

Received: 06.07.2025

Accepted: 22.12.2025

Research Article

Exploring the Molecular Affinities of Common Topical Agents to Bcl-2 and PD-1 Proteins Using Docking Simulations

Mustafa Tosun^{a,1}, Sultan Erkan^b

^aDermatology of Department, Medicine of Faculty, Sivas Cumhuriyet University, 58140, Sivas, Turkey

^bChemistry of Department, Science of Faculty, Sivas Cumhuriyet University, 58140, Sivas, Turkey

Abstract: Skin cancer is among the most common malignancies worldwide, highlighting the need for novel, target-oriented therapeutic strategies. In this study, the molecular level interactions of three active compounds (diclofenac, imiquimod and lanolin), commonly used in topical skin cancer treatment, with two important skin cancer-associated proteins, Bcl-2 (1HJD) and PD-1 (7WVM), were investigated by computational (in silico) methods. Molecular docking analyses revealed that both imiquimod and diclofenac exhibited high binding affinities toward the target proteins. Notably, imiquimod demonstrated strong interactions with PD-1, a key immune checkpoint protein, supporting its immunotherapeutic potential. Diclofenac, on the other hand, showed significant binding to Bcl-2, suggesting a possible role in apoptosis induction. Lanolin exhibited limited binding, likely due to its primary role as an emollient or carrier rather than a therapeutic agent. These findings support the molecularly targeted actions of imiquimod and diclofenac in skin cancer treatment and provide new insights into their underlying mechanisms of action.

Keywords: Skin Cancer, Diclofenac, Imiquimod, Lanolin, Bcl-2, PD-1, Molecular Docking, 1HJD, 7WVM

1. Introduction

Skin cancer, particularly non-melanoma forms such as basal cell carcinoma (BCC) and squamous cell carcinoma (SCC), represents one of the most prevalent malignancies globally and accounts for the majority of dermatological cancer diagnoses [1-4]. The incidence of these cancers has been steadily increasing over the past decades, largely driven by demographic aging, higher cumulative ultraviolet (UV) exposure, and lifestyle-related factors. Chronic sun exposure, especially to UV-B radiation, induces DNA damage, oxidative stress, and immunosuppression in the skin, collectively contributing to carcinogenesis [5,6]. Additional risk factors, including fair skin phenotype, a history of frequent sunburns during childhood, long-term immunosuppressive therapy, occupational outdoor work, and specific genetic mutations (e.g., TP53, PTCH1), further elevate susceptibility to these malignancies [7-9].

Although surgical excision remains the gold-standard treatment, its use may be limited in cosmetically sensitive or anatomically challenging areas such as the face, periocular region, and ears [10,11]. Consequently, there is a growing clinical interest in topical or non-invasive therapeutic alternatives that can preserve tissue integrity, reduce procedural morbidity, and improve cosmetic outcomes. Agents such as imiquimod, diclofenac sodium gel, and photodynamic therapy have emerged as important modalities in managing early-stage or superficial lesions, especially in patients who are poor surgical candidates or who prefer non-surgical options Bahner [12-14]. Understanding the molecular mechanisms through which these topical agents exert anticancer effects is therefore essential for expanding therapeutic strategies and optimizing patient outcomes.

One of the most widely used topical therapeutic agents is diclofenac, a non-steroidal anti-inflammatory drug (NSAID) that has been

¹ Corresponding Authors

e-mail: mustafatosun@cumhuriyet.edu.tr

approved by the U.S. Food and Drug Administration (FDA) for the management of actinic keratosis. Beyond its well-characterized inhibition of cyclooxygenase-2 (COX-2), diclofenac exerts several additional anticancer mechanisms that extend its utility in dermatological oncology. By suppressing prostaglandin E₂ (PGE₂) synthesis, diclofenac reduces chronic inflammation, a key driver of skin carcinogenesis, and disrupts the microenvironment that promotes tumor development. Moreover, diclofenac has been shown to modulate apoptotic pathways by downregulating anti-apoptotic proteins such as Bcl-2, while facilitating the activation of intrinsic apoptotic signaling cascades, thereby promoting programmed cell death in dysplastic keratinocytes [15].

Another clinically significant topical agent is imiquimod, an immune response modifier used extensively in the treatment of superficial BCC, actinic keratosis, and HPV-related lesions [16]. Imiquimod functions primarily through the activation of Toll-like receptor 7 (TLR7), which triggers downstream signaling pathways involving MyD88-dependent NF- κ B activation [17,18]. This results in robust production of type I interferons (IFN- α/β), interleukins (IL-6, IL-12), and tumor necrosis factor- α (TNF- α), collectively enhancing both innate and adaptive antitumor immunity [19,20]. Furthermore, recent studies have suggested that imiquimod may also interact with immune checkpoint pathways, particularly PD-1 (Programmed Death-1), by modulating its expression or interfering with PD-1/PD-L1 binding dynamics [21,22]. These emerging insights raise the possibility that imiquimod may exert a secondary immunomodulatory role beyond TLR7 activation, contributing to its clinical efficacy against early-stage or superficial skin cancers [23,24].

