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CHEMOINFORMATICS ANALYSIS OF TRITERPENOID DERIVATIVES AS ANTI-MELANOMA AGENTS

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ABSTRACT

Melanoma is an aggressive skin cancer with high mortality rates, necessitating the development of novel therapeutic agents. This study aims to identify potential anti-melanoma candidates from triterpenoid derivatives through an integrated chemoinformatics approach. A dataset of 35 triterpenoid compounds was analyzed using KNIME to build a Quantitative Structure-Activity Relationship (QSAR) model. The model demonstrated good predictive ability with $R^2 = 0.842$, RMSE = 0.38, and MAE = 0.30, validated through 5-fold cross-validation ($Q^2 = 0.78$). QSAR analysis identified five best candidates: cucurbitacin B ($IC_{50} = 0.015$ µM), betulin (15.61 µM), lupeol (66.59 µM), oleanolic acid (75 µM), and ursolic acid (75 µM). Lipinski's Rule of Five analysis revealed LogP violations in most compounds, though these are common for natural triterpenoids and can be addressed through formulation strategies. Molecular docking showed oleanolic acid had the best binding affinity against BCL-2 (-8.2 kcal/mol), while lupeol showed the highest affinity against BRAF (-8.9 kcal/mol). Based on the balance of predicted activity, pharmacokinetic profiles, and binding affinity, oleanolic acid and lupeol emerged as the most promising candidates for further experimental validation. This integrative approach demonstrates the efficiency of computational screening in prioritizing lead compounds for melanoma drug discovery.

Keywords: Melanoma, Triterpenoid, QSAR, Molecular Docking, Chemoinformatics

INTRODUCTION

Melanoma is the most aggressive and malignant type of skin cancer, originating from melanocytes. Melanoma cases have increased in recent years, especially in fair-skinned individuals, posing significant challenges to healthcare systems worldwide (Teixido et al., 2021). According to World Health Organization data for 2022, approximately 160,000 people are diagnosed with skin cancer annually, making it the second leading cause of death after cardiovascular disease. The most deadly skin cancer is melanoma, with 287,723 cases and 60,712 deaths recorded in 2020 (Sung et al., 2021). Melanoma is characterized by high metastatic potential and resistance to conventional therapies, necessitating the

development of novel therapeutic strategies (Moralev et al., 2024).

In Indonesia, skin cancer ranks third after cervical and breast cancer (Fu'adah et al., 2020). Recent studies from several referral hospitals in Indonesia provide updated epidemiological data. A study at Dr. Mohammad Hoesin General Hospital, Palembang (2019-2021) found that basal cell carcinoma (BCC) was the most common type (44.74%), followed by squamous cell carcinoma (31.57%), and malignant melanoma (13.16%) (Hardianto et al., 2025). Similar findings were reported at Dr. Hasan Sadikin General Hospital, Bandung, where BCC accounted for the majority of cases (Rulandani et al., 2025). Early symptoms of melanoma can be seen from the appearance of new moles or changes in existing moles, which can worsen with ultraviolet radiation exposure (Anwar et al., 2021).

Melanoma in Indonesia presents unique challenges. A study of 63 melanoma patients at Dr. Sardjito Hospital, Yogyakarta found that most patients were diagnosed at advanced stages (Stage III-IV: 77.8%), with Breslow thickness >4 mm (80.9%), and ulceration (55.6%) (Anwar et al., 2024). BRAF mutations, which are targetable with specific therapies, were found in 44.4% of patients and were associated with significantly lower overall survival (median survival 16.5 vs 31.4 months, P=0.001) (Anwar et al., 2024). These findings highlight the aggressive nature of melanoma in Indonesia and the urgent need for effective therapeutic options.

