

Phytochemical Composition and Cosmeceutical-Related Bioactivities of *Canscora lucidissima* (H. Lév. & Vaniot) Hand.-Mazz.

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Abstract

Canscora lucidissima (H. Lév. & Vaniot) Hand.-Mazz. is a Vietnamese ethnomedicinal plant traditionally associated with anti-inflammatory use, yet its cosmeceutical potential remains poorly defined. This study provides an integrated evaluation of the phytochemical composition and cosmeceutical-related bioactivities of *C. lucidissima* solvent extracts, including antioxidant capacity, enzyme inhibitory, and antibacterial effects, together with in silico analyses of the identified phytochemicals covering molecular interactions, electronic features, and predicted ADME properties. Among the extracts, ethyl acetate showed the most consistent bioactivity profile, with the strongest tyrosinase inhibition ($IC_{50} = 195.24 \mu\text{g/mL}$), α -amylase inhibition, DPPH and ABTS radical-scavenging activities, and antibacterial effects against *Staphylococcus aureus* and *Escherichia coli*. The ethanol extract exhibited the highest α -glucosidase inhibition ($IC_{50} = 96.46 \mu\text{g/mL}$). Phytochemical screening and UHPLC-based quantification revealed a solvent-dependent distribution of secondary metabolites. PCA and Pearson correlation analyses associated the enhanced responses of this fraction with phenolic/flavonoid enrichment, particularly catechin, chlorogenic acid, rutin, quercitrin, and quercetin. Molecular docking against tyrosinase 5NN8 identified rutin, caffeine, quercitrin, and chlorogenic acid as the most relevant candidate ligands, with rutin showing the strongest predicted affinity and favorable electronic responsiveness based on its HOMO-LUMO gap. ADME prediction indicated that quercetin and apigenin possessed the most balanced drug-likeness and permeability-related profiles, whereas highly polar glycosides were mainly limited by reduced passive absorption. Overall, this work provides the first integrated evidence linking the chemical profile of *C. lucidissima* with cosmeceutical-related bioactivities and supports its development as a multifunctional skin-protective botanical ingredient.

1. Introduction

Natural plant-based products have garnered considerable attention in global healthcare and disease management [1, 2]. It is estimated that nearly 80% of the world's population depends on plant-derived materials to support their health needs [3]. In Vietnam, traditional medicine remains widely practiced, with approximately 75% of the population relying on it for healthcare [4]. The country is recognized as one of the most biodiverse regions, hosting about 10,000 medicinal plant species. Among these, over 4000 species are employed in folk remedies, while around 700 are officially used in traditional medicine systems [4].

In addition to therapeutic applications, plant-derived natural products are increasingly utilized in the cosmetic field due to their natural origin and safety profile [5]. Various plant extracts have been incorporated into skincare formulations for purposes such as skin whitening, scar reduction, anti-aging, photoprotection, and the treatment of conditions like eczema and acne [6, 7]. In particular, the inhibition of tyrosinase (an essential enzyme in melanogenesis) has become a key target in the development of skin-whitening agents [8].

In traditional medicine, *Canscora lucidissima* (H. Lév. & Vaniot) Hand.-Mazz has been reported as a valuable ethnomedicinal plant with notable anti-inflammatory properties, as evidenced by its ability to inhibit ERK1/2 phosphorylation [9]. Phytochemical investigations have revealed that this species is rich in bioactive constituents, particularly xanthenes and iridoid glucosides, which contribute to diverse biological activities [10, 11]. Recent studies have further identified novel xanthone derivatives with significant anti-inflammatory and antitumor activities, reinforcing its pharmacological potential [12]. These compounds are well recognized for their antioxidant and anti-inflammatory effects, which are highly relevant to cosmeceutical applications, especially in mitigating oxidative stress and inflammation-associated skin aging [11, 13]. Therefore, *C. lucidissima* represents a promising natural source for the development of functional cosmetic ingredients.

Beyond tyrosinase inhibition, plant-derived extracts exhibit multiple bioactivities relevant to cosmeceutical applications. Antioxidant and antimicrobial effects contribute to skin protection and repair, while α -glucosidase and α -amylase inhibition may reduce glycation-related aging, a key factor associated with skin aging and loss of elasticity [13–15]. These multifunctional properties further support the potential of *C. lucidissima* as a valuable natural source for the development of cosmeceutical formulations [1].

Despite its traditional use and emerging pharmacological evidence, comprehensive studies on *C. lucidissima* remain limited, particularly regarding its potential as a cosmeceutical resource. To date, integrated investigations linking its solvent-dependent phytochemical composition with antioxidant, tyrosinase-inhibitory, carbohydrate-hydrolysing enzyme inhibitory, and antibacterial activities have not been systematically established. In addition, the molecular basis of its bioactive constituents and their physicochemical and permeability-related suitability remain insufficiently clarified. To address these gaps, this study evaluated the phytochemical profiles and cosmeceutical-relevant bioactivities of four solvent extracts of *C. lucidissima*. Multivariate correlation analysis was applied to associate quantified phytochemicals with biological responses, while molecular docking and frontier molecular orbital analysis were used to explore the interaction patterns and electronic features of the most relevant tyrosinase-binding ligands. Predicted ADME and drug-likeness parameters were further included as supportive descriptors for comparing the physicochemical suitability, permeability-related behavior, and developability potential of the identified phytochemicals, rather than as direct evidence of cosmetic efficacy.

2. Materials and Methods

2.1. Materials

Samples of *C. lucidissima* (H. Lév. & Vaniot) Hand.-Mazz. were collected in Cao Bang Province, Vietnam. Botanical identification was confirmed by Prof. Dr. Tran The Bach (Institute of Biotechnology, Vietnam Academy of Science and Technology). A voucher specimen (Hue29082024) was deposited at Thai Nguyen University-Ha Giang Campus, Vietnam. The air-dried plant materials were sealed in polyethylene bags and preserved at -30°C prior to analysis. Tyrosinase from mushroom, acarbose, trolox, chloramphenicol, kojic acid, DPPH, and intestinal acetone powders from rats were obtained from Sigma-Aldrich (USA or Singapore). Reference standards including gallic acid, chlorogenic acid, epicatechin, myricetin, quercetin, luteolin, and apigenin (purity 95–97%) were

also supplied by Sigma-Aldrich. The bacterial strains *Escherichia coli* ATCC 25922 and *Staphylococcus aureus* ATCC 6538 were maintained at the Institute of Biotechnology and Environment, Tay Nguyen University (Dak Lak, Vietnam). All additional reagents were of analytical grade.

2.2. Preparation of *C. lucidissima* extracts

Various solvents differing in polarity, namely n-hexane, ethyl acetate, ethanol, and distilled water, were employed to obtain extracts from the plant material. Briefly, 10 g of the air-dried sample was immersed in 100 mL of the selected solvent in an Erlenmeyer flask and maintained under continuous shaking at ambient temperature for 24 h to facilitate compound dissolution. The mixture was subsequently filtered using Whatman No. 1 filter paper (Whatman International Ltd., Maidstone, UK) to separate the liquid phase from the solid residue. To ensure exhaustive extraction, the residual plant material was re-extracted twice more under identical conditions, each time with an additional 100 mL of the same solvent. The combined filtrates were concentrated under reduced pressure at 60°C using a rotary evaporator to remove the solvent. The obtained crude extracts were kept at -30°C for preservation prior to subsequent analyses [16].

2.3. Bioactivity assays

Tyrosinase inhibitory assay: Tyrosinase inhibition was evaluated using a spectrophotometric method based on L-DOPA oxidation presented in a previous study [17]. The dried extracts were reconstituted in sterile DMSO to prepare stock solutions and then diluted to the required concentrations using sterile distilled water. The enzyme (mushroom tyrosinase) and substrate (L-DOPA) were prepared in 0.05 M sodium phosphate buffer (pH 6.8). In a 96-well microplate, 100 µL of sample solution was mixed with 100 µL of tyrosinase and pre-incubated at 25°C for 5 min. The reaction was initiated by adding 100 µL of L-DOPA and allowed to proceed for an additional 5 min at the same temperature. Dopachrome formation was monitored by measuring absorbance at 475 nm using a microplate reader. Kojic acid was employed as the reference inhibitor. Tyrosinase inhibition (%) was calculated as: Tyrosinase inhibition (%) = $[(C - E)/C] \times 100$. Where *E* represents the absorbance of wells containing enzyme, substrate, and test sample, and *C* corresponds to the control containing enzyme and substrate without inhibitor. Kojic acid was used as reference standard. The IC₅₀ value, defined as the concentration required to suppress 50% of tyrosinase activity, was determined from the dose–response relationship. Lower IC₅₀ values indicate stronger inhibitory potency.

α-Glucosidase inhibition assay: α-Glucosidase inhibitory activity was evaluated using a chromogenic method based on p-nitrophenyl-α-D-glucopyranoside (pNPG) presented in a previous study [17]. The enzyme was prepared in 0.1 M potassium phosphate buffer (pH 7.0). The extract solution was pre-incubated with α-glucosidase at 37°C for 15 min to allow potential enzyme-inhibitor interaction. The reaction was initiated by addition of pNPG (10 mM) and maintained at 37°C for 30 min. Sodium carbonate (1 M) was then added to terminate the reaction and promote formation of the yellow p-nitrophenolate product. Absorbance was recorded at 410 nm using a microplate reader. Enzyme inhibition (%) was calculated relative to the control without inhibitor: Inhibition (%) = $[(C - E)/C] \times 100$. Where *E* represents the absorbance of the reaction mixture containing the enzyme, extract, and substrate, whereas *C* denotes the absorbance of the control mixture consisting of the enzyme and extract without the addition of substrate. Acarbose was used as reference standard. IC₅₀ values were obtained from concentration-response analysis, with lower values indicating stronger inhibitory potency.

α-Amylase inhibitory assay: α-Amylase inhibitory activity was determined using a modified Bernfeld colorimetric method presented in a previous study [17]. Porcine pancreatic α-amylase (0.25 U/mL) and soluble starch (0.25%, w/v) were prepared in 0.1 M potassium phosphate buffer (pH 7.0). The assay was performed by pre-incubating 150 µL of enzyme solution with 50 µL of plant extract at 37°C for 10 min. The enzymatic reaction was initiated by adding 200 µL of starch solution and continued at 37°C for 20 min. The reaction was terminated with dinitrosalicylic acid (DNS) reagent, followed by heating at 100°C for 10 min to develop the colored complex. The formation of reducing sugars was quantified by measuring absorbance at 540 nm using a spectrophotometer. Enzyme inhibition was calculated as: Inhibition (%) = $[(C - E)/C] \times 100$, where *E* represents the absorbance of the reaction mixture containing enzyme, extract, and substrate, and *C* corresponds to the control without extract. Acarbose was used as reference standard. The IC₅₀ value, defined as the concentration required to inhibit 50% of α-amylase activity, was derived from the concentration–response curve. Lower IC₅₀ values indicate stronger inhibitory potency.

Antioxidant Activity Evaluation: The antioxidant effect was evaluated using the method previously presented in our earlier work [18] via DPPH radical scavenging assay and ABTS radical cation scavenging assay.