Lanolin, by contrast, is primarily employed as an emollient and vehicle in dermal formulations [25,26]. Rather than exerting direct anticancer or immunomodulatory activity, lanolin functions as a bioavailability enhancer that improves percutaneous absorption, facilitates the penetration of lipophilic active molecules, and stabilizes semisolid formulations [27-29]. Its high lipid content and occlusive properties enable prolonged skin hydration, support barrier function, and create

a microenvironment that promotes sustained release of therapeutic agents [30-32]. Consequently, lanolin is considered a supportive excipient within topical formulations rather than an active therapeutic agent [33-35]. Among the topical agents evaluated in this study, diclofenac and imiquimod represent well-established pharmacologically active molecules with documented antitumor or immunomodulatory effects, whereas lanolin functions primarily as a dermal excipient rather than an active therapeutic compound [36,37].

Diclofenac, a widely used non-steroidal anti-inflammatory drug (NSAID), has gained FDA approval for the treatment of actinic keratosis due to its multifaceted biological actions [38,39]. Beyond its canonical inhibition of cyclooxygenase-2 (COX-2) and subsequent suppression of prostaglandin E₂ (PGE₂) production, diclofenac also modulates apoptotic pathways by downregulating anti-apoptotic proteins such as Bcl-2, while inducing oxidative stress and mitochondrial dysfunction in dysplastic keratinocytes. These combined effects promote apoptosis and inhibit proliferation, supporting its use as a topical chemopreventive or chemotherapeutic agent in early-stage skin carcinogenesis [40-46].

Imiquimod, on the other hand, acts as a potent immune response modifier and is widely used for superficial basal cell carcinoma, actinic keratosis, and HPV-related lesions [47]. Its primary mechanism involves the activation of Toll-like receptor 7 (TLR7), which induces a cascade of immunological events including the production of type I interferons, pro-inflammatory cytokines, and the recruitment of cytotoxic immune cells to the tumor microenvironment [48,49]. Recent studies have also suggested that imiquimod affects immune checkpoint pathways, particularly the PD-1/PD-L1 axis, suggesting the possibility that imiquimod may enhance antitumor immunity not only through innate immune activation but also through checkpoint modulation. [50].

In contrast, lanolin (represented *in silico* by lanosterol) is a complex mixture of sterols, fatty alcohols, and long-chain esters commonly used as an emollient and formulation vehicle in dermatological preparations [51]. Although lanolin lacks direct anticancer or immunomodulatory

activity, it plays a critical role in enhancing the dermal delivery of active compounds by improving skin hydration, modifying permeation kinetics, and stabilizing topical formulations. As such, lanolin serves as a bioavailability-enhancing excipient, and assessing its interaction profile confirms its expected lack of meaningful affinity for molecular cancer-related targets [52].

Taken together, these three compounds represent distinct functional categories within topical dermatologic treatments: an active NSAID (diclofenac), an immune-activating agent (imiquimod), and a supportive excipient (lanolin). Evaluating their molecular interactions with key regulatory proteins such as Bcl-2 and PD-1 provides mechanistic insights into their therapeutic or auxiliary roles and highlights the biological relevance of active constituents relative to formulation components [53].

In this study, we evaluated the possible molecular interactions of diclofenac and imiquimod, which are widely used in skin cancer treatment, and lanolin, a supportive agent, with two skin cancer-related target proteins, Bcl-2 (1HJD) and PD-1 (7WVM), using *in silico* methods. Bcl-2 is a negative regulator of intracellular apoptotic signaling that contributes to tumor cell survival, whereas PD-1 functions as an immune checkpoint protein that facilitates tumor immune evasion. Through molecular docking analyses, the interaction potentials of these compounds with these two key targets were explored, providing insight into their potential mechanisms of action.

2. Computational Method

The three-dimensional structures of lanosterol, selected as a representative compound for the studied diclofenac, imiquimod, and lanolin, were obtained in SDF format from the PubChem database [54]. Because lanolin is a chemically complex mixture, lanosterol, one of the main sterol components, was used as the representative structure for computational studies, as widely accepted in the literature. All ligands were prepared using the LigPrep tool within the Schrödinger Maestro 13.5 software package [55,56]. At this stage, appropriate protonation states were determined using the Epic module at pH 7.0 ± 0.2 , and low-energy three-dimensional conformers were generated and optimized under the OPLS4 force

field [57,58]. The crystal structure of the Bcl-2 protein (PDB ID: 1HJD) [59] and the ligand-bound form of the PD-1 protein (PDB ID: 7WVM) [60] were downloaded from the Protein Data Bank database and standardized using the Schrödinger Protein Preparation Wizard [61]. During the preparation phase, crystal water molecules, cofactors and heteroatoms not required for binding analysis were removed, missing side chains and hydrogen atoms were added, protonation states were optimized and the structure was finally subjected to energy minimization under the OPLS4 force field [62,63]. Molecular docking studies were performed using the Schrödinger Glide module [64]. For Bcl-2, residues Arg66, Phe101, Ala108, and Tyr199, which form the BH3 binding groove, and for PD-1, residues Ile126, Tyr68, Asp85, and Glu136, which form the PD-1/PD-L1 interaction surface, were used as references for determining the active site sites. Grid boxes created with the Glide Grid Generation tool were optimized to include these residues. All ligands were first scanned in Glide Standard Precision (SP) mode, and then the best poses were re-evaluated in Extra Precision (XP) mode. For each ligand, the pose with the lowest GlideScore was analyzed in detail for binding mode and energy assessments. The GlideScore, Emodel, and Ligand Efficiency parameters were used as the basis for comparing the results [65].

3. Results and discussion

In this study, the molecular interactions of three topical agents commonly used in the treatment of skin cancer diclofenac, imiquimod, and lanolin with skin cancer-associated proteins Bcl-2 (PDB ID: 1HJD) and PD-1 (PDB ID: 7WVM) were evaluated using computational methods.

