

Biocomputational-mediated Screening for Discovery of Antimelanogenic and Antioxidant Agents from *Ficus carica L.*

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Abstract: Hyperpigmentation disorders caused by the overproduction of melanin and oxidative stress not only affect skin health but also contribute to psychological consequences such as low self-esteem and social anxiety. The desire to solve hyperpigmentation problems, as well as adverse effects associated with synthetic compounds in commercial skin-depigmenting products, has led to a growing demand for natural skin-depigmenting ingredients. The fig (*Ficus carica L.*) is a promising alternative as it is known to contain various bioactive compounds with excellent antioxidant properties. This study aims to identify safe yet effective antioxidant and antimelanogenic compounds from fig fruit for skin depigmentation purposes. Seventy-seven phytochemicals of *F. carica* were docked with four melanogenesis-related proteins (receptor tyrosine kinase, tyrosinase-related protein 1, cAMP-response element binding protein, endothelin receptor type-B) and two oxidative stress-associated proteins (mitogen-activated protein kinase, matrix metalloproteinase-1). The top five ligands for each target protein were analyzed for their pharmacokinetic characteristics (ADME and toxicity predictions). Several compounds showed strong binding affinities (-6.2 to -10.1 kcal/mol), with cynaroside demonstrating consistently high affinity across multiple targets and favorable pharmacokinetic profiles. Multiple-ligand simultaneous docking suggested possible synergistic interactions. Overall, these findings highlight cynaroside and several other fig-derived compounds as promising computational candidates for further experimental investigation toward depigmentation and antioxidant applications.

Keywords: hyperpigmentation; fig; melanogenesis.

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1. Introduction

Hyperpigmentation disorders are conditions where some parts of the skin are darker than the surrounding skin, usually caused by excess melanin synthesis and oxidative stress [1]. Some examples of common hyperpigmentation disorders include postinflammatory hyperpigmentation, ephelides, melasma, café au lait macules, and solar lentigines [2]. Melanin is a polymorphous pigment synthesized by melanocytes in the epidermal layer and is responsible for determining the color of the skin, hair, and eyes. Its production is influenced by genetics, hormones, and UV exposure [3]. Eumelanin and pheomelanin are the main types of melanin involved in human pigmentation of the skin.

The synthesis of melanin begins with the oxidation of L-tyrosine to L-3,4-dihydroxyphenylalanine (L-DOPA) and subsequently to dopaquinone by tyrosinase, the rate-limiting enzyme of melanogenesis. Dopaquinone may then proceed through pathways that produce eumelanin and pheomelanin, involving TRP1 and TRP2 enzymes [4]. Oxidative stress further contributes to pigmentation through excess reactive oxygen species (ROS), which damage skin components and activate melanogenic proteins such as CREB, MITF, and tyrosinase [5-10]. This well-established link between ROS and hyperpigmentation highlights the importance of integrating antioxidant ingredients into depigmenting formulations.

Most commercially available depigmenting agents inhibit tyrosinase [5]; however, compounds such as hydroquinone and mercury-containing agents pose risks of irritation, dermatitis, or systemic toxicity [11-13]. Increasing consumer preference for natural, safer alternatives has driven the search for plant-derived antimelanogenic compounds.

Figs (*Ficus carica* L.) have emerged as a promising natural repository with potential antimelanogenic effects, attributed to their rich composition of bioactive compounds, especially antioxidants. The fig is an edible syconium from the Moraceae family with a teardrop shape and a thick purple-brown outer skin [14-15]. They are widely known to be a great source of fiber, vitamins, and minerals such as calcium, iron, magnesium, and potassium; hence, they have a long history of use in treating various diseases related to the gastrointestinal, respiratory, inflammatory, and cardiovascular systems [16]. Besides having high nutritional value, figs are also known for containing various bioactive compounds, including polyphenols, flavonoids, and carotenoids with excellent antioxidant properties [17]. Several studies have highlighted its potential therapeutic benefits; however, their bioactive constituents have not been systematically screened for antimelanogenic or antioxidative effects at the molecular level.

Therefore, this research aims to identify the bioactive compound from *F. carica* with the best antioxidant and antimelanogenic properties for use in skincare through molecular docking, a time- and cost-saving *in silico* structure-based drug discovery approach [18]. The pharmacokinetic properties of the compounds will be assessed through absorption, distribution, metabolism, excretion, and toxicity (ADMET) tests to identify and eliminate weak or toxic compounds [19-20]. Four proteins associated with melanogenesis inhibition, which are endothelin receptor type B, cyclic adenosine monophosphate (cAMP) response element-binding protein, tyrosinase-related protein 1, and receptor tyrosine kinase, as well as two proteins associated with oxidative stress production, including mitogen-activated protein kinase and matrix metalloproteinase-1 (MMP-1), will be focused on in this study.

2. Materials and Methods

2.1. Retrieval of target proteins & ligands.

Four target proteins for inhibiting melanogenesis, including tyrosinase-related protein 1 (PDB ID: 5M8N), endothelin receptor type-B (PDB ID: 5XPR), receptor tyrosine kinase (PDB ID: 6XV9), cAMP-response element binding protein (PDB ID: 2L84), and two target proteins for inhibiting oxidative stress, mitogen-activated protein kinase (PDB ID: 1DI9) and matrix metalloproteinase-1 (PDB ID: 966C) were downloaded from the RCSB Protein Data Bank (<https://www.rcsb.org>) in PDB format. Seventy-seven (77) bioactive compounds found in fig fruit were selected through literature reviews of various journal publications. These compounds were chosen based on previously documented flavonoid, phenolic, and carotenoid

constituents known for antioxidant or biological activity. The 3D conformers of these compounds and the selected positive controls were downloaded from PubChem (<https://pubchem.ncbi.nlm.nih.gov>) in the structure data file (SDF) format.

2.2. Preparation of target proteins.

The target proteins were imported into BioVia Discovery Studio Visualizer to analyze ligand interactions and to identify their binding sites. The imported protein structures then underwent a cleaning process, which included the removal of water molecules, ligands, and heteroatoms. Polar hydrogens were added to the protein to stabilize it. The filtered protein structure is then saved in PDB format. Binding sites were confirmed based on literature-reported active sites and visual inspection of co-crystallized ligand environments.

