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Propolis bioactive compounds as potential topical agents for atopic dermatitis: an in silico pharmacokinetic screening and molecular docking

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ABSTRACT

Background: Atopic dermatitis (AD) is a common chronic inflammatory skin disease. Current treatments, including corticosteroids and calcineurin inhibitors, are effective but limited by long-term adverse effects. Propolis possesses antimicrobial, anti-inflammatory, antioxidant, and immunomodulatory properties. This study evaluated propolis bioactive compounds as topical therapeutic candidates for AD using molecular docking analysis.

Methods: Bioactive compounds from propolis were screened for pharmacokinetic and ADMET properties relevant to topical application. Molecular docking was performed against key protein targets implicated in AD pathogenesis to evaluate binding affinities and interaction profiles versus reference ligands.

Results: A total of 31 compounds fulfilled the pharmacokinetic and toxicity criteria for topical use. Tschimgin showed the strongest affinity toward secretory phospholipase A_2 (ΔG = −8.00 kcal/mol; Ki = 1.37 μM) and favorable binding to FK506-binding protein 12 (ΔG = −7.88 kcal/mol; Ki = 1.68 μM), suggesting multitarget potential. Suberosin showed the highest affinity toward PDE4 (ΔG = −6.86 kcal/mol; Ki = 9.35 μM), exceeding the reference drug roflumilast (ΔG = −6.47 kcal/mol; Ki = 18.06 μM).

Conclusion: These findings suggest propolis contains bioactive compounds relevant to multiple AD-associated targets. Tschimgin and suberosin may serve as lead compounds for developing safer topical therapies, pending further in vitro and in vivo validation.

Keywords: Propolis, atopic dermatitis, molecular docking, topical therapy

Introduction

Atopic dermatitis (AD) is a chronic, noninfectious inflammatory skin disease characterized by recurrent intense pruritus and eczematous lesions [1]. AD affects individuals across all age groups, with an estimated prevalence ranging from 2%–22% among children worldwide, particularly in industrialized countries and low-income populations [2]. According to the Global Burden of Disease study, AD is ranked among the most prevalent nonfatal skin diseases affecting both males and females globally [3]. In addition to its high prevalence, AD significantly reduces patients' quality of life through sleep disturbance, persistent itching, and psychosocial complications, including depression, social withdrawal, compulsive scratching behavior, and neuropsychiatric disorders associated with chronic visible skin lesions [4]. Furthermore, AD imposes substantial social and economic burdens due to reduced productivity and long-term treatment costs [5].

The pathogenesis of AD involves a complex interplay among epidermal barrier dysfunction, immune dysregulation, environmental factors, and alterations in the skin microbiome. The disease is characterized by high clinical and molecular heterogeneity, which

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may contribute to variable therapeutic responses and provides opportunities for the development of targeted therapies in the future [6]. Current treatment strategies for AD aim to reduce symptoms and prevent recurrent flare-ups. Topical therapy remains the primary treatment approach because it effectively alleviates clinical symptoms [7]. Available topical therapies include emollients, topical corticosteroids (TCS), topical calcineurin inhibitors (TCI), and immunosuppressive agents. However, prolonged use of TCS may increase the risk of adverse effects such as petechiae, telangiectasia, skin atrophy, and skin thinning, whereas long-term TCI administration may induce local irritation and burning sensations [8-9]. Phosphodiesterase-4 (PDE4) inhibitors have emerged as non-steroidal alternatives with improved tolerability [2]. Nevertheless, the FDA-approved PDE4 inhibitor crisaborole remains financially inaccessible for many patients due to its high cost [10].

These limitations have encouraged the exploration of safer and more affordable alternative therapies derived from natural products. Propolis, commonly known as "bee glue," is a resinous substance collected by bees from plant exudates and mixed with beeswax, pollen, and other minor constituents [11-12]. The selection of *Trigona* sp. propolis from Sumatra was based on both geographical and biological considerations. The chemical composition of propolis is highly dependent on the botanical sources available around the hive and the environmental characteristics of the collection area. Sumatra is one of the major tropical biodiversity hotspots in Indonesia, possessing abundant medicinal plant species that potentially contribute to the unique phytochemical profile of stingless bee propolis. Previous studies demonstrated that *Tetrigona apicalis* propolis originating from Sumatra contains diverse bioactive constituents, including flavonoids, phenolic compounds, terpenoids, and prenylated derivatives, which are strongly associated with antioxidant and anti-inflammatory activities. Furthermore, Indonesian stingless bee propolis has been reported to exhibit significant pharmacological potential due to its rich phenolic and flavonoid contents, which may modulate inflammatory signaling pathways relevant to atopic dermatitis pathogenesis. Therefore, the use of Sumatra-derived *Trigona* sp. propolis in this study is scientifically relevant, as its unique biodiversity-driven phytochemical composition may provide distinct therapeutic advantages for inflammatory skin disorders [13-14]. These characteristics suggest that Sumatran stingless bee propolis may serve as a promising natural source for the development of topical therapeutic agents for inflammatory skin disorders.

Several studies have demonstrated that propolis possesses multiple pharmacological activities relevant to AD management, including immunomodulatory, anti-inflammatory, antioxidant, antifungal, antibacterial, antiulcerogenic, and antimutagenic effects [7]. Previous studies reported that propolis exhibited anti-inflammatory activity of 71.14% at a concentration of 1000 µg/mL with an IC_{50} value of 68.52 µg/mL [15]. In vivo studies using 48/80-induced rat models further demonstrated that topical administration of propolis was more effective than oral administration for the treatment of AD [16]. However, previous studies have not comprehensively evaluated the bioactive compounds of propolis that fulfill the pharmacokinetic requirements for topical administration, nor specifically investigated their molecular mechanisms against AD-related targets. Since in vitro and in vivo drug screening require substantial time and financial resources, in silico approaches have become increasingly important as preliminary strategies in drug discovery to facilitate the identification and selection of potential drug candidates [17]. Therefore, this study aimed to investigate the potential bioactive compounds in propolis against several targets involved in AD pathogenesis, including phospholipase A_2 ($sPLA_2$), FK506-binding protein 12 (FKBP12), and phosphodiesterase-4 (PDE4), as potential topical therapeutic agents for atopic dermatitis.

Methods

Retrieval of propolis bioactive compounds

Bioactive compounds of propolis were identified through a literature review using the keyword "propolis bioactive compounds." A total of 41 compounds were collected and their chemical structures were subsequently retrieved in the form of SMILES codes from PubChem (www.pubchem.ncbi.nlm.nih.gov) [18].

Pharmacokinetic and toxicity profiling

The SMILES codes obtained from PubChem were used as input for pharmacokinetic and toxicity profiling in pkCSM (https://biosig.lab.uq.edu.au/pkcsm/) [19]. Screening criteria for topical drug candidates included molecular weight between 200 and 500 Da, Log P values ranging from 1.0 to 4.0, hydrogen bond donor and acceptor properties, skin permeation represented by Log Kp values, and non-sensitizing properties [20–22]. Compounds fulfilling

the predefined criteria were subsequently selected for molecular docking analysis.

Protein preparation

The 3D structure of sPLA2, FKBP12, and PDE4 with the ID 1KVO, 1FKJ, and 8WDN respectively, were obtained from PDB Database (https://www.rcsb.org/) [23]. This selection was based on four criteria: (1) high resolution (<2 Å); (2) human origin (*Homo sapiens*); (3) a high-affinity bound ligand; and (4) the absence of mutations at the catalytic or active site. Protein preparation was performed using AutoDock Tools 1.5.6 and included the removal of water molecules, ions, and native ligands, followed by the addition of polar hydrogen atoms, assignment of Kollman charges, and computation of Gasteiger charges [24].

