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BIOINFORMATICS STUDY: THE POTENCY OF *Syzygium samarangense* STEM BARK DICHLOROMETHANE EXTRACT AS ANTI-MELASMA AND ANTI-ACNE

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ABSTRAK

Syzygium samarangense mengandung senyawa flavonoid telah terbukti bermanfaat. Penelitian sebelumnya mengungkapkan bahwa aurentiacin, pinocembrin, stercurensin, dan uvangoletin sebagai bahan kimia bioaktif terdapat pada kulit batang tanaman. Senyawa ini terbukti memiliki aktivitas antioksidan yang sangat baik. Namun, belum ada penelitian mengenai potensinya sebagai agen anti melasma dan anti jerawat. Penelitian ini berupaya melihat keempat bahan kimia tersebut berpotensi sebagai penghambat tyrosinase (TYRP1) anti melasma dan penghambat androgen (AR) anti jerawat dengan menggunakan teknologi biokomputasi. Studi ini mencakup analisis *druglikeness* Lipinski dan *molecular docking* menggunakan protein TYRP1 dan AR dengan hidrokuinon dan clascoterone sebagai obat kontrol. Analisis lebih lanjut dilakukan dengan prediksi PASS-Online untuk mendukung potensi senyawa. Hasilnya menunjukkan bahwa semua senyawa berpotensi menjadi agen anti melasma dan anti jerawat yang efektif, dengan pinocembrin (-7.4 kkal/mol untuk TYRP1; -8.8 kkal/mol untuk AR) menjadi senyawa yang paling manjur. Senyawa ini memenuhi aturan kemiripan obat Lipinski dan didukung oleh prediksi PASSOnline bahwa senyawa tersebut berpotensi sebagai pemutih kulit dan antagonis androgen. Namun, penelitian lebih lanjut, termasuk penelitian *in vitro* dan *in vivo*, diperlukan untuk memastikan potensinya sebagai agen anti melasma dan anti jerawat.

Kata kunci: anti-jerawat, anti-melasma, jerawat, hiperpigmentasi, *molecular docking*.

ABSTRACT

Syzygium samarangense containing flavonoid compounds have been proven to be beneficial. Previous research revealed that the aurentiacin, pinocembrin, stercurensin, and uvangoletin as bioactive chemicals were present in the plant stem bark. These compounds have been found to have excellent antioxidant activity. However, there has been no research on their potential as anti-melasma and anti-acne agents. This research attempts to look into these four chemicals potential as anti-melasma tyrosinase inhibitors and anti-acne androgen inhibitors using biocomputation technology. The study included druglikeness and molecular docking analyses using TYRP1 and AR proteins with hydroquinone and clascoterone as control drugs. Further analysis was carried out with PASS-Online predictions to support the potency of compounds. The results indicated that all compounds have the potential to be effective anti-melasma and anti-acne agents, with pinocembrin (-7.4 kcal/mol for TYRP1; -8.8 kcal/mol for AR) being the most potent compound. These compounds fulfilled Lipinski's druglikeness rules and were supported by PASSOnline's predictions that they have potential as skin whiteners and androgen antagonists. However, further research, including *in vitro* and *in vivo* studies, is necessary to confirm their potential as anti-melasma and anti-acne agents.

Keywords: Anti-acne, anti-melasma, acne, hyperpigmentation, molecular docking.

INTRODUCTION

Skin problems are a problem that is often faced by everyone and is a stressor. Common skin problems are melanin and acne problems (Conforti et al., 2020; Sheth & Pandya, 2011). Melanin is a human black pigment produced in the body through the melanogenesis pathway by converting tyrosine to dihydroxyphenylalanine (DOPA), then DOPA is converted to dopaquinone (Nazir et al., 2021; Iraji et al., 2020; Zolghadri et al., 2019). In addition to being principally responsible for skin, hair, and eye colour, melanin also acts as a photo barrier in living things to prevent DNA destruction caused by ultraviolet (UV) radiation (Zolghadri et al., 2019; Baxter & Pavan, 2013). UV light initiates melanogenesis to protect skin cells from harmful effects (Hering et al., 2023). However, overexpression of tyrosinase in the brain can cause nerve damage, as well as neurodegenerative diseases such as Parkinson

and Huntington (Jin et al., 2024; Yue et al., 2024). Tyrosinase enzyme plays a role in this process and is commonly used as a target for hyperpigmentation treatment. There are reports of a number of tyrosinase inhibitors being used as both aesthetic and medicinal treatments for a variety of skin disorders and hyperpigmentation concerns (Kishore et al., 2018; Ashraf et al., 2015). Tyrosinase inhibitors possess the ability to effectively suppress elevated tyrosinase activity, hence assuming a significant therapeutic function as pharmaceutical agents for many skin conditions. Hydroquinone is a widely used receptor blocker (Carradori et al., 2024), but the use of this synthetic drug has side effects such as exogenous ochronosis (Olumide et al., 2008) and cancer (Polynice, 2024; Shivaram et al., 2024); so that the main alternative is needed from natural materials.