2.3. Single ligand molecular docking.

The filtered protein structures and the bioactive compounds were imported into PyRx (version 0.8) for single-ligand molecular docking. The proteins were converted to AutoDock macromolecules, while the bioactive compounds underwent energy minimization and were converted to AutoDock ligands (.pdbqt). Docking was performed using AutoDock Vina via Vina Wizard in PyRx. The grid box was adjusted to cover the binding sites of the protein. Grid dimensions were validated by ensuring complete coverage of the catalytic pocket and by redocking reference ligands to confirm pose consistency. The exhaustiveness value was set to the default of 8, as recommended for medium-throughput virtual screening, where increasing exhaustiveness offers diminishing returns in accuracy relative to computation time. For 5M8N, it was set to 23.6380 x 38.2752 x 31.2960, with the centers at -21.2855 x 23.7440 x -4.1922. For 5XPR, the grid box dimensions were set as -26.1085 x 33.3269 x 31.3000, with the centers at -32.9641 x 5.9931 x 11.2029. For 6XV9, the grid box dimensions were set as 33.1945 x 28.3220 x 38.9159, with the centers at 189.7714 x 10.5748 x 73.3879. For 2L84, the grid box dimensions were set as 20.5520 x 23.6773 x 26.1911, with the centers 13.2739 x 0.8396 x 1.2063. For 1DI9, the grid box dimensions were set as 24.9507 x 24.2271 x 24.7977 with the centers 41.2049 x 31.5530 x 32.4688, and for 966C, the grid box dimensions were set as 23.6575 x 22.0912 x 28.6739 with the centers 8.1531 x -8.7705 x 38.6855. Once the docking simulation was complete, the results were exported as CSV files.

2.4. Absorption, distribution, metabolism, excretion, and toxicity (ADMET) Analysis.

The top five compounds for each protein were selected for further pharmacokinetics assessment. The canonical Simplified Molecular Input Line Entry System (SMILES) of the compounds and positive controls were entered into SwissADME (<http://www.swissadme.ch>) and pkCSM (<https://biosig.lab.uq.edu.au/pkcsml/prediction>). SwissADME was used to obtain lipophilicity (log P_{ow}) and skin permeability (log K_p), while pkCSM provided total clearance, AMES toxicity, skin sensitization, and hepatotoxicity. Interpretation of ADMET parameters followed published guidelines: optimal dermal delivery typically corresponds to log P between 1–3, a compound with log K_p > -2.5 cm/s demonstrates favorable skin permeability, and AMES-negative, non-hepatotoxic, and non-sensitizing predictions were required for safety assessment.

2.5. Multiple ligand simultaneous docking.

After ADMET analysis, four compounds with desirable pharmacokinetic profiles were selected for multiple ligand simultaneous docking (MLSD). The compounds were paired based on complementary structural properties and strong individual docking scores. Pairings were chosen to evaluate whether combining ligands with overlapping active-site interactions may enhance theoretical binding affinity. Proteins were prepared using AutoDock Tools (version 1.5.7) by removing water molecules, adding polar hydrogens, and assigning Kollman charges. The structures were saved in.pdbqt format. Grid box parameters were optimized to ensure full active-site coverage. Docking simulations were executed using AutoDock Vina (version 1.2.5). MLSD poses were visually inspected to confirm that both ligands fit within the active pocket without steric clashes and demonstrated complementary interaction patterns, supporting the validity of the predicted synergistic interactions.

3. Results and Discussion

The 3D structures of the six target proteins downloaded from PDB were analyzed and cleaned using BIOVIA Discovery Studio (Figure 1). These structures were visually inspected to confirm correct folding and accessible active sites prior to docking. The binding sites for the six target proteins were then identified (Figure 2). The predicted binding pockets correspond to previously reported active regions associated with melanogenesis and oxidative-stress regulation.

To avoid redundancy and improve clarity, the amino-acid interaction profiles were refined to highlight only the key stabilizing residues that consistently contributed to ligand binding across the top-scoring compounds. For 5M8N, the main interacting residues were Thr69, Ser72, Val89, and Leu92, which frequently contributed hydrogen-bonding and hydrophobic interactions. In 5XPR, His150, Asp154, Lys182, and Trp336 were identified as the major hydrogen-bond donors and acceptors. For 6XV9, the ligand was mainly anchored by Glu671, Cys674, Gly676, and Asp810. In 2L84, the core hydrophobic and polar contacts involved Leu1109, Ile1122, Tyr1167, and Asn1168. For 1DI9, Gly33, Glu71, Thr68, and Phe169 were the key residues stabilizing ligand orientation, whereas in 966C, the principal interacting amino acids were Asn180, Arg214, Glu219, and Tyr237.

Table 1 summarizes the docking scores and major stabilizing interactions between selected *F. carica* phytochemicals and the six proteins involved in melanogenesis and oxidative stress pathways. Lower (more negative) binding affinities indicate stronger predicted interactions. Key residues mediating hydrogen bonding, hydrophobic contacts, or van der Waals stabilization are listed to highlight the molecular determinants of ligand binding. This comparative profile enables identification of compounds with the highest likelihood of functional inhibition relative to positive controls.

Table 1. Binding affinities and key interaction residues of the top five *F. carica* compounds and positive controls across six target proteins.

Protein	Ligands	Binding affinity (kcal/ mol)	Bond interactions		
			Van der Waals	Hydrogen bond	Hydrophobic interactions
5M8N	Pelargonidin 3-rutinoside	-9.4	A: Thr 69, Ser 72, Val 89, Leu 92 B: Ser 49, Gly 50, Pro 51 C: Ala 67, Thr 69, Ser 72, Asn 96, Arg 97	A: Val 68, Ala 70, Asn 96, Arg 97 B: Val 48 C: Ala 70	A: Ala 67 C: Leu 92
	Naringin	-9.2	A: Ala 67, Val 68, Thr 69, Asp 71, Ser 72,	C: Glu 88	B: Val 48