Based on data from the American Cancer Society (2024), melanoma treatment methods include surgery, chemotherapy, radiation, immunotherapy, and targeted therapy. Despite advances in immunotherapy and targeted therapy, effective treatment options for advanced-stage melanoma remain limited due to rapid resistance and significant side effects (Candra, 2021; Nigam et al., 2025). Targeted therapy, particularly BRAF inhibitors, has shown initial efficacy, but resistance develops in most patients within 6-12 months through various mechanisms including MAPK pathway reactivation and activation of alternative pathways such as PI3K/AKT/mTOR. The genetic heterogeneity of melanoma tumors further complicates treatment, as BRAF-mutant melanomas often harbor complex genetic backgrounds that enable multiple resistance mechanisms simultaneously (Valdez-Salazar et al., 2024). Therefore, there is an urgent need to discover novel anti-melanoma agents with improved efficacy, reduced side effects, and lower resistance potential.

Natural products have emerged as promising sources for anticancer drug discovery. One class of compounds reported to inhibit melanoma cell growth is triterpenoids. Triterpenoids can be found in fungi, bacteria, marine organisms, and plants (Olatunde et al., 2024). Pentacyclic triterpenoids (PTs) are a class of plant metabolites with a wide range of pharmacological activities, including strong antitumor potential against skin malignancies These compounds act on multiple signaling pathways that control key cellular processes, enabling complex effects on melanoma progression in vitro and in vivo (Moralev et al., 2024).

Plant-derived triterpenoid derivatives that have been reported to inhibit melanoma cells include betulin (IC_{50} 15.61 µM against C-32 cells), oleanolic acid (IC_{50} 75 µM against A375 cells) (Chrobak et al., 2021), ursolic acid (IC_{50} 75 µM against A375 cells) (Mahmoudi et al., 2022), cucurbitacin B (IC_{50} 0.015 µM against A375 cells) (Park et al., 2020), and lupeol (IC_{50} 66.59 µM against A375 cells) (Bociort et al., 2021). Recent reviews have evaluated the chemopreventive and anticancer activity of lupane-, oleanane, and ursane-type triterpenoids in melanoma, highlighting their mechanisms of action including cell viability inhibition, apoptosis induction, cell cycle regulation, and immune system modulation. Research by Li et al. (2023) showed that the presence of carbonyl groups at position C-3 and hydroxyl groups on the triterpenoid skeleton correlates with increased cytotoxic activity.

The selection of appropriate molecular targets is crucial in drug discovery for melanoma. Two key proteins are particularly relevant: BRAF and BCL-2. BRAF is a key component of the MAPK/ERK signaling pathway that regulates cell proliferation, differentiation, and survival. Approximately 40-60% of malignant melanoma cases carry BRAF V600E mutations, causing constitutive hyperactivation of the MAPK pathway (Anwar et al., 2024; Valdez-Salazar et al., 2024). In the Indonesian population, BRAF mutations were found in 44.4% of melanoma patients and were significantly associated with worse prognosis, with a median survival of 16.5 months compared to 31.4 months in patients without BRAF mutations ($P=0.001$). BCL-2 is an anti-apoptotic protein that functions as a key regulator of the intrinsic cell death pathway. Overexpression of BCL-2 is frequently found in various cancers including melanoma, contributing to treatment resistance and poor clinical outcomes. Together, BRAF and BCL-2 represent complementary pathways in melanoma pathogenesis—BRAF driving uncontrolled proliferation and BCL-2

enabling resistance to apoptosis—making them rational targets for screening potential anti-melanoma candidates (Anwar et al., 2024).

Research on triterpenoid compounds with potential to inhibit melanoma cells using integrated chemoinformatics approaches remains limited. Most previous studies have focused on individual triterpenoids or single computational methods, without integrating QSAR, drug-likeness evaluation, and molecular docking in a comprehensive workflow (Chrobak et al., 2019). Recent studies have emphasized that triterpenoids exert complex effects on melanoma through multiple signaling pathways, necessitating a systematic approach to identify the most promising candidates (Moralev et al., 2024). In silico methods are significantly faster and more cost-effective than in vitro methods, capable of processing thousands to millions of compounds virtually (Sekhar et al., 2021). An integrated chemoinformatics approach addresses the complexity of drug discovery through three complementary stages: Quantitative Structure-Activity Relationship (QSAR) for virtual prescreening, Lipinski's Rule of Five analysis for drug-likeness evaluation, and molecular docking to confirm candidate potential through binding affinity parameters.