Apart from hyperpigmentation, acne is a skin problem that almost everyone experiences. Acne, also known as acne vulgaris, is a multifactorial skin disorder that primarily affects the sebaceous glands and hair follicles (Tollenaere et al., 2022; Zaenglein et al., 2016). It is characterized by the development of comedones, papules, pustules, nodules, and cysts, which can lead to scarring if left untreated. The pathogenesis of acne involves a combination of factors such as increased sebum production, abnormal keratinization, bacterial colonization (often by *Propionibacterium acnes*), and inflammation (Dréno et al., 2015; Del Rosso et al., 2019), hormonal fluctuations, especially during adolescence, playing an important role in the development of acne. Androgens, like testosterone, stimulate sebum production and contribute to forming comedones and inflammatory lesions. Genetic factors can also influence a person's susceptibility to acne (Bataille et al., 2002; Alapatt & Matanaj, 2024). Hence, one way to deal with acne is to block androgen receptors (Bhat et al., 2017), the topical drug usually given is clascoterone, a steroid anti-inflammatory drug (Santhosh & George, 2021). The use of this drug has side effects such as hyperkalemia (Kalabalik-Hoganson et al., 2021), so it is needed other alternatives from natural materials. Plant predicted having the potency of that is Semarang Guava plant (*S. samarangense*), which is a local Indonesian plant.

This research is a follow-up to earlier investigations finding four flavonoid chemicals in the dichloromethane extract of a particular plant fraction, namely aurentiacin, pinocembrin, stercurensin, and uvangoletin, in which they have antifungal activity against *Candida albicans* (Tukiran et al., 2021) and potency as anti-inflammatory agent COX-2 inhibitor (Sururi et al., 2022). Based on this report, these compounds can be developed as natural ingredients for anti-acne and anti-melasma. The goal of this work was to define possible chemicals from the dichloromethane extract in selected fraction as a natural agent for anti-acne inhibitor testosterone and anti-melasma inhibitor tyrosinase as an *in silico.*

MATERIALS AND METHODS

Protein Receptor Preparation

Tyrosinase-related protein 1 (TYRP1), which functions as an anti-melanoma receptor and androgen receptor (AR), which functions as an anti-acne receptor, were both downloaded from the RCSB server (rcsb.org). In order to prepare a sterile protein and determine the binding locations (active site), the protein was generated using Discovery Studio (Sururi et al., 2023).

Ligand Preparation

The phytochemicals of the dichloromethane extract in selected fraction of the plant namely pinocembrin, uvangoletin, stercurensin, and aurentiacin that were reported in previous studies (Tukiran et al., 2021) were used as ligand. The control drugs used to compare the TYRP1 receptor and the AR receptor were hydroquinone and clascoterone, respectively. The 3D structure of the ligand was obtained from the PubChem server (pubchem.ncbi.nlm.nih.gov) which was then minimized using OpenBabel on the PyRx program to obtain a flexible structure (Pradeepkiran et al., 2016; Sururi et al., 2022).

Druglikeness Lipinski Analysis

An analysis was done using Lipinski's five rules to assess the pharmacological properties of compounds in the dichloromethane extract. This approach allowed thorough examination of the extract's therapeutic potential and identification of promising compounds for future studies. The following parameters are part of the rules: molecular weight (MW) < 500 Da, hydrogen bond acceptors (HBA) < 10, hydrogen bond

donors (HBD) < 5, molar refractivity (MR) 40–130, and lipophilicity < 5 (Lipinski, 2004; Lipinski et al., 2001). While, Druglikeness analysis was performed using the Scfbio web server (scfbioiitd.res.in) (Jayaram et al., 2012).

Molecular Docking and Visualization

Molecular docking assays were performed using the Vina Wizard (Trott & Olson, 2010) with docking coordinates for TYRP1 receptors (X: 15.993900; Y: -5.208800; and Z: 25.220400) and AR (X: 27.091714; Y: 2.278714; and Z: 4.949810). The conformer compounds obtained were then interacted with and visualized using PyMOL and Discovery Studio to determine the type and position of the interaction between the ligands and the receptors (Eberhardt et al., 2021).