Ligand preparation

3D structures of propolis bioactive compounds were retrieved from PubChem (https://pubchem.ncbi.nlm.nih.gov/) in the SDF format (*.sdf) [22]. Geometry optimization was carried out using Avogadro 1.2.0 with the MFF94 method and then converted into PDB files (*.pdb). The optimized ligands were subsequently imported into AutoDock Tools 1.5.6 for further preparation by defining rotatable bonds and converting the structures into PDBQT format (*.pdbqt) for docking analysis [25].

Molecular docking protocol and validation

Method validation was performed through a redocking procedure using AutoDock Tools 1.5.6, in which the co-crystallized (native) ligand was re-docked into the binding site of the target protein. The grid box was centered on the position of the native ligand and defined to adequately cover the binding pocket. The root-mean-square deviation (RMSD) between the predicted pose and the crystallographic conformation was then calculated, and the docking protocol was considered valid when the RMSD value was less than 2 Å [26].

Molecular docking analysis was performed for compounds that satisfied the physicochemical and skin sensitization criteria using the validated protocol. A total of 100 runs per ligand were executed using the Lamarckian Genetic Algorithm with a population size of 150, 2,500,000 energy evaluations, and 27,000 generations. The mutation rate was set to 0.02 and crossover rate to 0.8 with two-point crossover, while one elite individual was preserved.

For comparative analysis, known reference drugs for each target were incorporated as positive controls in the docking simulations. Reference drugs were assigned to each target based on their clinical relevance and mechanistic association, where clinical relevance refers to their widespread use in the management of atopic dermatitis. For the $sPLA_2$ target, hydrocortisone was selected due to its established use in atopic dermatitis, despite its primary mechanism as a corticosteroid being mediated through glucocorticoid receptor signaling rather than direct enzyme inhibition [27]. As a mechanistically relevant comparator for the same target, varespladib was also included, as it is a well-characterized inhibitor that directly targets $sPLA_2$ [28]. However, it is not clinically used in the management of atopic dermatitis. For the FKBP12 target, tacrolimus was assigned as the reference drug due to its established clinical use in atopic dermatitis and well-defined mechanism of action. Tacrolimus forms a complex with FKBP12, which subsequently inhibits calcineurin activity and suppresses T-cell activation [29]. For the phosphodiesterase 4 target, roflumilast was selected as the reference drug based on its clinical relevance in atopic dermatitis and its established role as a selective PDE4 inhibitor [30].

Analysis of interaction

Ligand–protein interactions were visualized using BIOVIA Discovery Studio 2021, generating both two-dimensional (2D) and three-dimensional (3D) representations [31]. These visualizations enabled detailed analysis of interactions between the ligand and amino acid residues within the binding site of the target protein. The overall workflow of compound screening and molecular docking analysis performed in this study is presented in Figure 1.

Results

Pharmacokinetics and toxicity prediction

Pharmacokinetic and toxicity screening was conducted to evaluate the suitability of propolis bioactive compounds for topical application. Table 1 presents the evaluated parameters, including molecular weight, Log P, hydrogen bond donor/acceptor, skin permeability (Log Kp), and skin sensitization. A total of 31 compounds met the predefined selection criteria and were selected for subsequent molecular docking analysis. Compounds

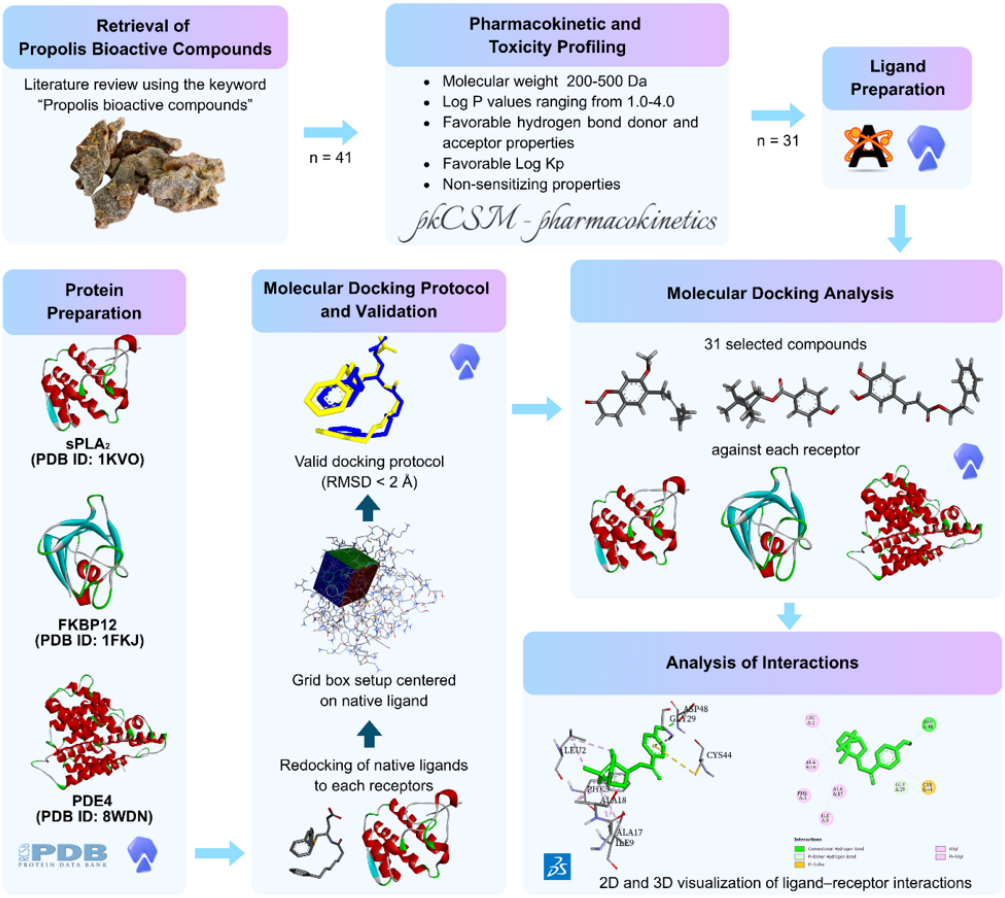

Figure 1. Overall workflow of the study. Propolis bioactive compounds were retrieved from the literature and screened for pharmacokinetic and toxicity properties, followed by protein and ligand preparation, docking protocol validation, molecular docking analysis against sPLA2, FKBP12, and PDE4, and analysis of ligand–protein interactions.

that did not meet the drug-likeness criteria were not included in further docking analysis, as compounds with poor drug-likeness are generally considered less suitable for downstream evaluation.

Method validation

Grid box dimensions and center coordinates used for redocking-based validation are summarized in Table 2. The docking grid was centered on the native ligand to define the binding site region for each receptor. The validation results showed that all receptor–native ligand complexes yielded RMSD values below 2 Å, indicating that the docking method was valid for subsequent molecular docking. These results are further supported by Figure 2, which shows minimal conformational deviation between native and re-docked ligands.

Molecular docking and analysis of interactions

Molecular docking analysis was performed to evaluate the binding affinity of propolis bioactive compounds against sPLA2, FKBP12, and PDE4. Tables 3–5 summarize the docking results, including binding energy (ΔG), inhibition constant (Ki), and amino acid residues involved in hydrogen bond and hydrophobic interactions. Figure 3 presents the chemical structures of tschimgin and suberosin, the two compounds that exhibited the most favorable molecular docking profiles against the evaluated targets, as detailed below.