Therefore, this study aims to screen triterpenoid derivatives as anti-melanoma candidates through an integrated chemoinformatics approach, including (1) building a QSAR model to predict anti-melanoma activity, (2) evaluating drug-likeness using Lipinski's Rule of Five, and (3) assessing binding affinity against BRAF and BCL-2, targets through molecular docking. The novelty of this study lies in the integration of these three computational methods and the identification of the most promising triterpenoid candidates with balanced potency, pharmacokinetic profiles, and target binding affinity for further experimental validation.

METHODS

Materials

The device used was an Axioo Slimbook Hype 10 laptop with 8 GB RAM, Intel Celeron Processor N4020. In silico testing used software and webservers that can be downloaded and accessed freely, including webserver Protein Data Bank *(https://www.wwpdb.org/*) for obtaining 3D protein structures, PubChem (*https://pubchem.ncbi.nlm.nih.gov/*) for compound structures, ChEMBL (*https://www.ebi.ac.uk/chembl/*) for bioactivity data, SwissADME (*https://www.swissadme.ch*) for

pharmacokinetic properties. Software: PyRx (*https://pyrx.sourceforge.io*) for molecular docking, PyMOL (*https://pymol.org*) for 3D protein preparation, Biovia Discovery Studio Visualizer (*https://discover.3ds.com*) for visualization, Chimera for docking visualization and amino acid identification, KNIME (Konstanz Information Miner) for QSAR workflow (KNIME, 2023), Toxtree for toxicity analysis.

The materials used were Macromolecular protein targets: BRAF (PDB ID: 3OG7) and BCL-2 (PDB ID: 4HW3), control ligand Erlotinib ($C_{22}H_{23}N_3O_4$), test ligands (triterpenoid compounds): betulin ($C_{30}H_{50}O_2$), cucurbitacin B ($C_{32}H_{46}O_8$), oleanolic acid ($C_{30}H_{48}O_3$), ursolic acid ($C_{30}H_{48}O_3$), and lupeol ($C_{30}H_{50}O$).

Research Path

1. QSAR Analysis

A dataset of 35 triterpenoid compounds with canonical SMILES and biological activity values (pIC_{50}) was imported using the Excel Reader node. The Molecule Type Cast and RDKit From Molecule nodes were used to convert canonical SMILES into RDKit-compatible molecular objects. The RDKit Descriptor Calculation node was used to calculate various physicochemical and structural descriptors including molecular weight, LogP, hydrogen bond donors/acceptors, TPSA, and rotatable bonds (Engel & Gasteiger, 2018). Column Filter, Missing Value, and Normalizer nodes were used for feature selection, handling missing values, and data normalization.

The dataset was divided into training and test sets using the Table Partitioner node with an (80:20 ratio), resulting in 28 compounds for training and 7 compounds for testing. The Tree Ensemble Learner node was used to build the QSAR model using Tree Ensemble Regression algorithm. The model was validated using 5-fold cross-validation to ensure robustness and prevent overfitting. The Tree Ensemble Predictor node was used to predict biological activity values (pIC_{50}) for each compound. Model performance was evaluated using the Numeric Scorer node, which calculated the coefficient of determination (R^2), Root Mean Square Error (RMSE), and Mean Absolute Error (MAE) (Ntie-Kang, 2024). The Scatter Plot was used to visualize the correlation between actual and predicted pIC_{50} values.