PASSOnline Prediction

PASS-Online prediction (way2drug.com) was carried out to determine the potency of the ligand compounds by looking at the potential value of the Pa and Pi ligand compounds. PASS-Online predictions are used to strengthen the potential compounds as anti-melasma and anti-acne agents (Lagunin et al., 2000; Rahmaningsih & Pujiastutik, 2019).

RESULT AND DISCUSSION

The receptors were prepared by removing unnecessary molecules such as water and other protein chains, and obtaining the active positions of each receptor using Discovery Studio. Determination of the active positions was based on the native ligand positions of each receptor, obtained from the RCSB server, namely for TYRP1 receptor (X: 15.993900; Y: -5.208800; and Z: 25.220400) and AR receptor (X: 27.091714; Y: 2.278714; and Z: 4.949810). Ligand preparation was performed by identifying the drug-likeness profile of each compound F1 fraction from the dichloromethane extract, using the Lipinski's of five rules to select compounds for molecular docking (Lipinski, 2004). The purposed compounds used in this study were pinocembrin, uvangoletin, stercurensin, and aurentiacin (Tukiran et al., 2021). The results of drug-likeness analysis using Lipinski's five rules present in Table 1 showed that these compounds have the potential to be promising drug candidates, as they meet at least 3 of the Lipinski's five rules (Lipinski, 2004; Lipinski et al., 2001)

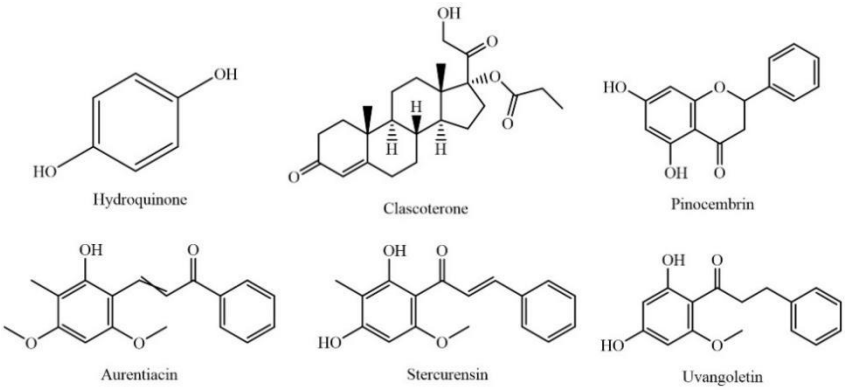

Figure 1. Ligand Structures in This Study

The aim of the molecular docking study is to evaluate a compounds potential as a medication with particular bioactivities by blocking the target protein receptors. Prior to the molecular docking analysis, the ligand structures are minimized using OpenBabel to achieve flexible ligands. When the ligands are flexible, they are expected to obtain minimal (stable) binding affinities (Pradeepkiran et al., 2016). The primary objectives of this study involved the investigation of bioactivities that specifically targeted the tyrosinase (TYRP1) receptor for anti-melasma effects and the androgen (AR) receptor for anti-acne effects. The TYRP1 receptor plays a role in the hyperpigmentation pathway through dopaquinone production (Carradori et al., 2024; Zolghadri et al., 2019), while AR receptor is involved in acne formation due to excessive androgen hormone production (Kircik, 2021;

Alapatt & Matanaj, 2024). The resulted molecular docking analysis (as seen in Table 1) revealed that all four compounds interact with the TYRP1 and AR receptors due to their negative binding affinity values. The outcomes indicated that these compounds exhibit lower binding affinities compared to the control drugs hydroquinone (-4.8 kcal/mol) and clascoterone (-5.9 kcal/mol), indicating their promising potential as anti-melasma and anti-acne agents. Binding affinity represents the stability value of the protein-ligand complex formed. A more negative value signifies greater stability of the complex. Enhanced stability of the formed complex leads to optimal inhibitory activity (Jensen, 2017; Pires et al., 2018). The findings of the investigation indicated that pinocembrin exhibits the most pronounced negative binding affinity for both receptors in a synergistic manner. These compounds are potential compounds that will be visualized to gather data on the positions and types of interactions within the formed receptor-ligand complexes.

