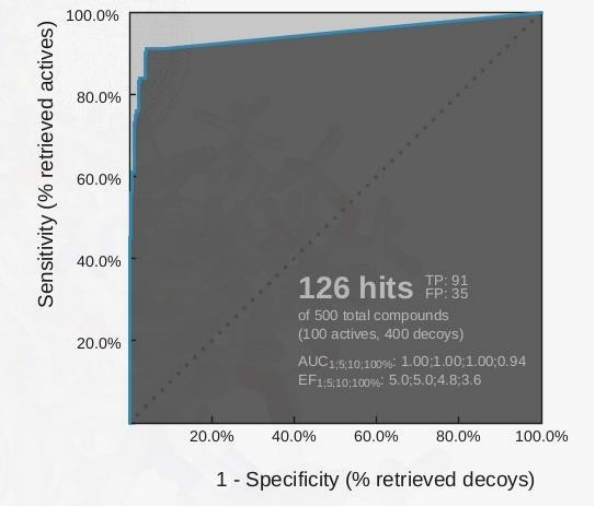


Figure 1. Pharmacophore screening ROC curve.

AUC Value of Pharmacophore Filtration Validation Results

Of the eleven test compounds, three were identified as hit compounds: isorhamnetin, kaempferol, and rutin (Figure 2). Each hit compound has a different fit score. Among the three, the test compounds, rutin and kaempferol, had the highest fit score, 47.21.

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After validation, followed by pharmacophore screening of the test compounds, 3 of 11 test compounds were found to hit the pharmacophore model. The three test compounds are isorhamnetin, kaempferol, and rutin. The pharmacophore model presents a three-dimensional array of chemical features and steric constraints required for small molecules to interact with specific proteins. The fit score is obtained based on the degree of compatibility between the features in the model and the features possessed by the compound, so that this score aims to sequence the hit molecules caused by each model (Vásquez et.al., 2021).

In the screening results (Table 3), two compounds had the same fit score: kaempferol and rutin, both with a fit score of 47.21. Both compounds have a better pharmacophore model resemblance than the other hit compound, namely, isorhamnetin. A higher fit score indicates a better fit for the targeted environment, suggesting the compound has the potential to show optimal activity against the target (Opo *et al*., 2021).

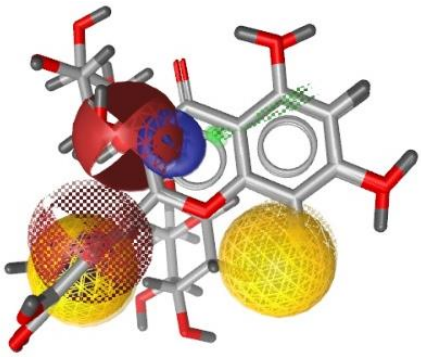


Figure 2. Results of screening of hit compounds (isoharmnetin, kaempferol, rutin).

Table 3. Pharmacophoretic screening fit score results.

No.	Compound Name	Fit Score
1.	Isorhamnetin	47.10
2.	Kaempferol	47.21
3.	Rutin	47.21

Molekuler Docking Validation

Validation of the docking process is carried out by redocking or re-docking ligands to the active site of the origin protein. By redocking, it means rematching the 3-dimensional conformation of the natural ligands of the receptor with the original conformation according to the one downloaded from the PDB site, with the conformation of the natural ligands resulting from the redocking process, which is run against the receptor 100 times to see the best conformation of the natural ligands to the receptor.

The aspects compared are the conformations of ligands between natural ligands (experimental poses) and those obtained from the redocking process (prediction poses). Then, the main quantitative metric used to determine validation success is the Root Mean Square Deviation (RMSD). Low RMSD (generally ≤ 2 Å) between natural ligands and redocked ligands indicates validation success. Visually, it can be seen whether the redocked ligands occupy a protein binding site with the same orientation as the natural ligand. In addition, amino acid residues that interact with natural ligands can also be compared to amino acid residues that interact with redocked ligands. This comparison is done to ensure that relatively the same interaction pattern still occurs.

Table 4. The result of the docking validation of the RMSD value.

Run	Binding Energy	Reference RMSD	Gridbox		
			X	Y	Z
48	-8,50	0,96	14.421	66.575	5.147

Docking validation of TGF-β compared to the experimental conformation of natural ligands, as shown in Table 4, yields an RMSD value of 0.96 Å, with the condition that the acceptance of the validation result is an RMSD value of 2 Å (Lestyawan *et al*., 2024). Based on the data, it can be concluded that the RMSD value is valid and obtained through a valid process, as reflected in the RMSD of less than 2 Å. It can also be seen visually in Figure 3 that the conformation of the natural ligand overlaps with the conformation of the retested natural ligand, thus

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indicating that the docking process produces a ligand that binds at the same natural site and is in accordance with the natural ligand from PDB, which means that the docking process against the hit test compound can be trusted for its accuracy.