2. Lipinski's Rule of Five Analysis

Canonical SMILES of test compounds (betulin, cucurbitacin B, oleanolic acid, ursolic acid, and lupeol) were prepared. The SwissADME webserver (*https://www.swissadme.ch*) was accessed, and SMILES were pasted to predict physicochemical properties, drug-likeness,

and pharmacokinetics. Parameters analyzed included molecular weight (MW < 500 Da), LogP (≤ 5), hydrogen bond donors (HBD ≤ 5), hydrogen bond acceptors (HBA ≤ 10), and topological polar surface area (TPSA) (Barret, 2018). Compounds were evaluated for Lipinski's Rule of Five compliance, which serves as a guideline for estimating oral bioavailability and drug-likeness (Raza, 2026).

3. Molecular Docking Analysis

- **Protein Preparation:** 3D structures of BRAF (PDB ID: 3OG7) and BCL-2 (PDB ID: 4HW3) were downloaded from the Protein Data Bank (*https://www.wwpdb.org/*). Water molecules and heteroatoms were removed using PyMOL v2.5. Hydrogen atoms and Kollman charges were added using AutoDockTools v1.5.7 to prepare the proteins for docking (Raza, 2026; Bhat et al., 2025)
- **Ligand Preparation:** 3D structures of test compounds (betulin, cucurbitacin B, oleanolic acid, ursolic acid, and lupeol) were downloaded from PubChem (https://pubchem.ncbi.nlm.nih.gov/). Energy minimization was performed in PyRx using the Universal Force Field (UFF) to obtain the most stable conformations.
- Docking Protocol Validation : Before performing docking with test compounds, the docking protocol was validated by re-docking the native ligand into the binding site of each protein (redocking). The Root Mean Square Deviation (RMSD) between the docked pose and the crystallographic pose was calculated using PyMOL. An RMSD value of < 2.0 Å was considered acceptable, confirming that the docking protocol accurately reproduced the crystallographic binding mode (Raza, 2026).
- Grid Box Parameters: The grid box was defined based on the position of the native ligand for BRAF and BCL-2. Grid box coordinates and dimensions used for docking were: BRAF (PDB ID: 3OG7): center (x=13.5, y=-2.8, z=18.7); size (25×25×25 Å). BCL-2 (PDB ID: 4HW3): center (x=-20.3, y=15.7, z=-3.2); size (20×20×20 Å).
- Docking Procedure: PyRx software was opened, and the AutoDock Vina Wizard was selected. Minimized ligands and prepared receptors were loaded. Docking was performed using AutoDock Vina with exhaustiveness = 8 (Raza, 2026). The binding affinity (ΔG) was calculated in kcal/mol, with more negative values indicating

stronger binding. Results were saved in PDB format for further analysis.

- Visualization: Docking results were visualized using Biovia Discovery Studio Visualizer and Chimera to identify amino acid residues and interaction types, including hydrogen bonds, hydrophobic interactions (van der Waals, alkyl, pi-alkyl, pi-sigma), and electrostatic interactions.

RESULTS AND DISCUSSION

1. QSAR Analysis

A dataset of 35 triterpenoid compounds with canonical SMILES and biological activity values (pIC_{50}) was imported using the Excel Reader node. The Molecule Type Cast and RDKit From Molecule nodes were used to convert canonical SMILES into RDKit-compatible molecular objects. The RDKit Descriptor Calculation node was used to calculate various physicochemical and structural descriptors including molecular weight, LogP, hydrogen bond donors/acceptors, TPSA, and rotatable bonds. Column Filter, Missing Value, and Normalizer nodes were used for feature selection, handling missing values, and data normalization.

The dataset was divided into training and test sets using the Table Partitioner node with an (80:20 ratio), resulting in 28 compounds for training and 7 compounds for testing. The Tree Ensemble Learner node was used to build the QSAR model using Tree Ensemble Regression algorithm.