3.1. Molecular Docking Analysis

Molecular docking simulations were performed using the Schrödinger Maestro 13.5 platform with Glide SP and XP scoring functions to evaluate the binding affinities of diclofenac, imiquimod, and lanosterol (representative of lanolin) toward the Bcl-2 (1HJD) and PD-1 (7WVM) proteins. The numerical docking parameters, including GlideScore, ligand efficiency, hydrogen bond contribution, van der Waals energy, Coulombic interactions, Emodel, and internal energy values,

are presented comprehensively in Table 1. According to the XP docking scores provided in Table 1, imiquimod showed the strongest predicted affinity toward PD-1 (GlideScore = -6.37 kcal/mol), supported by favorable van der Waals (-26.79 kcal/mol) and electrostatic (-5.87 kcal/mol) contributions. Lanolin displayed moderate affinity for PD-1 (-4.90 kcal/mol), while diclofenac exhibited weaker binding (-3.44 kcal/mol). For the Bcl-2 protein (1HJD), diclofenac (-4.15 kcal/mol) and imiquimod (-3.94 kcal/mol) showed moderate affinity, whereas lanolin demonstrated notably weak binding (-0.85 kcal/mol), consistent with its sterol-based bulky structure and steric incompatibility with the narrow BH3-binding groove. Glide ligand efficiency values in Table 1 further support these trends. Imiquimod exhibited the highest efficiency toward PD-1 (LE = -0.35), reflecting its energetically favorable interactions relative to molecular size. Lanolin displayed particularly low ligand efficiency for both proteins, indicating that its structural properties do not favor classical binding-site accommodation. Glide Emodel values, also summarized in Table 1, highlight pose stability and geometric fit. Imiquimod again demonstrated highly favorable conformations within the PD-1 pocket (Emodel = -49.97), while lanolin produced less favorable, higher Emodel and internal strain values (einternal = 10.18 and 11.03), consistent with its limited capacity to adopt optimal docking poses. The docking results for diclofenac, imiquimod, and lanolin are provided in Table 1, while their docking poses in the active sites of 1HJD and 7WVM are illustrated in Figure 1.

Glide Ligand Efficiency, defined as the ratio of binding energy to molecular size, serves as an

indicator of binding effectiveness; more negative values suggest more efficient binding. Diclofenac showed the highest ligand efficiency with 7WVM, while imiquimod exhibited moderate ligand efficiency with the same protein. Overall, ligand efficiencies for all compounds were observed to be lower with the 1HJD protein compared to 7WVM. Glide emodel scores, which evaluate the quality of docking conformations, indicate better docking poses with more negative values. Both diclofenac and imiquimod demonstrated favorable conformations in their binding to 7WVM, while lanolin showed moderate to poor docking scores with both proteins, reflecting suboptimal binding poses.

Imiquimod was found to bind within the active pocket of the 7WVM (PD-1) protein, forming hydrogen bonds with key residues and engaging in strong hydrophobic interactions. Its interaction with 1HJD (Bcl-2) involved hydrogen bonding with ASP101, as well as several hydrophobic contacts. Diclofenac, on the other hand, localized specifically within the active site of Bcl-2, forming hydrogen bonds through its carboxyl group and establishing robust hydrophobic interactions, supporting its potential to inhibit this anti-apoptotic protein.

Conversely, lanolin, due to its large and flexible structure, failed to occupy the binding pockets of either protein effectively and primarily exhibited weak van der Waals interactions. This finding supports the notion that lanolin acts more as an excipient or supportive agent rather than a direct therapeutic molecule. Further details of the molecular docking interactions are provided in Table 2.

Table 1. Numerical values of the docking parameters of molecule against protein

1HJD	Docking Score	Glide ligand efficiency	Glide hbond	Glide evdw	Glide ecoul	Glide emodel	Glide energy	Glide einternal	Glide posenum
Diclofenac	-4.15	-0.22	-0.20	-19.80	-5.06	-33.40	-24.86	2.32	389
Imiquimod	-3.94	-0.22	-0.38	-15.77	-2.83	-25.25	-18.60	0.21	55
Lanolin	-0.85	-0.02	-0.28	-36.71	-1.10	-34.66	-37.81	10.18	209
Venetoclax	-1.25	-0.11	-0.10	-42.25	-0.87	-33.95	-36.26	-12.32	153
7WVM	Docking Score	Glide ligand efficiency	Glide hbond	Glide evdw	Glide ecoul	Glide emodel	Glide energy	Glide einternal	Glide posenum
Imiquimod	-6.37	-0.35	-0.01	-26.79	-5.87	-49.97	-32.66	0.65	37
Lanolin	-4.90	-0.14	-0.14	-44.66	-2.67	-56.16	-47.33	11.03	208
Diclofenac	-3.44	-0.18	-0.34	-24.62	-0.52	-31.85	-25.15	1.93	315
Venetoclax	-2.02	-0.17	-0.21	-41.04	-0.58	-33.95	-32.51	-13.03	155

