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Computational Insights into Leucaena leucocephala Extract Shampoo as a Malassezia furfur Anti-Dandruff Agent

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Abstract

Dandruff is a scalp condition characterized by excessive flaking, commonly caused by colonization of the fungus Malassezia furfur. Chemical-based anti-dandruff shampoos often produce undesirable side effects, including irritation, hair discoloration, and resistance, and are further limited by reduced long-term efficacy. To address these limitations, this study investigates the potential of Leucaena leucocephala leaf extract as a natural anti-dandruff agent using an in-silico approach. Molecular modeling and docking assays targeted the 14-alpha lanosterol demethylase enzyme (CYP51), a primary antifungal target in M. furfur. The docking results revealed that squalene and lupeol, two active compounds in L. leucocephala, exhibit competitive binding affinity for CYP51. Squalene demonstrated polar interactions analogous to natural ligands, while lupeol displayed strong hydrophobic interactions, suggesting significant potential as enzyme inhibitors. These findings suggest that squalene and lupeol may serve as effective and safer antifungal agents, offering a promising natural alternative to synthetic treatments with fewer side effects. Further in vivo studies are needed to confirm their efficacy and safety in topical formulations.

Keywords: CYP51, Dandruff, *Leucaena leucocephala*, *Malassezia furfur*, Natural antifungal

Introduction

Dandruff is characterized by an overabundance of white or gray flakes on the scalp resulting from excessive shedding of dead skin cells. Dandruff is a significant issue as it can disrupt aesthetic appeal. Furthermore, if left unaddressed, dandruff may lead to even more serious problems, including hair loss, unpleasant odors, and scalp irritation (Putri et al., 2020). The incidence of individuals afflicted by dandruff is significant, both in Indonesia and globally. Fifty percent of the global population suffers from dandruff. According to the US International Data Base, 2004 Breu Census, Indonesia ranks fourth in the prevalence of dandruff patients. Dandruff is a prevalent issue throughout the population due to Indonesia's tropical climate, which is characterized by elevated humidity levels. (Sriwulan et al., 2023).

The shedding of the stratum corneum, which contributes to dandruff production, is caused by significant fungal colonization of the scalp. Research indicates that the primary cause of dandruff is Malassezia furfur (Rudramurthy et al., 2014). This fungus can infiltrate the pilosebaceous unit, leading to follicular dilatation, which facilitates sebum secretion from the oil glands at the follicle base to the scalp surface. The inflammatory reaction elicited by the colony causes damage to the skin layer (Billamboz & Jawhara, 2023). Presently, a broad array of anti-dandruff shampoos and treatments are available, yet studies indicate that these products exhibit limited efficacy like fungal resistance and induce numerous adverse effects (Leong et al., 2021; Tiwari et al., 2022). The adverse effects of anti-dandruff medications and shampoos result from the combination of chemical active components. The active chemical constituents

are ketoconazole, zinc pyrithione, tar derivatives, glycolic acid, salicylic acid, steroids, and selenium sulfide (Leong et al., 2021). Adverse effects resulting from the application of chemical active ingredients include irritation from zinc pyrithione, hepatitis and resistance from ketoconazole, increased sun sensitivity of the scalp from coal tar, hair discoloration from selenium sulfide, and dry scalp from salicylic acid (Tiwari et al., 2022). Ketoconazole is a commonly utilized active component for the treatment of dandruff issues. Ketoconazole blocks the enzyme 14-alpha lanosterol, an enzyme that forms sterols, which are components of fungal membrane lipids (Leong et al., 2021; Poojary et al., 2024).

In addressing the side effects associated with chemical active ingredients in dandruff treatments, several research studies have been conducted utilizing herbal plants as alternatives to natural active components in anti-dandruff shampoos. The utilization of herbs as active components demonstrates encouraging outcomes in addressing dandruff issues due to their efficacy, skin compatibility (pH of Skin, surface tension, viscosity) cost-effectiveness, and minimal risk of adverse effects (Umar et al., 2021). One of the prospective plants is Leucaena leucocephala, the primary causative agent of dandruff (Rudramurthy et al., 2014).