Table 3 presents the molecular docking results of compounds against sPLA2, using hydrocortisone and varespladib as reference compounds. All tested compounds exhibited negative binding energy values against sPLA2, indicating favorable interactions within the receptor binding pocket. Among the evaluated compounds, tschimgin exhibited more favorable binding energy than varespladib, although still lower than the native ligand and hydrocortisone. Figure 4 illustrates the 2D and 3D interaction profile of native ligand, hydrocortisone, varespladib, and tschimgin with sPLA2 (PDB ID: 1KVO).

Table 1. Pharmacokinetic and toxicity prediction of propolis bioactive compounds

Compounds	MW (g/mol)	Log P	HBA	HBD	Log Kp (cm/h)	Skin Sensitization	Selection Status
Ferulic Acid	194.186	1.4986	3	2	-2.72	No	Excluded
Hesperetin	302.282	2.5185	6	3	-2.737	No	Selected
Isoliquiritigenin	256.257	2.6995	4	3	-2.752	No	Selected
Naringenin	272.256	2.5099	5	3	-2.742	No	Selected
Pinobanksin	272.256	2.7751	5	3	-2.738	No	Selected
Pinocembrin	256.257	2.8043	4	2	-2.808	No	Selected
Sakuranetin	286.283	2.8129	5	2	-2.76	No	Selected
Acacetin	284.267	2.8798	5	2	-2.737	No	Selected
Apigenin	270.24	2.5768	5	3	-2.735	No	Selected
Chrysin	254.241	2.8712	4	2	-2.739	No	Selected
Fisetin	286.239	2.2824	6	4	-2.735	No	Selected
Galangin	270.24	2.5768	5	3	-2.735	No	Selected
Izalpinin	284.267	2.8798	5	2	-2.74	No	Selected
Kaempferide	300.266	2.5854	6	3	-2.735	No	Selected
Kaempferol	286.239	2.2824	6	4	-2.735	No	Selected
Luteolin	286.239	2.2824	6	4	-2.735	No	Selected
Macarangin	422.477	5.5176	6	4	-2.735	No	Excluded
Quercetin	302.238	1.988	7	5	-2.735	No	Selected
(3S)-Vestitone	286.283	2.4653	5	2	-2.83	No	Selected
Biochanin A	284.267	2.8798	5	2	-2.737	No	Selected
Calycosin	284.267	2.8798	5	2	-2.747	No	Selected
Daidzein	254.241	2.8712	4	2	-2.748	No	Selected
Formononetin	268.268	3.1742	4	1	-2.752	No	Selected
Medicarpin	270.284	3.0105	4	1	-2.819	No	Selected
Xenognosin B	284.267	2.8798	5	2	-2.747	No	Selected
Mucronulatol	302.326	2.8337	5	2	-2.795	No	Selected
Neovestitol	272.3	2.8521	4	2	-2.889	No	Selected
Vestitol	272.3	2.8251	4	2	-2.75	No	Selected
Ferruginol	286.459	5.5458	1	1	-2.606	No	Excluded
Junicedric Acid	336.472	4.7409	2	2	-2.735	No	Excluded
Pimaric Acid	302.458	5.2062	1	1	-2.727	No	Excluded
Sempervirol	286.459	5.5458	1	1	-2.638	Yes	Excluded
Ferutinin	358.478	4.4611	4	2	-3.318	No	Excluded
Suberosin	244.29	3.3103	3	0	-2.027	No	Selected
Teferin	388.504	4.4697	5	2	-3.297	No	Excluded
Tschimgin	274.36	3.7638	3	1	-3.006	No	Selected
Artepillin C	300.398	4.5074	3	2	-2.728	No	Excluded
CAPE	284.311	2.8969	4	2	-2.832	No	Selected
Cearoin	244.246	2.3374	4	2	-2.796	No	Selected
Copalol	290.491	5.504	1	1	-2.498	Yes	Excluded
Prenyletin	246.262	2.8436	4	1	-2.99	No	Selected

MW: Molecular weight; Log P: Partition coefficient; HBA: *Hydrogen bond acceptor*; HBD: *Hydrogen bond donor*; Log Kp: Skin permeability; CAPE: Caffeic acid phenethyl ester.

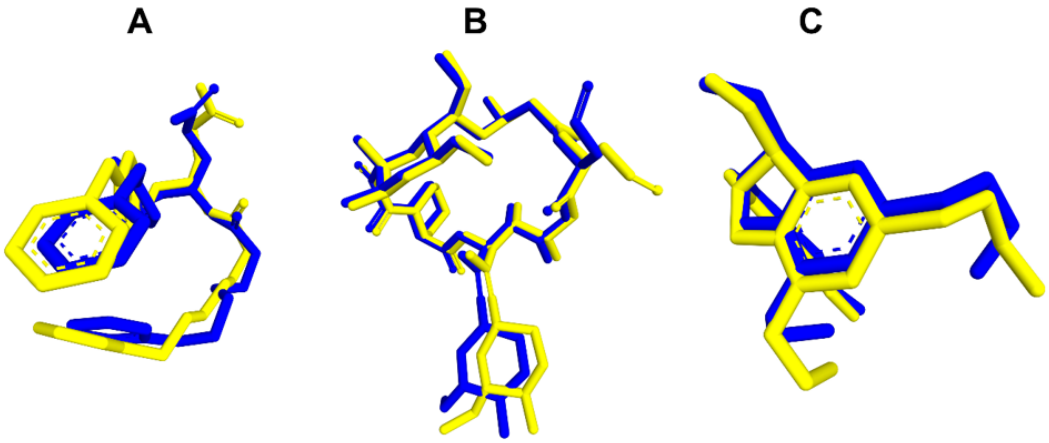

Figure 2. Redocking validation of native ligands. Overlapping redocking pose (blue) versus the native ligand pose (green) for (a) 1KVO, (b) 1FKJ, and (c) 8WDN.

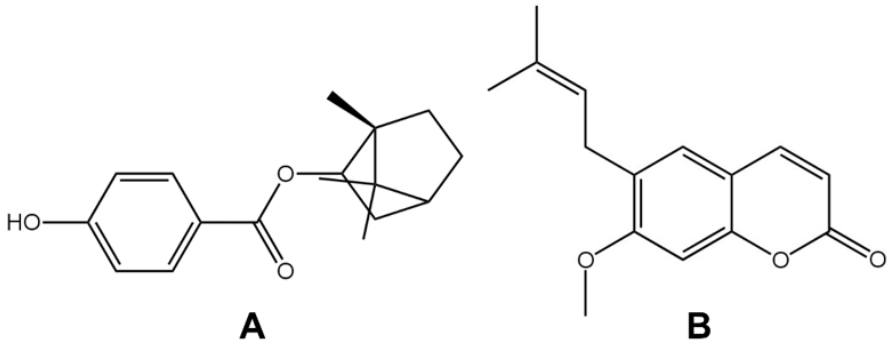

Figure 3. Chemical structures of the two most promising propolis bioactive compounds. (a) Tschimgin; (b) Suberosin.

Table 2. Grid box size and coordinates

PDB ID	Native Ligand	Grid Box Size	Grid Box Center	RMSD (Å)	ΔG (kcal/mol)
1KVO	FPL67047XX	x: 22 y: 26 z: 30	x: -39.919 y: 64.899 z: 34.843	0.96	-9.83
1FKJ	Tacrolimus	x: 36 y: 42 z: 22	x: 23.229 y: 29.106 z: 23.593	0.65	-9.47
8WDN	71-b	x: 22 y: 28 z: 28	x: 26.897 y: 77.245 z: 25.465	0.61	-7.66

RMSD: *Root Mean Square Deviation*; ΔG: free binding energy.

