In Silico Investigation of γ-Sitosterol Isolated from the Ethanol Extract of *Artocarpus camansi* Leaves as a Sunscreen Agent

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Abstract: *The activity test of sunscreen lotion from the ethanolic extract of* Artocarpus camansi *leaves was carried out. The activity of sunscreen lotion as sun protecting factor (SPF) is ranging from 28.716 ± 0.1557 to 29.740 ± 0.1360, while the SPF of pure compound is 28.483 ± 0.1422. The type of lotion is water in oil (w/o) with viscosity and pH values in the range of 3057.1–5001.1 cP and 6.86–7.89, respectively. The viscosity and pH values obtained were following the standard SNI 16-4399-1996. The value of dispersion is in the range of 4.60–6.90 cm, while the value of adhesion is in the range of 14.55–25.03 s. The pure compound is thought to be γ-sitosterol by analysis of its molecular weight similarity and positive ion fragment* m/z *with a melting point of 147 °C. From the molecular docking, it is known that γ-sitosterol has the highest binding affinity value of −7.4 and −8.2 kcal/mol to human neutrophile collagenase (PDB ID: 1BZS) and fibroblast collagenase-1 (PDB ID: 966C), respectively. The presence of active compounds in the ethanolic extract of* A. camansi *lotion can support the activity of the SPF so that it can be used as a sunscreen formula.*

Keywords: Artocarpus camansi*; sunscreen sun protection factor; γ-sitosterol*

■ INTRODUCTION

Ultraviolet (UV) rays from the sun have good benefits for the human body, such as the formation of cholecalciferol (vitamin D3), which plays a role in the metabolism of bone formation and as a defense of the immune system. However, excessive radiation can cause adverse effects that can harm humans [1]. UV radiation can cause sunburn [2], triggering skin problems such as cracks, burns, immune suppression, wrinkles, hypopigmentation, hyperpigmentation, dermatitis, urticaria, aging, and even cancer [3]. So that skin protection is needed, one of which is the use of sunscreen. Sunscreen is one of the solutions for self-protection against the dangers of exposure to UV rays [1]. The structure of compounds with conjugated double bonds or hydroxy groups can absorb high-energy UV rays and release the energy as lower-energy rays to prevent UV rays from damaging the skin [4]. Many of these compounds are contained in plants, one of which is *A. camansi*.

A. camansi, also called Kulu or Kluih, is a plant native to New Guinea and Indonesia that belongs to the family Moraceae. *A. camansi* plant is one of the plants that are well known to the public as a source of vegetables and medicine, the fruit is cooked as soup. Scientific research has been carried out on the leaves, bark, roots, and fruit, which can lower blood sugar [5-7]. There are so many chemical compounds found in *A. camansi*, i.e., beta-sitosterol propionate [8], beta-amirin acetate [6], and lupeol acetate [9].

A. camansi plant contains phenolic compounds, including flavonoids, stilbenoids, arylbenzofurones, and neolignans which are distributed in the leaves, fruit, flowers, and skin. The total phenol and total flavonoid content of the ethanol extract of *A. camansi* leaves was relatively high, namely 47.46 mg GAE/g and 79.094 CE/g, respectively [10]. The flavonoids in the leaves of *A.*

camansi are thought to play a significant role in increasing the activity of antioxidant enzymes. In addition, flavonoids and tannins are natural molecules with good UV protection activity [11].

Based on the description above, it is needed to test the sunscreen activity of the ethanol extract of the leaves of *A. camansi* in the form of a lotion dosage form. Lotion preparation has the advantage because it has properties such as a moisturizer on the skin, gives a soft feeling, and is easy to apply or clean.

■ EXPERIMENTAL SECTION

Materials

The Merck chemicals used in this study were stearic acid, cetyl alcohol, lanolin, triethanolamine (TEA), glycerin, methylparaben, silica gel 60, ethanol, *n*-hexane, chloroform, ethyl acetate, Mg metal, HCl, ammonia, and methanol. Reagents for phytochemicals analysis (Liebermann-Burchard, Dragendroff's, Mayer and Wagner) were purchased from Sigma-Aldrich.

The sample used in this research is *A. camansi* Blanco leaves collected from around Aceh Besar, Aceh. The sample was determined at the Herbarium Laboratory of the Biology Department, Faculty of Mathematics and Natural Sciences at Syiah Kuala University by Dr. Saida Rasnovi, S.Si., M.Si., showed that the plant was a plant from the Moraceae family, Genus Artocarpus J. R.Forst. & G. Forst, species *A. camansi* Blanco.