Leucaena leucocephala is a plant produced abundantly in tropical countries, mainly in the lowlands (CABI Compendium, 2023). Qualitative phytochemical analysis indicates that *Leucaena leucocephala* leaves possess active compounds, including lectins, tannins, saponins, coumarins, flavonoids, glycosides, steroids, phenols, carbohydrates, and amino acids, which may exhibit anti-inflammatory, antioxidant, antibacterial, and antifungal properties (Setiani, 2020). The phytochemical characteristics of *Leucaena leucocephala* have been evaluated in vitro against the fungal species *Candida albicans*. The study demonstrated substantial effects in fungal suppression of *Candida albicans* (Nova, 2020). While its interaction with Malassezia fungus remains unexamined. An in silico study can serve as the first approach to evaluate the interaction between the active constituents of *Leucaena leucocephala* plants and pathogen receptors (enzyme receptor 14-alpha-demethylase (CYP51)). This exploratory study intends to assess the ability of *Leucaena leucocephala* leaves to block the receptors of the *Malassezia furfur* dandruff pathogen in silico.

Method

This research started with a literature review to detect active dddcompounds in the leaves of *Leucaena leucocephala*. Squalene (41.02%), 1,2-benzenedicarboxylic acid mono(2- ethylhexyl) ester (17.7%), betulin (15.7%), lupeol (14.7%), and β-sitosterol (9.1%) were identified as the major component of *Leucaena leucocephala* leaves using gas chromatography-mass spectrometry (GC-MS) analysis in previous research (Zayed *et al*., 2019). The molecule will thereafter undergo phytochemical and binding affinity assessments. Literature reviews were employed to identify the natural receptors and ligands for utilization. This study selected the 14-alpha-demethylase enzyme receptor (CYP51) as it is the target responsible for dandruff (Saptarini *et al*., 2024).

Ligand Preparation

Leaf ligands of *Leucaena leucocephala*, including Squalene (ID: 638072), β-sitosterol (ID: 222284), lupeol (ID: 259846), 1,2-benzenedicarboxylic acid mono(2-ethylhexyl) ester (ID: 20393), and betulin (ID: 72326), were acquired from the PubChem database (https://pubchem.ncbi.nlm.nih.gov/) in *.sdf file format. The chosen ligands were subsequently evaluated according to Lipinski's Rule of 5 (RO5) by utilizing structure drawing on the Chemdraw Ultra platform in a simplified molecular-input line-entry system (SMILES) format. The ligand format was subsequently transferred to the Molecular Operating Environment (MOE) database software 2024.06 to get a 3D structural picture in *mdb format. The SMILES ligands were individually input into SwissADME (http://www.swissadme.ch) to assess the phytochemical properties of the test compounds, including lipophilicity (Log P), water solubility (Log S), topological polar surface area (TPSA), molecular refractivity (MR), molecular weight (MW), skin permeation (Log Kp), and binding affinity.

Protein Preparation

The protein structure of the enzyme 14-alpha-demethylase (CYP51) was obtained from the website (http://www.rcsb.org/) in PDB format, designated by the code 4XLJ. The protein's crystal structure was then constructed utilizing the Discovery Studio Visualizer (DSV) 2020 program and Molecular Operating Environment (MOE) 2024.06. Water molecules and natural ligands were removed from the protein. **Figure 1.** shows the interaction of the receptor and natural ligand before ligand cutting. The protein molecular structure was subsequently built with MOE 2024.06. Energy minimization was done on hydrogen atoms, alpha carbon, and backbone atoms. The constructed structure is then stored in PDB format and utilized as a receptor in the docking procedure.