Protein	Ligands	Binding affinity (kcal/ mol)	Bond interactions		
			Van der Waals	Hydrogen bond	Hydrophobic interactions
			Val 89, Leu 92, Asn 96 B: Ser 46, Pro 47 C: Ala 67, Val 68, Thr 69, Ala 70, Gly 83, Asn 96, Arg 97		C: Val 89, Leu 92, Arg 93
	Rutin	-8.9	A: Val 68, Thr 69, Ser 72, Val 89, Leu 92 B: Pro 47, Val 48, Gly 50, Pro 51 C: Val 68, Thr 69, Ser 72, Arg 97	A: Ala 70, Arg 97	A: Ala 67 C: Ala 67, Leu 92
	Cynaroside	-8.6	A: Val 68, Asp 71, Ser 72, Leu 92 B: Pro 47, Val 48, Pro 51, C: Val 68, Thr 69, Asp 71, Ser 72, Val 89, Leu 92	A: Asn 96, Arg 97 B: Gly 50 C: Ala 70, Asn 96	A: Ala 67, Ala 70, Val 89 C: Ala 67
	Zeaxanthin	-8.5	A: Leu 36, Arg 37, Ala 67, Val 68, Leu 92, Arg 93, Asn 96, Ser 166, Glu 167, Glu 168, Ile 169, Leu 170, Gly 171, Pro 172, Asp 173, Gly 174 B: Ser 49 C: Ala 67, Val 68, Leu 92, Asn 96, Arg 97	-	B: Val 48
	Ascorbic acid*	-5.4	A: Gln 29, Cys 30, Thr 32, Glu 34, Ser 38, Met 40, Asp 44, Gly 52	A: Ala 35, Cys 42, Arg 55	-
	Hydroquinone*	-4.7	A: Ser 72, Asp 82, Glu 88, Arg 93, Ile 432, Asn 435, Tyr 438 B: Gly 50	A: Asp 71	A: His 75, Val 89 B: Pro 51
5XPR	Proanthocyanidin	-9.1	A: Asn 104, Ser 108, Asp 154, Ile 157, Val 159, Leu 162, Glu 165, Trp 167, Val 177, Pro 178, Lys 273, Trp 336, Arg 343, Ile 372	A: Lys 97, Asn 158	A: Lys 161, Lys 182, Leu 277, Leu 339
	Rutin	-9.1	A: Ser 108, Asp 154, Ile 157, Leu 162, Trp 167, Phe 169, Val 177, Pro 178, Gln 181, Lys 182, Leu 256, Lys 273, Ile 372, Ser 376	A: Asn 104, Asn 158	A: Val 159, Lys 161, Phe 240
	Naringin	-9.0	A: Val 107, Ser 108, His 150, Asp 154, Asn 158, Lys 161, Leu 162, Pro 178, Gln 181, Glu 236, Phe 240, Leu 256, Leu 257, Lys 273, Leu 277, Trp 336, Leu 339, Arg 343, Asn 373, Ala 375, Ser 376	A: Asn 104, Lys 182	A: Val 159, Ile 372
	β-cryptoxanthin	-9.0	A: Phe 278, Cys 283, Ala 287, Thr 297, Met 300, Leu 301, Leu 337, Asn 1002, Trp 1115, Ala 1050, Val 1051	-	A: Phe 282, Leu 286, Ala 290, Tyr 293, Phe 326, Val 329, Leu 330, Ala 333
	Cyanidin 3,5-diglucoside	-8.8	A: Asn 104, Val 107, Ser 108, Val 111, His 150, Ile 155, Leu 162, Trp 167, Cys 174, Val 177, Pro 178, Gln 181, Lys 182, Phe 240, Cys 255, Leu 256, Trp 336, Leu 339, Ala 375, Ser 376	A: Asp 154, Asn 158, Asn 373	A: Val 159, Lys 161, Ile 372
	Ascorbic acid*	-5.0	A: Ser 108, Asn 158, Val 159, Leu 162, Ile 372, Asn 373, Ser 376	A: Asn 104, Asp 154	-
6XV9	Hydroquinone*	-4.7	A: Ile 103, Thr 105, Val 107, Ser 108, Asn 158, Leu 162, Asn 373, Ser 376	A: Asn 104	A: Val 159, Ile 372
	Naringin*	-11.2	A: Tyr 760, Asp 762 B: Ala 597, Lys 623, Thr 670, Cys 674, Gly 676, Arg 684, Arg 796, Leu 799, Asp 810, Ala 814, Arg 815	B: Leu 595, Gly 596, Tyr 672, Cys 673, Asp 677, Asn 680	B: Val 603, Ala 621, Cys 809, Phe 811
	Zeaxanthin	-11.1	A: Tyr 675, Gly 803, Asn 804 B: Glu 640, Val 643, Ile 653, Val 654, Thr 670, Glu 671, Cys 673, Cys 674, Gly 676, Asp 677, Leu 783, Cys 788, Ile 808, Asp 810	B: Ile 789	B: Leu 595, Val 603, Ala 621, Lys 623, Leu 644, Tyr 672, His 790, Leu 799, Cys 809, Phe 811
	Cynaroside	-10.8	A: Glu 640, Val 654, Val 668, Thr 670, Glu 671, Tyr 672, Cys 674, Gly 676, Asn 680, Arg 684	A: Cys 673, Tyr 675, Asp 677, Asp 810	A: Leu 595, Val 603, Ala 621, Lys 623, Leu 799, Cys 809, Phe 811
	Isoorientin	-10.7	A: Asp 762, His 802 B: Lys 623, Val 654, Thr 670, Cys 674, Tyr 675, Arg 684, Asp 810	A: Gly 803 B: Glu 605, Tyr 672, Cys 673, Gly 676, Asp 677	B: Leu 595, Val 603, Ala 621, Leu 799, Cys 809, Phe 811
	α-carotene	-10.5	A: Thr 607, Ile 612, Ala 616, Thr 619, Asn 649, His 650, Glu 651, Leu 657, Glu 671,	-	A: Ala 617, Met 618, His 802