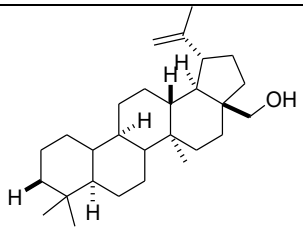
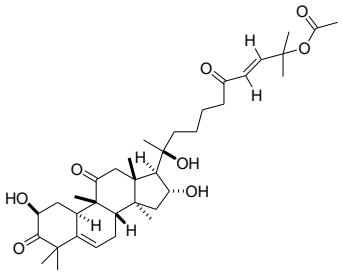
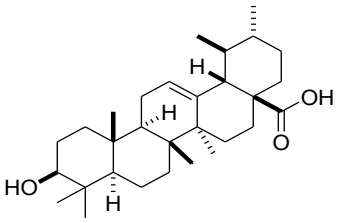
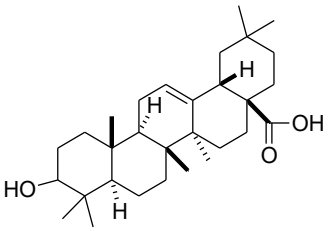
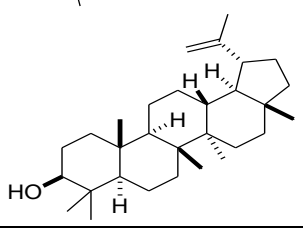
The model was evaluated using multiple complementary metrics to assess its predictive performance. The coefficient of determination (R^2) value of 0.842 indicates that the model explains 84.2% of the variance in the biological activity data. The Root Mean Square Error (RMSE) of 0.38 and Mean Absolute Error (MAE) of 0.30 further confirm the model's accuracy, with relatively low values indicating good prediction performance relative to the data range. Additionally, 5-fold cross-validation yielded a Q^2 value of 0.78, which exceeds the acceptable threshold of 0.5 and shows a small difference from R^2 ($R^2 - Q^2 = 0.062 < 0.2$), confirming the model's robustness and predictive power on unseen data.

The Tree Ensemble model provides insights into structure-activity relationships (SAR) through feature importance analysis. Key molecular descriptors identified as important contributors to anti-melanoma activity included LogP, molecular weight, and hydrogen bond donor/acceptor counts, which is consistent with previous findings that the presence of carbonyl groups at position C-3 and hydroxyl groups on the

triterpenoid skeleton correlates with increased cytotoxic activity (Li et al., 2023)

The QSAR model successfully identified five triterpenoid compounds with the best predicted pIC_{50} values: cucurbitacin B (0.015 µM), betulin (15.61 µM), lupeol (66.59 µM), oleanolic acid (75 µM), and ursolic acid (75 µM) (Table 1). Cucurbitacin B showed the highest predicted activity, consistent with previous studies reporting its potent antiproliferative effects against melanoma cells (Aiswarya et al., 2022; Mi et al., 2025).

Table 1. QSAR analysis results for top five compounds

No	Compound	Structure	Predicted IC_{50} (µM)	Activity Category
1	Cucurbitacin B		0.01	Very High
2	Betulin		15.61	High
3	Lupeol		66.59	Moderate
4	Oleanolic Acid		75.00	Moderate
5	Ursolic Acid		75.00	Moderate

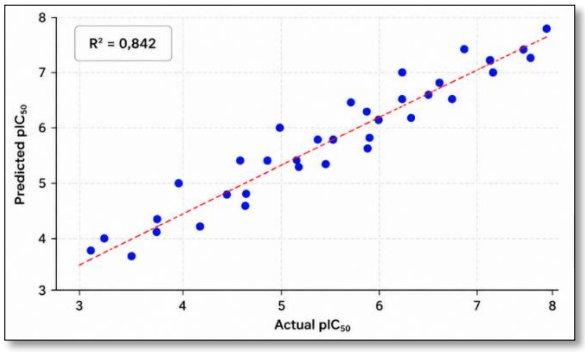


Figure 1. QSAR scatter plot comparison of actual vs predicted pIC_{50}

2. Lipinski's Rule of Five Analysis

The Lipinski's Rule of Five (RO5) analysis was performed using the SwissADME webserver to evaluate the drug-likeness and oral bioavailability potential of the five selected triterpenoid compounds. RO5 serves as a valuable guiding principle in early-stage drug discovery, helping to identify compounds with favorable physicochemical properties for oral administration.