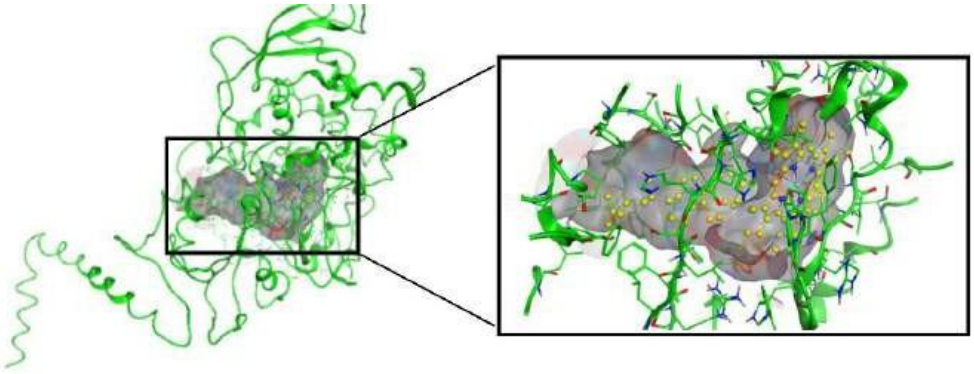

Figure 1. Receptor and natural ligand interactions before cutting

Molecular Docking Process

MOE 2024.06 was employed to examine the interaction. Prior to docking, the protein's active site was identified using the site finder, including many amino acid residues, and thereafter designated as a dummy atom for targeting during the docking procedure. Subsequently, in the dock menu, the site is designated as a dummy atom, and the MDB file with the created ligand structure is chosen as the ligand. During the docking phase, the placement technique employed was Alpha matcher. Scoring was conducted via the London dG technique, and 50 poses were preserved. During the refining phase, the receptor was deemed stiff, employing the GBVI/WSA dG scoring approach, and five poses were preserved.