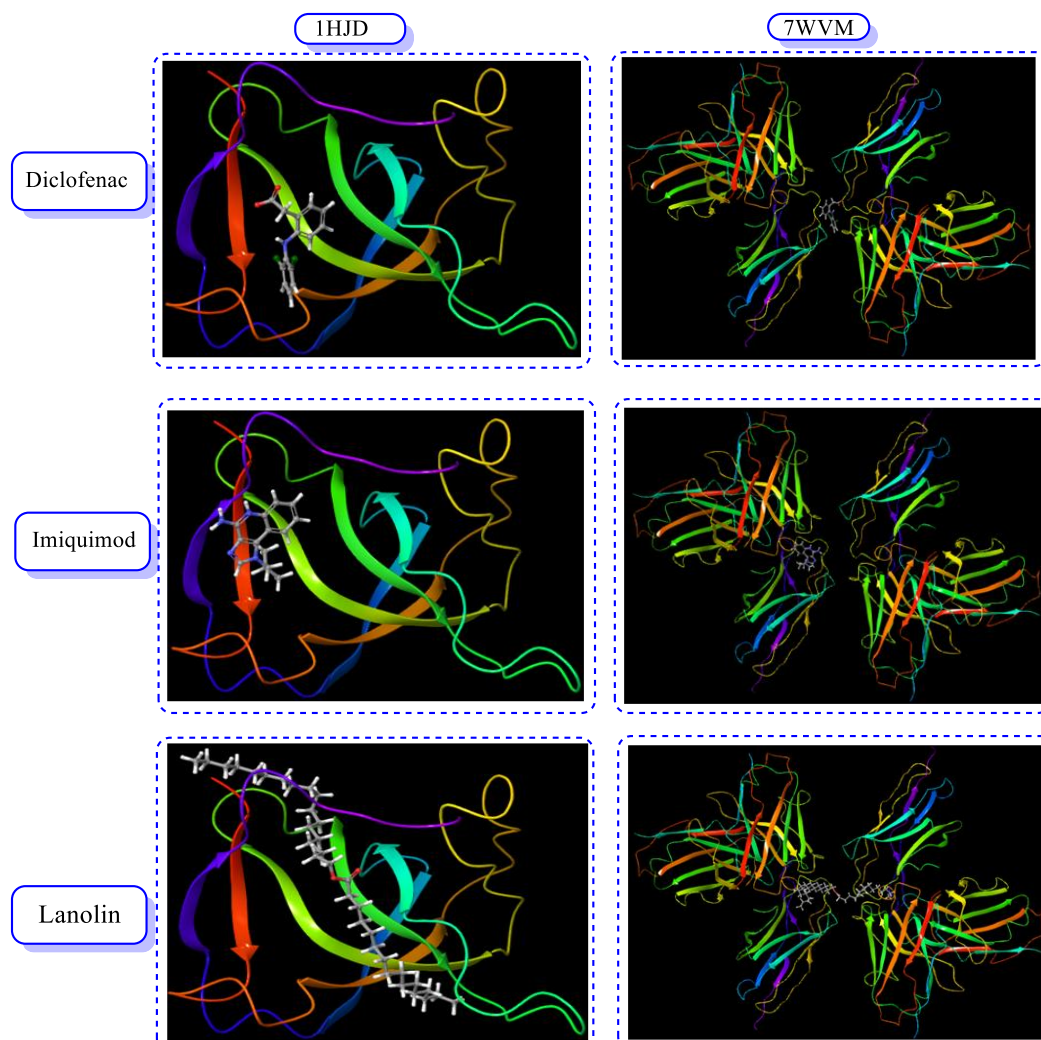


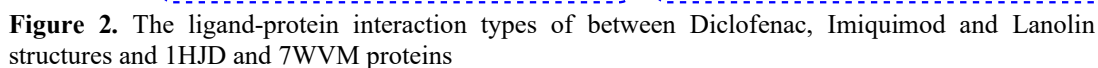
Figure 1. Docking poses between Diclofenac, Imiquimod and Lanolin structures and 1HJD and 7WVM proteins

The ligand-protein interaction types of Diclofenac, Imiquimod and Lanolin structures between the 1HJD and 7WVM proteins are given in Figure 2 and the ligand-protein interaction types are given in Table 2.

The docking poses illustrated in Figure 1 clearly support the numerical docking results. Diclofenac and imiquimod successfully position themselves within the BH3-binding region of Bcl-2, establishing compact and geometrically consistent orientations that align with their moderate GlideScore values. By contrast, lanolin—due to its elongated sterol structure—fails to enter the narrow binding pocket and instead aligns superficially along the protein surface. For the PD-1 protein, imiquimod fits directly into the PD-1/PD-L1 interface, adopting a stable and symmetrical pose

consistent with strong hydrophobic and electrostatic anchoring. Lanolin interacts primarily through surface hydrophobicity, while diclofenac remains peripherally located with minimal penetration into the regulatory interface. These pose differences visually reinforce the computational affinity trends presented in Table 1. The 2D interaction profiles presented in Figure 2 and summarized in Table 2 provide detailed insight into the molecular determinants of binding affinity. For Bcl-2 (1HJD), diclofenac forms multiple hydrogen bonds (e.g., Lys11, Ser19, His20) and hydrophobic contacts with Val98, Cys18, and Tyr79, supporting its moderate but meaningful binding energy. Imiquimod interacts with Lys11 and Asp101 while simultaneously engaging hydrophobic residues such as Val98 and Tyr79,

through hydrophobic patches but does not establish directional interactions, resulting in poor affinity.