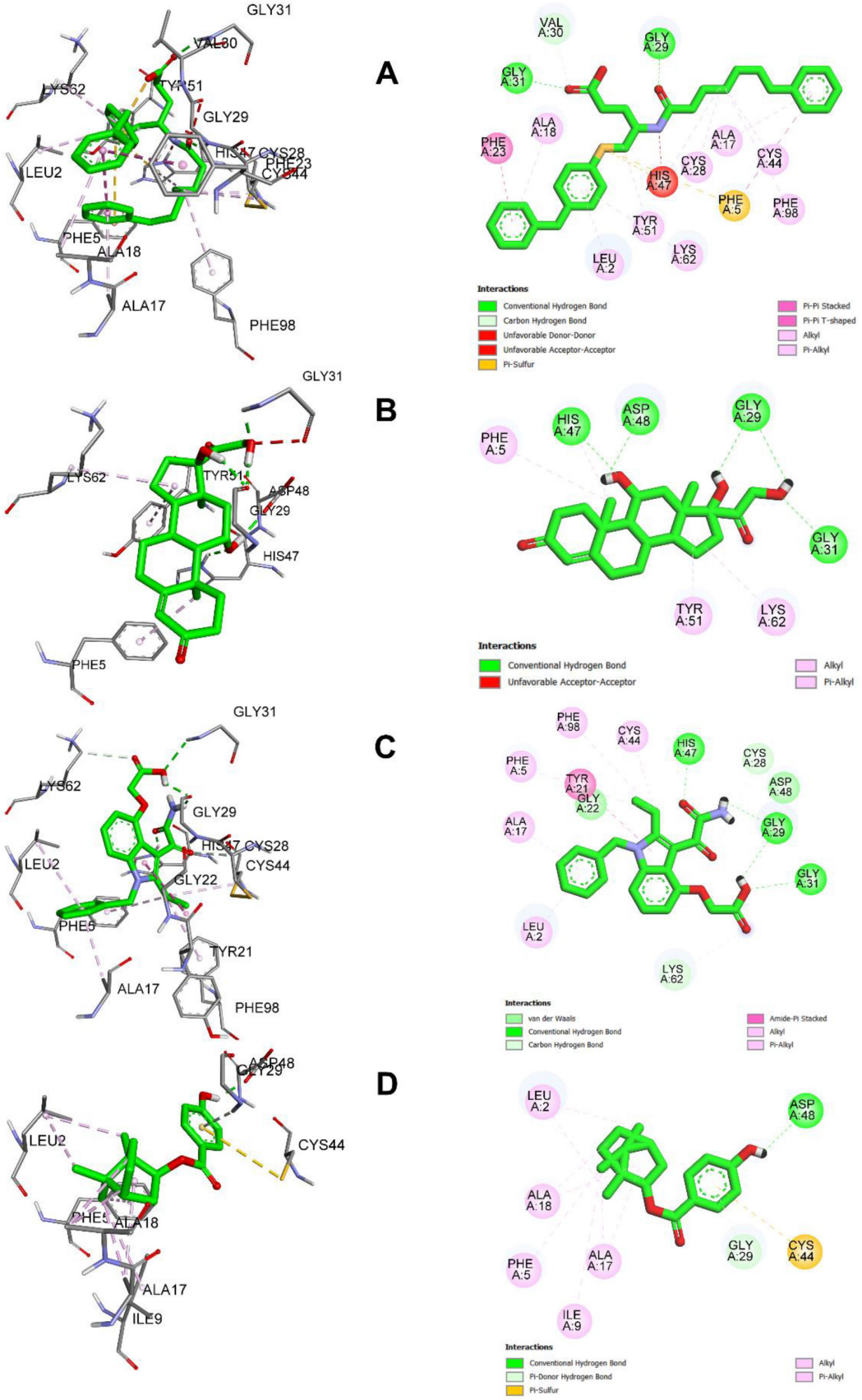

Figure 4. Two-dimensional and three-dimensional interaction profiles with secretory phospholipase A2 (sPLA2). (A) native ligand, (B) hydrocortisone, (C) varespladib, and (D) tschimgin within the binding pocket of sPLA2 (PDB ID: 1KVO).

Table 3. Molecular docking and interaction analysis of propolis bioactive compounds against $sPLA_2$

Compounds	ΔG (kcal/mol)	Ki (μM)	Hydrogen Bond	Hydrophobic Interactions
Native Ligand	-9.83	0.0627	Gly29, Gly31, Val30	Phe5, Phe23, Cys28, Cys44, His47, Tyr51, Phe98, Leu2, Lys62, Ala18, Ala17
Hydrocortisone	-9.20	0.17853	Gly31, His47, Gly29, Asp48	Lys62, Phe5, His47, Tyr51
Varespladib	-7.69	2.300	Gly31, His47, Gly29, Cys28, Lys62	Tyr21, Gly22, Cys44, Phe5, Phe98, Leu2, Ala17
Hesperetin	-6.61	14.39	His47, Asp48, Ala18, Gly29, Cys43, Gly29	Phe5, Ala94, Cys44, His47, Phe98, Cys28
Isoliquiritigenin	-6.00	40.26	His47, Gly22, Ala18, Asp48	Phe23, Gly29, Val30
Naringenin	-6.30	23.94	Ala18, Cys44, Asp48, Gly29	Cys28, Cys44, Ala18
Pinobanksin	-6.45	18.83	Asp48, Cys44, Ala17	Phe5, Cys28
Pinocembrin	-6.60	14.59	Cys44, Asp48, Gly29	Phe5, Cys28, Cys44, Ala18
Sakuranetin	-6.45	18.68	Asp48, Gly29	Cys44, Tyr21, Phe98, Cys28, Leu2, Val30, Lys62
Acacetin	-6.39	20.7	Cys44, Asp48, Ala18, Gly29	Phe5, Ala18, Cys28, Cys44
Apigenin	-6.16	30.66	Cys44, Asp48, Gly29	Phe5, Cys28, Cys44, Ala18
Chrysin	-6.52	16.74	Cys44, Asp48, Gly29	Phe5, Cys28, Cys44, Ala18
Fisetin	-7.24	4.91	Gly29, Gly31, Asp48, Ala17	Gly29, Phe5, Cys44
Galangin	-6.58	15.01	His47, Asp48	Gly29, Val30, Cys44
Izalpinin	-7.03	7.00	His47, Cys44, Asp48, Gly22, Ala17, Gly29	Gly29, Val30, Ala17, Ala18, Cys44, Cys28
Kaempferide	-5.92	45.7	Ala17, Asp48, Ala18, Gly29	Phe5, Ala18, Phe23, Cys44
Kaempferol	-6.24	26.57	His47, Asp48, Cys44, Ala17, Lys62, Gly29	Phe5, His47, Tys51, Lys62
Luteolin	-6.47	18.1	Asp48, Ala18, Gly29	Gly22, Tyr21, Gly22, Cys28
Quercetin	-5.91	46.71	Asp48, Ala18, Gly29	Gly22, Tyr21, Cys28, Cys44
(3S)-Vestitone	-6.25	26.21	Asp48, Ala17	Phe5, Leu2
Biochanin A	-6.00	40.22	Ala17	Tyr51
Calycosin	-6.51	17.01	Ala17	Tyr51
Daidzein	-6.36	21.65	Ala18, Asp48, Gly29	Gly29, Cys28, Cys44, Ala18
Formononetin	-6.22	27.74	Ala17, Asp48	Tyr51
Medicarpin	-7.21	5.16	His47, Tyr21, Gly31, Asp48, Gly29	Phe5, His47, Cys28, Cys44
Xenognosin B	-6.83	9.85	Gly29, His47, Asp48, Ala17	Gly29, Val30
Mucronulatol	-6.72	11.79	Gly29, Asp48, Ala18	Cys44, Phe5, His47, Tyr51, Ala18
Neovestitol	-6.13	32.02	Asp48, Cys44	His47, Gly29, Val30, Lys62, Cys44
Vestitol	-6.45	18.79	His47, Asp48, Ala17	
Suberosin	-6.92	8.44	Gly29	His47, Phe5, Gly29, Val30, Ala17, Ala94, Ile9, Cys44, Cys28
Tschimgin	-8.00	1.37	Asp48, Gly29	Ala17, Ala18, Leu2, Ile9, Phe5
CAPE	-7.37	3.96	Gly29, Asp48	Tyr21, Phe98, Cys28, Cys44
Cearoin	-6.49	17.46	Asp48, Gly29	Phe5, Ala17
Prenyletin	-6.59	14.86	Asp48, Gly29	Phe5, Cys28

