






Inhibitory Activities of Selected Phytochemicals in *Melaleuca alternifolia* (tea tree) Oil Against Receptors in *Tricophyton rubrum* (Dermatophytes)

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Abstract: The study investigates the inhibitory activities of several phytochemicals from the oil of *Melaleuca alternifolia* (tea tree) using molecular simulation and docking analysis against receptors 7PIS and 4ZHS, compared with common medications (Fluconazole and Griseofulvin). A total of 13 carefully selected phytochemicals were found to have binding affinities comparable to or superior to those of the standard medications. Of these, aromadendrene, myrcene, and globulol showed the highest level of affinity. Globulol exhibited a higher binding affinity (-7.0 kcal/mol) for receptor 7PIS compared to griseofulvin (-7.7 kcal/mol). In similar ways, with affinities of -6.3 kcal/mol, -6.2 kcal/mol, and -6.5 kcal/mol for receptor 4ZHS, respectively, Aromadendrene, Myrcene, and Globulol performed better than griseofulvin. The compound's affinities for 7PIS and 4ZHS varied from -5.2 to -7.7 kcal/mol and -5.2 to -6.5 kcal/mol, respectively. Myrcene, globulol, and aromadendrene are supported as possible therapeutic agents by the Lipinski rule of 5, favorable inhibition constants, molecular interactions, and ADMET calculations, all of which call for more research.

Keywords: *Melaleuca alternifolia*; molecular simulation; Lipinski rule of 5; docking analysis; aromadendrene; myrcene; phytochemicals; globulol and receptors 7PIS and 4ZHS.

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1. Introduction

The public's health is seriously threatened by dermatophytes, especially “ringworm,” a common and painful fungal skin condition. This dermatophytosis, named for the circular, red, and itchy rash that develops on the skin, surfaces, and common household items like garments and towels [1,2], is caused by fungi. Ringworm has nothing to do with real worms, despite its deceptive name. Depending on where in the body it resides, the illness goes by several names. For example, jock itch (in the groin and inner thighs) and athlete's foot (in the feet). Itching, redness, scaliness, and the formation of a characteristic ring-shaped rash are characteristic

symptoms. Depending on the affected area, hair loss may also occur. A precise diagnosis is made more difficult by the symptoms' resemblance to those of conditions such as eczema [3]. Furthermore, because of their weakened immune systems, people living with HIV are more vulnerable to infections like ringworm [4,5], which could accelerate the development of HIV into AIDS if appropriate treatment is not received. When treating ringworm, especially in immunocompromised patients, the need for novel therapeutic approaches cannot be overstated. Within this framework of study, investigating plant secondary metabolites—also known as phytochemicals—obtained from natural sources offers a new therapeutic option. Many of the medications currently on the market are either derived directly from plants or inspired by substances found in plants, demonstrating the value of phytochemicals as sources of medicinal compounds [6,7]. The main group consists of phenolics, alkaloids, and terpenoids, each with distinct pharmacological characteristics, and is native to the marshy coast of southeast Australia, making it an interesting plant. The aromatic qualities of tea tree oil, which is made from the tree's leaves, have long been known. Tea tree oil's chemical components have antibacterial, antifungal, and anti-inflammatory [8,9] properties, making it a viable option for the development of new pharmaceuticals. According to the reports of [10], phytochemicals such as tannins, saponins, alkaloids, cardiac glycosides, terpenes, flavonoids, and phenols have been revealed to be the major significant components that are capable of causing varied physiochemical and pharmacological effects based on [11], an antimycotic assay carried out. A report on the synergistic interactions among several phytochemicals found in TTO demonstrates that they enhance antifungal activity and reduce the likelihood of resistance development [12]. Furthermore, TTO's synergistic actions with other antifungal drugs improve treatment efficacy and shorten therapy time, resulting in better patient outcomes and quality of life [13]. It was observed that α -terpineol inhibits fungal cytochrome P450 enzymes involved in ergosterol biosynthesis, thereby affecting fungal growth and replication [14].