Instrumentation

The tools used in this study were UV-vis spectrophotometer (1240 Shimadzu UV-vis mini), electric balance (Mettler Toledo, Japan), column chromatography, GC-MS (Shimadzu QP 2010 Ultra), pH meter (710 A Thermo electron Orion), viscometer (Thermo scientific Haake viscometer c), and rotary evaporator (Buchi R-300).

Procedure

Extraction and fractionation of ethanolic extract of leaves of A. camansi

First, 1 kg of *A. camansi* leaves was cleaned, dried at room temperature, mashed, macerated using methanol for 3 × 24 h, and stirred several times. Then, it was filtered, and the filtrate obtained was evaporated resulting in 13.370 g of methanol extract. The methanol extract obtained was then partitioned with *n*-hexane as the solvent. The extract was evaporated, resulting in the *n*-hexane extract being obtained in as much as 29.386 g. The residue was then re-partitioned with an ethanol solvent, and an ethanol extract of 65.944 g was obtained with a yield of 6.5944%, with brown color. The ethanol extract was characterized by GC-MS and tested for its sunscreen activity, with a concentration of 2.0, 2.5, 5.0, 7.5, and 12%. Furthermore, the ethanol extract was made into a lotion with the same concentration as the extract and tested for its sunscreen activity and physical properties. The ethanol extract was separated using gravity column chromatography to obtain the subfraction. The resulting subfraction was made into lotion. Subfraction and subfraction lotion were also tested for their sunscreen activity. The most active subfraction was re-chromatographed using gravity column chromatography until a pure compound was obtained. Then it was made into a lotion and tested for sunscreen activity. Then, phytochemical analysis in the ethanol extract of *A. camansi* was carried out using the appropriate method [12].

Making sunscreen lotion

The manufacture of sunscreen lotion with an ethanol extract of *A. camansi* leaves was carried out based on the method used in several previous research [13-15] with slight modifications. The formulation of *A. camansi* leaf ethanol extract lotion can be seen in Table 1. The oil-soluble material in the form of cetyl alcohol, stearic acid, and lanolin is called the oil phase. In contrast, the water-soluble material in the form of methylparaben, TEA, and distilled water is called the water phase. The oil phase was put into a porcelain cup and heated using a water bath at 70 °C for 10 min, while the water phase was dissolved in hot distilled water for 25 min. After dissolving, the oil phase is mixed with the water phase and stirred again until the temperature drops to 40 °C. Then, *A. camansi* leaf extract was added, mixed with glycerin, and stirred until homogeneous [13-15]. The lotion formulation was tested for sunscreen activity by measuring its SPF value and physical properties. The

Table 1. Lotion formulation of *A. camansi* leaf ethanol extract

Phase	Ingredient	Concentration (%)					
Oil phase	Cetyl alcohol	0.5	0.5	0.5	0.5	0.5	0.5
	Stearic acid	3	3	3	3	3	3
	Lanolin	1	1	1	1	1	1
Water phase	Methyl paraben	0.1	0.1	0.1	0.1	0.1	0.1
	Triethyleneamine (TEA)	0.75	0.75	0.75	0.75	0.75	0.75
	Aquadest	92.65	90.65	90.15	87.65	85.15	80.65
Leaf extract/subfraction *A. camansi*		-	2	2.5	5	7.5	12
Glycerin		2	2	2	2	2	2

*The composition of all ingredients is made in the composition of v/v except the extract using the composition of w/v

positive control used was a commercial lotion with an SPF30 value.

Determination of SPF value of extract, subfraction, and lotion of A. camansi *leaves*

Extracts and subfractions, pure compounds of *A. camansi* leaves were made with variations in concentration from 2.0, 2.5, 5.0, 7.5, and 12%. Then the absorbance value was measured using a UV spectrophotometer at a wavelength of 290–320 nm with intervals of 5 nm. Fraction and subfraction lotion were made as much as 0.5 g dissolved in 25 mL ethanol (20.000 ppm) and tested for SPF [16]. All measurements were repeated 3 times. The effectiveness of the extract/subfraction/pure compound as a sunscreen can be seen from the SPF value, which can be measured using the Mansur equation in Eq. (1) [17];

$$\mathrm{SPF} = \mathrm{CF} \times \sum_{290}^{230} \mathrm{EE}(\lambda) \times \mathrm{I}(\lambda) \times \mathrm{Abs}(\lambda) \quad (1)$$

where EE (λ) = spectrum of erythermal effects, I (λ) = solar intensity, Abs (λ) = absorbance of sunscreen product, CF = correction factor (=10), and the values of EE × I are constants (Table 2) [18].

Table 2. Values of EE × I

Wavelength (nm)	EE × I (normalized)
290	0.0150
295	0.0817
300	0.2874
305	0.3278
310	0.1864
315	0.0839
320	0.0180

The examination of the lotion

The examination of the lotion is carried out on sunscreen activity as well as the physical properties of the lotion, i.e., pH [19], the power of spreadability [20], type emulsion [21], viscosity [15], and the power of adhesive [22].

