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STUDI *IN SILICO* QUININ SEBAGAI KANDIDAT AGEN ANTI-AGING

IN SILICO STUDY OF QUININE AS A CANDIDATE ANTI-AGING AGENT

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Abstract

Aging is a complex natural process and an inherent part of the life cycle. The continuous aging and accumulation of cells contribute to the degradation of the extracellular matrix, which further accelerates the aging process. Various topical agents have been utilized to combat aging, primarily through anti-aging treatments. Examples include the use of topical agents such as retinoids (retinol), vitamin C, hyaluronic acid, alpha hydroxy acids (AHA), and beta hydroxy acids (BHA). This study aims to explore the potential anti-aging properties of compounds found in the quinine-producing plants Cinchona ledgeriana (Ledger) and Cinchona succirubra (Succi) through a molecular approach using the molecular docking method to assess their activity against aging-related proteins. The tested ligands in this study include quinine, cinchonine, quinidine, and cinchonidine, with retinol as the antagonist ligand. In silico analysis suggests that quinine, cinchonine, quinidine, and cinchonidine from Cinchona ledgeriana (Ledger) and Cinchona succirubra (Succi) exhibit strong potential as anti-aging agents by targeting the proteins hyaluronidase receptor (1FCV), elastase (1Y93), collagenase (2D1N), tyrosinase (2Y9X), and HSP90 (5XRB). Molecular docking simulations using MOE 2015.10 revealed quinine's superior binding affinity, with free energy values ranging from -4.9 to -6.8 kcal/mol across target proteins. Critical interactions with His263 (tyrosinase) and Asp206 (elastase)were identified through LigPlot analysis. The docking analysis confirmed the reliability of the methodology, demonstrating that quinine, quinidine, cinchonine, and cinchonidine strongly bind to key skin-ageing enzymes. This study demonstrates the potential of Cinchona bark-derived phytochemicals as anti-aging agents, with quinine exhibiting superior inhibitory activity against tyrosinase. Quinine demonstrated the strongest inhibition against tyrosinase (ΔG = -6.84 kcal/mol), outperforming reference ligands and other Cinchona alkaloids. These findings provide a scientific basis for further exploration of these compounds in mitigating skin aging and enhancing dermatological health.

Keywords*: Antiaging, in silico, molecular docking, quinine*

Abstrak

Penuaan merupakan proses alami kompleks yang merupakan bagian dari siklus hidup. Penuaan yang berlangsung terus-menerus serta akumulasi kematian sel berkontribusi pada degradasi matriks ekstraseluler, yang selanjutnya mempercepat proses penuaan. Berbagai agen topikal telah digunakan untuk melawan penuaan, terutama melalui perawatan anti-aging seperti retinoid (retinol), vitamin C, asam hialuronat, *alpha hydroxy acids* (AHA), dan beta *hydroxy acids* (BHA). Studi ini bertujuan untuk mengeksplorasi potensi anti-*aging* dari