DPPH radical scavenging assay: The free radical scavenging capacity was assessed using the 2,2-diphenyl-1-picrylhydrazyl (DPPH) assay. Briefly, 100 µL of sample solution at different concentrations was combined with 25 µL of 0.75 mM DPPH in methanol in a 96-well microplate. The reaction mixture was incubated in the dark at ambient temperature for 30 min, and the absorbance was recorded at 517 nm using a microplate reader. Trolox served as the positive control. Radical inhibition (%) was calculated as following equation: % inhibition = $(\text{Abs control} - \text{Abs sample})/\text{Abs control} \times 100$. The IC₅₀ value, defined as the concentration required to scavenge 50% of DPPH radicals, was obtained from the concentration–response curve. All measurements were performed in triplicate using Trolox as reference standard.

ABTS radical cation scavenging assay: The antioxidant potential was further determined using the ABTS•⁺ decolorization assay. The ABTS radical cation was generated by reacting 7 mM ABTS with 2.45 mM potassium persulfate, followed by incubation in the dark at 37°C for 16 h. Prior to use, the radical solution was diluted with methanol to an absorbance of 0.70 ± 0.02 at 734 nm. For the assay, 2 mL of the prepared ABTS•⁺ solution was mixed with 0.2 mL of the test sample at various concentrations and incubated in the dark at 37°C for 10 min. The scavenging activity was calculated using the same equation as described for the DPPH assay. IC₅₀ values were determined to compare antioxidant efficacy. Trolox was employed as the reference standard. All experiments were conducted in triplicate to ensure reproducibility.

Antibacterial assay: The antibacterial activity of *C. lucidissima* extracts was evaluated using a modified agar disc diffusion assay [19]. Briefly, the dried extracts were reconstituted in DMSO to prepare stock solutions and then diluted to the required concentrations (5, 10, 20, 30, and 40 mg/mL) using sterile distilled water. Sterile paper discs with a diameter of 6 mm were impregnated with 50 µL of each extract solution and allowed to dry under aseptic conditions before being used for antibacterial testing. Bacterial suspensions were prepared and adjusted to a final density of approximately 10⁶ CFU/mL. An aliquot of

100 μ L of each bacterial suspension was uniformly spread onto tryptic soy agar (TSA) plates supplemented with 2% NaCl. The inoculated plates were left to dry for 3–5 min under aseptic conditions, then sample-loaded paper discs were placed on the surface of these plates. Positive controls, including chloramphenicol for *Staphylococcus aureus* and gentamicin for *Escherichia coli*, were used at 1 mg/mL. The plates were incubated at 28°C for 24 h. After incubation, antibacterial activity was determined by measuring the diameter of the clear inhibition zone around each disc, and the results were expressed in millimeters (mm). All experiments were performed in triplicate.

2.4. Determination of phytochemical composition of *C. lucidissima* extracts

Preliminary phytochemical screening: A qualitative phytochemical investigation was conducted on different solvent extracts of *C. lucidissima*. Crude extracts were obtained using solvents with different polarities, including diethyl ether, ethanol, and distilled water, following a modified procedure adapted from the method originally described by Culey. The prepared extracts were subsequently subjected to standard qualitative assays for the identification of major classes of secondary metabolites. The screening aimed to detect the presence of quinones, terpenoids, glycosides, alkaloids, saponins, coumarins, tannins, flavonoids, and other phenolic constituents. The identification of these phytochemical groups was based on characteristic colorimetric changes and/or precipitate formation according to established phytochemical testing protocols [20].

Ultra-high performance liquid chromatography (UHPLC) analysis: Plant-derived extracts were reconstituted in HPLC-grade methanol to obtain a final concentration of 10 mg/mL, followed by clarification through a 0.45 μ m polyvinylidene fluoride syringe filter (MilliporeSigma, USA) to remove particulate matter. An aliquot of 2 μ L of the filtered solution was injected into a Thermo Scientific Ultimate 3000 ultra-high-performance liquid chromatography system for chromatographic analysis. Chromatographic separation of the phytochemical constituents was performed on a Hypersil GOLD aQ reversed-phase column (150 $\times$ 2.1 mm i.d., 3 μ m particle size). The mobile phase comprised methanol and water containing 0.1% (v/v) phosphoric acid, delivered under a programmed gradient elution. The gradient profile was set as follows: 0.0–0.5 min, 5% methanol; 0.5–8.0 min, linear increase to 30% methanol; 8.0–13.0 min, 30–45%; 13.0–18.0 min, 45–65%; 18.0–22.0 min, 65–95%; and 22.0–23.0 min, re-equilibration from 95% to 5% methanol. The column oven temperature was maintained at 30°C, and the flow rate was fixed at 0.2 mL/min. UV detection was carried out at 265 nm, consistent with previously reported analytical conditions [21].

To examine the association between the phytochemical composition and biological activities of *C. lucidissima* extracts, multivariate and correlation-based analyses were performed following a previous report [22]. Principal component analysis (PCA) and multiple factor analysis were used to visualize the distribution of solvent extracts and to evaluate the contribution of quantified compounds to the observed bioactivity profiles. In parallel, Pearson's correlation analysis was conducted to estimate the strength and direction of relationships between individual phytochemicals and biological endpoints.

2.5. Computational Protocols

Docking study: Computational docking analyses were carried out based on a previously reported workflow [18, 21, 23], with minor adjustments to improve consistency and structural fidelity. The crystal structure of tyrosinase (PDB ID: 5NN8) was retrieved from the Protein Data Bank. The ligand dataset consisted of metabolites tentatively identified from the plant extract via phytochemical screening, whereas kojic acid was included as a standard inhibitor for reference comparison. Prior to docking calculations, both receptor and ligands were prepared using UCSF Chimera (version 1.19). Protein preparation involved elimination of non-essential crystallographic water molecules, retention of catalytically relevant ones, addition of hydrogen atoms, assignment of partial charges, and structural relaxation through energy minimization. Ligand structures were optimized using an appropriate force field to obtain low-energy conformations suitable for binding simulations. The docking region was defined by a grid box centered at $x = -9.36$, $y = -24.35$, and $z = -39.34$, with dimensions of $18.25 \times 17.42 \times 14.64$ Å, following previously validated parameters [23]. This binding pocket includes key residues associated with catalytic function and substrate recognition, notably histidine residues coordinating the dinuclear copper center (Cu400 and Cu401), along with adjacent residues such as Ala286 and Val283 that contribute to ligand stabilization. Docking outputs provided both energetic and structural insights, including predicted binding affinities (kcal/mol), binding orientations, and interaction patterns. Detailed analysis focused on non-covalent interactions such as hydrogen bonds, π - π interactions, hydrophobic contacts, and coordination with metal ions. The 3D structure of the protein and the defined docking grid are presented in Fig. 1.

Density functional theory (DFT) and in silico pharmacokinetic prediction: Quantum chemical computations were carried out using Gaussian 09 within the density functional theory (DFT) framework to elucidate the structural and electronic properties of the selected phytoconstituents. Geometry optimization was performed at the M05-2X/6-311 + + G(d,p) level of theory [24]. To verify that the optimized structures corresponded to true local minima on the potential energy surface, vibrational frequency analyses were subsequently conducted, ensuring the absence of imaginary frequencies. A frozen-core approximation was employed to describe inner-shell electrons, while the resolution-of-identity approach was applied to accelerate the calculations. Frontier molecular orbital characteristics were further examined using NBO 5.1 at the M05-2X/def2-TZVPP level [25]. The convergence of optimized geometries was confirmed based on four criteria: maximum force, root-mean-square (RMS) force, maximum displacement, and RMS displacement, as obtained from both optimization and frequency calculations.

The drug-likeness of the studied natural compounds was assessed according to Lipinski's Rule of Five using an online prediction tool [9]. In addition, key pharmacokinetic and toxicity-related properties, including absorption, distribution, metabolism, excretion (ADME), were predicted to provide preliminary insights into their potential bioavailability and safety profiles.

3. Results and Discussion

3.1. Potential cosmeceutical-related bioactivities of *C. lucidissima* extracts

3.1.1. Evaluation of enzymes inhibitory activities *C. lucidissima* extracts

To evaluate the skin-whitening potential of *C. lucidissima* extracts, their tyrosinase inhibitory activity was determined, and the results are summarized in Table 1. All tested extracts exhibited detectable inhibition, with IC₅₀ values ranging from 195.24 to 255.61 µg/mL. Among the extracts, the ethyl acetate fraction showed the strongest activity, with an IC₅₀ value of 195.24 µg/mL, followed by the ethanol (220.56 µg/mL) and aqueous (222.34 µg/mL) extracts, whereas the n-hexane extract was the least active (255.61 µg/mL). As expected, kojic acid, used as the reference inhibitor, displayed markedly higher potency, with an IC₅₀ value of 87.92 µg/mL. These results indicate that although *C. lucidissima* extracts were less active than the standard compound, they still exhibited moderate tyrosinase inhibitory potential. The stronger activity of the ethyl acetate extract may suggest the involvement of moderately polar constituents; however, further phytochemical profiling and bioassay-guided fractionation would be required to identify the compounds responsible for this effect.

Table 1
Enzyme inhibitory activities of *C. lucidissima* extracts

Samples	IC50 (µg/mL)		
	Anti-tyrosinse	aGI	aAI
n-Hexane extract	255.61	140.05	195.56
Aqueous extract	222.34	118.25	149.39
Ethyl acetate extract	195.24	119.09	125.68
Ethanol extract	220.56	96.46	149.09
Kojic acid	87.92	ND	ND
Acarbose	ND	13.09	25.44
<i>aGI: α-glucosidase inhibition; aAI: α-amylase inhibition; ND: no determine</i>			

The inhibitory activities of *C. lucidissima* extracts against carbohydrate-hydrolyzing enzymes, namely α-glucosidase and α-amylase, were also examined because these enzymes are indirectly associated with postprandial glucose regulation and glycation-related skin aging. All extracts inhibited both enzymes, although their potency varied depending on the extraction solvent. For α-glucosidase, the ethanol extract was the most active, with an IC₅₀ value of 96.46 µg/mL, followed by the aqueous (118.25 µg/mL), ethyl acetate (119.09 µg/mL), and n-hexane (140.05 µg/mL) extracts. Nevertheless, acarbose showed substantially stronger inhibition, with an IC₅₀ value of 13.09 µg/mL. In the α-amylase assay, the ethyl acetate extract exhibited the highest inhibitory effect, with an IC₅₀ value of 125.68 µg/mL, followed by the ethanol (149.09 µg/mL), aqueous (149.39 µg/mL), and n-hexane (195.56 µg/mL) extracts; acarbose again served as the most potent reference inhibitor, with an IC₅₀ value of 25.44 µg/mL. Taken together, these findings suggest that *C. lucidissima* extracts possess moderate inhibitory effects on α-glucosidase and α-amylase. Although these activities are not direct markers of cosmetic efficacy, they may support the potential role of the extracts in mitigating glycation-associated processes relevant to skin aging.