Molecular docking simulations demonstrated the binding interactions between terpinen-4-ol and ergosterol receptors in fungal cell membranes, highlighting their selectivity and affinity [15]. Furthermore, *in vitro* investigations have shown that tea tree oil components act synergistically to enhance antifungal activity against *Trichophyton rubrum* [16]. The clinical implications of the inhibitory activities of selected phytochemicals in tea tree oil against *Trichophyton rubrum* receptors were reported, and it was demonstrated that it has significant clinical implications for the treatment of dermatophytosis as TTO-based formulations, including creams, gels, and shampoos, offer safe and effective alternatives to conventional antifungal agents, with fewer side effects and a lower risk of resistance development [17]. According to recent research on the specific mechanisms underlying the inhibitory effects of selected phytochemicals in tea tree oil on receptors in *Trichophyton rubrum*, the interaction of terpinen-4-ol with ergosterol, a vital component of fungal cell membranes, destabilizes the membrane and causes fungal cell death [18]. The present study aims to determine the potency of phytochemicals derived from *Melaleuca alternifolia* (tea tree) using molecular docking, one of the most advanced computational tools in drug design and discovery. Molecular docking is a crucial tool in drug design because it enables the determination of the strongest protein-ligand interactions and identification of optimal ligand poses within protein binding sites [19-22]. The efficiency of screening procedures is increased by the use of computer-aided drug design and discovery technologies, which makes it easier to identify potential targets for additional biological testing [23].

This research aims to develop novel therapeutic interventions against dermatophytes, such as ringworm, and other fungal causes of cutaneous infections, providing potential benefits to a wide range of individuals, including those with compromised immune systems, as we investigate tea tree phytochemicals through molecular docking. The information provided here opens new avenues for research and shows potential to improve pharmaceutical approaches to treat fungal infections and to confirm the effect of the plant compound previously reported.

2. Materials and Methods

Melaleuca alternifolia bark was used to identify 13 phytochemicals previously found in only 5 in anti-ringworm medicines. Two important medications, griseofulvin and fluconazole for the treatment of dermatophytes caused by Trichophyton species (rubrum or mentagrophytes), were purchased, and the structures of the active ingredients were obtained from PubChem (<https://pubchem.ncbi.nlm.nih.gov>). Biovia Discovery Studio translated SDF data from PubChem into Protein Data Bank format. Reliability was ensured by using PubChem as the sole database for ligand retrieval. Our Materials and Methods include a full description of this standardized procedure, which sets the stage for transparent, repeatable research on anti-ringworm activity.

2.1. Preparation of receptors.

In this study, *Trichophyton rubrum* receptors—Aspartate semialdehyde dehydrogenase (PDB ID 4ZHS, Figure 1A) and KDNase (PDB ID 7P1S, Figure 1B)—were targeted. 3D structures were retrieved from the Protein Data Bank (<http://www.rcsb.org/pdb>). The dimeric forms of 4ZHS and 7P1S were employed, with Chain A extracted for docking. Using Biovia Discovery Studio software, extraneous entities were removed. This ensured precision in exploring molecular interactions with major *Melaleuca alternifolia* phytochemicals. Adhering to transparency principles, this concise methodology outlines the systematic acquisition and preparation of molecular components for subsequent analyses.

2.2. Determination of active site.

The protein's active site was identified using the Discovery Studio program. Building on literature findings that identified key amino acid residues, our method aimed to validate the binding pocket [24]. As components of the active site, the amino acid residues MET343, LEU346, THR347, LEU349, GLU353, LEU387, MET388, LEU391, ARG391, ARG394, PHE404, MET421, ILE424, PHE425, LEU428, HIS524, and LEU525 have been found. To ensure precision and reliability in determining the current site setup, the validation procedure used the Discovery Studio platform. This data provides a framework for the following analysis and interpretations in this study.