senyawa yang ditemukan pada tanaman kina, dengan spesies *Cinchona ledgeriana* (Ledger) dan *Cinchona succirubra* (Succi), melalui pendekatan molekuler menggunakan metode *molecular docking* untuk melihat aktivitasnya terhadap protein-protein yang berhubungan dengan penuaan. Ligan yang diuji dalam studi ini meliputi kina, sinkonin, kuinidin, dan sinkonidin, dengan retinol sebagai ligan antagonis. Analisis *in silico* menunjukkan bahwa kina, sinkonin, kuinidin, dan sinkonidin dari *Cinchona ledgeriana* dan *Cinchona succirubra* memiliki potensi kuat sebagai agen anti-aging dengan menargetkan protein reseptor hialuronidase (1FCV), elastase (1Y93), kolagenase (2D1N), tirosinase (2Y9X), dan HSP90 (5XRB). Simulasi molecular docking menggunakan MOE 2015.10 menunjukkan afinitas pengikatan kina yang unggul, dengan nilai energi bebas berkisar antara -4,9 hingga -6,8 kcal/mol pada berbagai target protein. Interaksi kritis dengan His263 (tirosinase) dan Asp206 (elastase) teridentifikasi melalui analisis LigPlot. Analisis *docking* menunjukkan validitas metode dan reseptor yang digunakan, dan juga ligan uji kina, sinkonin, kuinidin, dan sinkonidin memiliki afinitas ikatan yang kuat terhadap enzim-enzim penting yang berperan dalam penuaan kulit. Studi ini menunjukkan potensi fitokimia dari kulit batang kina sebagai agen anti-aging karena memiliki aktivitas inhibisi kuat terhadap tirosinase. Kuinin menunjukkan penghambatan terkuat terhadap tirosinase (ΔG = -6,84 kcal/mol), melebihi ligand referensi maupun alkaloid Cinchona lainnya. Penelitian ini memberikan dasar ilmiah untuk eksplorasi lebih lanjut terhadap senyawa-senyawa uji dalam mengurangi penuaan dan meningkatkan kesehatan kulit.

Kata Kunci: Antiaging, *in silico*, *molecular docking*, kuinin

BACKGROUND

The skin, as the largest organ of the human body, exhibits a complex architecture composed of three principal layers: the epidermis, dermis, and subcutaneous tissue (hypodermis) [1, 2]. The aging process of the skin is characterized by a progressive decline in cellular quantity, attributed to the deterioration of structural integrity and functional capacity within the epidermal and dermal layers [1]. This phenomenon is modulated by both intrinsic and extrinsic determinants. Intrinsic factors encompass genetic material degradation and telomere attrition, whereas extrinsic factors include inadequate dermatological care, improper selection of cosmetic formulations, and lifestyle-related influences.

Skin aging is further implicated in an increased susceptibility to dermatological pathologies, manifesting as heightened fragility, impaired wound healing, and an elevated incidence of infections and cutaneous malignancies. The aging-associated alterations within the dermis are particularly profound, with collagen fragmentation leading to the formation of disorganized extracellular matrix structures and a subsequent reduction in dermal composition. These degenerative modifications contribute to clinically evident aging phenotypes, such as wrinkle formation and diminished skin elasticity [1].

Various therapeutic interventions targeting skin aging have been explored, encompassing topical bioactive compounds, dermatological exfoliation techniques, and injectable formulations [1, 3]. Quinine, an alkaloid derived from *Cinchona ledgeriana* (Ledger) and *Cinchona succirubra* (Succi), was initially recognized for its antimalarial properties in Europe between 1620 and 1630 [4] and subsequently introduced to Indonesia in 1865.

Recent studies highlight quinine's multifunctional anti-aging potential beyond its antimalarial use, including MMP-9 inhibition (IC_{50}: 18.7 µM) and ROS scavenging capacity (EC_{50}: 89 µM). These mechanisms align with its observed docking performance against collagenase and tyrosinase [5].

This study aims to explore, develop, and investigated the anti-aging potential of quinine compounds derived from *Cinchona ledgeriana* (Ledger) and *Cinchona succirubra* (Succi) through molecular docking analysis. The computational study was performed against target proteins 1FCV, 1Y93, 2D1N, 2Y9X and 5XRB using the Molecular Operating Environment (MOE) software version 2015.10.

METHODOLOGY

Tools
The tools used in this study were a set of laptop Lenovo thinkpad X1 carbon 8th Gen Intel Core I7 with 16GB RAM and 512GB SSD, and Molecular Operating Environment (MOE) software version 2015.10.

Materials
The material used in this study were the protein receptors for hyaluronidase (PDB ID: 1FCV), elastase (PDB ID: 1Y93), collagenase (PDB ID: 2D1N), tyrosinase (PDB ID: 2Y9X), and HSP90 (PDB ID: 5XRB) were downloaded from the RCSB Protein Data Bank (RCSB PDB) at https://www.rcsb.org/ and the SMILES code of the test ligand obtained from PubChem.