3.1.2. Evaluation of antioxidant and antibacterial activities *C. lucidissima* extracts

Oxidative stress and microbial colonization are major factors contributing to skin aging and various dermatological disorders. Excessive production of reactive oxygen species (ROS) can accelerate cellular damage, inflammatory responses, and melanogenesis, whereas the proliferation of pathogenic or opportunistic bacteria may aggravate skin inflammation and impair barrier function. In this context, plant-derived extracts possessing both antioxidant and antibacterial properties are of considerable interest for the development of multifunctional cosmeceutical ingredients.

As summarized in Table 2, *C. lucidissima* extracts exhibited evident antioxidant activity, although the magnitude of activity varied depending on the extraction solvent and assay system. In the radical-scavenging assays, the ethyl acetate extract showed the highest potency, with IC₅₀ values of 51.79 µg/mL for DPPH and 34.02 µg/mL for ABTS. Its ABTS-scavenging activity was relatively close to that of Trolox, suggesting a marked capacity to neutralize ABTS radicals. The aqueous and ethanol extracts also displayed moderate antioxidant effects, with DPPH IC₅₀ values of approximately 68 µg/mL and ABTS IC₅₀ values of approximately 50 µg/mL, whereas the n-hexane extract was consistently the least active. In the FRAP assay, the polar extracts showed comparable reducing capacity, with values of approximately 51–52 µg/mL, although their activity remained weaker than that of Trolox (9.23 µg/mL). These findings indicate that the antioxidant potential of *C. lucidissima* is more pronounced in polar and moderately polar extracts, particularly the ethyl acetate fraction. However, further phytochemical profiling is required to clarify which classes of constituents are primarily responsible for this activity.

Table 2
Antioxidant activities of *C. lucidissima* extracts

Samples	IC50 (µg/mL)		
	DPPH	ABTS	FRAP
n-Hexane extract	120.81	76.75	61.48
Aqueous extract	68.36	50.68	51.58
Ethyl acetate extract	51.79	34.02	51.73
Ethanol extract	68.39	50.05	51.54
Trolox	58.55	36.19	9.23
DPPH: 2,2-diphenyl-1-picrylhydrazyl radical scavenging assay; ABTS: 2,2'-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid) radical cation decolorization assay; FRAP: ferric reducing antioxidant power assay			

The antibacterial activity of *C. lucidissima* extracts was first evaluated against *Staphylococcus aureus*, a bacterium commonly associated with inflammatory skin conditions and barrier dysfunction. As shown in Table 3 and Fig. 2a, all extracts displayed concentration-dependent inhibitory effects, with higher extract concentrations generally producing larger inhibition zones. The ethyl acetate extract exhibited the strongest activity, with inhibition zones increasing from 4 to 28 mm as the concentration increased from 5 to 40 mg/mL. This was followed by the ethanol extract (2–25 mm) and the aqueous extract (0–20 mm), while the n-hexane extract showed comparatively weaker activity (0–15 mm). Although these effects were lower than those of the positive control chloramphenicol, the observed inhibition suggests that *C. lucidissima* extracts, especially the ethyl acetate fraction, may possess potential for controlling *S. aureus*-associated microbial proliferation.

Table 3
Anti-*S. aureus* effect of *C. lucidissima* extracts

Samples	Zone inhibition (mm)				
	5 mg/mL	10 mg/mL	20 mg/mL	30 mg/mL	40 mg/mL
n-Hexane extract	0	1	5	9	15
Aqueous extract	0	4	10	15	20
Ethyl acetate extract	4	9	15	20	28
Ethanol extract	2	9	12.7	18	25
Chloramphenicol, a positive control was tested at 1mg/mL					30

A similar concentration-dependent pattern was also observed against *Escherichia coli* (Table 4 and Fig. 2b), which was used as a representative Gram-negative bacterium to further assess the antibacterial spectrum of the extracts. The ethyl acetate extract again showed the strongest inhibitory effect, with inhibition zones increasing from 4 to 28 mm across the tested concentrations of 5–40 mg/mL. The ethanol extract also displayed marked activity, with inhibition zones ranging from 2 to 25 mm, followed by the aqueous extract (0–24 mm). The n-hexane extract was the least active, although its inhibition zone increased from 0 to 16 mm at the highest tested concentration. Compared with gentamicin, which produced an inhibition zone of 32 mm at 1 mg/mL, the extracts were less potent; nevertheless, the clear dose-dependent inhibition indicates that *C. lucidissima* contains antibacterial constituents active against both Gram-positive and Gram-negative bacteria. The consistently stronger activity of the ethyl acetate extract against both *S. aureus* and *E. coli* further suggests that moderately polar compounds may contribute substantially to the antibacterial effects.

Table 4
Anti-*E. coli* effect of *C. lucidissima* extracts

Samples	Zone inhibition (mm)				
	5 mg/mL	10 mg/mL	20 mg/mL	30 mg/mL	40 mg/mL
n-Hexane extract	0	1	5	9	16
Aqueous extract	0	5	12	18	24
Ethyl acetate extract	4	10	16	20	28
Ethanol extract	2	8.7	14	19	25
Gentamicin, a positive control was tested at 1mg/mL					32

Overall, the antioxidant and antibacterial activities observed in this study support the potential use of *C. lucidissima* as a multifunctional botanical ingredient for skin-protective formulations. In particular, the ethyl acetate extract showed the most consistent performance across antioxidant and antibacterial assays, indicating that this fraction may be a promising candidate for further phytochemical and biological investigation. These findings are also consistent with previous reports showing that *C. lucidissima* contains bioactive xanthone glycosides and related xanthone derivatives with antioxidant and anti-inflammatory activities [9, 11, 12]. The 85% ethanol extract of *C. lucidissima* was previously reported to suppress LPS-induced inflammatory responses in RAW264.7 macrophages by reducing NO production and down-regulating iNOS, TNF-α, IL-6, MCP-1, and IL-1β, mainly through inhibition of ERK1/2 phosphorylation; the

extract showed no cytotoxicity up to 400 µg/mL and reduced inflammatory cytokines in an LPS-induced endotoxemia mouse model at doses of 75–300 mg/kg [9]. In another study, three new xanthone glycosides, namely canlucosides A-C, were isolated from the ethanol extract of *C. lucidissima* [11]. Among them, canlucosides B and C exhibited notable antioxidant activity, with IC₅₀ values of 33.64 µM and 36.63 µM, respectively, while canlucoside B also showed potent NO-inhibitory activity, with an IC₅₀ value of 0.92 µM. More recently, canlucones A-I and related xanthenes isolated from the whole plant of *C. lucidissima* were reported to exert anti-inflammatory effects in LPS-stimulated RAW264.7 cells, with compounds 7 and 11 inhibiting NO production with IC₅₀ values of 23.39 µM and 13.90 µM, respectively, and reducing TNF-α and IL-6 production in a concentration-dependent manner [12]. Prior to the present study, however, direct evidence for tyrosinase inhibition, α-glucosidase/α-amylase inhibition, and antibacterial activity of *C. lucidissima* had not been systematically documented in the accessible literature. Therefore, the current findings expand the novel known bioactivity profile of this species and provide additional support for its potential application in cosmeceutical research.

3.2. Phytochemical composition of *C. lucidissima* extracts

3.2.1. Preliminary phytochemical groups screening

The preliminary phytochemical screening of *C. lucidissima* extracts (as shown in Table 5) revealed a clear solvent-dependent distribution of secondary metabolite groups. This pattern appears to be closely associated with the polarity of the extraction solvents, which ranged from non-polar n-hexane to moderately polar ethyl acetate and highly polar ethanol and water. The n-hexane extract showed a selective affinity for less polar constituents, as indicated by the strong presence of terpenoids (+++), while polar metabolite groups such as glycosides, saponins, and tannins were not detected. In contrast, the ethyl acetate and ethanol extracts exhibited broader phytochemical profiles, particularly with respect to phenolic compounds and flavonoids. Notably, the ethyl acetate fraction showed the most intense response for phenolics (++++) and a high level of flavonoids (+++), suggesting that this solvent was especially effective in recovering compounds of intermediate polarity, including polyphenolic structures bearing aromatic rings and hydroxyl groups. Meanwhile, the aqueous extract was characterized by the strongest detection of glycosides (++++) and marked signals for saponins (+++) and tannins (+++), which is consistent with the high polarity and possible sugar-containing or highly hydroxylated nature of these compounds. The absence of terpenoids in the aqueous fraction further supports the selective partitioning of hydrophobic constituents into less polar solvents. Overall, these findings indicate that the phytochemical composition of *C. lucidissima* extracts is strongly influenced by solvent polarity, with ethyl acetate and ethanol being more favorable for phenolic- and flavonoid-rich fractions, whereas water preferentially extracts highly polar constituents such as glycosides, saponins, and tannins.

Table 5
Qualitative phytochemical groups screening of *Canscora lucidissima* extracts

Compound group	<i>n</i> -Hexane extract	Ethyl acetate extract	Ethanol extract	Aqueous extract
Phenolic	(±)	(++++)	(+++)	(++)
Flavonoid	(±)	(+++)	(++)	(++)
Quinone	(±)	(+)	(+)	(+)
Coumarin	(+)	(+)	(++)	(±)
Alkaloid	(±)	(+)	(++)	(+)
Glycosides	(-)	(++)	(+++)	(++++)
Terpenoid	(+++)	(++)	(+)	(-)
Saponin	(-)	(+)	(+)	(+++)
Tannin	(-)	(++)	(++)	(+++)
(-) Not present; (±) Not clear; (+) Slightly present; (++) Present; (+++) Abundantly present; (++++) Highly abundant.				

3.2.2. Determination of phytochemicals by UHPLC analysis

Quantitative UHPLC profiling (Table 6, Fig. 3) detected nine phytochemicals in *C. lucidissima* extracts, further substantiating the solvent-dependent distribution observed in the preliminary phytochemical screening. These markers included phenolic acids, flavonoids, and a non-phenolic methylxanthine alkaloid. The variation in individual compound levels among the extracts indicates that solvent polarity strongly influenced the extraction and partitioning of structurally different phytochemicals, particularly phenolic acids and flavonoids.