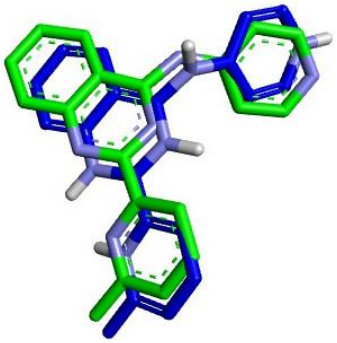


Figure 3. Comparison of natural ligand conformations (green) versus redocked natural ligands (blue).

Molecular Docking

Docking of 11 test compounds against TGF-β receptors was performed to identify the best test compounds, as indicated by increasingly negative binding energies and the lowest inhibition constants. If the bond energy of the bond between the receptor and the ligand of the test compound becomes negative, then the bond is becoming more stable. The value of the inhibition constant (K_i) indicates how strong the bond between the receptor and the ligand is, as well as the ligand's ability to inhibit the interaction between the enzyme and the substrate. If the K_i is lower, the bonds between the receptor and the ligand become stronger (Cahyaningrum *et al*., 2024). The docking results of the test compound molecules are shown in Table 5.

Molecular docking is a structure-based method for drug development. Thus, this method assesses the compatibility of the interaction between the test compound and the target receptor's structure. The molecular docking method is suitable for this study because, for a test compound to be identified as a potential drug, it must have a sufficiently strong interaction with the target receptor (Lestyawan *et al*., 2024). Therefore, to identify compounds that play an active role in the TGF-β pathway, docking and bond-energy analysis of each hit compound with the TGF-β receptor are performed. The results of molecular docking show that isorhamnetin has the lowest binding energy and inhibition constant.

Based on the data shown in Table 5, the compound with the lowest binding energy and the smallest inhibition constant is Isorhamnetin, with a binding energy of -8.18 kcal/mol and an inhibition constant of 1.02 µM. When compared to the other 2 hit compounds, namely rutin and kaempferol, the test compound, isorhamnetin, had the lowest inhibition constant, despite its binding energy being larger than that of rutin. Rutin has a binding energy of -9.24 kcal/mol, but the highest inhibition constant among the hit compounds is 168.78 µM. Meanwhile, kaempferol has a binding energy of -5.24 kcal/mol (greater than isorhamnetin) and an inhibition constant of 143.35 µM. Lower inhibition constant values indicate that the ligand binds to the receptor more strongly, and the bonds between the protein and the resulting ligand are more stable (Manna *et al*., 2017; Muttaiqn, 2019). High KI values indicate weak binding of the rutin and kaempferol compounds to receptors. Therefore, the isorhamnetin assay was chosen because it demonstrated a strong, stable interaction with TGF-β receptors and the potential to suppress liver cell overgrowth. Based on the results of the previous parameter tests, isorhamnetin met the established criteria and was selected as the main candidate.

In vivo testing conducted by Susanto *et al*. (2021), which examined the antiproliferation effect of moringa leaf powder on progressive hepatocellular carcinoma, it is known that moringa leaves can reduce liver cell proliferation by reducing TGF-β expression in the liver by suppressing HSC activation, which is associated with the reduction of oxidative stress and inflammation by inhibition of the TGF-β/Smad3 pathway. However, it is not known specifically which compounds in moringa leaves have this ability, beyond a hypothesis. When compared to the standard drug compound metformin, which has a binding energy of -2.96 kcal/mol and an inhibition constant of 6.81 µM, isorhamnetin's binding energy is greater. This value indicates that the bond between TGF-β and the hit compound Isorhamnetin will be more stable than the bond between metformin and the TGF-β receptor. This can be used as a separate advantage to select the test compound, Isorhamnetin, contained in moringa leaves, as an antiproliferative agent for liver cancer.