Protein	Ligands	Binding affinity (kcal/ mol)	Bond interactions		
			Van der Waals	Hydrogen bond	Hydrophobic interactions
			Lys 807 B: Ser 590, Thr 607, Gln 609, Thr 619, Asn 649, Glu 651, Asn 655, Glu 671, Thr 801, Ile 805, Lys 807		B: Ala 617, Met 618, Tyr 672, His 802
	Ascorbic acid*	-5.7	A: Met 618, Thr 619, Cys 674, His 802 B: Met 618, Glu 671, Cys 674, His 802	A: Glu 671, Tyr 672 B: Thr 619, Tyr 672	-
	Hydroquinone*	-5.1	A: Val 622, Ile 669, Leu 799, Cys 809, Asp 810, Phe 811	A: Val 668, Thr 670	A: Val 603, Ala 621, Lys 623
2L84	Vitexin	-9.2	A: Pro 1106, Phe 1111, Ile 1122, Pro 1132, Met 1133, Asp 1134, Met 1160, Asn 1163, Tyr 1167, Asn 1168, Phe 1177	A: Leu 1109, Gln 1113, Tyr 1125, Asn 1168, Arg 1173	A: Pro 1110, Val 1115, Leu 1120, Ala 1164, Val 1174
	Cynaroside	-8.7	A: Leu 1109, Ile 1122, Asn 1163, Tyr 1167, Asn 1168	A: Pro 1110, Gln 1113, Tyr 1125, Asp 1134, Met 1160, Arg 1173	A: Phe 1111, Val 1115, Leu 1120, Ala 1164, Val 1174
	Orientin	-8.7	A: Pro 1106, Leu 1109, Phe 1111, Gln 1113, Leu 1119, Ile 1122, Met 1133, Tyr 1167, Asn 1168, Arg 1173, Phe 1177	A: Pro 1110, Tyr 1125, Asp 1134, Met 1160	A: Val 1115, Leu 1120, Ala 1164, Val 1174
	Cyanidin 3-malonyl glucoside	-8.6	A: Leu 1109, Phe 1111, Pro 1114, Leu 1119, Ala 1164, Phe 1177	A: Gln 1113, Asp 1116, Asn 1168, Arg 1173	A: Pro 1110, Val 1115, Leu 1120, Ile 1122, Tyr 1125, Tyr 1167, Val 1174
	Naringin	-8.6	A: Pro 1106, Leu 1109, Phe 1111, Pro 1114, Leu 1119, Ile 1122, Asp 1134, Met 1160, Asn 1163, Tyr 1167, Asn 1168, Phe 1177	A: Pro 1110, Gln 1113, Tyr 1125, Pro 1132, Met 1133, Arg 1173	A: Val 1115, Leu 1120, Ala 1164, Val 1174
	Ascorbic acid*	-5.2	A: Gly 1077, Ser 1078, Ile 1084, Phe 1085, Glu 1089, Leu 1196	A: His 1079, Met 1080, Arg 1081, Ser 1195	-
	Hydroquinone*	-4.8	A: Phe 1111, Leu 1120, Ile 1122, Met 1160, Tyr 1167, Asn 1168	A: Pro 1110, Tyr 1125, Asp 1134	A: Val 1115, Ala 1164, Val 1174
1DI9	Rutin	-9.3	A: Gly 31, Ser 32, Gly 33, Gly 36, Ser 37, Val 38, Lys 53, Leu 55, Ser 56, Arg 57, Pro 58, Thr 68, Glu 71, Asp 168, Gly 170, Thr 175	A: Ala 34, Phe 169, Leu 171, Ala 172, Glu 178	A: Tyr 35, His 64, Arg 67
	Cyanidin 3-malonyl glucoside	-9.2	A: Ser 32, Gly 33, Tyr 35, Ser 37, Ala 51, Leu 55, Pro 58, His 64, Glu 71, Leu 75, Ile 84, Thr 106, His 107, Phe 169, Ala 172	A: Gly 36, Lys 53, Arg 67, Thr 68, Leu 171	A: Val 38, Leu 167, Asp 168
	Proanthocyanidin	-9.2	A: Gly 33, Tyr 35, Gly 36, Arg 57, Pro 58, Glu 71, Gly 170, Arg 173, Thr 175, Glu 178	A: Ser 56, His 64, Phe 169	A: Ala 34, Leu 55, Arg 67, Ala 172, His 174
	Isoorientin	-8.8	A: Ser 56, Pro 58, Thr 68, Glu 71, Asp 150, Lys 152, Asn 155, Gly 170, Leu 171	A: Lys 53, Arg 57, Asp 168, Phe 169, His 174	A: Tyr 35, Leu 55, His 64, Arg 67, Ala 172
	Pelargonidin 3-rutinoside	-8.8	A: Lys 53, Leu 55, Pro 58, Thr 68, Gly 170, Leu 171, His 174, Thr 175, Glu 178	A: Ala 34, Arg 57, His 64, Arg 67, Asp 168, Phe 169	A: Tyr 35, Ala 172
	Cynaroside	-8.8	A: Gly 33, Tyr 35, Lys 53, Leu 55, Arg 57, Pro 58, Glu 71, Phe 169, Gly 170, Thr 175, Glu 178	A: Ala 34, Ser 56, Asp 168, His 174	A: His 64, Arg 67, Leu 171, Ala 172
	Ascorbic acid*	-5.8	A: Tyr 35, Lys 53, Leu 55, Ser 56, Arg 57, His 64, Leu 171	A: Ala 34, Pro 58, Arg 67, Thr 68, Glu 71	-
966C	Hydroquinone*	-5.1	A: Ala 34, Tyr 35, Arg 57, Pro 58, Glu 71, Leu 171	A: Ser 56, His 64	A: Leu 55, Arg 67
	Cynaroside	-10.2	A: Asn 180, Arg 214, Glu 219, Ala 234, Met 236, Tyr 237, Thr 241	A: Gly 179, Ala 182, Leu 235, Ser 239	A: Leu 181, Val 215, His 218, Tyr 240
	Luteolin	-10.0	A: Asn 180, Arg 214, Glu 219, Ala 234, Leu 235, Pro 238, Thr 241	A: Ala 182, Tyr 237, Ser 239	A: Leu 181, Val 215, His 218, Tyr 240
	Quercetin	-10.0	A: Gly 179, Asn 180, Arg 214, Glu 219, Ala 234, Leu 235, Thr 241	A: Leu 181, Ala 182, Tyr 237, Ser 239	A: Val 215, His 218, Tyr 240
	Eriodictyol	-10.0	A: Asn 180, Arg 214, Glu 219, Ala 234, Met 236, Ser 239, Thr 241	A: Ala 182, Leu 235, Tyr 237	A: Leu 181, Val 215, His 218, Tyr 240

Protein	Ligands	Binding affinity (kcal/ mol)	Bond interactions		
			Van der Waals	Hydrogen bond	Hydrophobic interactions
Isoorientin		-9.9	A: Asn 180, Arg 214, Glu 219, Ile 232, Gly 233, Ala 234, Tyr 237, Pro 238, Ser 239, Val 246, Leu 248, Ala 249, Asp 252	A: Ala 182, Leu 235, Thr 241, Gln 247	A: Leu 181, Val 215, His 218, Tyr 240
Ascorbic acid*		-6.2	A: Arg 214, Val 215, His 218, Gly 233, Leu 235, Tyr 240, Ser 243	A: Ile 232, Ala 234, Tyr 237, Ser 239, Thr 241	-
Hydroquinone*		-5.3	A: Leu 181, Arg 214, Leu 235, Pro 238, Ser 239, Tyr 240, Thr 241	A: Tyr 237	A: Val 215, His 218

Positive controls are marked with *.