Table 6
Nine major phenolics of *Canscora lucidissima* extracts determined by UHPLC analysis

No.	Compound	RT (min)	Content (mg/g dry extract)			
			n-Hexane extract	Ethyl acetate extract	Ethanol extract	Aqueous extract
(1)	Gallic acid	7.3	-	0.002	0.051	-
(2)	Catechin	13.5	-	0.010	0.005	0.003
(3)	Chlorogenic acid	14.1	0.085	3.234	0.255	1.022
(4)	Caffeine	14.8	0.004	0.025	0.008	0.039
(5)	Rutin	18.9	0.015	0.218	0.096	0.022
(6)	Ellagic acid	19.3	-	0.229	0.231	0.095
(7)	Quercitrin	20.0	-	0.158	0.205	0.066
(8)	Quercetin	20.6	0.187	0.229	0.201	0.235
(9)	Apigenin	21.3	-	-	0.023	-
(-): Not detected						

The n-hexane extract showed a markedly limited capacity to recover phenolic constituents, as most target phenolic compounds were either not detected or present only at trace levels. This observation is consistent with the predominantly polar nature of phenolic acids and flavonoids, which generally contain multiple hydroxyl groups and therefore exhibit poor solubility in non-polar solvents. Only small amounts of quercetin and chlorogenic acid were detected in this fraction, at 0.187 and 0.085 mg/g, respectively. In contrast, the recovery of phenolic acids and flavonoids increased substantially in the ethyl acetate, ethanol, and aqueous extracts, confirming the greater suitability of polar and moderately polar solvents for extracting polyphenolic constituents. Among the quantified phenolics, chlorogenic acid was the predominant compound across the extracts, reaching its highest level in the ethyl acetate fraction at 3.234 mg/g and remaining abundant in the aqueous extract at 1.022 mg/g. This distribution suggests that chlorogenic acid possesses favorable solubility in solvents of intermediate to high polarity, likely due to the structural balance between its caffeoyl and quinic acid moieties. The distribution of flavonoids also revealed structure-dependent extraction behavior. Glycosylated flavonoids, such as rutin and quercitrin, were preferentially recovered in the ethyl acetate and ethanol fractions, with rutin reaching 0.218 mg/g and quercitrin reaching 0.158 mg/g. Their poor detection in the n-hexane extract is consistent with the increased polarity imparted by sugar residues. By contrast, the aglycone flavonol quercetin showed a more even distribution among the polar extracts, with comparable contents in the ethyl acetate, ethanol, and aqueous extracts at 0.229, 0.201, and 0.235 mg/g, respectively. While apigenin was detected only in the ethanol extract at 0.023 mg/g.

Overall, the UHPLC results provide quantitative support for the phytochemical screening data and show that the quantified profile of *C. lucidissima* was dominated by phenolic acids, particularly chlorogenic acid, together with selected flavonoid derivatives. These findings indicate that ethyl acetate and ethanol are suitable solvents for enriching phenolic- and flavonoid-containing fractions, supporting their potential use in the targeted recovery of bioactive constituents from this species. These findings appear to represent the first UHPLC-based comparative quantification of selected phenolic acids, flavonoids, and caffeine in different solvent extracts of *C. lucidissima*, thereby extending the current phytochemical knowledge of this species.

3.2.3. Correlation between phytochemical profiles and biological activities via multivariate analysis

The Pearson correlation heatmap and PCA biplot in Fig. 4 provide an integrated interpretation of the relationships between quantified phytochemical markers and the biological responses of *C. lucidissima* extracts. The first two principal components explained 91.28% of the total variance, with PC1 and PC2 accounting for 69.73% and 21.55%, respectively, indicating that the major chemical and bioactivity-related differences among the solvent extracts were well represented in the PCA space. The distribution of samples was broadly consistent with the activity profiles reported in Tables 1–4. The n-hexane extract was clearly separated on the negative side of PC1 and was generally associated with weaker biological responses, whereas the ethyl acetate and ethanol extracts were positioned on the positive side of PC1, reflecting their stronger association with the quantified phytochemical markers and their comparatively higher bioactivities.

The ethyl acetate extract was closely associated with catechin, chlorogenic acid, caffeine, rutin, quercetin, and antibacterial activity, particularly against *E. coli*. This pattern is consistent with the experimental results showing that the ethyl acetate fraction exhibited the strongest tyrosinase, α -amylase, DPPH, ABTS, and antibacterial activities. Ellagic acid and quercitrin were also located on the positive side of PC1 and showed strong positive correlations with antibacterial activity, especially against *S. aureus*. These findings suggest that the antibacterial effects of *C. lucidissima* extracts may be partly related to the enrichment of moderately polar phenolic and flavonoid constituents in the ethyl acetate fraction.

The ethanol extract was positioned in the upper-right quadrant and was more closely aligned with gallic acid and apigenin. This agrees with the bioactivity data showing that ethanol was the most active extract against α -glucosidase. In the correlation matrix, gallic acid and apigenin showed marked negative correlations with α -glucosidase IC₅₀ values, suggesting that these compounds may be selectively associated with stronger α -glucosidase inhibition. By contrast, their relationships with several other endpoints were weaker or more selective, indicating that they may not be the main contributors to the broader antioxidant and antibacterial profiles.

For enzyme inhibitory and antioxidant assays expressed as IC₅₀ values, the negative correlations between phytochemical markers and bioactivity variables should be interpreted as favorable associations, because lower IC₅₀ values indicate stronger activity. Under this interpretation, catechin, chlorogenic acid, rutin, ellagic acid, quercitrin, and quercetin were associated with improved tyrosinase, α-amylase, DPPH, ABTS, and FRAP responses, particularly in the ethyl acetate fraction. This interpretation is consistent with the experimental finding that ethyl acetate generally showed the lowest IC₅₀ values across most assays. In contrast, antibacterial activity was evaluated using inhibition zone diameters, where higher values indicate stronger activity; therefore, the positive correlations between several phytochemical markers and anti-*S. aureus* or anti-*E. coli* activity directly support their possible contribution to antibacterial effects.

Overall, the multivariate and correlation analyses are consistent with the biological evaluation of the solvent extracts. Nevertheless, these correlations remain exploratory and should not be interpreted as direct evidence of causality without further validation using purified compounds or bioassay-guided fractionation.

3.3. Molecular docking, pharmacokinetic properties, and electronic features of phytochemicals from *C. lucidissima* extracts

3.3.1. Molecular docking analysis of identified phytochemicals against tyrosinase 5NN8

Molecular docking was performed to elucidate potential interactions between the identified phytochemicals from *C. lucidissima* extracts and tyrosinase 5NN8. As shown in Table 7, the docking scores ranged from – 5.389 to -8.426 kcal/mol, indicating clear differences in the predicted binding affinity of the tested ligands. Rutin (5) showed the most favorable docking score, followed by Caffeine (4), Quercitrin (7), Chlorogenic acid (3), Apigenin (9), Quercetin (8), Catechin (2), Ellagic acid (6), and Gallic acid (1). Notably, Rutin (5), Caffeine (4), and Quercitrin (7) exhibited stronger predicted binding than Kojic acid (10), the reference inhibitor, whereas Chlorogenic acid (3) showed a comparable affinity. The interaction profiles further revealed that several residues were repeatedly involved in ligand binding, particularly His84, His262, Phe263, Val282, Ser281, Gly280, Met256, and Val247. Among these, His262 appeared in the complexes of Chlorogenic acid (3), Caffeine (4), Quercitrin (7), Quercetin (8), Apigenin (9), and Kojic acid (10), suggesting its importance in ligand stabilization within the tyrosinase binding pocket. The recurrent participation of Phe263, Val282, Gly280, and Ser281 also indicates that both polar contacts and hydrophobic/aromatic interactions contribute to stabilizing the docked conformations.

Table 7
The interaction of the identified phytochemicals from *Canscora lucidissima* extracts (ligand 1–9) and kojic acid (ligand 10) toward tyrosinase (5NN8)

Symbol of Ligad-enzyme	DS (Kcal/mol)	Key Interacting residues
(1)-5NN8	-5.389	His 60, His 84, Glu 255, His 258, Asn 259, His 262, Ser 281, Val 282
(2)-5NN8	-6.671	His 84, Val 247, Asn 259, His 262, Met 279, Ser 281, Val 282, Ala 285
(3)-5NN8	-7.347	His 243, Met 256, Asn 259, His 262, Phe 263
(4)-5NN8	-8.12	His 84, His 262, Met 279, Gly 280, Ser 281, Val 282, Arg 287
(5)-5NN8	-8.426	Asn 80, His 84, Val 247, Met 256, Phe 263, Val 282
(6)-5NN8	-6.519	His 60, His 84, Glu 255, His 262, Met 279, Val 282
(7)-5NN8	-7.565	Val 247, Met 256, His 262, Phe 263, Gly 280, Ser 281, Val 282
(8)-5NN8	-6.775	His 84, His 243, Val 247, His 262, Phe 263, Ser 281, Val 282, Ala 285
(9)-5NN8	-6.797	His 84, Val 247, His 262, Ser 281, Val 282, Ala 285
(10)-5NN8	-7.423	His 262, Gly 280, Val 282, Ala 285

The detailed 2D and 3D interaction maps of the best-performing ligands provided further support for this binding pattern (Fig. 5). Chlorogenic acid (3) interacted with His243, Met256, Asn259, His262, and Phe263, suggesting that its caffeoyl and quinic acid moieties may stabilize binding through a combination of polar contacts and aromatic interactions. The presence of His262 and Phe263 in this complex is notable because these residues were also involved in several higher-affinity ligands. Caffeine (4), despite lacking phenolic hydroxyl groups, displayed strong affinity through interactions with His84, His262, Met279, Gly280, Ser281, Val282, and Arg287. Its compact planar xanthine scaffold may therefore allow efficient accommodation within the binding pocket, explaining its docking score superior to Kojic acid (10). Rutin (5), the strongest ligand, formed interactions with Asn80, His84, Val247, Met256, Phe263, and Val282. Its extended flavonoid glycoside structure provides a larger molecular surface and multiple hydroxyl groups, enabling simultaneous polar and hydrophobic/aromatic contacts. Similarly, Quercitrin (7) interacted with Val247, Met256, His262, Phe263, Gly280, Ser281, and Val282. The combination of polar contacts with Gly280 and Ser281 and hydrophobic/aromatic contacts with Val247, Phe263, and Val282 suggests stable accommodation of Quercitrin (7) in the enzyme pocket.

Overall, the docking results support the contribution of multiple phytochemicals to the anti-tyrosinase activity of *C. lucidissima* extracts. Rutin (5), Caffeine (4), Quercitrin (7), and Chlorogenic acid (3) appear to be the most relevant candidate ligands, as they combined favorable docking scores with interactions involving key residues in the tyrosinase binding pocket.

3.3.2. Frontier molecular orbital analysis of the most active ligands

Frontier molecular orbital analysis was conducted to further interpret the electronic features of the four most relevant ligands identified from *C. lucidissima* extracts, in comparison with Kojic acid (10) as the reference inhibitor. As shown in Table 9 and Fig. 6, the HOMO–LUMO energy gaps of Chlorogenic acid (3), Caffeine (4), Rutin (5), and Quercitrin (7) were 4.00, 4.99, 3.77, and 4.10 eV, respectively, whereas Kojic acid (10) exhibited a markedly lower gap of 2.39 eV. Among the phytochemicals, Rutin (5) showed the smallest energy gap, indicating the highest electronic reactivity and charge-transfer potential within this group. This result is consistent with its strongest docking affinity, suggesting that both electronic responsiveness and multiple interaction sites contribute to its stable accommodation within the tyrosinase binding pocket.

Table 9
Frontier molecular orbital energies and energy gap values of the major compounds

Compound	E _{HOMO} (eV)	E _{LUMO} (eV)	ΔE _{gap} (eV)
3	-6.12	-2.12	4.00
4	-6.16	-1.17	4.99
5	-5.65	-1.88	3.77
7	-5.94	-1.84	4.10
10	-8.42	-5.49	2.93

Chlorogenic acid (3) and Quercitrin (7) showed intermediate energy gaps of 4.00 and 4.10 eV, respectively, reflecting moderate electronic reactivity. Their DFT profiles support the docking results, in which both ligands were able to interact with relevant residues in the tyrosinase pocket, although their binding strength may be influenced by molecular size, conformational flexibility, and spatial complementarity. In contrast, Caffeine (4) displayed the largest energy gap among the tested phytochemicals, suggesting lower intrinsic electronic reactivity. Nevertheless, its favorable docking score indicates that its binding may be driven primarily by its compact planar scaffold and efficient fitting within the active pocket rather than by strong charge-transfer capacity.