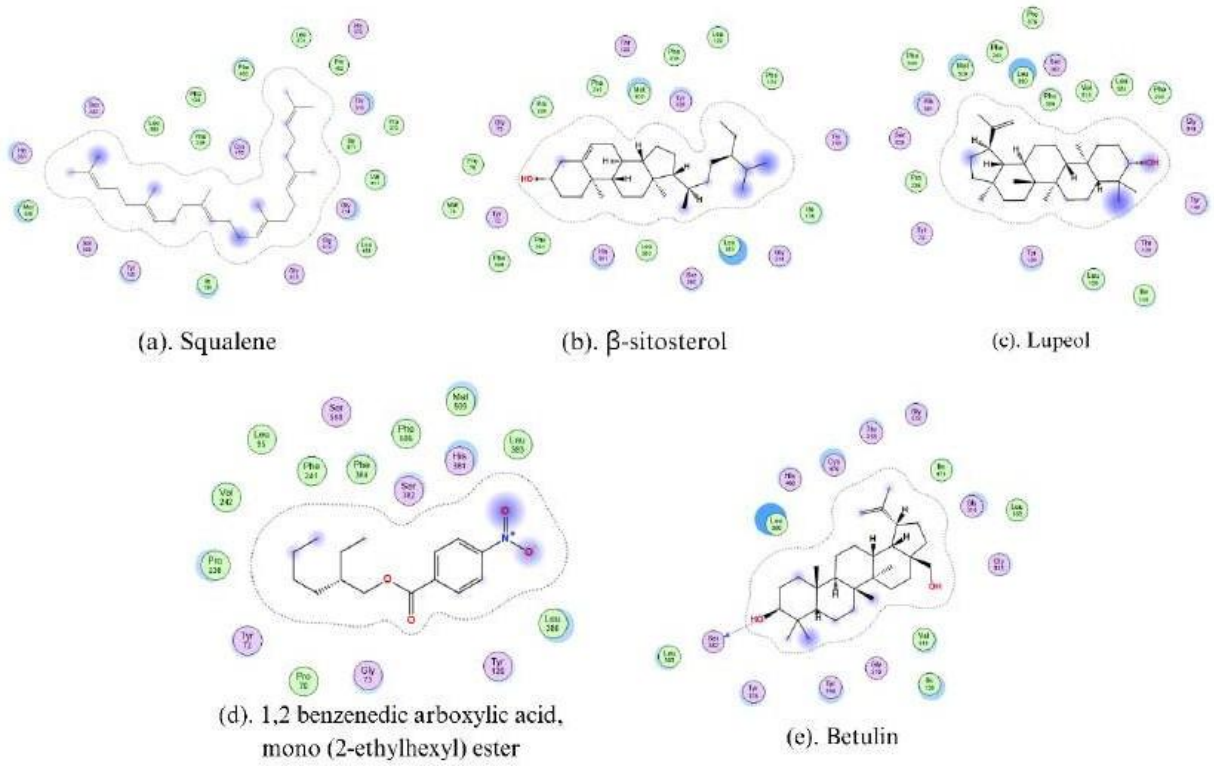

Figure 2. Compounds 2D interaction with 14-alpha lanosterol demethylase

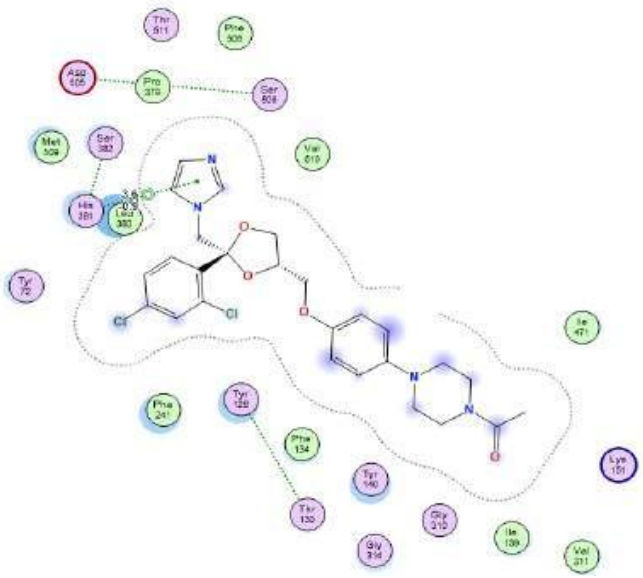

Figure 3. Ketoconazole 2D interaction with 14-alpha lanosterol demethylase

Results and Discussion

A principal mechanism of antifungal therapy, the inhibition of 14-alpha lanosterol demethylase (CYP51) disrupts the ergosterol biosynthesis uppercase pathway of *Malassezia furfur*. This enzyme is responsible for converting lanosterol precursors into ergosterol — a key component of fungal cell membranes that helps the microbes keep their membranes fluid. Inhibition of ergosterol biosynthesis inhibits fungal proliferation, making CYP51 a high-value drug target pursuant to antifungal therapeutics (Lepesheva & Waterman, 2007; Agnello *et al*., 2019). For this purpose, ketoconazole was used as a reference

ligand due to its known antifungal indication and high utilization in commercial anti-dandruff shampoos. However, ketoconazole presents several limitations. From a chemical standpoint, it suffers from poor solubility and limited skin permeability due to its high molecular weight. Clinically, resistance to ketoconazole has been increasingly reported. Furthermore, ketoconazole is associated with side effects such as skin irritation, which restrict its usability in some individuals.

Pharmacokinetics and Permeability Analysis

The successful treatment of skin diseases using topical antifungal formulations highly relies on predicting the permeability of the skin. While passive chemical constituents in anti-dandruff shampoos may be useful, the active compounds must reach the layers of the skin where the concentrations of Malassezia are the highest, which includes the hair follicles and interfollicular epidermis (Sala *et al*., 2018); Mangion *et al*., 2021). The permeability model of Potts (1992) shows that two basic parameters play a central role in skin permeability (Log Kp), namely molecular weight (MW) and lipophilicity.

As shown in **Table 2**, the calculated permeability showed a moderate to high permeability of betulin (-3.12 cm/s), which may facilitate its accumulation at the epidermis. In comparison, lupeol, squalene, and beta-sitosterol exhibit good permeability to penetrate deep while localizing on the scalp surface owing to their relatively larger molecular sizes. Because their lipophilic nature provides skin penetration for enduring antifungal action, betulin, lupeol, squalene, and beta-sitosterol were determined to be appropriate actives for anti-dandruff shampoos. On the other hand, 2-ethylhexyl ester and ketoconazole have low skin permeation, restricting their action on the skin surface. In moderate-molecular size, 2-ethyl hexyl ester has limited penetration in wounded skin. Conversely, due to ketoconazole's large molecular weight and poor permeability, it struggles to diffuse through the skin and solubilize in aqueous solution.