ΔG: Binding free energy; Ki: Inhibition constant; CAPE: Caffeic acid phenethyl ester

Table 4. Molecular docking and interaction analysis of propolis bioactive compounds against FKBP12

Compounds	ΔG (kcal/mol)	Ki (μM)	Hydrogen Bond	Hydrophobic Interactions
Tacrolimus	-9.47	0.11404	Ile56, Asp37, Glu54	Ile91, Tyr26, Phe36, Phe46, Trp59, Tyr82, His87, Phe99
Hesperetin	-5.51	91.91	Gln53, Asp37	Ile56
Isoliquiritigenin	-6.18	29.67	Tyr82, Asp37, Gln53	Phe99, Val55
Naringenin	-5.64	73.31	Gln53, Asp37	Val55
Pinobanksin	-5.61	76.86	Ile56, Asp37	Ile56
Pinocembrin	-5.70	66.2	Asp37	Ile56
Sakuranetin	-5.51	91.11	Tyr82, Gln53	Ile91, Phe36, Tyr82, Val55
Acacetin	-5.55	85.06	Tyr82, Asp37, Gln53	Trp59, Val55, Ile56
Apigenin	-5.60	78.86	Tyr82, Gln53, Asp37	Trp59, Val55, Ile56
Chrysin	-5.67	69.34	Tyr82, Asp37	Ile56, Trp59, Val55
Fisetin	-5.79	57.44	Ile56, Glu54, Asp37	Ile56
Galangin	-5.70	66.03	Ile56, Glu54, tyr82, Tyr26, Asp37	
Izalpinin	-5.34	122.8	Ile56, Glu54, Val55	Val55, Ile56
Kaempferide	-5.50	92.71	Tyr82, Gln53, Ile56	Val55, Ile56, Tyr26, Trp59, Phe99, Ile56
Kaempferol	-5.37	116.15	Ile56, Glu54, Tyr82, Tyr26, Asp37	Phe46
Luteolin	-5.40	110.81	Tyr82, Gln53, Asp37	Trp59, Val55, Ile56
Quercetin	-4.99	221.37	Ile56, Tyr26, Gln53, Asp37	Ile56
(3S)-Vestitone	-5.93	44.92	Ile56, Gln53, Asp37	Phe46, Trp59, Tyr26, Phe36, Phe99, Val55
Biochanin A	-5.72	64.03	Tyr82, Glu54, Gln53	Val55, Tyr26, Ile56
Calycosin	-6.22	27.38	Ile56, Gln53, Tyr26, Asp37, Val55	Trp59, Val55, Ile56
Daidzein	-6.16	30.69	Ile56, Gln53, Tyr26, Asp37	Trp59, Val55, Ile56
Formononetin	-5.87	49.72	Ile56, Tyr26, Asp37, Val55	Trp59, Tyr82, Val55, Ile56
Medicarpin	-7.49	3.25	Ile56, Glu54	Val55, Trp59, Phe99, Val55, Ile56, Ile91, Phe36, Tyr82, His87
Xenognosin B	-6.02	38.49	Ile56, Glu54, Tyr26, Asp37	Trp59, Val55, Ile56
Mucronulatol	-5.47	62.41	Ile56, Gln53, Asp37	Trp59, Tyr82, Val55, Ile56, Tyr26, Phe36, Phe99
Neovestitol	-5.86	50.58	Glu54, Gln53, Asp37	Tyr26, Trp59, Val55, Ile56, Phe36, Phe99
Vestitol	-5.60	78.54	Tyr82	Ile56, Tyr26, Val55, Tyr82
Suberosin	-6.21	28.17	Ile56, Tyr82	Trp59, Phe99, Ile91, Phe36, Tyr82, Val55, Ile56
Tschimgin	-7.88	1.68	Ile56, Tyr82, Gln53	Tyr26, Trp59, Val55, Ile56, Phe46, Tyr82, Phe99
CAPE	-6.44	19.03	Ile56, Tyr26, Asp37, Val55	Trp59, Tyr26, Phe46, Phe99
Cearoin	-6.02	38.85	Tyr82, Tyr26, Asp37	Trp59, Tyr26, Val55
Prenyletin	-6.99	7.52	Ile56, Asp37, Tyr82	Trp59, Tyr26, Phe99, Ile90, Phe36, His87, Ile56

ΔG: Binding free energy; Ki: Inhibition constant; CAPE: Caffeic acid phenethyl ester

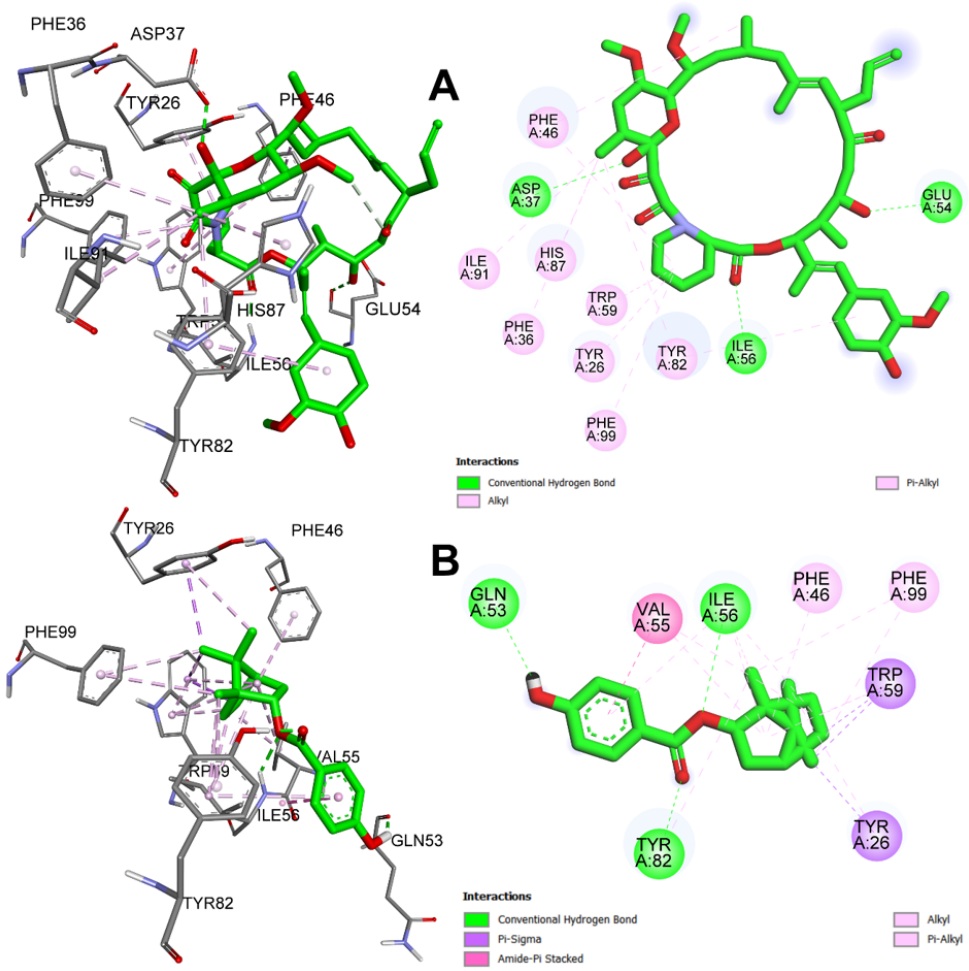

Figure 5. Two-dimensional and three-dimensional interaction profiles with FK506-binding protein 12 (FKBP12). (A) tacrolimus, and (B) tschimgin within the binding pocket of FKBP12 (PDB ID: 1FKJ).