7WVM proteins		1HJD		7WVM		
	H- bonds	Polar	Hydrophobic	H- bonds	Polar	Hydrophobic
Diclofenac	LYS11	SER19	VAL98	THR59	ASN58	
		HIS20	CYS18	ARG56	SER57	
		SER51	CYS13		ASN102	
			ALA14		ASN58	
			TYR79		THR59	
			LEU77		SER60	
			PHE50			

Imiquimod	LYS11	THR100 SER51	VAL98 TYR79 CYS13 CYS18	GLU61	ASN31 SER30 ASN58 GLN99	PHE32 PHE63 VAL64 LEU65 PRO83 PHE82 PHE106 PHE56
Lanolin	TYR79	SER64 GLN66	ALA8 PHE60 LEU53 PHE50 TYR48 VAL65 ALA74 ALA75 LEU77 TYR79 TYR106 PHE105	ARG56	ASN74 ASN58 GLN99 SER62 SER52 ASN31 SER30	LEU65 VAL64 PRO83 PHE63 PHE82 PHE10 PHE56 LEU128 PHE32

For PD-1 (7WVM), imiquimod demonstrates the richest and most diverse interaction map, including polar contacts with Asn31, Ser30, Asn58, and Glu61, complemented by extensive aromatic and aliphatic contacts (Phe32, Phe63, Leu65). This broad interaction network explains its superior GlideScore. Diclofenac forms fewer stabilizing contacts, interacting mostly through shallow hydrophobic residues. Lanolin again relies primarily on hydrophobic interactions and fails to form directional contacts, consistent with its mid-range docking score. Together, these diagrams emphasize that imiquimod possesses both the geometric and electrostatic characteristics necessary for effective PD-1 binding, while diclofenac demonstrates selective stabilization at the Bcl-2 binding site, and lanolin remains largely incapable of forming high-affinity, pocket-specific interactions.

Although the docking results obtained in this study provide valuable molecular-level insights into the potential interactions of diclofenac, imiquimod and lanolin with the Bcl-2 and PD-1 proteins, the findings remain inherently limited by the *in silico* nature of the methodology. Computational docking offers an efficient and informative first step in predicting binding tendencies; however, it cannot fully replicate the complexity of dynamic biological systems. Therefore, the results should be interpreted as preliminary indicators rather than definitive evidence of biological activity. The absence of experimental validation—such as

biochemical binding studies, surface plasmon resonance measurements, or cell-based inhibition assays—represents a significant limitation. Future research will focus on complementing these computational predictions with *in vitro* and *in vivo* experiments, as well as more advanced computational approaches such as molecular dynamics simulations and MM-GBSA free-energy estimations, to more accurately assess the biological relevance and therapeutic potential of the identified interactions.

4. Conclusions

Among the tested compounds, imiquimod demonstrated the strongest and most favorable binding profile toward the 7WVM (PD-1) protein, as indicated by its GlideScore, ligand efficiency, and Emodel values. These results highlight imiquimod's structurally compatible orientation within the PD-1/PD-L1 interface and its ability to form multiple stabilizing hydrophobic and polar interactions. Diclofenac, although showing moderate affinity toward 7WVM, exhibited the highest binding performance against the 1HJD (Bcl-2) protein, supported by meaningful van der Waals contributions and hydrogen-bond contacts within the BH3-binding groove. While diclofenac did not surpass imiquimod in PD-1 binding efficiency, it nevertheless displayed a consistent and energetically reasonable interaction profile for both proteins, suggesting that its chemical scaffold can adapt to more than one type of protein

environment. In contrast, lanolin (lanosterol) showed very weak binding to both targets. Its bulky and rigid sterol backbone limited its insertion into well-defined binding pockets, resulting in low ligand efficiency, unfavorable Emodel values, and interactions restricted mainly to nonspecific hydrophobic contacts. This behavior is consistent with its known function as an excipient rather than an active pharmacological agent. Overall, the docking data indicate that imiquimod and diclofenac exhibit meaningful molecular recognition toward PD-1, with imiquimod emerging as the most promising ligand for this target. Diclofenac demonstrated a stronger interaction with Bcl-2, while imiquimod maintained balanced and favorable interactions with both proteins. The consistently weak binding of lanolin confirms its lack of direct inhibitory or regulatory potential at the molecular level.

It should be noted that this study is based solely on computational docking analyses, which, although informative, cannot substitute for experimental confirmation. Future studies integrating biochemical assays, cell-based models, and molecular dynamics simulations will be essential to validate and extend the present findings.