However, it is important to note that RO5 is a guideline rather than an absolute rule, and an increasing number of approved drugs no longer adhere to these criteria, particularly those derived from natural sources (Yang et al., 2025).

The analysis revealed that none of the compounds perfectly satisfied all RO5 parameters (Table 2). Cucurbitacin B had an ideal LogP (3.50) but exceeded molecular weight (558.70 > 500) and had TPSA approaching the upper limit (138.20 Å²). Betulin, oleanolic acid, ursolic acid, and lupeol had molecular weights below 500 g/mol and acceptable HBD/HBA values but exhibited LogP values exceeding the recommended limit (5.82-7.91), indicating excessive lipophilicity that may lead to poor aqueous solubility and reduced oral absorption (Dai et al., 2023; Sahu et al., 2025).

The observed violations are not uncommon for triterpenoid natural products. Compounds derived from natural sources often possess complex structures and violate Lipinski's guidelines, yet they have historically been a rich source of therapeutic agents. For instance, many plant-derived compounds like paclitaxel or antibiotics like vancomycin have high molecular weights and numerous hydrogen bond donors and acceptors. Despite these violations, they exhibit potent biological activity and acceptable pharmacokinetic profiles. The high LogP values observed in this study are characteristic of pentacyclic triterpenoids, which are highly lipophilic by nature and

often require specialized formulation strategies to achieve therapeutic efficacy.

3. Molecular Docking Analysis

The molecular docking results showed that all five compounds exhibited strong binding affinity against the two target proteins: BRAF and BCL-2. Oleanolic acid showed the best binding affinity against BCL-2 (-8.2 kcal/mol), surpassing the native ligand (-7.2 kcal/mol) and erlotinib (-6.0 kcal/mol) (Table 3). Lupeol showed the highest binding affinity against BRAF (-8.9 kcal/mol), superior to erlotinib (-8.8 kcal/mol) (Table 4).

Table 2. QSAR analysis results for top five compounds

No	Compound	Molecular Formula	MW (g/mol)	LogP	HBD	HBA	TPSA (A^0)
1	Cucurbitacin B	$C_{32}H_{46}O_8$	558.70	3.50	3	8	138.20
2	Betulin	$C_{30}H_{50}O_2$	442.72	7.00	2	2	40.46
3	Lupeol	$C_{30}H_{50}O$	426.70	7.91	1	1	20.23
4	Oleanolic Acid	$C_{30}H_{48}O_3$	456.70	7.23	2	3	57.53
5	Ursolic Acid	$C_{30}H_{48}O_3$	456.70	5.82	2	3	57.53

Table 3. Summary of best binding affinity per receptor

No	Reseptor	Best Ligand	Binding Affinity (kcal/mol)
1	BCL-2	Oleanolic Acid	-8.2
2	BRAF	Lupeol	-8.9

Table 4. Comparison with native ligand and control

No	Reseptor	Native Ligand (kcal/mol)	Best Ligand (kcal/mol)	Erlotinib Control (kcal/mol)
1	BCL-2	-7.2	-8.2	-6.0
2	BRAF	-10.4	-8.9	-8.8