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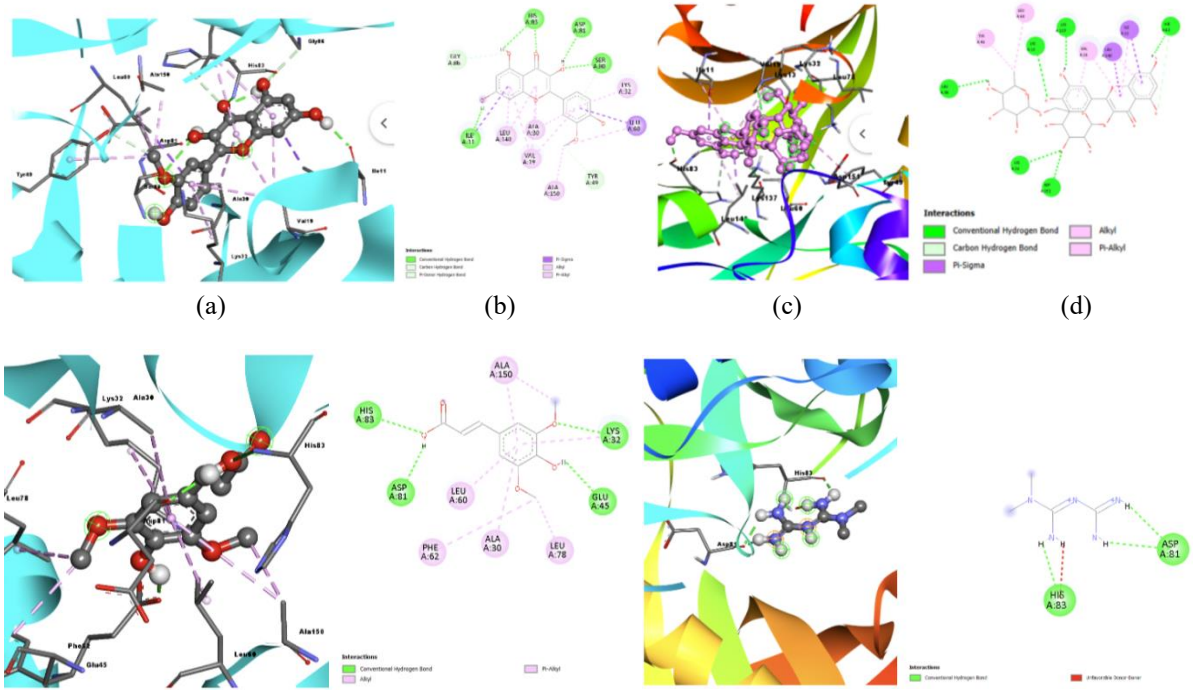
Table 5. Molecular docking results of compound tests.

Compounds	Binding Energy (kcal/mol)	K_i (μM)	Interaction with Amino Acids		
			Hydrogen Bonding	Van der Waals Interaction	Other Interactions
Rutin	-9.24	168.78	Leu A:78 Lys A:32 Asp A:151 Lys A:13 Lys A:137	-	pi-alkyl (Tyr A:49, Leu A:60, Val A:19) pi-sigma (Leu A:140, Ile A:11)
Kaempferol	-5.24	143.35	His A:83 Asp A:81 Lys A:32 Glu A:45	-	pi-alkyl (Ala A:150, Leu A:60, Phe A:62, Ala A:30, Leu A:78)
Quercetin	-7.87	1.69	Glu A:45 Ile A:11 Ser A:80 Asp A:81 His A:83	-	pi-alkyl (Lys A:32, Ala A:150, Leu A:140, Ala A:30, Val A:19, Leu A:60)
o-Coumaric Acid	-6.45	18.67	Lys A:32 Asp A:151		pi-alkyl (Leu A:78) Pi-Pi T-shaped (Tyr A:49)
Myrisetin	-7.45	3.47	Ile A:11 Glu A:45 Leu A:78 Ser A:80 Asp A:81 His A:83 Gly A:86 Lys A:32	-	pi-sigma (Leu A:60, Leu A:140, Ile A:11) pi-alkyl (Ala A:30 Val A:19)
Ellagic Acid	-6.75	11.3	Ile A:11 Gly A:12 Gly A:86 His A:83 Ser A:80 Asp A:81	-	pi-sigma (Leu A:140, Val A:19) pi-alkyl (Ala A:30)
Ferulic Acid	-5.00	216.9	Lys A:32	-	pi-Sigma (Leu A:60), Unfavorable Donor-donor (Val A:79) Alkyl (Ala A:30)
Synaptic Acid	-5.86	50.92	Lys A:32 Asp A:151 Asp A:81 His A:83 Gly A:86 Ile A:11	-	pi-Sigma (Leu A:140) alkyl dan pi-alkyl (Ala A:30, Val A:19, Leu A :60)
Gallic Acid	-4.63	405.42	Ser A:80 Lys A:32 Glu A:45	-	pi-sigma (Leu A:78) pi-alkyl (Leu A:60)
Syringic Acid	-6.49	17.37	Lys A:32 Glu A:45 Asp A:151 Tyr A:49 Ser A:80 Ala A:30	-	pi-sigma (Leu A:60) alkyl and pi-alkyl (Val A:19, Ala A:62, Leu A:78)
Isorhamnetin	-8.18	1.02	His A:83 Asp A:81 Ser A:80 Ile A:11 Gly A:86 Tyr A:49	-	pi-sigma (Leu A: 60) alkyl dan pi-alkyl (Leu A: 140, Ala A:30, Val A:19, Ala A:150, Lys A:32)
Metformin	-2.96	6.81	His A:83 Asp A:81	-	-

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Visualization of Test Results

TGF-β receptors interact with the test compounds Isorhamnetin, rutin, and Kaempferol through binding with amino acids. The visualization process is assisted by the BIOVIA Discovery Studio Visualizer software. 2D and 3D visualizations, as shown in Figure 4, aim to observe bond interactions with amino acid residues of all test compounds and compare them with interactions observed with natural ligand compounds.