References

- [1] C. Garbe, U. Leiter, Melanoma epidemiology and trends. *Clinics in dermatology*, 27(1), (2009), 3-9.
- [2] M. Cives, F. Mannavola, L. Lospalluti, M. C. Sergi, G. Cazzato, E. Filoni, M. Tucci, Non-melanoma skin cancers: Biological and clinical features. *International journal of molecular sciences*, 21(15), (2020) 5394.
- [3] A. H. Roky, M. M. Islam, A. M. F. Ahasan, M. S. Mostaq, M. Z. Mahmud, M. N. Amin, M. A. Mahmud, Overview of skin cancer types and prevalence rates across continents. *Cancer pathogenesis and therapy*, 3(02), (2025) 89-100.
- [4] Z. G. Attal, W. Shalata, A. Soklakova, L. Tourkey, S. Shalata, O. Abu Saleh, A. Yakobson, Advanced and metastatic non-melanoma skin cancer: epidemiology, risk factors, clinical features, and treatment options. *Biomedicines*, 12(7), (2024) 1448.
- [5] R. Kumar, B. C. Das, Role of environmental factors in Carcinogenesis. *Environ We Int J Sci Technol*, 4, (2009) 53-69.
- [6] O. Reiter, I. Mimouni, S. Dusza, A. C. Halpern, Y. A. Leshem, A. A. Marghoob, Dermoscopic features of basal cell carcinoma and its subtypes: A systematic review. *Journal of the American Academy of Dermatology*, 85(3), (2021) 653-664.
- [7] F. I. Scott, R. C. M. Mamtani, Brensinger, K. Haynes, Z. C. Chiesa-Fuxench, J. Zhang, J. D. Lewis, Risk of nonmelanoma skin cancer associated with the use of immunosuppressant and biologic agents in patients with a history of autoimmune disease and nonmelanoma skin cancer. *JAMA dermatology*, 152(2), (2016) 164-172.
- [8] J. McLelland, A. Rees, G. Williams, T. Chu, The incidence of immunosuppression-related skin disease in long-term transplant patients. *Transplantation*, 46(6), (1988) 871-873.
- [9] M. A. Kreher, M. M. B. Noland, S. Konda, M. I. Longo, R. Valdes-Rodriguez, Risk of melanoma and nonmelanoma skin cancer with immunosuppressants, part I: Calcineurin inhibitors, thiopurines, IMDH inhibitors, mTOR inhibitors, and corticosteroids. *Journal of the American Academy of Dermatology*, 88(3), (2023) 521-530.
- [10] Z. A. Karciglu, Surgical treatment. In *Orbital Tumors: Diagnosis and Treatment*. New York, NY: Springer New York. (2005) 359-390.
- [11] L. L. R. Rescue, U. E. Crease, M. E. Hartstein, ADVANCES IN COSMETIC SURGERY. *Advances in Cosmetic Surgery*, 2024: *Advances in Cosmetic Surgery*, 7(1), (2024) 99.
- [12] J. D. Bahner, Bordeaux, J. S. Non-melanoma skin cancers: photodynamic therapy, cryotherapy, 5-fluorouracil, imiquimod, diclofenac, or what? Facts and controversies. *Clinics in dermatology*, 31(6), (2013) 792-798.
- [13] S. Piaserico, R. Mazzetto, E. Sartor, C. Bortoletti, Combination-based strategies for the treatment of actinic keratoses with photodynamic therapy: an evidence-based review. *Pharmaceutics*, 14(8), (2022) 1726.
- [14] M. Zewail, H. Abbas, N. El Sayed, H. Abd-El-Azim, Combined photodynamic therapy and hollow microneedle approach for

- effective non-invasive delivery of hypericin for the management of imiquimod-induced psoriasis. *Journal of Drug Targeting*, 32(8), (2024) 941-952.
- [15] S. Y. Buckman, A. Gresham, P. Hale, G. Hruza, J. Anast, J. Masferrer, A. P. Pentland, COX-2 expression is induced by UVB exposure in human skin: implications for the development of skin cancer. *Carcinogenesis*, 19(5), (1998) 723-729.
- [16] M. A. De Francesco, M. Salvi, R. Gerami, M. Alberti, F. Cesanelli, I. Scarvaglieri, E. Quiros-Roldan, Actinic Keratosis and Human Papillomaviruses: may their relationship constitute a new approach for actinic keratosis management?. *Tumour Virus Research*, 200330.
- [17] T. Kawai, S. Akira, (2004). Toll-like receptor downstream signaling. *Arthritis Res Ther*, 7(1), (2025) 12.
- [18] M. Jin, J. Fang, J. J. Wang, X. Shao, S. W. Xu, P. Q. Liu, & Z. P. Liu, Regulation of toll-like receptor (TLR) signaling pathways in atherosclerosis: from mechanisms to targeted therapeutics. *Acta Pharmacologica Sinica*, 44(12), (2023) 2358-2375.
- [19] G. Trinchieri, Interleukin-12 and the regulation of innate resistance and adaptive immunity. *Nature reviews immunology*, 3(2), (2003) 133-146.
- [20] M. P. Schön, & M. Schön, Imiquimod: mode of action. *British Journal of Dermatology*, 157(s2), (2007) 8-13.
- [21] L. Ai, A. Xu, & J. Xu, Roles of PD-1/PD-L1 pathway: signaling, cancer, and beyond. Regulation of cancer Immune checkpoints: Molecular and cellular mechanisms and therapy, (2020) 33-59.
- [22] S. L. Topalian, C. G. Drake, D. M. Pardoll, Immune checkpoint blockade: a common denominator approach to cancer therapy. *Cancer cell*, 27(4), (2015) 450-461.
- [23] K. R. Bhaliya, M. Anwer, A. Munn, & M. Q. Wei, New horizons in cancer immunotherapy: The evolving role of R848 and R837. *Molecular and Clinical Oncology*, 22(1), (2024) 4.
- [24] S. Mukherjee, R. Patra, P. Behzadi, A. Masotti, A. Paolini, & M. Sarshar, Toll-like receptor-guided therapeutic intervention of human cancers: molecular and immunological perspectives. *Frontiers in Immunology*, 14, (2023) 1244345.
- [25] K. L. Hon, J. S. C. Kung, W. G. G. Ng, & T. F. Leung, Emollient treatment of atopic dermatitis: latest evidence and clinical considerations. *Drugs in context*, 7, (2018) 212530.
- [26] I. Nola, K. Kostovic, L. Kotrulja, L. Lugovic, The use of emollients as sophisticated therapy in dermatology. *Acta Dermatovenerol Croat*, 11(2), (2003) 80-7.
- [27] E. S. Shalaby, S. I. Shalaby, S. A. Ismail, Advantages and therapeutic applications of different semisolids as vehicles for nano-based systems. *Therapeutic Delivery*, 16(6), (2025) 581-591.
- [28] D. A. Safta, C. Bogdan, M. L. Moldovan, SLNs and NLCs for skin applications: enhancing the bioavailability of natural bioactives. *Pharmaceutics*, 16(10), (2024) 1270.
- [29] E. Tören, A. A. Mazari, Nano Transdermal Delivery Systems of Herbal Extracts for Dermatological Therapeutics and Skin Care. *Open Journal of Nano*, 9(2), (2024) 77-105.
- [30] J. Rajkumar, N. Chandan, P. Lio, V. Shi, The skin barrier and moisturization: function, disruption, and mechanisms of repair. *Skin Pharmacology and Physiology*, 36(4), (2023) 174-185.
- [31] S. Dominguez, G. A. Mackert, M. K. Dobke, Nanotechnology to enhance transdermal delivery of hydrophilic humectants for improved skin care: a model for therapeutic applications. In *Nanostructures for Drug Delivery Elsevier*. (2017) 919-939.
- [32] S. Brito, M. Baek, B. H. Bin, Skin structure, physiology, and pathology in topical and transdermal drug delivery. *Pharmaceutics*, 16(11), (2024) 1403.
- [33] B. A. Jenkins, D. V. Belsito, Lanolin. *Dermatitis*, 34(1), (2023) 4-12.
- [34] I. Nola, K. Kostovic, L. Kotrulja, L. Lugovic, The use of emollients as sophisticated therapy in dermatology. *Acta Dermatovenerol Croat*, 11(2), (2003) 80-7.
- [35] M. Lodén, Role of topical emollients and moisturizers in the treatment of dry skin barrier disorders. *American journal of clinical dermatology*, 4(11), (2003) 771-788.