Solubility and Lipophilicity Considerations

Solubility remains a key property in the drug formulation process concerning bioavailability and therapeutic effect. **Table 1** summarizes the solubility and lipophilicity profiles of the compounds tested. With moderate lipophilicity (Log P = 3.57) and TPSA of 69.06 Å², ketoconazole bridges the characteristics of hydrophilic and lipophilic nature during membrane interactions. However, it possesses low aqueous solubility (Log S = −5.69), which complicates achieving suitable therapeutic concentrations (Daina, 2017). Similarly, 2-ethylhexyl ester has moderate lipophilicity and polarity (Log P = 3.42, Log S = -4.41), indicating its potential stability as an ingredient in shampoo products.

On the other hand, betulin, lupeol, squalene, and beta-sitosterol are highly lipophilic and poorly soluble in water, which is a common issue in the case of poorly water-soluble drugs (Xie *et al*., 2024). One of the major challenges in drug delivery is the low aqueous solubility of azole antifungals, which leads to a possible risk of resistance development (Verweij *et al*., 2015). One advantage is that herbal-derived compounds possess a wide range of pharmacological properties to suppress the growth of fungi and obstruct the pathogen potentials, reducing the chances of fungal resistance (Anand *et al*., 2019).

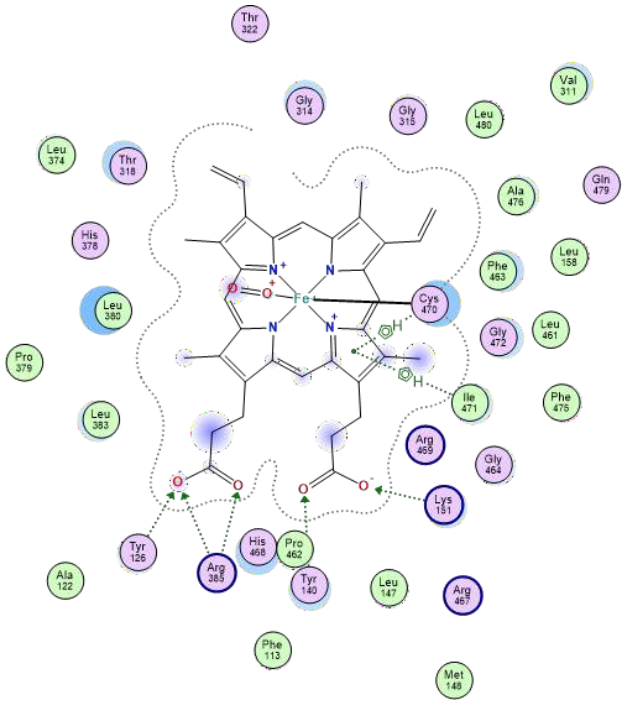

Figure 4. 14-alpha lanosterol demethylase and natural ligand 2D interaction

Molecular docking and binding affinity

The binding affinity data in **Table 2** indicates that ketoconazole (-9.6328) has a pronounced binding affinity to CYP51, in accordance with its significant antifungal activity. CYP51 (−11.4861) has higher receptor binding affinity, thus maintaining its dominance as a natural ligand for 14-alpha lanosterol demethylase. Of the natural compounds evaluated, betulin (-

7.4096), lupeol (-8.8341), and squalene (-9.3428) showed competitive binding. However, squalene demonstrates the least affinity, suggesting lower fungicidal ability than ketoconazole and CYP51.

Molecular refractivity (MR) and permeability (Log Kp) are important pharmacokinetic parameters that can further the distribution after binding affinity. Ketoconazole (MW = 144.44, Log Kp = -6.46) shows good skin permeability when used for local topical administration. Betulin (molecular weight = 136.30), squalene (MW = 143.48), and lupeol (MW = 135.14) have molecular properties that could be suited for enhancement of formulation efficiency.