2.3. Molecular docking simulations.

In the pursuit of molecular insights, AutoDock Vina, Vina Wizard, and PyRx's open Babel module were utilized for docking studies, engaging both phytochemicals and drug compounds with *Trichophyton rubrum*. Grid coordinates of -1.35, 6.09, 29.39 (x, y, z) and dimensions of 76, 78, 86 ensured comprehensive exploration. Ligands, under flexible conditions, underwent meticulous scrutiny. These methods conform to guidelines, fostering transparency and reproducibility.

2.4. Pharmacokinetics (ADMET) and drug-likeness parameters analysis.

The eligibility of a compound as a lead candidate hinges on meeting predefined parameters, such as molecular weight, logP, HBA, HBD, rotatable bonds, and water solubility [25]. Evaluation methods include octanol/water partitioning, liposome partitioning, IAM retention, PAMPA, and SPR biosensor analysis, providing a thorough understanding of pharmacokinetics and drug-likeness

2.5. Preparation of ligands.

Melaleuca alternifolia bark was used to identify 13 phytochemicals previously found in only 5 in anti-ringworm medicines. Two important medications, griseofulvin and fluconazole for the treatment of dermatophytes caused by Trichophyton species (rubrum or mentagrophytes), were purchased, and the structures of the active ingredients were obtained from PubChem (<https://pubchem.ncbi.nlm.nih.gov>). Biovia Discovery Studio translated SDF data from PubChem into Protein Data Bank format. Table 1 presents the molecular weight, formula, 2D structure, and molecular structure of ligands, including recognized phytochemicals and medications. Reliability was ensured by using PubChem as the sole database for ligand retrieval. Our Materials and Methods include a full description of this standardized procedure, which sets the stage for transparent, repeatable research on anti-ringworm activity.

3. Results and Discussion

3.1. Molecular docking.

Melaleuca alternifolia bark (Figure 1) was used to uncover thirteen phytochemicals (Table 1).



Figure 1. *Melaleuca alternifolia*.

Trichophyton rubrum receptors—Aspartate semialdehyde dehydrogenase (PDB ID 4ZHS, Figure 2a) and KDNase (PDB ID 7P1S, Figure 2b) were used. Early drug discovery virtual screening is made easier by molecular docking, a critical tool in computer-aided drug design. It places molecules at the target site and assesses binding effectiveness by analyzing interactions between the ligand and receptor proteins [26, 27].

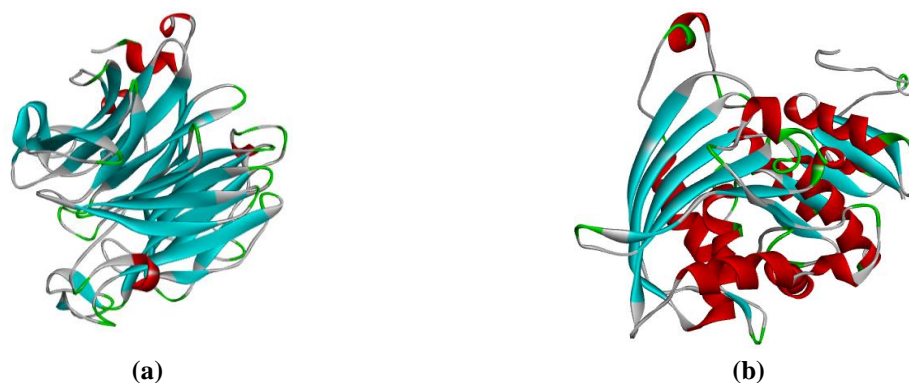
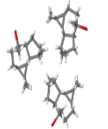
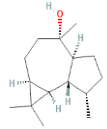
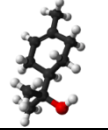
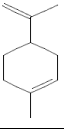
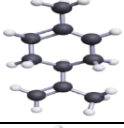

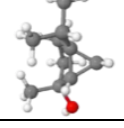
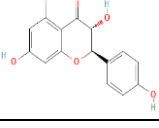
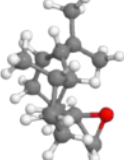

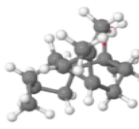
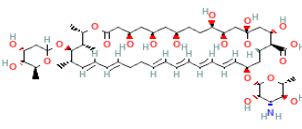


Figure 2. (a) Crystal Structure of KDNase (PDB ID: 7PLS); (b) Crystal structure of aspartate dehydrogenase from trichophyton rubrum (PDB ID: 4ZHS).