Table 4 summarizes the docking results against FKBP12, in which tacrolimus, which also serves as the native ligand of 1FKJ, was used as the reference drug. All evaluated compounds exhibited negative binding energy values against FKBP12. Among the tested compounds, tschimgin demonstrated a notable, though weaker, binding affinity relative to tacrolimus. Together with its favorable interaction profile against sPLA2, these findings suggest that tschimgin may interact with several targets involved in inflammatory signaling pathways, although further experimental validation is required to confirm these interactions. Figure 5 shows the 2D and 3D interaction profile of tacrolimus and tschimgin with FKBP12 (PDB ID: 1FKJ).

The docking results against PDE4 using roflumilast as the reference drug are shown in Table 5. All tested compounds also exhibited negative binding energy values against PDE4. Among the evaluated compounds, suberosin demonstrated more favorable binding affinity than roflumilast. Figure 6 presents the 2D and 3D interaction profile of native ligand, roflumilast, and suberosin with PDE4 (PDB ID: 8WDN).

Discussion

This study demonstrated that tschimgin and suberosin, two propolis-derived bioactive compounds identified among the 31 screened candidates, exhibited the most favorable binding affinities toward the atopic dermatitis (AD)-related targets sPLA2, FKBP12, and PDE4, suggesting their potential as multitarget topical candidates for AD management. The physicochemical properties of drug candidates can also influence their pharmacokinetic profile and bioavailability in pharmaceutical applications [32]. Unfavorable pharmacokinetic characteristics of a drug candidate, as well as its toxic properties, can significantly reduce

Table 5. Molecular docking and interaction analysis of propolis bioactive compounds against PDE4

Compounds	ΔG (kcal/mol)	Ki (μM)	Hydrogen Bond	Hydrophobic Interactions
Native Ligand	-7.66	2.44	His160, Gln369	Ile336, Phe372, Met357, Tyr329, Phe340
Roflumilast	-6.47	18.06	Gln369, Ser368	Phe372, Phe340, Ile336, Met357, His160
Hesperetin	-5.38	113.62	His160, Gln369, Met357, Met337	Phe372, Met273, His160, Ile336
Isoliquiritigenin	-5.59	79.31	Gln369, Gln343	Ile336, Phe372, Phe340
Naringenin	-5.45	100.37	His160, Gln369, Met337	Phe372, Tyr159, met357, Ile336
Pinobanksin	-5.58	81.34	Gln369, Met337	Ser368, Met357, Ile336, Phe372, Tyr159
Pinocembrin	-6.00	40.24	Gln369, Met357	Ile336, Met357, Phe372, Phe340
Sakuranetin	-5.83	53.55	His204, Gly206	Ile336, Phe372, Phe340
Acacetin	-5.48	96.55	His160, Gln369, Met337	Phe372, Tyr159, Met273, His160, Met357, Ile336
Apigenin	-5.36	118.63	Met337, Ser368	Phe340, Phe372, Ile336, Met357
Chrysin	-5.82	54.47		Ile336, Met357, Phe372, Phe340
Fisetin	-5.05	199.41	Met337, Ser368	Phe340, Phe372, Ile336, Met357
Galangin	-5.66	71.37	His160	Ile336, Phe372, Tyr159, Phe340
Izalpinin	-5.94	44.57	Gln369	Ile336, Phe372, Phe340, Met273, His160
Kaempferide	-5.22	148.88	His160	Ile336, Phe372, Tyr159, Phe340
Kaempferol	-5.13	175.05	Met337, Ser368	Phe340, Phe372, Ile336, Met357
Luteolin	-5.06	194.07	His160, Gln369	Ile336, Phe372, Tyr159
Quercetin	-4.45	545.00	His160, Gln369, Met337	Met357, Phe372
(3S)-Vestitone	-5.68	68.65	Gln369, Asn321, Trp332	Ile336, Met357, Phe372, Ile376
Biochanin A	-5.71	65.10	Gln369, Asn321	Ile336, Met357, Phe372, Phe340
Calycosin	-5.68	68.92	Gln369, Asn321	Ile336, Met357, Phe372, Phe340, Pro356
Daidzein	-5.88	49.21	Gln369, Asn321	Ile336, Met357, Phe372, Phe340
Formononetin	-6.06	36.13	Gln369, Asn321	Ile336, Met357, Phe372, Phe340
Medicarpin	-5.90	46.96	Gln369, Ser208	Ile336, Phe372, Tyr159, Phe340, His160
Xenognosin B	-5.70	66.71	Gln369, Asn321	Ile336, Met357, Phe372, Phe340, Pro356
Mucronulatol	-5.63	74.66	Gln369, Asn321	Ile336, Met357, Phe372, Met273, Ile376, Phe340
Neovestitol	-5.68	68.46	Gln369	Ile336, Met357, Phe372, Phe340
Vestitol	-5.77	58.85	Gln369, Asn321	Ile336, Met357, Phe372, Phe340
Suberosin	-6.86	9.35	Gln369, Ser368	Ile336, Phe372, Phe340, Met273, Ile376, Met357
Tschimgin	-6.11	33.02	Met337	Phe340, Ile336, Leu319, Met273, Phe372, Met357
CAPE	-6.34	22.71	His160	Ile336, Phe372, Phe340
Cearoin	-5.54	86.89	Met357, Ser368	Ile336, Phe372, Phe340, Met357
Prenyletin	-6.41	20.1	Ser368	Pro322, Ile336, Tyr159, Tyr329, Phe372, Met357

ΔG: Binding free energy; Ki: Inhibition constant; CAPE: Caffeic acid phenethyl ester

effectiveness and increase costs [22]. Therefore, predicting the pharmacokinetic profile and toxicity of compounds can serve as an effective approach to screening drug candidates with the greatest potential. For drug candidates intended for topical application, pharmacokinetic and toxicity tests conducted include molecular weight, Log P, Hydrogen Bond Acceptor (HBA), and Hydrogen Bond Donor (HBD) as criteria for drug-likeness, Log Kp to analyze skin permeability, and skin sensitization to analyze toxicity towards the skin.

For effective skin permeability, the optimal molecular weight is between 200 and 500 Da [32]. In addition, Log P value becomes one of the factors that must be considered because it affects permeability to the skin. A higher Log P value indicates that the compound is more lipophilic, and vice versa. The higher the lipophilicity, the greater the permeability through the skin. However, excessively high lipophilicity may potentially cause toxicity and decrease permeability through the skin [33]. The optimal log P value for topical drug delivery is between 1.0 and 4.0. A lower number of HBA and HBD in drug candidates is desirable as it affects membrane permeability, especially in the skin [34]. Log Kp describes the permeability to the skin, particularly for topical use. A more negative log Kp value indicates lower skin permeability [22]. Additionally, skin sensitization is a category that measures a compound's ability to irritate the skin, making it unsuitable for topical application [34].