Table 1. Druglikeness and Molecular Docking Analysis using TYRP1 and AR Receptors

Ligands	Lipinski Parameter					Binding affinity (kcal/mol)	
	MW[1]	AH[2]	DH[3]	MR[4]	Log P[5]	TYRP1	AR
Hydroquinone	-	`-	-	-	-	-4.8	-
Clascoterone	-	-	-	-	-	-	-5.9
Pinocembrin	256.25	4	2	69.55	2.48	-7.4	-8.8
Uvangoletin	272.30	3	2	76.47	2.92	-6.7	-8.1
Stercurensin	284.31	3	2	81.75	3.20	-6.9	-8.1
Aurentiacin	298.33	4	1	86.22	3.51	-6.3	-7.2

Note: [1]MW = molecular weight $\leq$ 500 Da; [2]AH= Hydrogen Bond Acceptor $\leq$ 10; [3]DH = Hydrogen Bond Donor $\leq$ 5; [4]MR = Molar Refractivity 40 – 130; [5]Log P = liphopility $\leq$ 5

The four potential compounds are then visualized, and the results of the 2D visualization are presented in Figure 2a for the TYRP1 complex and Figure 2b for the AR complex. The outcomes revealed the formation of various types of interactions, including hydrogen bonding, hydrophobic interactions, and electrostatic bonding. These interactions can be observed in Figure 2a and Figure 2b above; surface area interaction can be observed in Figure 3. Hydrogen bonding refers to the intermolecular interactions that occur between hydrogen atoms and highly electronegative atoms, such as fluorine, oxygen, and nitrogen (Sururi et al., 2024). Hydrophobic interactions occur between hydrophobic groups of the receptor and ligand (King et al., 2014). Electrostatic bonding arises from charges between the receptor and ligand (Kamila et al., 2024; Njoroge et al., 2008).