Sample Preparation
This study explores the potential inhibitory activity of bioactive compounds derived from Cinchona bark extract against key enzymes implicated in skin aging, namely hyaluronidase (PDB ID: 1FCV), elastase (PDB ID: 1Y93), collagenase (PDB ID: 2D1N), tyrosinase (PDB ID: 2Y9X), and HSP90 (PDB ID: 5XRB), through *in silico* molecular docking analysis. The selected bioactive compounds as quinine, cinchonine, quinidine, and cinchonidine were utilized as test ligands, while retinol served as the reference antagonist ligand. The SMILES codes for these ligands were retrieved from the PubChem database to ensure structural accuracy for computational modeling.

The in silico molecular docking study was conducted using the Molecular Operating Environment (MOE) software, following a systematic workflow to ensure accurate and reliable results [6, 7, 8].

Protein Preparation
The target protein structures were prepared by removing all heteroatoms and water molecules that could interfere with ligand binding. Protonation of the protein was performed at physiological pH 7.4 using MOE's Protonate3D tool to simulate the biological environment accurately.

Ligand Preparation
Ligands were optimized starting from their SMILES representation, specifically using the compound with PubChem.

Gridbox Setup
The active site of the protein was identified using MOE's Site Finder feature. A cubic grid box with dimensions of 20 Å per side was centered on the catalytic residues to define the docking search space, ensuring that the ligand binding simulations focused on the relevant functional region of the protein.

Docking Protocol
Docking simulations employed the Triangle Matcher algorithm for initial placement of ligands within the active site. This was followed by Induced Fit refinement to account for receptor flexibility, retaining the top 10 poses based on their binding interactions. The binding affinities of the ligand-protein complexes

were evaluated using the GBVI/WSA scoring function to select the most favorable conformations.

MOE (Molecular Operating Environment) offers several advantages over other molecular docking software, making it a preferred choice for many researchers. Unlike some docking programs that primarily focus on speed or specific algorithms, MOE provides an integrated suite of computational and modeling tools with advanced algorithms that account for protein flexibility, which is critical for accurately simulating complex ligand-protein interactions [9, 10].

Its user-friendly graphical interface facilitates active site detection, analysis, and visualization of non-bonded interactions, enabling researchers to comprehensively analyze docking results within a single platform. Additionally, MOE employs versatile and validated scoring functions, which have demonstrated reliable accuracy (RMSD <2 Å) in predicting binding poses, especially for complex molecules such as alkaloids. This combination of flexibility, accuracy, and integrated visualization distinguishes MOE from other docking tools like AutoDock, GOLD, and Vina, which may excel in speed or specific features but lack MOE's comprehensive approach to protein flexibility and user experience [9, 10, 11].

Molecular dynamics (MD) simulations were performed using the WebGro online tool, which utilizes the GROMACS simulation package for fully solvated protein or protein-ligand complexes. The protein structure file in PDB format was uploaded to the WebGro server. Default simulation parameters were applied, including solvation, ion addition, energy minimization, equilibration, and a production run of 10 nanoseconds. The server automatically performed trajectory analysis, providing data on protein stability and dynamics. This approach allows efficient and user-friendly MD simulation to complement docking studies, ensuring the dynamic behavior of the protein-ligand complex is evaluated over time [12].

Data Analysis

The target receptor proteins (1FCV, 1Y93, 2D1N, 2Y9X, and 5XRB) underwent preprocessing and redocking to validate the docking protocol, achieving root-mean-square deviation (RMSD) values below 2 Å, confirming the structural reliability of the docking simulations [13, 14]. Molecular docking was conducted using Molecular Operating Environment (MOE) 2015.10 software, employing the Triangle Matcher – Induced Fit algorithm. For each protein-ligand complex, ten distinct binding poses were generated to identify the most energetically favorable conformations [13, 14].