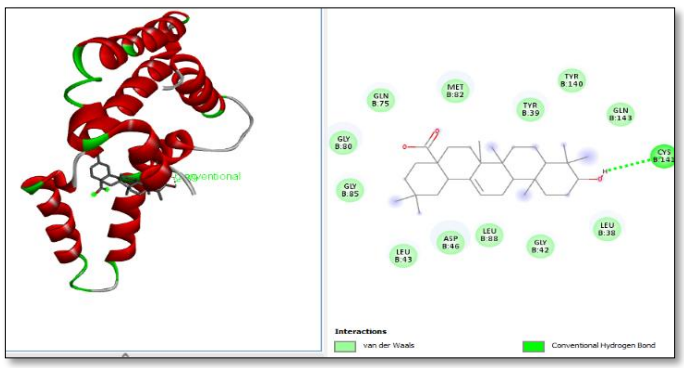


Figure 2. Docking interaction of oleanolic acid with BCL-2

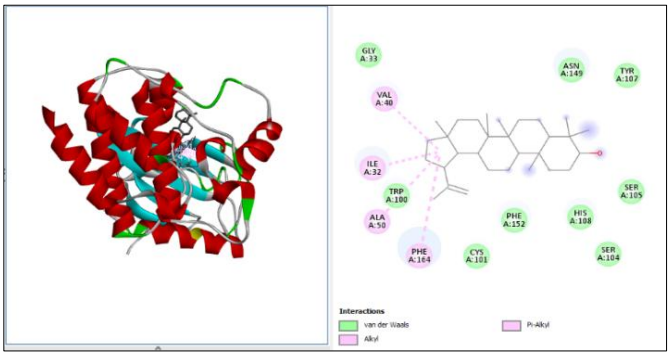


Figure 3. Docking interaction of lupeol with BRAF

To provide a meaningful interpretation of the docking results, the binding affinity values were evaluated based on established guidelines for AutoDock Vina scores. According to recent molecular docking protocols, docking scores can be categorized as follows: scores below -9.0 kcal/mol indicate excellent binding potential (typically associated with high-affinity ligands in the nM range), scores between -7.0 and -9.0 kcal/mol indicate good binding potential (often seen with moderate to high-affinity ligands in the nM to low µM range), scores between -5.0 and -7.0 kcal/mol indicate moderate binding potential (common for lower-affinity compounds in the µM range), and scores above -5.0 kcal/mol indicate weak binding potential (Raza, 2026).

Based on this classification, the binding affinities observed in this study fall within the good binding potential category (-7.0 to -9.0 kcal/mol). Oleanolic acid (-8.2 kcal/mol) and lupeol (-8.9 kcal/mol) demonstrate strong interactions with their respective targets, suggesting that these compounds have favorable binding characteristics comparable to known active compounds.

The docking results are further supported by the biological relevance of the selected targets. BCL-2 (B-cell lymphoma 2) is an anti-apoptotic protein that functions as a key regulator of the intrinsic cell death pathway. Its overexpression is frequently found in various cancers including melanoma, contributing to resistance to apoptosis and poor clinical outcomes . BRAF is a key component of the MAPK/ERK signaling pathway that regulates cell proliferation, differentiation, and survival. Approximately 40-60% of malignant melanoma cases carry BRAF V600E mutations, causing constitutive hyperactivation of the MAPK pathway (Anwar et al., 2024; Valdez-Salazar et al., 2024). In the Indonesian population, BRAF

mutations were found in 44.4% of melanoma patients and were significantly associated with worse prognosis (Anwar et al., 2024). The strong binding affinity of lupeol to BRAF suggests its potential as a BRAF inhibitor, which could be particularly relevant for BRAF-mutant melanoma patients.

Before performing docking with test compounds, the docking protocol was validated by re-docking the native ligand into the binding site of each protein (redocking). The Root Mean Square Deviation (RMSD) between the docked pose and the crystallographic pose was calculated using PyMOL. An RMSD value of < 2.0 Å was considered acceptable, confirming that the docking protocol accurately reproduced the crystallographic binding mode (Raza, 2026; Sousa et al., 2024). Notably, the RMSD values for all test compounds were 0.00 Å, indicating that the docking protocol produced consistent and reproducible binding poses for each ligand, further confirming the reliability of the docking procedure (Ibrahim et al., 2024; Raza, 2026). This validation step is crucial to ensure that the docking procedure reliably predicts binding poses and affinities.