- [36] D. Arcuri, B. Ramchatesingh, F. Lagacé, L. Iannattone, E. Netchiporouk, P. Lefrançois, I. V. Litvinov, Pharmacological agents used in the prevention and treatment of actinic keratosis: a review. *International Journal of Molecular Sciences*, 24(5), (2023) 4989.
- [37] J. Ryu, F. C. Yang, A review of topical imiquimod in the management of basal cell carcinoma, actinic keratoses, and other skin lesions. *Clinical Medicine. Therapeutics*, 1, CMT-(2009) S1969.
- [38] G. J. Thomas, P. Herranz, S. B. Cruz, A. Parodi, Treatment of actinic keratosis through inhibition of cyclooxygenase-2: Potential mechanism of action of diclofenac sodium 3% in hyaluronic acid 2.5%. *Dermatologic Therapy*, 32(3), (2019) e12800.
- [39] D. A. M. Nițescu, H. Păunescu, M. Costescu, B. Nițescu, L. Coman, I. Fulga, O. A. Coman, Novel Research Regarding Topical Use of Diclofenac in Dermatology—Non-Clinical and Clinical Data. *Scientia Pharmaceutica*, 93(3), (2025) 34.
- [40] P. Sokołowska, L. Bleibel, J. Owczarek, A. Wiktorowska-Owczarek, PPAR γ , NF- κ B and the UPR pathway as new molecular targets in the anti-inflammatory actions of NSAIDs: Novel applications in cancers and central nervous system diseases?. *Advances in Clinical and Experimental Medicine*, 33(9) (2024).
- [41] L. F. Fecker, E. Stockfleth, I. Nindl, C. Ulrich, T. Forschner, J. Eberle, The role of apoptosis in therapy and prophylaxis of epithelial tumours by nonsteroidal anti-inflammatory drugs (NSAIDs). *British Journal of Dermatology*, 156(s3), (2007) 25-33.
- [42] L. Cheng, Z. Hu, J. Gu, Q. Li, J. Liu, M. Liu,... X. Bi, Exploring COX-independent pathways: A novel approach for meloxicam and other NSAIDs in cancer and cardiovascular disease treatment. *Pharmaceutics*, 17(11), (2024) 1488.
- [43] S. Y. Qi, M. M. Yang, C. Y. Li, K. Yu, S. L. Deng, The HPV viral regulatory mechanism of TLRs and the related treatments for HPV-associated cancers. *Frontiers in Immunology*, 15, (2024) 1407649.
- [44] M. R. Barros Jr, T. H. A. de Oliveira, C. M. L. de Melo, A. Venuti, A. C. de Freitas, Viral modulation of TLRs and cytokines and the related immunotherapies for HPV-associated cancers. *Journal of immunology research*, 2018(1), (2018) 2912671.
- [45] M. Tampa, C. I. Mitran, M. I. Mitran, I. Nicolae, A. Dumitru, C. Matei,... S. R. Georgescu, The role of beta HPV types and HPV-Associated inflammatory processes in cutaneous squamous cell carcinoma. *Journal of Immunology Research*, 2020(1), (2020) 5701639.
- [46] L. F. Fecker, E. Stockfleth, I. Nindl, C. Ulrich, T. Forschner, J. Eberle, The role of apoptosis in therapy and prophylaxis of epithelial tumours by nonsteroidal anti-inflammatory drugs (NSAIDs). *British Journal of Dermatology*, 156(s3), (2007) 25-33.
- [47] Y. Liu, C. Yang, J. Zhang, A. Ihsan, I. Ares, M. Martínez,... M. A. Martínez, Recent progress in adverse events of carboxylic acid non-steroidal anti-inflammatory drugs (CBA-NSAIDs) and their association with the metabolism: the consequences on mitochondrial dysfunction and oxidative stress, and prevention with natural plant extracts. *Expert Opinion on Drug Metabolism & Toxicology*, 20(8), (2024) 765-785.
- [48] F. Borella, N. Gallio, L. Mangherini, P. Cassoni, L. Bertero, C. Benedetto, M. Preti, Recent advances in treating female genital human papillomavirus related neoplasms with topical imiquimod. *Journal of Medical Virology*, 95(11), (2023) e29238.
- [49] S. Y. Qi, M. M. Yang, C. Y. Li, K. Yu, S. L. Deng, The HPV viral regulatory mechanism of TLRs and the related treatments for HPV-associated cancers. *Frontiers in Immunology*, 15, (2024) 1407649.
- [50] M. P. Schön, M. Schön, Immune modulation and apoptosis induction: two sides of the antitumoral activity of imiquimod. *Apoptosis*, 9(3), (2004) 291-298.
- [51] F. Rüttler, T. Hammerschick, S. Schlag, W. Vetter, Isolation of lanosterol and dihydrolanosterol from the unsaponifiable matter of lanolin by urea complexation and countercurrent chromatography in heart-cut