Table 1. Displays the components found in *Melaleuca alternifolia* (tea tree) oil and the molecular weight, 2D structure, and molecular structure of two pharmaceuticals used to treat Trichophyton rubrum (dermatophytes).

S/N	Ligands	Pubchem cid	Molecular weight (g/mol)	Molecular formula	2D structure	Molecular structure
1.	Terpinolene	11463	136.23	C ₁₀ H ₁₆		
2.	α-terpinene	7462	136.23	C ₁₀ H ₁₆		
3.	γ-terpinene	7461	136.23	C ₁₀ H ₁₆		
4.	Para-cyme	7463	134.23	C ₁₀ H ₁₄		
5.	1,8-cineol	46781028	157.27	C ₁₀ H ₁₈ O		
6.	Terpinen-4-ol	11230	154.25	C ₁₀ H ₁₈ O		
7.	α-terpineol	17100	154.25	C ₁₀ H ₁₈ O		
8.	α-pinene	6654	136.23	C ₁₀ H ₁₆		
9.	Ladene (syn. Viridiflorene)	10910653	204.35	C ₁₅ H ₁₄		

S/N	Ligands	Pubchem cid	Molecular weight (g/mol)	Molecular formula	2D structure	Molecular structure
10.	Globulol	101716	222.37	C ₁₅ H ₂₆ O		
11.	Limonene	22311	136.23	C ₁₀ H ₁₆		
12.	Sabinene	18818	136.23	C ₁₀ H ₁₆		
13	Aromadendrene	91354	204.35	C ₁₅ H ₂₄		
14.	Fluconazole	441005	204.35	C ₁₅ H ₂₄		
15.	Griseofulvin	11996452	222.5	C ₁₅ H ₂₆ O		

The results (Table 2) show that 13 ligands exhibit binding affinities exceeding the predetermined threshold of -5 kcal/mol. In comparison to fluconazole's -6.6 kcal/mol, Aromadendrene, Myrcene, and Globulol either match or surpass it. For receptor 7PIS, globulin also has a -7.7 kcal/mol match with griseofulvin. In a similar vein, griseofulvin's -6.1 kcal/mol is exceeded by aromadendrene, myrcene, and globulol for receptor 4ZHS. The range of apparent intensities, or affinity values, is -5.2 to -7.7 kcal/mol (7PIS) and -5.2 to -6.5 kcal/mol (4ZHS), confirming and validating candidates for further drug investigation.

3.2. Determination of inhibition constant.

The inhibition constant (K_i) (Table 2) is determined by the docking scores of the ligands, which provide information for the calculation (Equation 1). Increased potency is indicated by a lower K_i value, expected to be between 0.1 μM and 1.0 μM for hits or leads and not more than 10nM for medications [28]. Based on their binding affinities, Table 2 presents K_i values (Equation 1) for all molecules within the docked ligands, ranging from 2.24μM to 152.74μM post-comprehensive screening. This research helps determine the effectiveness of inhibition, which is important in order to comprehend these compounds' potential as pharmacological agents.

$$K_i = e^{\left[\frac{-\Delta G}{RT}\right]} \quad (1)$$

R = Gas constant (1.987 × 10⁻³ kcal/K-mol); T = 298.15 (absolute temperature); k_i = Inhibition constant.

Table 2. Shows the ligands, their binding affinity, and inhibition constant values.