Molecular interaction analysis revealed that hydrophobic interactions (van der Waals, alkyl, pi-alkyl, and pi-sigma) dominated the binding modes, with additional conventional hydrogen bonds contributing to binding specificity in some complexes (Figure 2-3). The presence of amino acid residues such as Gln, Tyr, Asp, and Arg in the binding pockets facilitated stable complex formation through hydrogen bonding and hydrophobic interactions (Srinivas et al., 2025; Aguilera-Durán et al., 2024).

The interaction profile of lupeol with BRAF reveals key contacts with residues ILE463, THR529, GLN530, TRP531, CYS532, and PHE583, which contribute to stabilizing the conformation of triterpenes within the catalytic binding site of the protein . These residues are known to be important for BRAF inhibitor binding, supporting the potential of lupeol as a BRAF-targeting agent.

The binding affinities observed in this study are comparable to those reported in recent triterpenoid research. A study on Eucalyptus tereticornis essential oils reported the strongest binding affinity to BRAF at -8.5 kcal/mol, which is similar to our findings for lupeol (-8.9 kcal/mol) . Another study on caffeoyl triterpenes demonstrated that molecular docking studies suggested cytotoxic activity was strongly attributed to interactions between triterpene compounds and molecular targets of importance for melanoma treatment (Sousa et al., 2024).

Furthermore, research on triterpenes as potential BRAF inhibitors showed that lupeol exhibited binding affinity comparable to known BRAF inhibitors .

The ideal drug candidate cannot be determined by a single parameter alone but requires an integrative approach that balances potency (low IC_{50}), strong binding affinity, and a favorable Lipinski's Rule of Five profile. In this study, oleanolic acid emerged as the most balanced candidate due to its superior docking affinity against BCL-2 (-8.2 kcal/mol). Although it has a high logP value, this limitation can be addressed through formulation strategies such as prodrug formation or nanoparticle encapsulation (Raza, 2026). Meanwhile, cucurbitacin B requires further structural optimization to address its molecular weight issue, whereas lupeol requires modification to reduce its extreme logP value.

This integrative approach aligns with expert recommendations that multidimensional evaluation combining QSAR predictions, Lipinski's Rule of Five parameters, and molecular docking is essential for comprehensive assessment before proceeding to laboratory testing (Prodea et al., 2025; Banjare et al., 2024).

CONCLUSIONS

Based on the chemoinformatics screening of triterpenoid derivatives as anti-melanoma candidates through QSAR, Lipinski's Rule of Five, and molecular docking approaches, the following conclusions can be drawn:

The quantitative relationship between molecular descriptors and anti-melanoma activity was successfully determined through the QSAR model, with an R^2 value of 0.842, RMSE of 0.38, and MAE of 0.30, indicating good predictive ability.

Lipinski's Rule of Five analysis showed that none of the compounds perfectly satisfied all parameters, with LogP values being the most common violation. However, as natural products, these compounds remain promising candidates, and the observed violations can be addressed through advanced formulation strategies such as nanoparticle encapsulation, prodrug formation, or topical administration.

Oleanolic acid and lupeol showed the most promising potential as anti-melanoma candidates based on the balance of biological activity, binding affinity, and pharmacokinetic profiles. Oleanolic acid showed the best binding affinity against BCL-2 (-8.2 kcal/mol), while lupeol showed the highest affinity against BRAF (-8.9 kcal/mol).

The QSAR model was built on a relatively small dataset of 35 compounds, which may limit its generalizability. Additionally, in silico predictions require experimental validation through in vitro and in vivo studies before clinical translation. The use of static protein structures in molecular docking does not account for protein flexibility and solvation effects.

Based on these findings, the following recommendations are proposed: in vitro validation, formulation development, molecular dynamics simulations and in vivo studies.

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