Notably, Kojic acid (10) presented the lowest HOMO–LUMO gap overall, indicating high electronic softness and a strong tendency toward electronic interaction. However, its docking affinity was lower than those of Rutin (5), Caffeine (4), and Quercitrin (7), and was comparable to Chlorogenic acid (3). This observation suggests that electronic reactivity alone is insufficient to determine tyrosinase binding efficiency. Instead, ligand size, functional-group distribution, conformational adaptability, and spatial matching within the binding pocket collectively govern the predicted inhibitory potential. Therefore, the combined docking and DFT results indicate that Rutin (5) is the most promising candidate, while Caffeine (4), Quercitrin (7), and Chlorogenic acid (3) may also contribute to the anti-tyrosinase activity of *C. lucidissima* through distinct but complementary interaction mechanisms.

3.3.3. Predicted ADME and physicochemical suitability of phytochemicals from *C. lucidissima* extracts

Although conventional ADME and drug-likeness parameters are mainly designed for oral drug discovery, they were used here as supportive descriptors to compare the physicochemical suitability, permeability-related behavior, and developability potential of the identified phytochemicals. Accordingly, these predictions should not be regarded as direct evidence of cosmetic efficacy, but as complementary criteria for prioritizing compounds for topical formulation, cellular validation, and subsequent experimental safety assessment.

3.3.3.1. Bioavailability radar plot for physicochemical drug-likeness

The bioavailability radar (Fig. 7) provides an immediate visual summary of drug-likeness by comparing six molecular properties against the optimal range for oral absorption. The hexagon's vertices correspond to lipophilicity (LIPO), molecular size (SIZE), polarity (POLAR), aqueous solubility (INSOLU), molecular unsaturation (INSATU), and conformational flexibility (FLEX). The coloured zone represents the physicochemical space favourable for oral absorption. Overall, Gallic acid (1), Catechin (2), Quercetin (8), Apigenin (9), and Kojic acid (10) showed relatively favorable radar profiles, with most parameters falling within or close to the optimal physicochemical space. Their molecular size, lipophilicity, polarity, solubility, and flexibility were generally compatible with oral bioavailability, which is consistent with their predicted high gastrointestinal absorption. Among these compounds, Apigenin (9) exhibited one of the most balanced radar patterns, particularly in terms of lipophilicity, polarity, size, and flexibility. Quercetin (8) also showed a favorable profile, although its polarity was close to the upper acceptable limit. Catechin (2) displayed an acceptable radar distribution, with moderate polarity and suitable molecular size. Gallic acid (1) and Kojic acid (10) were highly soluble and flexible, but their small molecular size and low saturation slightly reduced their lead-like radar balance. In contrast, Chlorogenic acid (3), Caffeine (4), Rutin (5), and Quercitrin (7) showed less favorable radar profiles, mainly due to excessive polarity. Their high TPSA and extensive hydrogen-bonding capacity caused the POLAR axis to extend beyond the optimal region, explaining their predicted low gastrointestinal absorption. This limitation was most evident for Rutin (5), which also exceeded the preferred molecular size range, reflecting its large glycosylated structure and poor passive permeability. Ellagic acid (6) presented an intermediate profile. Although its molecular size, lipophilicity, and flexibility were acceptable, its polarity was slightly above the optimal range and its aromatic, highly unsaturated structure affected the saturation-related parameter. Therefore, despite its predicted high gastrointestinal absorption, its radar plot suggests some physicochemical constraints that may influence permeability. Overall, the radar analysis indicates that Apigenin (9), Quercetin (8), and Catechin (2) possess the most balanced bioavailability-related profiles, whereas Rutin (5), Quercitrin (7), Chlorogenic acid (3), and Caffeine (4) are mainly limited by excessive polarity and reduced permeability.

3.3.3.2. Boiled-egg plot for passive gastrointestinal absorption and blood-brain barrier penetration

The BOILED-Egg plot (Fig. 8) provided a visual prediction of gastrointestinal absorption and blood-brain barrier (BBB) permeability. By plotting the calculated lipophilicity (WlogP) against the topological polar surface area (TPSA), the model separates compounds likely to be well absorbed from those expected to cross the BBB. Most compounds were located within or near the white region, indicating a certain degree of compatibility with passive gastrointestinal absorption. Gallic acid (1), Catechin (2), Ellagic acid (6), Quercetin (8), Apigenin (9), and Kojic acid (10) were positioned in the HIA-favorable area, consistent with their predicted high GI absorption in SwissADME. None of the compounds was located within the yellow BBB region, indicating that they are unlikely to cross the blood-brain barrier. This agrees with the pharmacokinetic prediction that all compounds were non-BBB permeant. For cosmeceutical or peripheral enzyme-inhibitory applications, this limited CNS exposure may be considered favorable rather than disadvantageous. In particular, Rutin (5) was outside the plotted range, reflecting its very high TPSA and large molecular size.

Regarding P-glycoprotein interaction, Catechin (2) was marked as PGP-positive, suggesting possible efflux-mediated limitation of intracellular or systemic exposure. The remaining displayed compounds were mainly PGP-negative, implying that P-gp efflux may not be a major restriction for these molecules. However, for highly polar compounds such as Rutin (5) and Quercitrin (7), poor absorption appears to be driven primarily by physicochemical constraints rather than efflux alone.

Overall, the BOILED-Egg plot confirms that Apigenin (9), Quercetin (8), Ellagic acid (6), Gallic acid (1), Catechin (2), and Kojic acid (10) possess more favorable absorption-related profiles, whereas Rutin (5), Quercitrin (7), Chlorogenic acid (3), and Caffeine (4) are mainly limited by excessive polarity and reduced passive permeability.

3.3.3.3. Comprehensive summary of ADME and drug-likeness parameters

A detailed ADME (Absorption, Distribution, Metabolism, Excretion)-related evaluation, covering physicochemical, lipophilicity, water solubility, pharmacokinetics, druglikeness, and medicinal chemistry properties of compounds 1–9 (from *C. lucidissima* extracts) and Kojic acid (10) is provided in Table 8.

Table 8
SwissADME/ADMET-related parameters of phytochemicals (1–9) from *C. lucidissima* extracts and Kojic acid (10)

Property	Molecule 1	Molecule 2	Molecule 3	Molecule 4	Molecule 5	Molecule 6	Molecule 7	Molecule 8
PHYSICOCHEMICAL PROPERTIES								
Formula	C ₇ H ₆ O ₅	C ₁₅ H ₁₄ O ₆	C ₁₆ H ₁₈ O ₉	C ₂₂ H ₁₈ O ₁₁	C ₂₇ H ₃₀ O ₁₆	C ₁₄ H ₆ O ₈	C ₂₁ H ₂₀ O ₁₁	C ₁₀ H ₆ O ₄
Molecular weight	170.12 g/mol	290.27 g/mol	354.31 g/mol	458.37 g/mol	610.52 g/mol	302.19 g/mol	448.38 g/mol	302.07 g/mol
Num. heavy atoms	12	21	25	33	43	22	32	22
Num. arom. heavy atoms	6	12	6	18	16	16	16	16
Fraction Csp ³	0.00	0.20	0.38	0.14	0.44	0.00	0.29	0.00
Num. rotatable bonds	1	1	5	4	6	0	3	1
Num. H-bond acceptors	5	6	9	11	16	8	11	7
Num. H-bond donors	4	5	6	8	10	4	7	5
Molar refractivity	39.47	74.33	83.50	112.06	141.38	75.31	109.00	78.07
TPSA	97.99 Å ²	110.38 Å ²	164.75 Å ²	197.37 Å ²	269.43 Å ²	141.34 Å ²	190.28 Å ²	130.40 Å ²
LYPOPHILICITY								
Log <i>P</i> _{o/w} (iLOGP)	0.21	1.33	0.87	1.53	0.46	0.79	1.60	1.60
Log <i>P</i> _{o/w} (XLOGP3)	0.70	0.36	-0.42	1.17	-0.33	1.10	0.86	1.50
Log <i>P</i> _{o/w} (WLOGP)	0.50	1.22	-0.75	1.91	-1.69	1.31	0.49	1.50
Log <i>P</i> _{o/w} (MLOGP)	-0.16	0.24	-1.05	-0.44	-3.89	0.14	-1.84	-0.01
Log <i>P</i> _{o/w} (SILICOS-IT)	-0.20	0.98	-0.61	0.57	-2.11	1.67	0.01	1.50
Consensus Log <i>P</i> _{o/w}	0.21	0.83	-0.39	0.95	-1.51	1.00	0.22	1.20
WATER SOLUBILITY								
Log S (ESOL)	-1.64	-2.22	-1.62	-3.56	-3.30	-2.94	-3.33	-3.00
Solubility (ESOL)	3.90e+00 mg/mL; 2.29e-02 mol/L	1.74e+00 mg/mL; 5.98e-03 mol/L	8.50e+00 mg/mL; 2.40e-02 mol/L	1.27e-01 mg/mL; 2.76e-04 mol/L	3.08e-01 mg/mL; 5.05e-04 mol/L	3.43e-01 mg/mL; 1.14e-03 mol/L	2.08e-01 mg/mL; 4.64e-04 mol/L	2.10e-01 mg/mL; 6.90e-04 mol/L
Solubility class (ESOL)	Very soluble	Soluble	Very soluble	Soluble	Soluble	Soluble	Soluble	Soluble
Log S (Ali)	-2.34	-2.24	-2.58	-4.91	-4.87	-3.66	-4.44	-3.00
Solubility (Ali)	7.86e-01 mg/mL; 4.62e-03 mol/L	1.66e+00 mg/mL; 5.72e-03 mol/L	9.42e-01 mg/mL; 2.66e-03 mol/L	5.64e-03 mg/mL; 1.23e-05 mol/L	8.30e-03 mg/mL; 1.36e-05 mol/L	6.60e-02 mg/mL; 2.18e-04 mol/L	1.62e-02 mg/mL; 3.63e-05 mol/L	3.70e-02 mg/mL; 1.20e-04 mol/L
Solubility class (Ali)	Soluble	Soluble	Soluble	Moderately soluble	Moderately soluble	Soluble	Moderately soluble	Soluble
Log S (SILICOS-IT)	-0.04	-2.14	0.40	-2.50	-0.29	-3.35	-2.08	-3.00