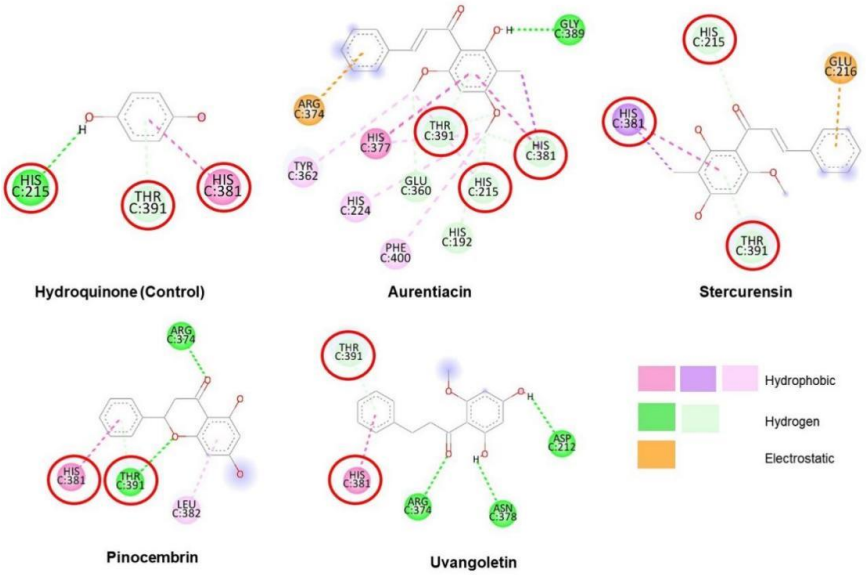

Figure 2a. Visualization 2D of Drug and Potential Compounds of TYRP1 Complex

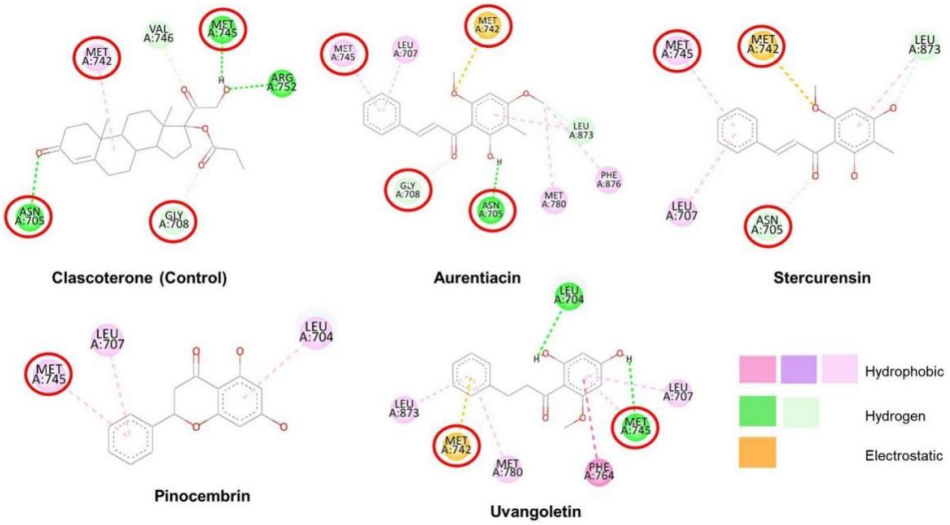

Figure 2b. Visualization 2D of Drug and Potential Compounds of AR Complex

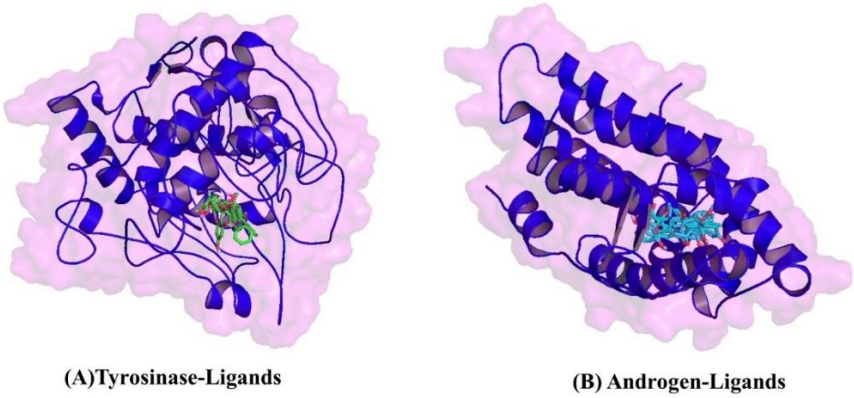

Figure 3. Visualization 3D (Surface Area Interaction) of Each Complexes

Based on the visualization results as shwon in Figure 2a for the TYRP1 receptor, it is evident that there are identical amino acid residues to the hydroquinone control drug, specifically residues at positions His 215, Thr 391, and His 381. As known that aurentiacin, sterecurensin, pinocembrin, and uvangoletin exhibits 3, 3, 2, and 2 amino acid similarities, respectively. This representation indicated that four potential compounds have inhibitory positions similar to the control compound's active site, providing support for their potential as anti-melasma inhibitors targeting tyrosinase (Kharisma et al., 2021). While the AR receptor (as displayed in Figure 2b), it is found that the amino acid is identical to the drug clascoterone at positions Met 742, Met 745, Glu 708, and Asn 705. As shown that aurentiacin, sterecurensin, pinocembrin, and uvangoletin have 3, 3, 1, and 2 amino acid similarities, respectively. This also provided support that four potential compounds synergistically have potential as anti-androgens and as anti-acne agents because they have the same inhibitory position like the drug clascoterone (Nugroho et al., 2023). Amino acid residues and types of interactions that are identical to the control can be seen in Figure 2a and Figure 2b as well.

The evaluation of the outcomes of molecular docking was conducted utilizing PASS-Online in order to substantiate the potential of the four compounds for anti-melasma and anti-acne actions, by examining the Pa and Pi values associated with each molecule. The evaluation results as seen in Table 2 showed that each compound with the highest probability as an anti-melasma (skin whitener) is stercurnesin (Pa=0.764; Pi=0.001); while only 1 compound with anti-acne potential (androgen antagonist) is pinocembrin (Pa=0.127; Pi=0.018). A Pa value > 0.7 has a high probability; while Pa > 0.3 has a moderate probability (Kharisma et al., 2021; Rahmaningsih & Pujiastutik, 2019).

Table 2. PASS-Online Analysis of Potential Compounds

Potential Compounds	Skin Whitening		Androgen Antagonist	
	Pa	Pi	Pa	Pi
Pinocembrin	0.729	0.002	0.127	0.018
Uvangoletin	0.446	0.004	-	-
Stercurensin	0.764	0.001	-	-
Aurentiacin	0.746	0.002	-	-

CONCLUSION

There are four compounds found in selected fraction of *S. samarangense* stem bark dichloromethane extract had the potential as anti-melasma tyrosinase inhibitors and anti-acne inhibitors androgens with the most potent compound being pinocembrin (-7.4 kcal/mol for TYRP1; -8.8 kcal/mol for AR). The resulted PASS-Online analysis provided support so that this compound has the potential as an anti-melasma and anti-acne.

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