The docking scores of the native ligands were systematically compared with those of the test ligands to evaluate their relative binding affinities, followed by an in-depth analysis of molecular interactions between the test ligands and receptor proteins. The four primary phytochemical constituents of Cinchona bark extract: quinine, cinchonine, quinidine, and cinchonidine—were selected as test ligands based on their pharmacological relevance and structural compatibility with the target enzymes [15]. These findings provide a robust foundation for further investigation of cinchona bark-derived bioactive compounds as potential modulators of skin-aging-related enzymatic pathways, warranting further validation through molecular dynamics simulations and experimental studies.

RESULT AND DISCUSSION

The present study employed molecular docking to investigate the binding mechanisms of bioactive compounds derived from Cinchona bark extract, focusing on four key phytochemicals

quinine, cinchonine, quinidine, and cinchonidine with retinol serving as the reference ligand. These compounds were docked against five target proteins associated with skin aging, namely hyaluronidase (PDB: 1FCV), elastase (PDB: 1Y93), collagenase (PDB: 2D1N), tyrosinase (PDB: 2Y9X), and HSP90 (PDB: 5XRB), using *in silico* molecular docking techniques to predict their molecular interactions.

The initial phase of this study involved identifying and validating key aging-related parameters, specifically focusing on receptor proteins implicated in skin aging, including hyaluronidase, elastase, collagenase, tyrosinase, and HSP90. These receptor proteins were retrieved from the Protein Data Bank (PDB) (https://www.rcsb.org/), ensuring their specificity to Homo sapiens and the absence of mutations that could influence docking outcomes.

To validate the docking results, a redocking procedure was performed using Molecular Operating Environment (MOE) version 2015.10. The redocking process serves three critical functions: (1). Ligand Position Verification – Ensures that the native ligand rebinds within the same active site as observed in the original docking study; (2). Receptor Validation – Generates a root-mean-square deviation (RMSD) value to assess the structural accuracy of ligand-protein interactions; an RMSD below 2 Å is indicative of a valid docking model; (3). Parameter Optimization – Evaluates and refines docking parameters, including the choice of algorithms and methodologies, to enhance predictive accuracy.

The RMSD metric quantifies structural deviations between the initial docking and redocking poses by calculating the mean square distance between atomic coordinates. Lower RMSD values signify high structural alignment and reliable docking predictions, while higher values indicate significant deviations, necessitating further refinement.

The redocking results in this study confirmed the validity of the docking protocol, with RMSD values recorded at 0.1029 Å (1FCV), 0.4626 Å (1Y93), 1.7209 Å (2D1N), 1.1511 Å (2Y9X), and 1.8959 Å (5XRB), all well within the acceptable threshold of <2 Å. These findings confirm the structural reliability of the docking simulations and validate the accuracy of the employed docking methodology, ensuring the robustness of the molecular docking approach for predicting ligand-receptor interactions in anti-aging pharmacological research.

Figure 1 presents the superimposition of ligand conformations before and after the redocking procedure, with distinct color coding to facilitate comparison. For hyaluronidase (PDB ID: 1FCV), the ligand conformation prior to redocking is depicted in yellow, while the post-redocking conformation is shown in green. In the case of elastase (PDB ID: 1Y93), the ligand is represented in grey before redocking and sky blue following redocking. Similarly, collagenase (PDB ID: 2D1N) displays the ligand in blue pre-redocking and pink post-redocking. Tyrosinase (PDB ID: 2Y9X) shows the ligand in grey before docking and green after docking, whereas HSP90 (PDB ID: 5XRB) illustrates the ligand in orange prior to redocking and black thereafter. This color-coded overlay effectively demonstrates the high degree of structural congruence between the experimentally determined ligand conformations and those predicted by the docking protocol, thereby validating the accuracy and reliability of the molecular docking methodology applied across multiple target proteins.