Property	Molecule 1	Molecule 2	Molecule 3	Molecule 4	Molecule 5	Molecule 6	Molecule 7	Molecule 8
PHYSICOCHEMICAL PROPERTIES								
Solubility (SILICOS-IT)	1.55e + 02 mg/mL; 9.10e-01 mol/L	2.09e + 00 mg/mL; 7.19e-03 mol/L	8.94e + 02 mg/mL; 2.52e + 00 mol/L	1.46e + 00 mg/mL; 3.18e-03 mol/L	3.15e + 02 mg/mL; 5.15e-01 mol/L	1.36e-01 mg/mL; 4.49e-04 mol/L	3.69e + 00 mg/mL; 8.22e-03 mol/L	1.7e + 00 mg/mL; 5.7e-03 mol/L
Solubility class (SILICOS-IT)	Soluble	Soluble	Soluble	Soluble	Soluble	Soluble	Soluble	Soluble
PHARMACOKINETICS								
GI absorption	High	High	Low	Low	Low	High	Low	High
BBB permeant	No	No	No	No	No	No	No	No
P-gp substrate	No	Yes	No	No	Yes	No	No	No
CYP1A2 inhibitor	No	No	No	No	No	Yes	No	Yes
CYP2C19 inhibitor	No	No	No	No	No	No	No	No
CYP2C9 inhibitor	No	No	No	No	No	No	No	No
CYP2D6 inhibitor	No	No	No	No	No	No	No	Yes
CYP3A4 inhibitor	Yes	No	No	No	No	No	No	Yes
Log Kp (skin permeation)	-6.84 cm/s	-7.82 cm/s	-8.76 cm/s	-8.27 cm/s	-10.26 cm/s	-7.36 cm/s	-8.42 cm/s	-7.36 cm/s
DRUGLIKENESS								
Lipinski	Yes; 0 violation	Yes; 0 violation	Yes; 1 violation: NHorOH > 5	No; 2 violations: NorO > 10, NHorOH > 5	No; 3 violations: MW > 500, NorO > 10, NHorOH > 5	Yes; 0 violation	No; 2 violations: NorO > 10, NHorOH > 5	Yes; 1 violation: NorO > 10
Ghose	No; 2 violations: MR < 40, #atoms < 20	Yes	No; 1 violation: WLOGP < -0.4	Yes	No; 4 violations: MW > 480, WLOGP < -0.4, MR > 130, #atoms > 70	Yes	Yes	Yes
Veber	Yes	Yes	No; 1 violation: TPSA > 140	No; 1 violation: TPSA > 140	No; 1 violation: TPSA > 140	No; 1 violation: TPSA > 140	No; 1 violation: TPSA > 140	Yes
Egan	Yes	Yes	No; 1 violation: TPSA > 131.6	No; 1 violation: TPSA > 131.6	No; 1 violation: TPSA > 131.6	No; 1 violation: TPSA > 131.6	No; 1 violation: TPSA > 131.6	Yes
Muegge	No; 1 violation: MW < 200	Yes	No; 2 violations: TPSA > 150, H-don > 5	No; 3 violations: TPSA > 150, H-acc > 10, H-don > 5	No; 4 violations: MW > 600, TPSA > 150, H-acc > 10, H-don > 5	Yes	No; 3 violations: TPSA > 150, H-acc > 10, H-don > 5	Yes
Bioavailability score	0.56	0.55	0.11	0.17	0.17	0.55	0.17	0.55
MEDICINAL CHEMISTRY								
PAINS	1 alert: catechol_A	1 alert: catechol_A	1 alert: catechol_A	1 alert: catechol_A	1 alert: catechol_A	1 alert: catechol_A	1 alert: catechol_A	1 alert: catechol_A

Property	Molecule 1	Molecule 2	Molecule 3	Molecule 4	Molecule 5	Molecule 6	Molecule 7	Molecule 8
PHYSICOCHEMICAL PROPERTIES								
Brenk	1 alert: catechol	1 alert: catechol	2 alerts: catechol, michael_acceptor_1	1 alert: catechol	1 alert: catechol	3 alerts: catechol, coumarine, polycyclic_aromatic_hydrocarbon_3	1 alert: catechol	1 alert: catechol
Leadlikeness	No; 1 violation: MW < 250	Yes	No; 1 violation: MW > 350	No; 1 violation: MW > 350	No; 1 violation: MW > 350	Yes	No; 1 violation: MW > 350	Yes
Synthetic accessibility	1.22	3.50	4.16	4.20	6.52	3.17	5.28	3.2

All compounds exhibited distinct physicochemical profiles, reflecting differences in molecular size, polarity, hydrogen-bonding capacity, and structural complexity. The molecular weights ranged from 142.11 g/mol for Kojic acid (10) to 610.52 g/mol for Rutin (5). Smaller phenolic compounds, including Gallic acid (1), Catechin (2), Ellagic acid (6), Quercetin (8), Apigenin (9), and Kojic acid (10), generally showed molecular weights within a favorable range for drug-like molecules. In contrast, Chlorogenic acid (3), Caffeine (4), Rutin (5), and Quercitrin (7) displayed higher molecular weights and/or greater polarity. A major physicochemical limitation was associated with the high topological polar surface area of several compounds. Rutin (5) showed the highest TPSA value (269.43 Å²), followed by Caffeine (4), Quercitrin (7), and Chlorogenic acid (3). These compounds also possessed high numbers of hydrogen-bond donors and acceptors, which may restrict passive membrane diffusion. By contrast, Gallic acid (1), Catechin (2), Quercetin (8), Apigenin (9), and Kojic acid (10) had more moderate TPSA values, suggesting more favorable physicochemical properties for absorption.

The predicted lipophilicity values indicated that most compounds were weakly to moderately lipophilic. The consensus Log P values ranged from -1.51 for Rutin (5) to 2.11 for Apigenin (9). None of the compounds showed excessive lipophilicity, suggesting a low risk of poor solubility caused by hydrophobicity. Apigenin (9) showed the highest consensus Log P, indicating the strongest tendency toward membrane partitioning among the tested compounds. Ellagic acid (6) and Quercetin (8) also showed moderate lipophilicity, which may support their predicted gastrointestinal absorption. In contrast, Chlorogenic acid (3) and especially Rutin (5) had negative consensus Log P values, reflecting strong hydrophilic character. This is consistent with their high polarity and extensive hydrogen-bonding capacity, which may limit membrane permeability despite favorable aqueous compatibility.

The predicted water solubility profiles were generally acceptable, although model-dependent differences were observed. Gallic acid (1), Chlorogenic acid (3), and Kojic acid (10) showed particularly favorable solubility profiles. Kojic acid (10) was predicted as very soluble by both ESOL and Ali models, consistent with its low molecular weight and moderate polarity. By contrast, larger polyphenolic compounds such as Rutin (5), Quercitrin (7), Caffeine (4), and Apigenin (9) showed lower solubility in the Ali model, with several classified as moderately soluble. This may reflect the influence of molecular size, aromaticity, and intermolecular interactions. Overall, however, poor aqueous solubility does not appear to be the main limitation for most compounds. For highly polar molecules such as Chlorogenic acid (3), Caffeine (4), Rutin (5), and Quercitrin (7), the more relevant concern is likely limited permeability rather than insufficient dissolution.

The pharmacokinetic predictions showed clear differences in gastrointestinal absorption. Gallic acid (1), Catechin (2), Ellagic acid (6), Quercetin (8), Apigenin (9), and Kojic acid (10) were predicted to have high GI absorption, suggesting more favorable oral absorption potential. In contrast, Chlorogenic acid (3), Caffeine (4), Rutin (5), and Quercitrin (7) showed low GI absorption, which is consistent with their high TPSA values and high hydrogen-bonding capacity. None of the compounds was predicted to be blood-brain barrier permeant, indicating limited central nervous system exposure. This may be advantageous for peripheral or cosmeceutical applications, where CNS penetration is generally unnecessary. Catechin (2) and Rutin (5) were predicted as P-glycoprotein substrates, suggesting that active efflux may reduce their intracellular accumulation or systemic exposure. Regarding CYP inhibition, most compounds showed limited predicted CYP liability. However, Gallic acid (1) was predicted to inhibit CYP3A4, while Ellagic acid (6), Quercetin (8), and Apigenin (9) were predicted to inhibit CYP1A2. In addition, Quercetin (8) and Apigenin (9) were predicted to inhibit CYP2D6 and CYP3A4, indicating a higher theoretical risk of metabolic interaction for these two flavonoids. Predicted skin permeability was low across all compounds. Apigenin (9) showed the least negative Log Kp value, suggesting comparatively better skin permeation potential, whereas Rutin (5) showed the poorest predicted skin permeability. This trend is consistent with their contrasting lipophilicity and polarity profiles.

For druglikeness, this evaluation further separated smaller phenolic compounds from larger and highly polar structures. Gallic acid (1), Catechin (2), Ellagic acid (6), Quercetin (8), Apigenin (9), and Kojic acid (10) complied with Lipinski's rule without violations, supporting their general drug-like characteristics. Chlorogenic acid (3) showed one Lipinski violation due to excessive hydrogen-bond donors, while Caffeine (4), Rutin (5), and Quercitrin (7) failed Lipinski criteria mainly because of excessive oxygen atoms and/or hydrogen-bond donors. Veber and Egan filters were more restrictive for compounds with high TPSA. Chlorogenic acid (3), Caffeine (4), Rutin (5), Ellagic acid (6), and Quercitrin (7) violated at least one permeability-related rule, mainly due to TPSA values above the recommended thresholds. Conversely, Catechin (2), Quercetin (8), Apigenin (9), and Kojic acid (10) satisfied Veber and Egan criteria, indicating more favorable predicted permeability. The bioavailability scores were also consistent with these trends. Gallic acid (1), Catechin (2), Ellagic acid (6), Quercetin (8), Apigenin (9), and Kojic acid (10) showed relatively favorable scores of approximately 0.55–0.56, whereas Chlorogenic acid (3), Caffeine (4), Rutin (5), and Quercitrin (7) showed lower scores, reflecting their higher polarity, larger molecular size, and reduced predicted gastrointestinal absorption.

Medicinal chemistry alerts were mainly associated with catechol-containing structures. Gallic acid (1), Catechin (2), Chlorogenic acid (3), Caffeine (4), Rutin (5), Ellagic acid (6), Quercitrin (7), and Quercetin (8) showed PAINS alerts, mostly related to catechol_A. In contrast, Apigenin (9) and Kojic acid (10) showed no PAINS alerts, indicating a cleaner medicinal chemistry profile in this respect. Brenk alerts followed a similar pattern. Catechol-related alerts were observed for several phenolic compounds, while Ellagic acid (6) showed additional alerts related to coumarin and polycyclic aromatic hydrocarbon motifs. These alerts

do not exclude biological relevance, but they indicate that some activities may require careful experimental validation to rule out assay interference or nonspecific reactivity. Leadlikeness was favorable for Catechin (2), Ellagic acid (6), Quercetin (8), and Apigenin (9). Gallic acid (1) and Kojic acid (10) failed leadlikeness mainly because of their low molecular weights, whereas Chlorogenic acid (3), Caffeine (4), Rutin (5), and Quercitrin (7) failed primarily due to excessive molecular weight and/or polarity. Synthetic accessibility scores indicated that Gallic acid (1) and Kojic acid (10) were the simplest structures, while Rutin (5) had the highest synthetic complexity.