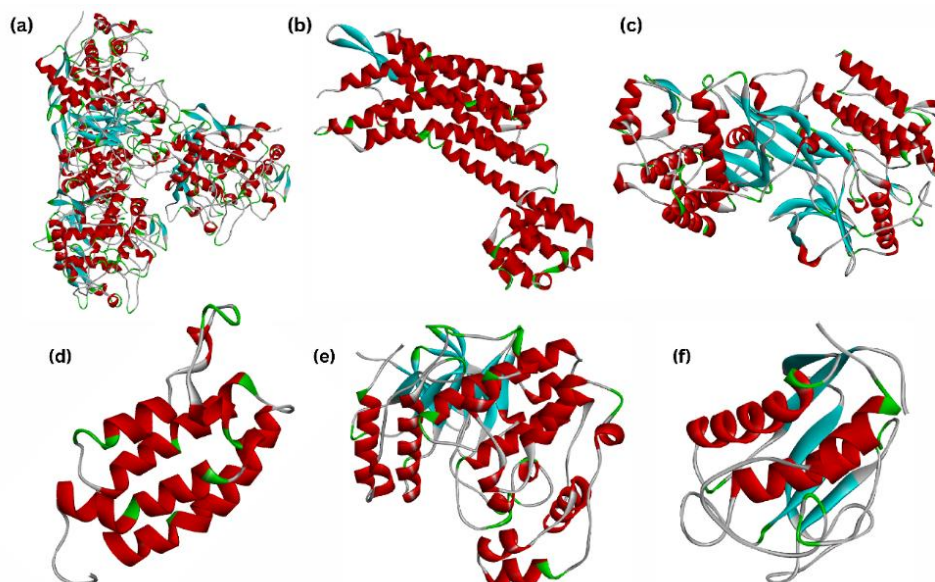


Figure 1. 3D structures of target proteins (a) 5M8N; (b) 5XPR; (c) 6XV9; (d) 2L84; (e) 1DI9; (f) 966C. These structures were used as the basis for molecular docking. Visualizing the protein folds and surface topography helps confirm that the binding pockets are structurally accessible and suitable for ligand interaction analysis, thereby validating the reliability of subsequent docking simulations.

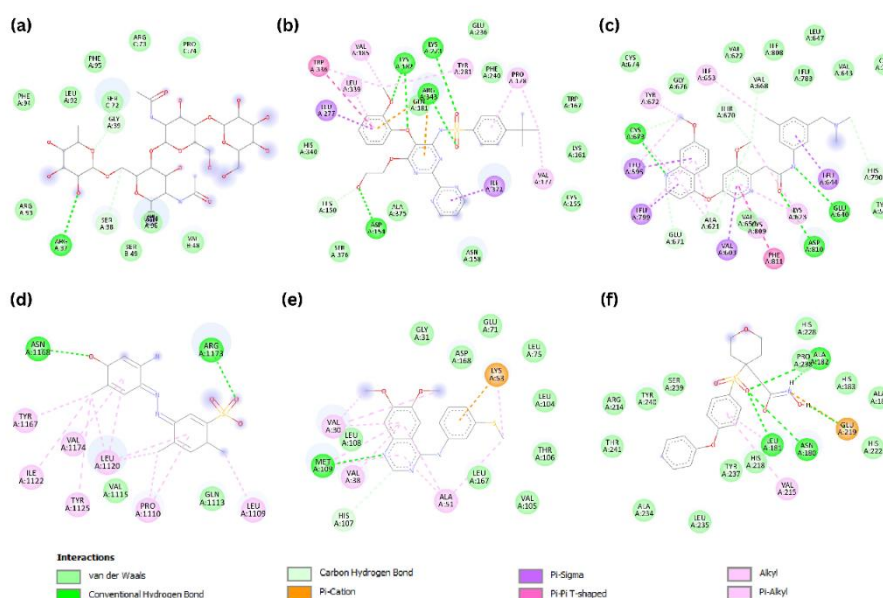


Figure 2. 2D visualisation of binding sites of (a) 5M8N; (b) 5XPR; (c) 6XV9; (d) 2L84; (e) 1DI9; (f) 966C. Highlighted regions represent key residues known or predicted to participate in ligand binding. Mapping these active sites provides essential context for interpreting docking affinity results and helps explain why certain phytochemicals demonstrate stronger interactions with specific targets.

Based on the results of the single ligand molecular docking (Table 1), the compounds with the best binding affinity in each protein include pelargonidin 3-rutinoside with a binding affinity of -9.4 kcal/mol in 5M8N, proanthocyanidin with a binding affinity of -9.1 kcal/mol in 5XPR, naringin with a binding affinity of -11.2 kcal/mol in 6XV9, vitexin with a binding affinity of -9.2 kcal/mol in 2L84, rutin with the binding affinity of -9.3 kcal/mol in 1DI9, and cynaroside with the binding affinity of -10.2 kcal/mol in 966C. Among all the proteins of interest, 6XV9 showed the strongest binding affinity with the compounds of interest, followed by 966C, 5M8N, 1DI9, 2L84, and then 5XPR.

The best five ligands for each protein were exported and analyzed for their interactions with the protein, along with the positive controls. The superimposed docking visualization in 3D shows the binding sites of ligands and positive controls with the target proteins (Figure 3). This alignment supports the validity of the docking predictions and suggests similar inhibitory potential.