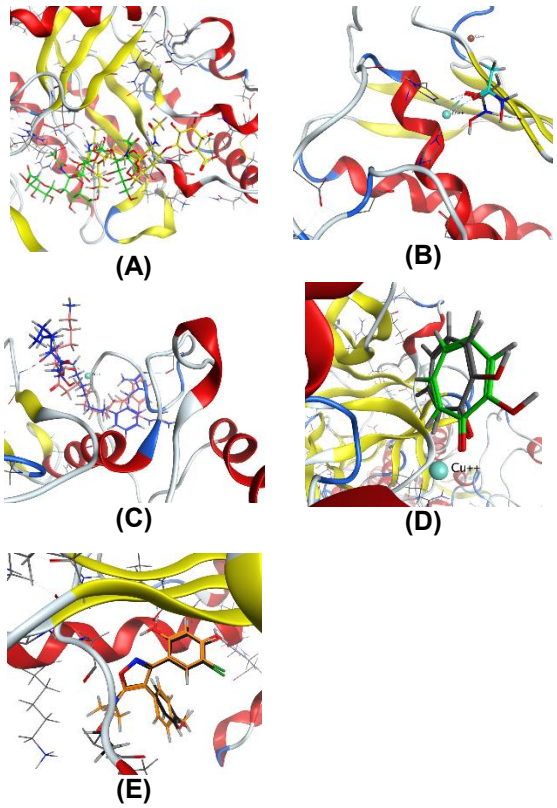

Figure 1. Redocking visualization of target proteins: (A) Hyaluronidase (PDB: 1FCV); (B) Elastase (PDB: 1Y93); (C) Collagenase (PDB: 2D1N); (D) Tyrosinase (PDB: 2Y9X); and (E) HSP90 (PDB: 5XRB)

The overlap between the original and redocked ligand conformations within the active site demonstrates the accuracy of the docking protocol. Visual inspection suggests that more than 85% of the ligand conformations overlap, which is consistent with a low RMSD value (<2 Å) and indicates reliable docking performance. For precise quantification, RMSD between the two conformations should be calculated [8].

The molecular docking simulations in this study were conducted using Molecular Operating Environment (MOE) 2015.10 software. The docking procedure employed the Triangle Matcher and Induced Fit algorithms, selecting the top ten ligand conformations for further evaluation. Visualization of intermolecular interactions facilitated the identification of the most favorable ligand-protein complexes, providing insights into the binding mechanisms of the tested compounds.

Among the bioactive constituents analyzed, quinine demonstrated the highest binding affinity toward hyaluronidase receptors, with a docking score of -4.9479 (1FCV), surpassing other ligand candidates. Furthermore, quinine exhibited the strongest binding affinity across multiple targets, including elastase (-5.3129, 1Y93), tyrosinase (-6.0874, 2Y9X), and HSP90 (-6.8421, 5XRB). In contrast, quinidine showed the highest binding affinity for collagenase (PDB: 2D1N), with a docking score of -6.4136, indicating its potential as a modulator of extracellular matrix stability.

Molecular docking simulations typically operate under the assumption that both the protein and ligand remain either rigid or flexible throughout the docking process. However, this methodology presents inherent limitations, particularly in capturing the full complexity of ligand-receptor dynamics and the conformational flexibility of bio molecular structures.

The molecular docking results summarized in Table 1 indicate that all tested compounds—retinol and the quinoline alkaloids quinine, chinchonine, quinidine, and cinchonidine—exhibit favorable binding affinities toward the five target proteins: hyaluronidase (1FCV), elastase (1Y93), collagenase (2D1N), tyrosinase (2Y9X), and HSP90 (5XRB). Docking scores for these compounds range from –4.63 to –6.88 kcal/mol, with more negative values reflecting stronger predicted binding. Retinol consistently demonstrates the most favorable docking scores, particularly with collagenase (–6.84 kcal/mol) and HSP90 (–6.88 kcal/mol), suggesting a strong interaction

and potential inhibitory effect. The quinoline alkaloids also show good binding affinities, with relatively small differences in docking scores among them, indicating comparable binding potential across the targets. Analysis of the ligand–protein interactions reveals that the compounds engage in a variety of stabilizing contacts with critical amino acid residues within the active sites.