Overall, Quercetin (8) and Apigenin (9) displayed the most balanced ADME-related profiles, combining acceptable physicochemical properties, high predicted GI absorption, favorable druglikeness, and reasonable synthetic accessibility. Catechin (2) and Ellagic acid (6) also showed generally favorable profiles, although medicinal chemistry alerts should be considered. In contrast, Chlorogenic acid (3), Caffeine (4), Rutin (5), and Quercitrin (7) were mainly limited by high polarity, low predicted GI absorption, and reduced druglikeness. Gallic acid (1) and Kojic acid (10) showed favorable solubility and absorption but may be less suitable as lead-like compounds because of their relatively small molecular size.

4. Conclusions

This study demonstrates that *C. lucidissima* is a promising botanical source of multifunctional cosmeceutical ingredients. Among the four solvent extracts, the ethyl acetate fraction exhibited the most favorable bioactivity profile, including the strongest tyrosinase inhibition, α -amylase inhibition, antioxidant activity, and antibacterial effects against both *S. aureus* and *E. coli*. The ethanol extract showed the highest α -glucosidase inhibitory activity. Phytochemical screening and UHPLC analysis revealed a clear solvent-dependent distribution of bioactive constituents. The ethyl acetate and ethanol extracts were particularly enriched in phenolic and flavonoid compounds. PCA and Pearson correlation analyses further supported the association between phenolic/flavonoid enrichment and enhanced antioxidant, enzyme inhibitory, and antibacterial activities, especially in the ethyl acetate extract. Molecular docking and frontier molecular orbital analysis indicated that rutin, caffeine, quercitrin, and chlorogenic acid may contribute to the observed anti-tyrosinase activity, with rutin showing the strongest predicted affinity and favorable electronic responsiveness. In parallel, ADMET prediction highlighted quercetin and apigenin as the most balanced compounds in terms of drug-likeness and permeability-related properties, whereas highly polar compounds such as rutin, quercitrin, and chlorogenic acid were mainly limited by reduced passive absorption. Overall, this work provides the first integrated evidence linking the phytochemical profile of *C. lucidissima* with cosmeceutical-related bioactivities, molecular interactions, electronic features, and ADMET properties. These findings support further bioassay-guided fractionation, cellular validation, formulation development, and safety assessment to advance *C. lucidissima*-derived extracts or compounds as functional skin-protective ingredients.

Declarations

Ethical approval:

Not applicable.

Conflicts of Interest:

The authors declare no conflict of interest.

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Author Contribution

Conceptualization, Van Bon Nguyen (V.B.N.), Thi Thu Le Vu (T.T.L.V.); San-Lang Wang (S.-L.W.), methodology, V.B.N. and T.T.L.V.; software and validation, Tu Quy Phan (T.Q.P.), and Manh Dung Doan (MDD); formal analysis, Thanh Hue Pham (T.H.P.), Dao Viet Hung (D.V.H.), Van Quynh Giang (V.Q.G.), Thi Kim An Nguyen (T.K.A.N.), Minh Quy Bui (M.Q.B.); writing-original draft preparation, V.B.N.; writing-review and editing, V.B.N., T.T.L.V. and S.-L.W.; supervision, V.B.N. and S.-L.W., visualization and project administration, T.T.L.V.. All authors have read and agreed to the published version of the manuscript.

Availability of data and materials:

All relevant data are within the manuscript and available from the corresponding author upon request

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Figures

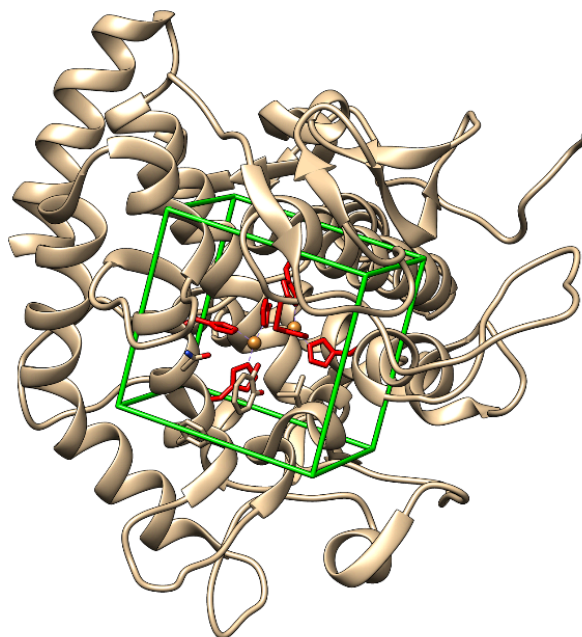


Figure 1

The 3D structure of protein 2Y9X and its docking grid box

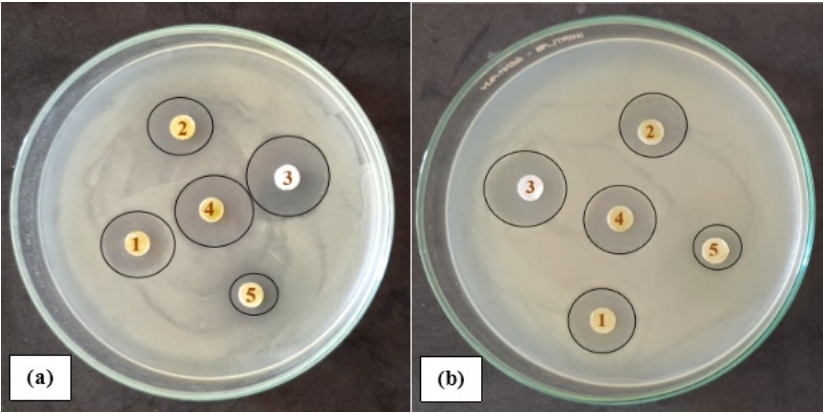


Figure 2
Antibacterial activity of *C. lucidissima* extracts at 30 mg/mL against *S. aureus* (a) and *E. coli* (b) of ethanol (1), aqueous (2), antibiotic control (3), ethyl acetate (4), and n-hexane (5) extracts

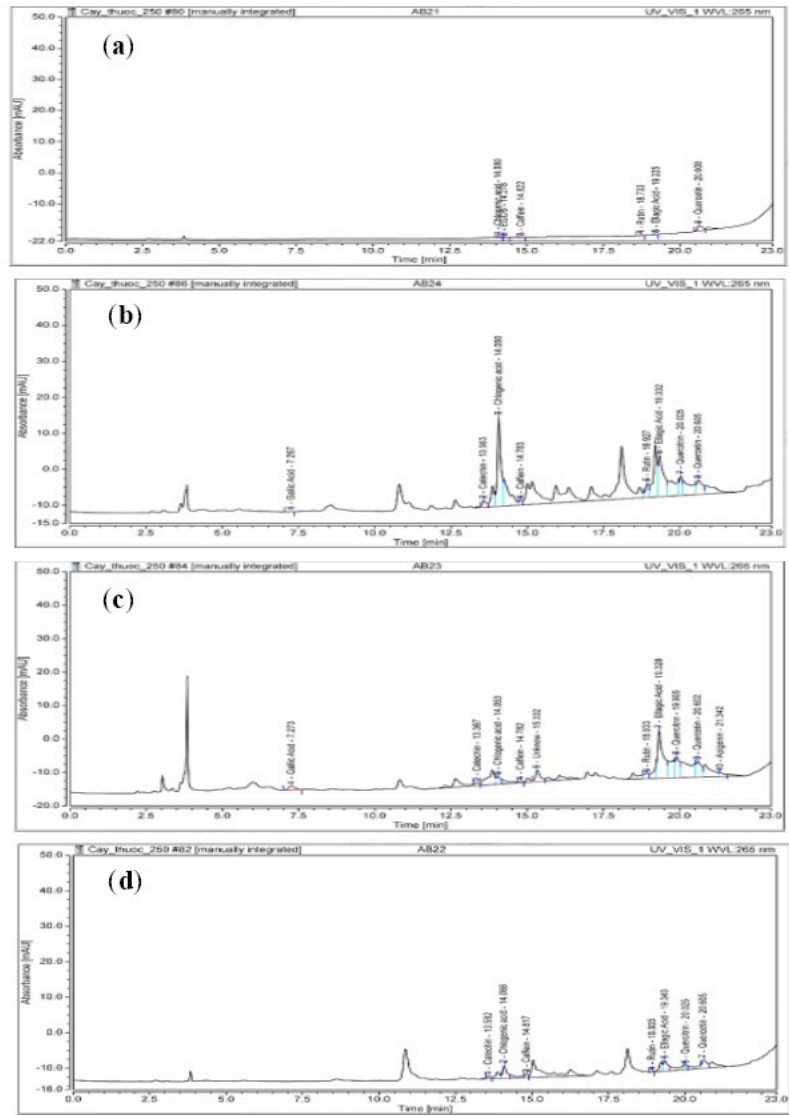


Figure 3
Representative HPLC-UV chromatogram of (a) n-hexane, (b) ethyl acetate, (c) ethanol, and (d) aqueous extracts of *Canscora lucidissima*

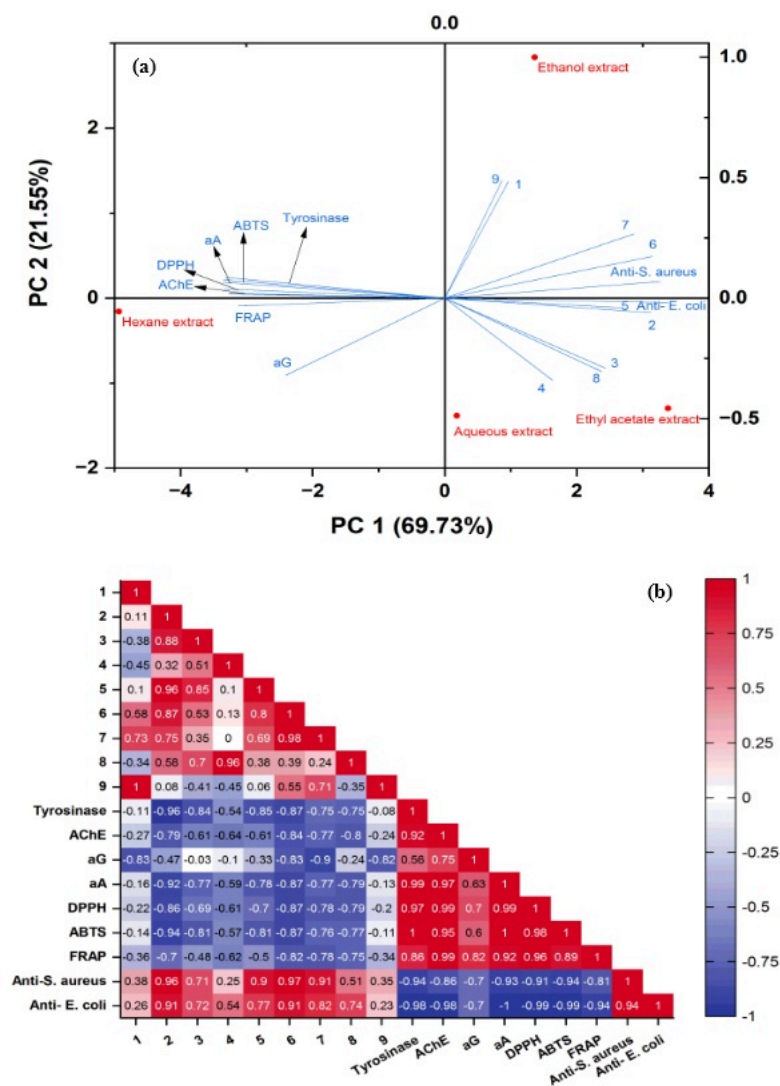


Figure 4

PCA biplot (a) and Pearson correlation heatmap (b) illustrating the phytochemicals-bioactivities relationship and discrimination of solvent extracts from *C. lucidissima*