Based on the pharmacokinetic and toxicity prediction results, 31 propolis bioactive compounds fulfilled the predefined criteria and were subsequently selected for molecular docking analysis. Several compounds did not satisfy the drug-likeness criteria due to physicochemical properties falling outside the recommended range for topical delivery. In addition, sempervirol and copalol were predicted to exhibit skin sensitization potential, which may limit their suitability for topical application.

In silico drug discovery is a method to identify and design a novel using additional molecular modelling tools as well as computer-aided drug design (CADD) methods. Computational techniques such as virtual ligand screening, molecular modeling, and docking-based virtual screening can assist in predicting binding modes and interaction patterns of potential drug candidates. The in silico approach aims to identify potential compounds with less time and cost, but it cannot completely replace necessary in vitro and in vivo studies [17]. However, the selection of potential hit compounds remains relatively uncertain, owing to the lack of consensus regarding binding energy and ligand efficiency [35].

Validation of the docking protocol is an essential step to ensure the reliability of molecular docking results. The re-docking of the native ligand into its respective protein binding site yielded an RMSD value, where an RMSD of less than 2.0 Å is considered the accepted threshold for validating the docking method [36]. In this study, the results of the docking protocol validation are shown in Table 2. The re-docking validation process for each native ligand produced an RMSD value of less than 2.0 Å. This indicates that the grid box parameters and other parameters used are valid. In addition, the binding energy (ΔG) obtained from the re-docking validation process is used as a reference value to evaluate the affinity of the test compounds.

The data obtained from molecular docking include binding energy value (ΔG, kcal/mol), inhibitory constant (Ki, μM), the number of hydrogen bonds and hydrophobic interaction, as well as amino acids residues. Free binding energy is calculated including ionic bonds, hydrogen bonds, hydrophobic contacts, and van der Waals interactions. It determines the binding affinity between the ligand and the receptor, where the lower values indicate stronger binding affinity [37]. Inhibition constant represents the dissociation constant of the enzyme-inhibitor complex. The smaller Ki value represents the higher binding affinity and stronger interaction between the protein and the ligand [38]. Interactions between native ligand-receptor and test ligand-receptor through similar amino acids might imply that the interactions played important roles in desired activity [26].

In this study, we performed molecular docking between propolis bioactive compounds and sPLA2, an enzyme expressed in the epidermis that plays a crucial role in maintaining skin barrier homeostasis. sPLA2 generates bioactive lipids that support stratum corneum acidification, keratinocyte differentiation and barrier recovery after disruption. Dysregulation of the sPLA2 secretion leads to impaired lipid balance, increased skin surface pH, and weakened epidermal barrier function, which facilitates allergen and microbial penetration to the skin. Experimental studies in mice have shown that loss of sPLA2 expression causes barrier defects and skin abnormalities, such as psoriasis-like epidermal hyperplasia and alopecia [39-40]. These findings are relevant to atopic dermatitis, which is also characterized by epidermal barrier disruption and epidermal thickening.

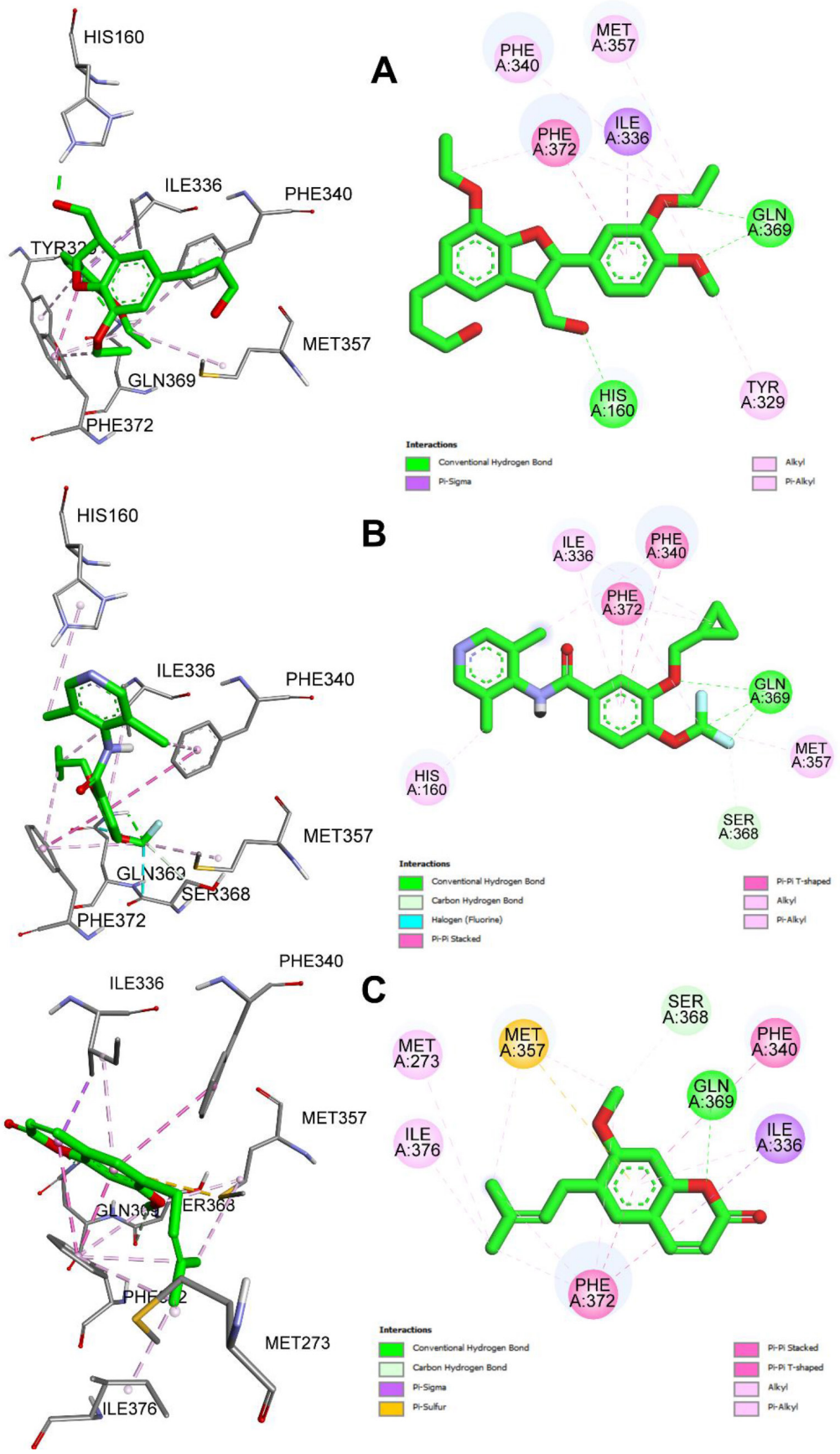

Figure 6. Two-dimensional and three-dimensional interaction profiles with phosphodiesterase-4 (PDE4). (A) native ligand, (B) roflumilast, and (C) suberosin within the binding pocket of PDE4 (PDB ID: 8WDN).