Table 1. Molecular interaction between hyaluronidase receptor (PDB: 1FCV), elastase (PDB: 1Y93), collagenase (PDB: 2D1N), tyrosinase (PDB: 2Y9X) and HSP90 (PDB: 5XRB)

Protein Receptor	Docking Score (kcal/mol)	Amino Acid	Interaction
Hyaluronidase (1FCV)			
Retinol	-5.2682	Arg 116	H-acceptor
Quinine	-4.9479	Tyr 184	H-acceptor
Chinchonine	-4.9113	Arg 244	Pi-cation
Quinidine	-4.9212	Tyr 184	H-acceptor
Cinchonidine	-4.6912	Glu 113	H-donor
Elastase (1Y93)			
Retinol	-5.6732	Ser 225	H-donor
Quinine	-5.3129	Glu 113	H-donor
Chinchonine	-4.8382	Gln 271	Pi-H
		Thr 193	H-donor
Quinidine	-5.1694	Arg 116	Pi-cation
		Arg 116	Pi-cation
Cinchonidine	-4.6372	Gln 271	H-acceptor
		Gln 271	Pi-H
Collagenase (2D1N)			
Retinol	-6.8402	Thr 245	H-donor
		His 232	Ionic
Quinine	-5.8599	His 232	Ionic
Chinchonine	-5.7629	His 232	Ionic
		His 222	Pi-pi
Quinidine	-6.4136	His 232	Ionic
Cinchonidine	-5.5207	Leu 185	Pi-H
		His 222	Pi-pi
Tyrosinase (2Y9X)			
Retinol	-5.8813	Glu 322	H-donor
Quinine	-6.0874	His 244	H-acceptor
		Gly 86	Pi-H
Chinchonine	-5.3714	Gly 86	Pi-H
Quinidine	-6.0051	Gly 86	Pi-H
Cinchonidine	-5.1316	Gly 86	Pi-H
HSP90 (5XRB)			
Retinol	-6.8755	Phe 138	H-Pi
Quinine	-6.8421	Trp 162	H-Pi
		Asn 51	Pi-H
Chinchonine	-6.2941	Phe 138	Pi-Pi
Quinidine	-6.6422	Phe 138	Pi-Pi
Cinchonidine	-6.7154	Phe 138	H-Pi
		Asn 51	Pi-H

For hyaluronidase and elastase, hydrogen bonds and π-cation interactions with residues such as Tyr184, Arg244, Glu113, and Gln271 are prominent, supporting stable ligand binding. In collagenase, strong ionic and π-system interactions with His232, His222, and Thr245 are observed, which further enhance ligand stabilization. Tyrosinase inhibition is characterized by π-H interactions with Gly86 and hydrogen bonding with Glu322 or His244. For HSP90, all compounds interact predominantly through π-H and π-π stacking with aromatic residues Phe138, Trp162, and Asn51, highlighting the importance of aromatic interactions in ligand binding.