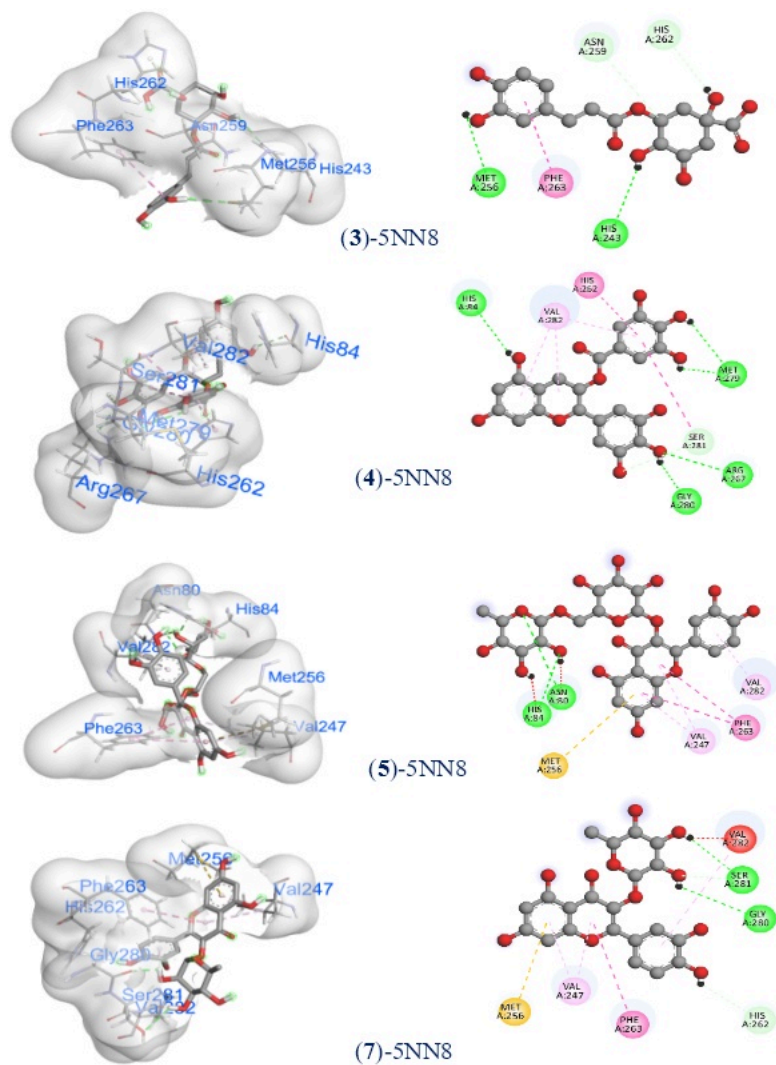


Figure 5

The 3D and 2D interaction diagrams of potential phytochemicals from *C. lucidissima* extracts with tyrosinase (5NN8)

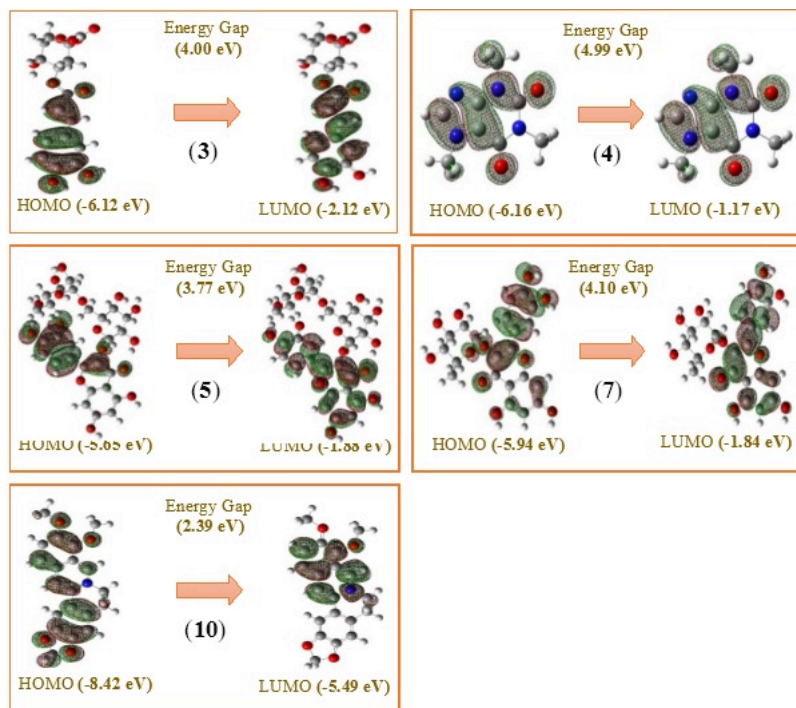


Figure 6

HOMO-LUMO energy gaps of the most active ligands (3, 4, 5, 7) and Kojic acid (10) analyzed by DFT at theory level of B3LYP/6-31G

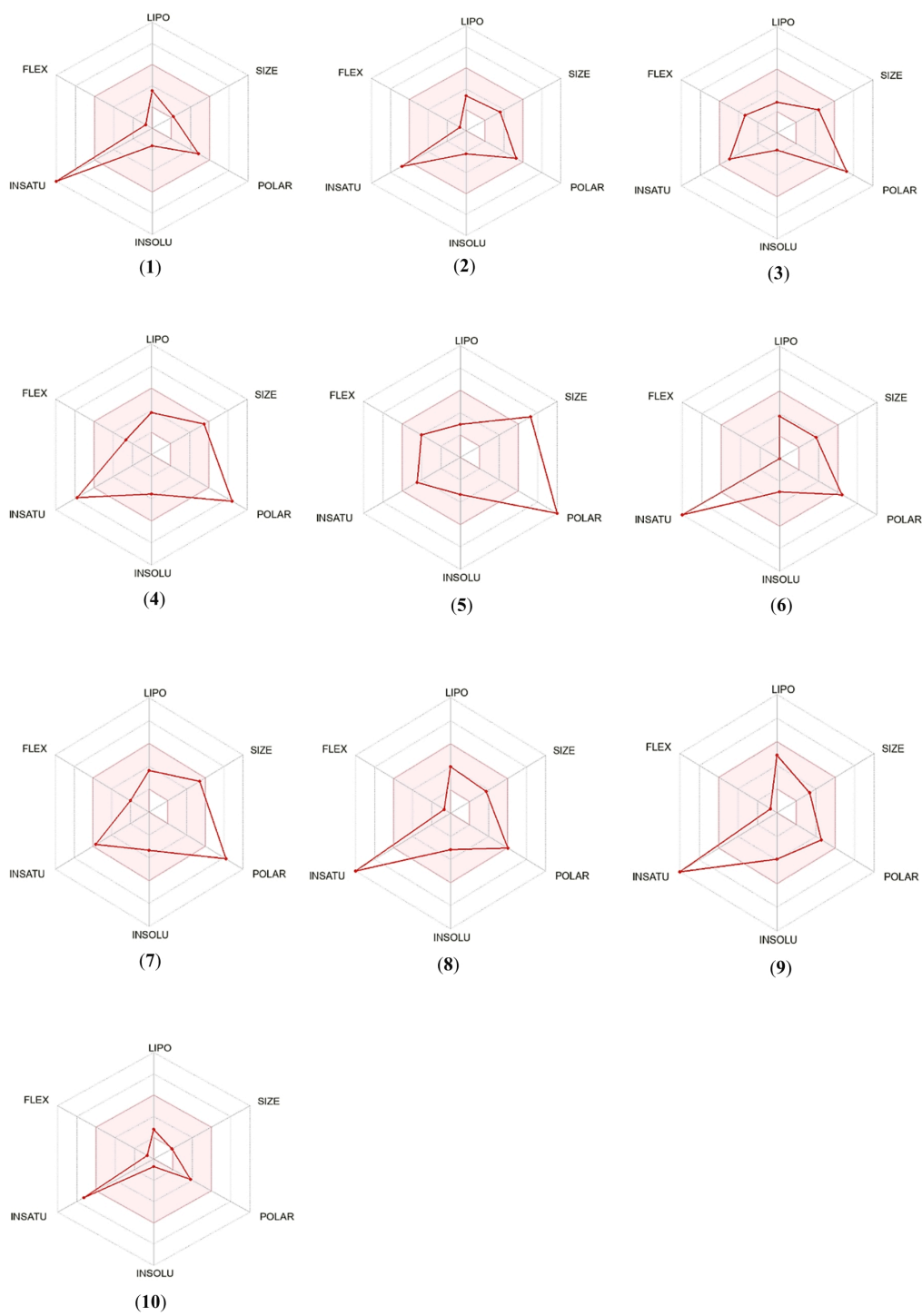


Figure 7

The bioavailability radar plots of phytochemicals(1-9) from *C. lucidissima* extracts and Kojicacid (10)

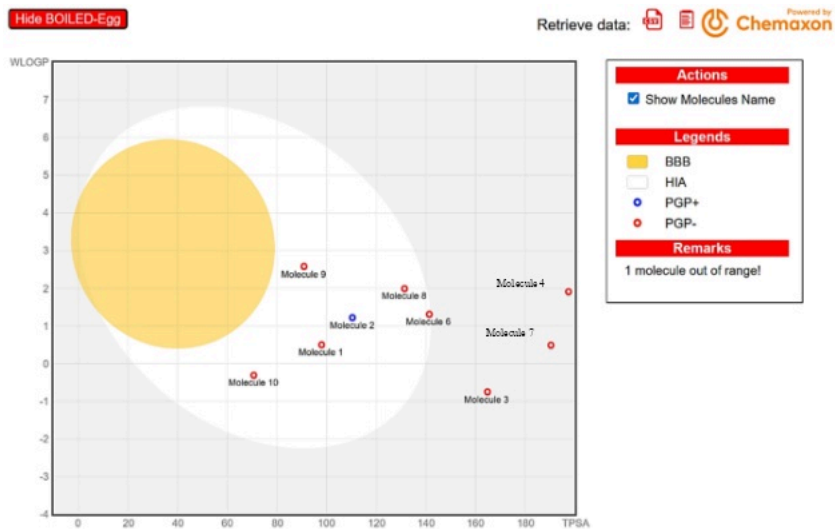


Figure 8

BOILED-Egg plot of gastrointestinal absorption and blood-brain barrier permeation of phytochemicals(1-9) from *C. lucidissima* extracts and Kojicacid (10)