(a) (b) (c) (d)

(e) (f) (g) (h)

Figure 4. Molecular docking visualization (a) 3D diagram of isorhamnetin at TGF-β active site, (b) 2D diagram of isorhamnetin at TGF-β active site, (c) 3D diagram of rutin at TGF-β active site, (d) 2D diagram of rutin at TGF-β active site, (e) 3D diagram of Kaempferol at TGF-β active site, (f) 2D diagram of Kaempferol at TGF-β active site, (g) 3D diagram of metformin as a standard drug, and (h) 2D drawings of metformin as a standard drug.

Based on the visualization results, the interactions formed will be visible, for example, hydrogen bonds, van der Waals bonds, pi-Sigma, pi-Alkyl, and Alkyl (Cahyaningrum *et al*., 2024). Isorhamnetin forms hydrogen bond interactions with His A:83, Asp A:81, Ser A:80, Ile A:11, Gly A:86, and Tyr A:49, pi-Sigma bonds with Leu A:60, pi-Alkyl bonds with Leu A:140, Ala A:30, Val A:19, Ala A:150, and Lys A:32. Rutin forms interactions with receptors through hydrogen bonds with Leu A:78, Lys A:32, Asp A:151, Lys A:13, and Lys A:137; Pi-Sigma bonds with Leu A:140 and Ile A:11, pi-Alkyl bonds with Tyr A:49, Leu A:60, and Val A:19. Kaempferol forms hydrogen bonds with His A:83, Asp A:81, Lys A:32, and Glu A:45 as well as pi-Alkyl bonds with Ala A:150, Leu A:60, Phe A:62, Ala A:30, and Leu A:78. The three hit compounds do not show any van der waals bonds with the receptor.

In all three compounds, hydrogen bonds showed a stronger affinity than Van der Waals bonds. This is because hydrogen bonds can be formed even if the distance between the ligand and the receptor is quite far. The more hydrogen bonds formed between amino acid residues, the more stable the interaction will be (Frimayanti *et al*., 2021). The pi-Sigma and pi-Alkyl interactions are part of the aromatic interaction that helps to direct the position of the ligand precisely and maintain its stability at the active site of the protein. Variations in bond types provide an interpretation of the relationship between ligands and target proteins: the more and stronger the bonds formed, the greater the potential of a compound to exhibit meaningful biological activity. Therefore, the analysis of these bonds is an important parameter in evaluating molecular docking results (Amin *et al*., 2024). Compared with standard drug compounds, namely metformin, the metformin visualization results showed interactions with receptors via hydrogen bonding at amino acid residues His A:83 and Asp A:81. All three hit compounds form hydrogen bonds with His A:83 and Asp A:81, suggesting they may interact well with TGF-β receptors.

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CONCLUSION

The results of predicting the activity of compounds in Moringa leaves (*Moringa oleifera* L.) against TGF-β receptors as antiproliferation agents for liver cancer using the *in silico* approach show that Isorhamnetin is the most potent compound. This compound has a fit score of 47.10, a binding energy of -8.18 kcal/mol, an inhibition constant of 1.02 μM, can interact with important amino acid residues such as HIS83 and ASP81, and exhibits an acceptable pharmacokinetic and toxicity profile. This study uses an *in silico* approach, so the results remain predictive. Testing aspects such as the affinity and stability of compound–receptor interactions obtained from the test may differ from actual biological conditions, so further validation through *in vitro* and *in vivo* studies is needed.

CONFLICT OF INTEREST

There are no conflicts of interest in this article.

AUTHOR CONTRIBUTION

AA: Conceptualization, Methodology, Data Analysis, Editor, Software, Manuscript Draft Writing, Manuscript Editing; DME: Data Analysis, Manuscript Draft Writing, Editor; KPA: Data Analysis, Manuscript Draft Writing, Editor, Software, ALP: Conceptualization, Data Analysis, Software, Manuscript Draft Writing, Editor, Manuscript Editing, JFS: Data Analysis, Software, Manuscript Draft Writing, Editor, Manuscript Editing, NF: Manuscript Review and Editing; SS: Manuscript Review and Editing; MM: Supervision.

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