S/N	Ligands	Binding affinity		Inhibition constant	
		7PIS	4ZHS	7PIS	4ZHS
1	1,8-cineol	-5.4	-5.3	108.94	128.99
2	Alpha-pinene	-5.2	-5.2	152.74	152.74
3	Alpha-terpinene	-5.2	-5.4	152.74	108.94
4	Alpha-terpineol	-5.4	-5.5	108.94	92.00
5	Aromadendrene	-6.6	-6.3	14.35	23.82
6	Fluconazole	-6.6	-6.9	14.35	8.64
7	Gamma-terpene	-5.3	-5.3	128.99	128.99
8	Globulol	-7	-6.5	7.30	16.99
9	Griseofulvin	-7.7	-6.1	2.24	33.37
10	Myrcene	-6.6	-6.2	14.35	6.34
11	Limonene	-5.2	-5.3	152.74	128.99
12	Para-cymene	-5.3	-5.4	128.99	108.94
13	Sabinene	-5.4	-5.9	108.94	46.80
14	Terpinene-4-ol	-5.5	-5.4	92.00	108.94
15	Terpinolene	-5.4	-5.3	108.94	128.99

3.3. Pharmacokinetics (ADMET) and drug likeness analysis.

Prior to drug discovery, it is essential to evaluate physicochemical properties and drug similarity. According to Lipinski's "rule of five," for a chemical to be an effective oral medicinal medication, it must satisfy certain requirements, such as having a molecular weight of less than 500Da, an HBD of less than 5, an HBA of less than 10, and a log P of less than 5. The ligands myrcene, globulol, and aromadendrene showed encouraging inhibition constants and binding affinities, making them eligible to be classified as hit compounds (L13, L10, L9). All ligands will go through additional analysis using the ADMET SAR-2 web server and Molinspiration online to verify safety and efficacy. The evaluation of drug-likeness showed no violations of the "rule of five," indicating that all ligands had adequate oral bioavailability and permeability (Table 3).

Table 3. Shows the ligands and their drug-like parameters.

Ligands	Compound	Molecular weight (g/mol)	Hydrogen bond acceptor (HBA)	Hydrogen bond donor (HBD)	Log P	Rule of Five violation	Heavy atom
L1	Terpine-4-ol	154.25	1	1	2.60	0	11
L2	γ -terpine	136.24	0	0	3.36	0	10
L3	α -terpinene	136.24	0	0	3.36	0	14
L4	1,8-cineol	168.28	1	1	2.96	0	12
L5	Para-cymene	134.22	0	0	3.90	0	10
L6	α -terpineol	154.25	1	1	2.60	0	11
L7	α -terpinolene	136.24	0	0	3.67	0	10
L8	α -Pinene	178.28	0	0	3.03	0	13
L9	Globulol	170.25	2	1	1.2	0	12
L10	Myrcene	136.24	0	0	3.99	0	10
L11	β -pinene	194.36	0	0	4.92	0	14
L12	Sabinene	152.28	0	0	3.78	0	11
L13	Aromadendrene	204.35	0	0	4.7	0	15
L14	Fluconazole	306.27	7	1	0.4	1	22
L15	Griseofulvin	1056.2	21	13	-0.3	1	74

3.4. Pharmacokinetics (ADMET) analysis of the selected compounds.

The Pharmacokinetics (ADMET) analysis of selected compounds is pivotal in early drug discovery, influencing molecule selection and minimizing attrition. Utilizing the ADMET SAR-2 web server, the ADMET profiles of potent phytochemicals (L-9, L-10, and L-13) were evaluated (Table 4). These compounds demonstrated favorable characteristics, including good human intestinal absorption, suitable solubility (log S between -1 and -5), and no toxicity.

Notably, all hits were well absorbed in the human intestine, crossed the blood-brain barrier, and did not inhibit cytochrome P450, indicating robust metabolic activity [29]. Predictive assessments revealed non-mutagenic properties (Ames toxicity) and type III acute oral toxicity (slightly toxic). These findings guide the early-phase drug discovery process, steering towards compounds with optimal safety and therapeutic profiles. Acknowledging the importance of ADMET parameters in mitigating later-stage failures, this analysis streamlines resource allocation, avoiding investment in potentially discarded drug candidates. Overall, the ADMET analysis underscores the potential of the selected compounds and provides a foundation for subsequent drug development steps.