Molecular docking analysis explains ligand-receptor interaction. Squalene forms an arene-H bond with TyrA126 (**Figure 2a**), which is an analog of the interaction of the natural ligand at Tyr126 (**Figure 4**), suggesting competitive inhibition of the receptor (Guedes *et al*., 2014). Hydrogen bonding is an important interaction that determines binding affinity and specificity. These bonds are stronger than van der Waals interactions. The arene-H acts as a hydrogen bond donor in the interaction between the squalene compounds and receptors. Consequently, hydrogen bonds formed via O-H and N-H donor groups are expected to be weaker than those formed during conventional hydrogen bonds. Arene-H interactions showed medium to large strength hydrogen bonds (Hay & Bryantsev, 2008). Lupeol makes hydrophobic interactions with SerA508 (**Figure 2c**). These interactions are essential as they provide thermodynamic stability by removing water structuring, thus increasing entropy, and strengthening the bond between ligand and receptor (Ferenczy & Kellermayer, 2022). Beta-sitosterol, betulin, and 2-ethylhexyl ester are poorly interacting with the receptors.

The comparative ligand ketoconazole forms arene-H hydrogen bonds with Leu380 and His381 (**Figure 3**), while the natural ligand forms several conventional hydrogen bonds with Tyr126, Arg205, Pro452, and Lys151. Natural ligand also shows cysteine-Fe interactions at Cys470 that are required for lanosterol demethylation (Hargrove *et al*., 2012). Alternatively, a comparison of binding interactions between ketoconazole and the natural ligand revealed that ketoconazole does not fully mimic the binding interactions of the natural ligand, suggesting that squalene has potentially greater receptor inhibition than ketoconazole due to structural similarity to endogenous ligands.

Table 1. Phytochemical analysis

Compounds	Log S (ESOL)	Con. Log P	TPSA (Å²)	MR	Log Kp cm/s
Betulin	-7.67	6.39	40.46	136.30	-3.12
2-ethylhexyl ester	-4.41	3.42	72.12	80.19	-4.39
Lupeol	-8.64	7.27	20.23	135.14	-1.90
Squalene	-8.64	7.27	0.00	143.48	-1.90
Beta-sitosterol	-7.90	7.24	20.23	133.23	-2.20
Ketoconazole	-5.69	3.57	69.06	144.44	-6.46
Cyp51	-4.56	3.48	115.98	160.25	-7.73

Log P, Lipophilicity; Con. Log S, Consensus water solubility; TPSA, topological polar surface area;
MR, Molecular refractivity; MW, Molecular weight; Log Kp, Skin permeation

Table 2. Binding affinity

Compounds	Molecular Formula	MW g/mol	Binding affinity
Betulin	C30H50O2	442.72	-7.4096
2-ethylhexyl ester	C15H21NO4	279.33	-6.9651
Lupeol	C30H50O	426.72	-8.8341
Squalene	C30H50	410.72	-9.3428
Beta-sitosterol	C29H50O	414.71	-8.8022
Ketoconazole	C26H28Cl2N4O4	531.4	-9.6328
Cyp51	C30H40F2N6O4	586.7	-11.4861

Conclusion

This study demonstrates that active compounds in Leucaena leucocephala, particularly squalene and lupeol, have the potential to block the CYP51 receptor of Malassezia furfur, the primary target in dandruff pathogenesis. Squalene interacts with CYP51 through polar binding similar to the natural ligand, while lupeol forms stable hydrophobic interactions, both indicating strong inhibitory potential. These findings suggest that L. leucocephala extract may serve as a natural alternative to

chemical-based antifungals. Further experimental and formulation studies are necessary to validate its safety and efficacy for topical antifungal applications through in vitro, in vivo and clinical trial exploration.

Conflict of Interest

The author stated that there was no conflict of interest.

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Author Contribution

MFH designed the research design, performed molecular modelling, and wrote the Introduction and Discussion sections. TN was responsible for literature search, phytochemical analysis, and writing the Methods section. MSA performed molecular docking simulation, ligand- receptor interaction analysis, and wrote the Results section. MPA processed the in silico data, compiled tables and figures, and provided interpretation of the results. CALW edited the entire manuscript, ensured formatting compliance with journal guidelines, and made revisions based on peer review feedback. DDW acted as research supervisor, provided conceptual and methodological guidance, and critically reviewed all parts of the manuscript.

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