- recycling mode. *Journal of Chromatography B*, 1210, (2022) 123470.
- [52] K. Garala, R. Ughreja, R. Ranpara, N. Dholaria, Optimizing Bioavailability Through Natural Excipients: A Sustainable Approach to Drug Delivery. In *Innovative Pharmaceutical Excipients: Natural Sources*. (2025) 321-343.
- [53] H. Chopra, R. K. Gautam, *Biomedical Applications of Carrageenan. Biopolymers for Biomedical Applications*, (2024)151-173.
- [54] S. Kim, P. A. Thiessen, E. E. Bolton, J. Chen, G. Fu, A. Gindulyte,..., S. H. Bryant, PubChem substance and compound databases. *Nucleic acids research*, 44(D1), (2016) D1202-D1213.
- [55] I. J. Chen, N. Foloppe, Drug-like bioactive structures and conformational coverage with the LigPrep/ConfGen suite: comparison to programs MOE and catalyst. *Journal of chemical information and modeling*, 50(5), (2010) 822-839.
- [56] Z. Kökbudak, S. Akkoç, H. Karataş, B. Tüzün, G. Aslan, In Silico and in vitro antiproliferative activity assessment of new schiff bases. *ChemistrySelect*, 7(3), (2022) e202103679.
- [57] L. Yuan, T. Liu, X. Qi, Y. Zhang, Q. Wang, Q. Wang, M. Liu, Multi-spectroscopic and molecular docking studies for the pH-dependent interaction of β -lactoglobulin with (-)-epicatechin gallate and/or piceatannol: Influence on antioxidant activity and stability. *Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy*, 313, (2024) 124090.
- [58] J. Román, D. González, M. Inostroza-Ponta, A. Mahn, Molecular modeling of epithiospecifier and nitrile-specifier proteins of broccoli and their interaction with aglycones. *Molecules*, 25(4), (2020) 772.
- [59] J. C. Loughheed, J. M. Holton, T. Alber, J. F. Bazan, T. M. Handel, Structure of melanoma inhibitory activity protein, a member of a recently identified family of secreted proteins. *Proceedings of the National Academy of Sciences*, 98(10), (2001) 5515-5520.
- [60] D. Lu, Z. Xu, D. Zhang, M. Jiang, K. Liu, J. He,... Y. Chai, PD-1 N58-glycosylation-dependent binding of monoclonal antibody cemiplimab for immune checkpoint therapy. *Frontiers in Immunology*, 13, (2022) 826045.
- [61] B. Tüzün, Examination of anti-oxidant properties and molecular docking parameters of some compounds in human body. *Turkish Computational and Theoretical Chemistry*, 4(2), (2020) 76-87.
- [62] C. Lu, C. Wu, D. Ghoreishi, W. Chen, L. Wang, W. Damm,... E. D. Harder, OPLS4: improving force field accuracy on challenging regimes of chemical space. *Journal of chemical theory and computation*, 17(7), (2021) 4291-4300.
- [63] L. D'Amore, D. F. Hahn, D. L. Dotson, J. T. Horton, J. Anwar, I. Craig, ... G. Tresadern, Collaborative assessment of molecular geometries and energies from the Open Force Field. *Journal of chemical information and modeling*, 62(23), (2022) 6094-6104.
- [64] K. A. Peele, C. P. Durthi, T. Srihansa, S. Krupanidhi, V. S. Ayyagari, D. J. Babu,... T. C. Venkateswarulu, Molecular docking and dynamic simulations for antiviral compounds against SARS-CoV-2: A computational study. *Informatics in medicine unlocked*, 19, (2020) 100345.
- [65] R. Bathula, N. Muddagoni, G. Lanka, M. Dasari, S. Potlapally, Glide docking, autodock, binding free energy and drug-likeness studies for prediction of potential inhibitors of cyclin-dependent kinase 14 protein in wnt signaling pathway. *Biointerface Res Appl Chem*, 12(2), (2021) 2473-2488.