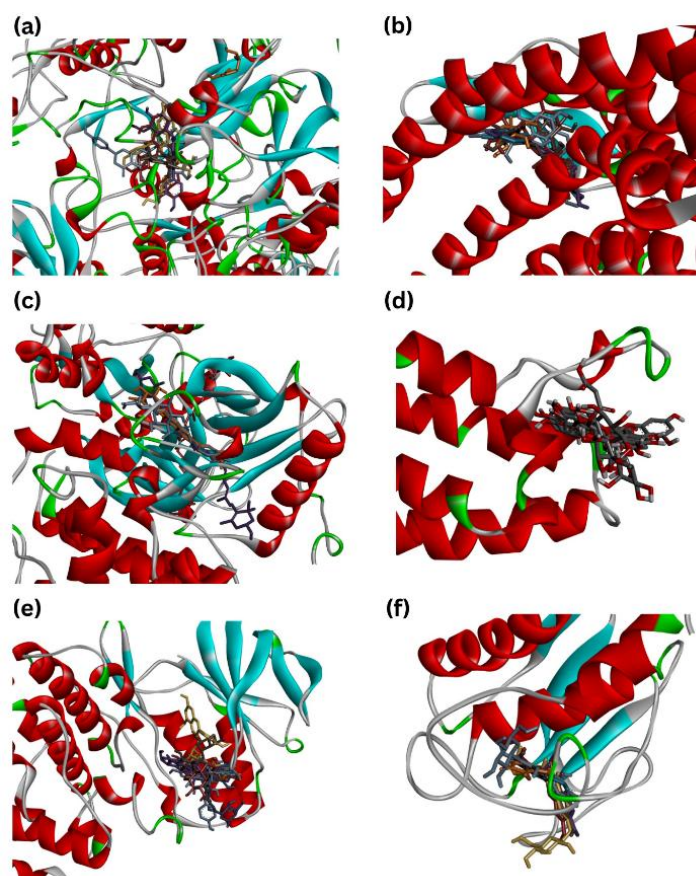


Figure 3: Superimposition of ligands and positive controls binding to the active site of proteins (a) 5M8N; (b) 5XPR; (c) 6XV9; (d) 2L84; (e) 1DI9; (f) 966C. This figure compares the docked positions of the top-performing *F. carica* compounds (colored structures) with their corresponding positive controls (gray structures) in proteins (a) 5M8N, (b) 5XPR, (c) 6XV9, (d) 2L84, (e) 1DI9, and (f) 966C. The close overlap between ligand and control binding poses indicates that many phytochemicals occupy the same functional pockets as known inhibitors, supporting their potential to modulate melanogenesis and oxidative-stress pathways. This structural alignment strengthens confidence in the docking predictions.

Table 2. Summary of ADMET properties of selected *F. carica* compounds and positive controls.

Ligands	Lipophilicity	Log Kp (cm/s)	Total clearance (log/min/kg)	AMES toxicity	Hepatotoxicity	Skin sensitization
Proanthocyanidin	1.85	-8.00	0.054	No	No	No
Rutin	-1.29	-10.26	-0.369	No	No	No
Naringin	-0.79	-10.15	0.318	No	No	No
β -cryptoxanthin	10.19	-0.98	0.923	No	No	No
Cyanidin 3,5-diglucoside	-3.76	-12.05	-0.164	No	No	No

Ligands	Lipophilicity	Log Kp (cm/s)	Total clearance (log/min/kg)	AMES toxicity	Hepatotoxicity	Skin sensitization
Zeaxanthin	9.31	-2.02	1.039	No	No	No
Cynaroside	0.16	-8.00	0.478	No	No	No
Isoorientin	-0.24	-9.14	0.372	No	No	No
α -carotene	11.03	0.12	0.947	Yes	No	No
Vitexin	-0.07	-8.79	0.444	No	No	No
Orientin	-0.41	-9.14	0.374	No	No	No
Cyanidin 3-malonylglucoside	-1.31	-9.67	0.66	No	No	No
Pelargonidin 3-rutinoside	-1.73	-10.66	-0.065	No	No	No
Luteolin	1.73	-6.25	0.495	No	No	No
Quercetin	1.23	-7.05	0.407	No	No	No
Eriodictyol	1.45	-6.62	-0.013	No	No	No
Hydroquinone*	0.87	-6.55	0.52	No	No	Yes
Ascorbic acid*	-1.28	-8.54	0.631	No	No	No

Positive controls are marked with *.

Sixteen compounds with the strongest binding affinity were selected for the ADMET analysis along with the positive controls (Figure 4). According to the results (Table 2), α -carotene has the highest lipophilicity of 11.03, while cyanidin 3,5-diglucoside has the lowest lipophilicity of -3.76 among all the compounds. Alpha-carotene also showed the highest skin permeability, 0.12 cm/s. Meanwhile, cyanidin 3,5-diglucoside showed the lowest skin permeability of -12.05 cm/s. The highest total clearance rate was seen in zeaxanthin, with a rate of 1.039, while rutin has the lowest total clearance rate, which is -0.369. Alpha-carotene is the only compound that possesses AMES toxicity, and none of the compounds were found to cause hepatotoxicity or skin sensitization.

Table 2 also presents predicted pharmacokinetic and safety parameters—including lipophilicity (logP), skin permeability (logKp), total clearance, and toxicity endpoints—for the top-performing compounds. These results provide insight into their suitability for topical application. Compounds showing acceptable lipophilicity, low toxicity, and favorable clearance values are considered more promising for dermal formulations. The comparison with positive controls facilitates evaluation of relative safety and absorption potential.

Table 3. Binding affinities of paired ligands in multiple ligand simultaneous docking (MLSD) across all target proteins.

Ligand 1	Ligand 2	Binding affinity (kcal/mol)					
		5M8N	5XPR	6XV9	2L84	1DI9	966C
Cynaroside	Vitexin	-13.45	-11.48	-14.90	-12.17	-12.44	-12.60
	Luteolin	-13.46	-13.32	-15.52	-12.23	-13.23	-14.35
	Quercetin	-13.87	-12.62	-15.99	-12.04	-12.54	-14.20
Vitexin	Luteolin	-13.42	-11.85	-14.65	-12.72	-13.32	-13.67
	Quercetin	-13.45	-12.05	-14.52	-12.44	-12.98	-14.24
Luteolin	Quercetin	-14.69	-12.86	-14.33	-12.45	-13.78	-14.85
Hydroquinone*	Ascorbic acid*	-9.197	-7.841	-8.673	-7.458	-9.030	-9.891

Positive controls are marked with *

Four compounds with potential pharmacological properties, including cynaroside, vitexin, luteolin, and quercetin, were chosen for the multiple ligand simultaneous docking. Based on the results (Table 3), the combination of cynaroside and quercetin with 6XV9 produced the strongest binding affinity (-15.99 kcal/mol), followed by the combination of cynaroside and luteolin (-15.52 kcal/mol), and the combination of cynaroside and vitexin with 6XV9, with a binding affinity of -14.90 kcal/mol. These enhanced affinities suggest potential synergistic occupation of overlapping sub-pockets within the active site. MLSD poses were

checked for steric compatibility and demonstrated consistent binding orientation across repeated runs.

Table 3 displays the predicted synergistic effects of combining two phytochemicals simultaneously within the active sites of the six proteins. MLSD binding affinities show whether paired compounds achieve stronger interactions than single-ligand docking or known positive controls. Lower affinity values indicate enhanced theoretical binding stability, allowing identification of compound combinations—particularly those involving cynaroside—that may exert amplified inhibitory effects on melanogenesis or oxidative-stress-related targets.