Table 4. Shows the ADMET Analysis of the ligands.

Absorption and distribution	L1	L2	L3	L4	L5	L6	L7	L8	L9	L10	L11	L12	L13	L14	L15
GI absorption (high/low)	High	High	High	High	High	High	High	High	High	High	High	High	High	High	High
BBB (yes/no)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Pgp substrate	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No
Metabolism															
CY450 2C9 substrate	0.837	0.181	0.831	0.843	0.846	0.86	0.781	0.86	0.87	0.9	0.832	0.867	0.73	0.98	0.473
CYP450 2D6 substrate	0.876	0.867	0.765	0.865	0.081	0.814	0.896	0.777	0.986	0.973	0.764	0.672	0.765	0.642	0.874
CYP450 3A4 substrate	0.624	0.692	0.865	0.435	0.567	0.876	0.456	0.872	0.832	0.735	0.872	0.845	0.567	0.956	0.863
CYP450 1A2 substrate	0.674	0.784	0.745	0.864	0.746	0.745	0.864	0.856	0.967	0.976	0.567	0.745	0.634	0.864	0.645
CYP450 2C9 inhibitor	0.876	0.864	0.834	0.856	0.894	0.538	0.867	0.987	0.864	0.844	0.834	0.421	0.856	0.745	0.934
CYP450 2C19 inhibitor	0.986	0.856	0.884	0.832	0.812	0.844	0.875	0.826	0.934	0.976	0.186	0.876	0.764	0.873	0.886
CYP4503A4 inhibitor	0.857	0.756	0.874	0.634	0.887	0.667	0.994	0.664	0.563	0.754	0.674	0.748	0.834	0.895	0.874
toxicity	L1	L2	L3	L4	L5	L6	L7	L8	L9	L10	L11	L12	L13	L14	L15
Human ether-related gene inhibition	0.89	0.86	0.89	0.74	0.98	0.88	0.78	0.98	0.67	0.78	0.89	0.56	0.29	0.87	0.56
AMES toxicity	0.886	0.897	0.786	0.786	0.670	0.385	0.47	0.547	0.954	0.862	0.437	0.234	0.546	0.785	0.768
Fish toxicity	0.665	0.764	0.754	0.754	0.653	0.678	0.674	0.745	0.567	0.758	0.578	0.868	0.745	0.875	0.564
Honey toxicity (BEE)	0.966	0.934	0.932	0.934	0.932	0.936	0.843	0.347	0.947	0.658	0.943	0.867	0.767	0.877	0.877
Biodegradation	0.667	0.743	0.854	0.843	0.464	0.453	0.546	0.867	0.984	0.548	0.435	0.463	0.693	0.548	0.965
Acute oral toxicity	0.986	0.473	0.439	0.326	0.432	0.548	0.569	0.234	0.576	0.756	0.895	0.437	0.987	0.857	0.344

4. Conclusions

This study analyzed the phytochemicals of *Melaleuca alternifolia* and used molecular docking to elucidate the molecular mechanisms underlying dermatophyte infections, such as ringworm. Tested against the receptors 4ZHS and 7PIS were thirteen substances in addition to prescription medications. The findings showed affinities higher than the baseline of -5 kcal/mol; in particular, globulol, myrcene, and aromadendrene matched or exceeded fluconazole. Griseofulvin's affinity for receptor 7PIS was likewise matched by globulol. These ligands demonstrated good inhibitory constants and confirmed previous reports in an antimycotic assay against cutaneous mycosis by [10], met ADMET calculations molecular interaction requirements, and obeyed Lipinski's rule. As potential treatments for ringworm, aromadendrene, myrcene, and globulol represent a promising avenue for the development of

novel antifungal therapies and warrant further investigation to elucidate their precise mechanisms of action and optimize the therapeutic potential of TTO-based formulations for the treatment of dermatophytosis.

Author Contributions

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

Institutional Review Board Statement

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Informed Consent Statement

Not applicable.

Data Availability Statement

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

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Conflicts of Interest

The authors declare no conflicts of interest related to this article.

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