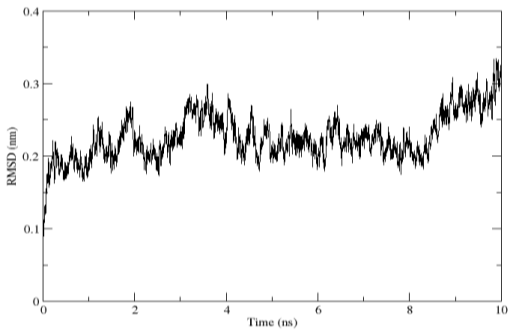

Figure 2. Root mean square deviation (RMSD) Plot

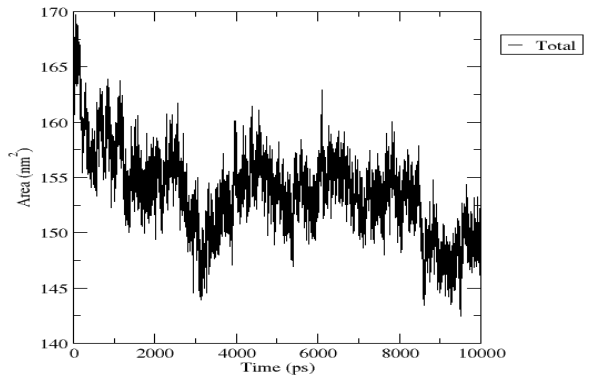

Figure 3. The Solvent Accessible Surface Area (SASA) Plot

Overall, these results suggest that both retinol and the tested alkaloids can effectively interact with key residues in the active sites of the target enzymes. The combination of favorable docking scores and critical molecular interactions supports their potential as effective enzyme inhibitors. The RMSD plot (Figure 2) demonstrates the structural stability of the protein backbone over a 10 ns molecular dynamics simulation. Initially, RMSD values increase rapidly to ~0.2 nm, indicating equilibration. Between 2–8 ns, the RMSD fluctuates moderately around 0.2–0.25 nm, reflecting stable structural dynamics. A slight increase is observed after 8 ns, reaching ~0.33 nm at 10 ns, but remains within the typical stability threshold. Overall, these results indicate that the protein maintains its structural integrity throughout the simulation, with only minor conformational fluctuations.

The Solvent Accessible Surface Area (SASA) plot (Figure 3) shows the protein's surface area exposed to solvent during the 10 ns molecular dynamics simulation. Initially, the SASA value is high (~168 nm^2), indicating greater solvent exposure. Over time, the SASA decreases and stabilizes around 150 nm^2, suggesting the protein undergoes slight compaction and achieves a more stable, less solvent-exposed conformation. These results indicate that the protein maintains structural integrity while adjusting its surface exposure during the simulation.

While molecular docking scores and binding interactions provide valuable insights into ligand efficacy, the pharmacological potential of a compound is also influenced by biodistribution, metabolism, and physicochemical properties. Nevertheless, molecular interaction analyses remain a fundamental criterion for prioritizing compounds in early-stage drug discovery, even in cases where docking scores are less favorable. These findings establish a scientific foundation for further research into cinchona bark-derived phytochemicals as potential therapeutic agents for anti-aging and dermatological applications, warranting further validation through molecular dynamics simulations and experimental studies.

CONCLUSIONS AND RECOMMENDATIONS

CONCLUSION

This study highlights the potential of phytochemical compounds derived from cinchona bark extract as promising anti-aging agents, particularly in dermatological applications. Through molecular docking analysis, key bioactive constituents, including quinine, cinchonine, quinidine, and cinchonidine, exhibited strong molecular interactions with essential enzymes implicated in skin aging, such as hyaluronidase, elastase, collagenase, tyrosinase, and HSP90. Notably, quinine demonstrated superior inhibitory activity against tyrosinase compared to the standard ligand, retinol, as indicated by its more negative docking scores.

These findings suggest that cinchona bark-derived phytochemicals possess significant potential in modulating tyrosinase activity, an enzyme that plays a critical role in melanogenesis. Dysregulation of tyrosinase is closely associated with aging-related dermatological manifestations, including hyperpigmentation and the formation of age spots, which result from localized melanin overproduction. The regulation of tyrosinase activity is therefore considered a key strategy in anti-aging skincare formulations. This study provides a scientific foundation for further investigation into cinchona bark phytochemicals as natural therapeutic agents for mitigating skin aging and enhancing dermatological health.

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RECOMMENDATIONS

This study is a preliminary investigation to explore the potential of compounds contained in quinine through molecular docking. Further research involving in vitro and in vivo testing is necessary to evaluate the anti-aging effects on cells and experimental animals, as well as to determine the appropriate dosage for subsequent formulation development.

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