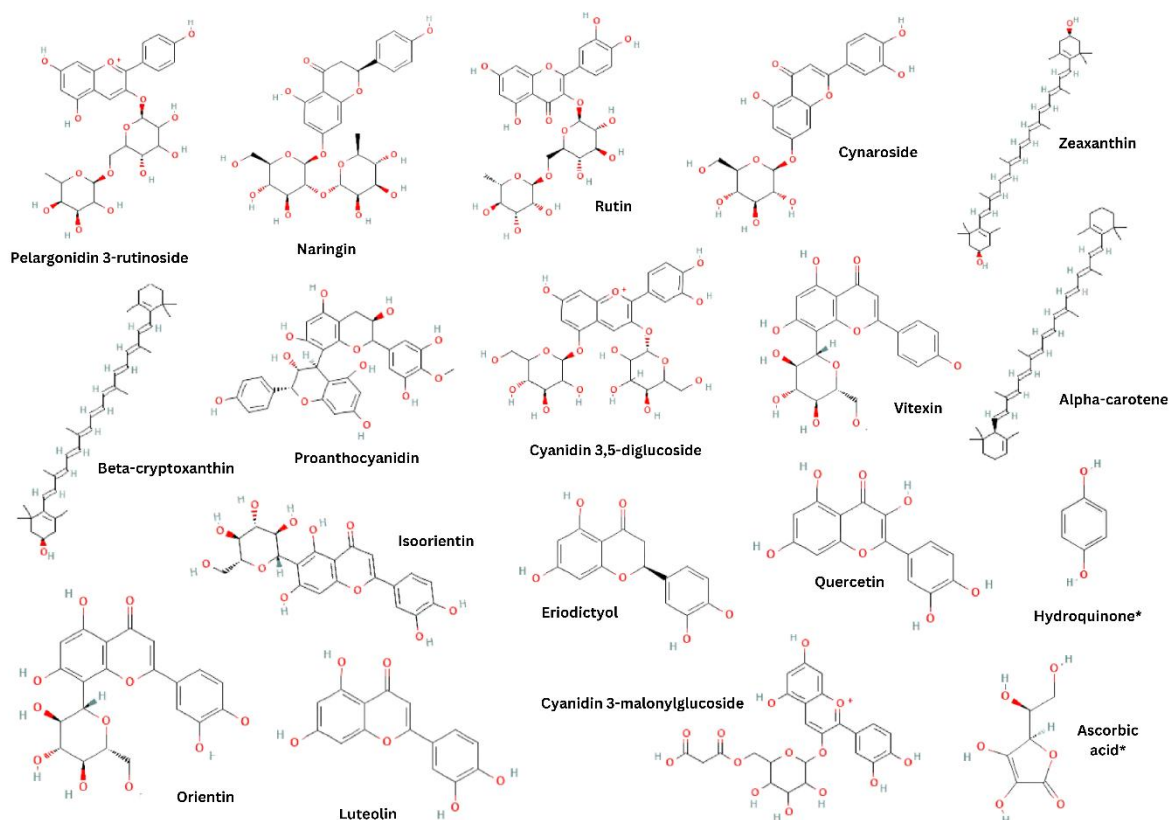


Figure 4. 2D structures of selected ligands and positive controls for ADMET analysis, obtained from PubChem. Note: Positive controls are marked with *. Visual comparison of molecular features—such as ring systems, glycosylation, and hydrophobic moieties—provides insight into the observed ADMET trends, including lipophilicity, permeability, and safety predictions. These structures help explain why certain molecules (e.g., carotenoids) exhibit higher skin permeability or why polyphenolic compounds tend to show favorable toxicity profiles.

3.1. Discussion.

The process of melanogenesis involves three major enzymes: tyrosinase, tyrosinase-related protein 1 (TRP-1), and dopachrome tautomerase (TRP-2). As tyrosine enzymes are produced solely by melanocytes, direct inhibition of their activity is the most used method to inhibit melanogenesis without adverse effects in cosmetic and pharmaceutical applications [21]. In this study, TRP-1 was targeted due to its role in 5,6-dihydroxyindole-2-carboxylic acid (DHICA) oxidation and eumelanin synthesis [22-23].

Melanogenesis is also regulated by several interconnected signaling pathways mediated by receptors such as melanocortin 1 receptor (MC1R), c-kit receptor, and endothelin receptor type B (ETBR). These upstream signaling molecules converge on the melanocyte-inducing

transcription factor (MITF), which governs the transcription of tyrosinase, TRP-1, and TRP-2. Activation of MC1R by α -MSH elevates intracellular cyclic AMP, subsequently activating cAMP response element-binding protein (CREB) through the PKA pathway and increasing MITF expression [24]. The binding of stem cell factor (SCF) to c-kit and endothelin-1/endothelin-3 to ETBR can also enhance MITF levels through phosphorylation of MAPKs such as p38, JNK, and ERK [24]. While our docking study predicts strong ligand interactions with CREB, c-kit, and ETBR, any subsequent impact on MITF expression remains theoretical and would require experimental confirmation.

In addition to regulating melanogenesis, MAPKs are involved in oxidative stress responses, including cell survival, apoptosis, and extracellular matrix remodeling. p38 MAPK, in particular, is activated by UV radiation and elevated reactive oxygen species (ROS) [25-26]. Once activated, it promotes the expression of matrix metalloproteinase (MMP-1), which degrades collagen, elastin, and other extracellular matrix proteins, contributing to photoaging and pigmentary disorders [27-28]. It is believed that downregulating the activity of p38 MAPK can reduce the expression of MMP-1, thus strengthening the skin barrier and preventing skin aging. Some evidence from studies includes the discovery that scopoletin extracted from *Artemisia capillaris* and antioxidants derived from *Haematococcus* successfully inhibit MMP-1 production by suppressing the p38 MAPK pathway [29-30]. Therefore, both p38 MAPK and MMP-1 are targeted in this study, as suppressing their activity can be crucial in alleviating the effects caused by skin oxidative stress. Although our computational findings show strong predicted interactions between several fig-derived compounds and both p38 MAPK and MMP-1, suppression of oxidative stress or matrix degradation cannot be inferred directly from docking and requires biochemical verification.

Molecular docking provides insights into the potential of compounds to bind target proteins by estimating the strength and stability of predicted ligand–protein complexes [28,31]. In AutoDock Vina, a more negative binding affinity value indicates stronger predicted binding [32-33]. In this study, many *F. carica* compounds exhibited stronger predicted binding affinities than hydroquinone and ascorbic acid, which are commonly used in skin-depigmenting and antioxidant controls. While these results support the theoretical potential of fig-derived compounds to modulate melanogenesis and oxidative-stress pathways, docking predictions alone cannot confirm biological inhibition and should be interpreted cautiously [34-36].