According to the molecular docking results on Table 3, all of the test compounds exhibited negative binding energy values, indicating favorable interactions with $sPLA_2$ (PDB ID: 1KVO). Tschimgin demonstrated the lowest free binding energy (ΔG = -8.00 kcal/mol) among the tested compounds. Although the binding affinity of tschimgin was still lower than that of the native ligand (ΔG = -9.83 kcal/mol) and hydrocortisone (ΔG = -9.20 kcal/mol), it exhibited a more favorable binding energy than varespladib (ΔG = -7.69 kcal/mol). The corresponding inhibition constant (Ki = 1.37 µM) of tschimgin further supported this observation, indicating a higher predicted inhibitory potential compared to the majority of other compounds. Detailed interaction analysis revealed that tschimgin engaged in hydrogen bonding with Asp48 and Gly29 and formed extensive hydrophobic interactions with Ala17, Ala18, Leu2, Ile9, and Phe5, as shown in Figure 4. These residues overlap with the binding environment of the native ligand, suggesting that tschimgin adopts a comparable binding mode.

We also performed molecular docking between propolis bioactive compounds and FKBP12, a binding protein that forms a complex with tacrolimus to inhibit the calcium- and calmodulin-dependent serine/threonine phosphatase calcineurin, which normally activates the nuclear factor of activated T-cells (NFAT) and triggers transcription of pro-inflammatory cytokines that exacerbate skin inflammation; dysregulation of this pathway is a hallmark of immune disorders [41]. By inhibiting calcineurin, the FKBP12–tacrolimus complex prevents nuclear translocation of NFAT and thereby suppresses NFAT-mediated transcription of pro-inflammatory cytokines in T cells [8].

The docking simulations against the FKBP12 target (PDB ID: 1FKJ), tschimgin again exhibited one of the most favorable binding energies (ΔG = -7.88 kcal/mol), which was lower than most test compounds but weaker than tacrolimus (ΔG = -9.47 kcal/mol) (Table 4). The inhibition constant (Ki = 1.68 µM) supported this result, being smaller than many other candidates but larger than that of tacrolimus (0.97 µM). Interaction mapping revealed that tschimgin established hydrogen bonds with Ile56 and Tyr82, together with hydrophobic contacts involving Tyr26, Trp59, Val55, Phe46, and Phe99 (Figure 5). Several of these residues overlapped with those targeted by the native ligand, suggesting a partially similar binding conformation.

In addition to sPLA2 and calcineurin, molecular docking analysis was also performed against PDE4, another key enzyme involved in the pathogenesis of AD. PDE4 works by converting the cellular secondary messenger cyclic adenosine monophosphate (cAMP) into 5'-adenosine monophosphate, which play a role in pro-inflammatory cytokine responses expression such as interleukin (IL)-4, IL-13, and IL-31. Inhibition of PDE activity can reduce the expression of pro-inflammatory cytokines by increasing intracellular cAMP [5].

Molecular docking analysis towards PDE4 (PDB ID: 8WDN) shown in Table 5. Suberosin exhibited a binding energy of -6.86 kcal/mol, which was lower than roflumilast (-6.47 kcal/mol), although not as favorable as the native ligand (-7.66 kcal/mol). The Ki value further supported this trend, as suberosin exhibited smaller Ki value (9.35 µM) than reference drug (18.06 µM), yet larger than the native ligand (2.44 µM). Further analysis of interactions demonstrated that all of the test compounds, especially suberosin interacted with PDE4 protein through similar amino acid residues also targeted by the native ligand and the reference drug, as shown in Figure 6. Specifically, hydrogen bond interactions were observed with Gln369, while hydrophobic contacts were observed with Ile336, Phe372, Met357, and Phe340.

Overall, the docking results indicate that tschimgin and suberosin are among the most promising propolis compounds for modulating pathways associated with AD pathogenesis, including the sPLA2-mediated lipid barrier pathway, the calcineurin–NFAT signaling pathway, and the PDE4–cAMP regulatory pathway. These findings support the potential of propolis-derived compounds for further investigation as topical agents for AD treatment. Nevertheless, additional experimental studies are required to validate their therapeutic relevance and biological activity.

To contextualize our findings with previous studies, several reports have demonstrated the anti-inflammatory and anti-atopic potential of propolis through both in silico and in vitro approaches. A comparative study of Korean and Brazilian propolis showed that propolis-derived flavonoids, including CAPE and pinocembrin, interacted with inflammatory targets related to atopic dermatitis and suppressed inflammatory responses in HaCaT keratinocytes [42]. These findings are consistent with our results, where tschimgin, suberosin, formononetin, CAPE, and pinocembrin exhibited favorable binding affinities toward sPLA2, FKBP12, and PDE4, suggesting their potential role in modulating inflammatory and immune-related pathways in AD. In addition, previous studies have reported that propolis compounds can inhibit mast cell activation and reduce pro-inflammatory

cytokines through regulation of NF-κB, MAPK, and calcineurin-NFAT signaling pathways [16]. Furthermore, recent network pharmacology studies highlighted that propolis exerts therapeutic effects through multitarget and multipathway mechanisms, supporting the present findings and strengthening the potential of propolis-derived compounds as topical therapeutic candidates for atopic dermatitis treatment [43]

This study has several limitations that should be considered. First, the molecular docking analysis employed a rigid docking approach, which does not fully account for protein flexibility and dynamic conformational changes during ligand–receptor interactions [44]. Second, the ADMET and skin permeability evaluations were based solely on computational predictions and therefore may not completely reflect the actual pharmacokinetic and toxicological behavior of compounds in biological systems. In addition, the present study lacked in vitro and in vivo experimental validation to confirm the biological activity of the identified compounds against atopic dermatitis-related targets. Furthermore, the behavior of propolis compounds in real topical formulations may differ due to factors such as formulation composition, skin penetration, and compound stability, which were not evaluated in this study. Therefore, further experimental and formulation studies are required to validate the therapeutic potential of these compounds for topical treatment of atopic dermatitis.

Future studies should focus on experimental validation of the identified compounds using both in vitro and in vivo models relevant to atopic dermatitis. In vitro studies using TNF-α/IFN-γ- or IL-4/IL-13-stimulated HaCaT keratinocytes are recommended to evaluate the effects of propolis compounds on inflammatory cytokines, oxidative stress, and skin barrier-related proteins such as filaggrin and involucrin [45-46]. Furthermore, in vivo validation using established AD mouse models, particularly DNCB-induced BALB/c or NC/Nga mice, would be valuable to assess anti-inflammatory activity, epidermal thickness, mast cell infiltration, and skin barrier recovery following topical administration [47-48]. These approaches may provide stronger evidence for the therapeutic potential of propolis-derived compounds in atopic dermatitis treatment.

Conclusion

Among the thirty-one selected compounds, tschimgin and suberosin demonstrated the most favorable binding affinities, with tschimgin showing strong interactions against sPLA2 (ΔG = −8.00 kcal/mol) and FKBP12 (ΔG = −7.88 kcal/mol), while suberosin exhibited the best binding affinity toward PDE4 (ΔG = −6.86 kcal/mol). These findings suggest that propolis-derived compounds may modulate inflammatory, immune, and skin barrier-related pathways implicated in atopic dermatitis pathogenesis. Further in vitro, in vivo, and topical formulation studies are recommended to validate the therapeutic efficacy and safety of these compounds for atopic dermatitis treatment.

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Ethics statement

Ethical approval was not required for this study because no human participants, animal subjects, or clinical samples were involved.

Conflict of interest

The authors declare no conflict of interest.

Author contributions

Conceptualization, T.L.N. and N.N.; methodology, N.N. and T.L.N.; software, N.N.; validation, N.N., A.S. and I.A.H.; formal analysis, N.N. and M.U.; investigation, N.N., A.S., I.A.H., R.A., M.U., T.S. and Y.O.; resources, T.L.N.; data curation, N.N.; writing—original draft preparation, N.N.; writing—review and editing, T.L.N. and A.S.Z.; visualization, N.N.; supervision, T.L.N.; project administration, T.L.N.; funding acquisition, T.L.N. All authors have read and agreed to the published version of the manuscript.

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