Among all ligand-protein interactions (Table 1) in this study, naringin exhibited the strongest affinity with receptor tyrosine kinase (PDB ID: 6XV9) at -11.2 kcal/mol. Compounds binding to 6XV9 also showed generally stronger affinities, suggesting that fig flavonoids may theoretically interact with RTK more effectively than other targets. This observation aligns with previous reports describing the ability of flavonoids to inhibit melanocyte activation and melanin synthesis through modulation of RTK-related pathways [37]. In addition, naringin showed high predicted affinity across multiple melanogenesis-associated proteins, suggesting strong theoretical potential as an antimelanogenic agent. Meanwhile, cynaroside exhibits the strongest docking affinities toward MAPK (1DI9) and MMP-1 (966C), which suggests potential antioxidant activity through modulation of oxidative-stress pathways. Because cynaroside also showed strong affinities toward melanogenic targets (5M8N, 6XV9, 2L84), it appears to be the most promising multitarget ligand from this dataset. These conclusions are consistent with previous computational and experimental studies reporting strong biological activity of related fig-derived polyphenols, such as quercetin and luteolin.

ADMET analysis (Table 2) further evaluated the suitability of promising compounds for topical application. Lipophilicity, skin permeability, clearance, and toxicity predictions indicated that luteolin, cynaroside, vitexin, and quercetin possess favorable pharmacokinetic and safety profiles compared to the positive controls [38-39]. Most compounds demonstrated acceptable lipophilicity (logP 1–3) and low predicted toxicity, supporting their theoretical suitability for dermal formulations. Nevertheless, these parameters are computational estimates and require validation through in vitro skin permeation assays and cytotoxicity testing [40-43].

Furthermore, the ability of the compounds to penetrate the stratum corneum is measured and presented as the log Kp value. A compound with log Kp > -2.5 is considered to have good skin permeability [44]. The positive controls in this study, hydroquinone and ascorbic acid, are proven to have rapid absorption across the skin through various studies [45-46]. Therefore, the log Kp values of these compounds can be taken as a reference. Based on Table 2, hydroquinone has a log kp value of -6.55, while ascorbic acid has a log kp value of -8.54. Most compounds investigated showed a greater log Kp value compared to the positive controls, with cyanidin 3,5-diglucoside having the strongest skin permeability with a log Kp value of -12.05.

The total clearance is another important parameter in pharmacokinetics as it affects both half-life and bioavailability. It determines the rate at which chemicals are removed from the blood by different organs, primarily the liver and the kidneys [47-48]. A lower clearance rate indicates a lower bioavailability and a longer half-life, which means more time is required to reduce the concentration of a chemical in blood by 50% [49]. Therefore, a higher total clearance rate is preferred. According to our results, hydroquinone and ascorbic acid showed total clearance of 0.52 and 0.631, respectively. Zeaxanthin, α -carotene, β -cryptoxanthin, and cyanidin 3-malonylglucoside showed values of 1.039, 0.947, 0.923, and 0.66, which are higher than those of the positive controls. However, these compounds have unsatisfactory lipophilicity values, which may result in adverse effects. Hence, compounds with ideal lipophilicity and skin permeability, as well as similar total clearance to the positive controls, are considered. These compounds include luteolin, cynaroside, vitexin, and quercetin.

In addition, the toxicity of the compounds is evaluated by AMES toxicity, hepatotoxicity, and skin sensitization. The AMES test predicts whether the compounds are mutagenic and carcinogenic using the bacterial strains of *Salmonella typhimurium*. A positive AMES test indicates the potential of a chemical compound to cause gene mutation and, therefore, may lead to cancer [50]. The hepatotoxicity parameter predicts the potential of a compound to cause damage or impaired function of the liver [51]. Skin sensitization test is crucial for developing topically applied products as it examines the possibility of a substance causing allergic reactions such as contact dermatitis [52]. For compounds to be incorporated into skincare products, they must show a negative result for these parameters to ensure the safety of use. Almost all compounds investigated passed these three tests, except α -carotene, which tested positive for AMES toxicity.

Overall, it was found that cynaroside, vitexin, luteolin, and quercetin are more effective in inhibiting melanogenesis and oxidative stress while also having safe pharmacokinetic properties compared to the positive controls, hydroquinone and ascorbic acid. These four compounds were further investigated to identify if combining them in pairs would enhance their binding to the proteins through multiple ligand simultaneous docking (MLSD). Table 3 showed that the binding affinity significantly increased when the ligands were combined in pairs, indicating an improved interaction with the target proteins and hence a greater inhibition of melanin and oxidative stress production. Furthermore, all ligand pairings had higher binding

affinities for all target proteins than the pairing of positive controls. This finding indicates that the selected fig compounds will show a greater effect when used in pairs compared to the positive controls, hydroquinone and vitamin C, which are often used in combinations in skin-depigmenting products. The pairing of cynaroside and quercetin showed the most promising results (-15.99 kcal/mol) among the other pairings, suggesting its potential for effective skin depigmenting solutions. Further laboratory studies—including enzymatic assays, cell-based melanogenesis models, and oxidative-stress response assays—are essential to validate the biological relevance of the predicted interactions and to confirm the feasibility of developing fig-derived compounds as natural skin-depigmenting agents.

4. Conclusions

This study identified several *F. carica* phytochemicals - particularly cynaroside, vitexin, luteolin, and quercetin - as promising computationally predicted inhibitors of melanogenesis and oxidative-stress-related targets based on molecular docking and ADMET analysis. Among these, cynaroside showed the strongest predicted multi-target interactions, along with favorable pharmacokinetic properties. Paired-ligand simulations also suggested potential cooperative binding effects.

However, these findings represent *in silico* predictions and should not be interpreted as confirmed biological activity. Experimental validation through *in vitro* enzymatic assays, cell-based melanogenesis models, skin permeation studies, and eventually *in vivo* evaluations will be essential to determine the true efficacy and safety of these compounds. Overall, this computational analysis provides a foundational framework for prioritizing *F. carica*-derived bioactives for further investigation in the development of natural depigmenting and antioxidant agents.

Author Contributions

Conceptualization, Z.W.L. and Y.Q.T.; methodology, W.X.C. and Y.Q.T.; investigation, writing—original draft preparation, W.X.C.; writing—review and editing, Z.W.L. and Y.Q.T.; supervision, Y.Q.T. All authors have read and agreed to the published version of the manuscript.

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Data supporting the findings of this study are available upon reasonable request from the corresponding author..

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Conflicts of Interest

The authors declare no conflict of interest.

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