Molecular docking and physicochemical analysis

Molecular docking was performed to study the molecular interactions of active compounds from the ethanolic extract of *A. camansi* with two selected human skin proteins. The receptors are human neutrophile collagenase (PDB ID: 1BZS) and fibroblast collagenase-1 (PDB ID: 966C) The 3D structures of macromolecules were obtained from the Protein Data Bank (http://www.rcsb.org/pdb/) accessed on September 01, 2022. Meanwhile, the 3D form of the compound of *A. camansi* was obtained from PubChem (https://pubchem.ncbi.nlm.nih.gov/). The docking process is carried out using Autodock Vina, emulated with PyRx software, and using a blind docking type. The ligand molecule will interact on the receptor's active site and give the binding affinity value. The interaction of the ligand with the receptors was visualized using Discovery Studio Visualizer [23]. The physicochemical activity of the compound from *A. camansi* extract was then evaluated using SwissADME [24]. Chemical characteristics such as lipophilicity (log P) and skin permeability (log K_p) were determined using the simplified molecular input line entry system (SMILES) structure of the active compounds.

■ RESULTS AND DISCUSSION

Phytochemical Profile of *A. camansi* Leaves Extract

A phytochemical test is a preliminary stage in identifying the content of secondary metabolites of a natural material [25]. The results of the phytochemical test of the leaves of *A. camansi* can be seen in Table 3. Table 3 shows that the leaves of *A. camansi* contain secondary metabolites of alkaloids, steroids, tannins/phenolics, flavonoids, and saponins. The presence of steroids is indicated by the formation of a green color when reacted with Liebermann-Burchard reagent. Phenolic compounds were characterized by a dark blue color formation when the extract was reacted with $FeCl_3$. This is due to the formation of a coordinating covalent bond between the iron(III) ion and the phenolic OH group. The reaction equation is as shown in Eq. (2) [26];

$$FeCl_3 + 6[ArOH] \rightarrow 6H^+ + 3Cl^- + [Fe(OAr)_6]^{3+} \quad (2)$$

The presence of flavonoids in the leaves of *A. camansi* was indicated by the formation of a red precipitate when reacted with Mg and HCl metals. This change was caused by the formation of a coordinating covalent bond between the magnesium ion and the OH group in the flavonoid compound [27].

The *A. camansi* plant contains phenolic compounds, including flavonoids, stilbenoids, arylbenzofurones, and neolignans which are distributed in the leaves, fruit, flowers, and skin. Total phenol and total flavonoid content of the ethanol extract of *A. camansi* leaves was relatively high, i.e., 47.46 mg GAE/g and 79.094 CE/g, respectively [10]. The flavonoids contained in the leaves of *A. camansi* are thought to play a significant role as antioxidants. Flavonoids and tannins/phenolics are well known natural molecules with good UV protection [11]. *A. camansi* can be used as a sunscreen to protect the skin from exposure to UV rays.

SPF of Extract and Lotion of *A. camansi* Leaves

The sunscreen activity test on the ethanolic extract of *A. camansi* leaves was carried out to examine the sunscreen activity of the crude extract before being used as a lotion. In comparison, the sunscreen activity test on lotion was carried out to see the effect of the addition of a mixture of lotion ingredients on the activity of secondary metabolites as sunscreens. The graph of SPF values of crude extract and lotion containing ethanolic extract of *A. camansi*'s leaves was presented in Fig. 1. The ethanolic extract of *A. camansi* leaves has the highest SPF value with a concentration of 12% (36.520 ± 1.4445) while the lowest SPF value is owned by the extract with a concentration of 2% (32.205 ± 0.3621). Lotion from the ethanol extract has the highest SPF value with a concentration of 12% (29.740 ± 0.1360), while the lowest SPF value is owned by lotion with a concentration of 2% (28.716 ± 0.1557).

The SPF value is directly proportional to the concentration of the tested extract, the higher the concentration value of the tested extract, the higher the SPF value produced. This proves that the sample contains secondary metabolites with conjugated double bonds or OH groups directly related to their activity as sunscreens. The electronic transition in the conjugated

Table 3. Types of secondary metabolites in the ethanol extract of *A. camansi* leaves

Test	Observation	
	Color	Results
Alkaloids	Dragendorff: brown precipitate	(+)
	Mayer: white precipitate	(–)
	Wagner: reddish brown precipitate	(+)
Steroids	Green/blue	(+)
Terpenoids	Red/purple	(–)
Tannins/Phenolic	Dark blue	(+)
Flavonoids	Red precipitate	(+)
Saponins	There is foam	(+)

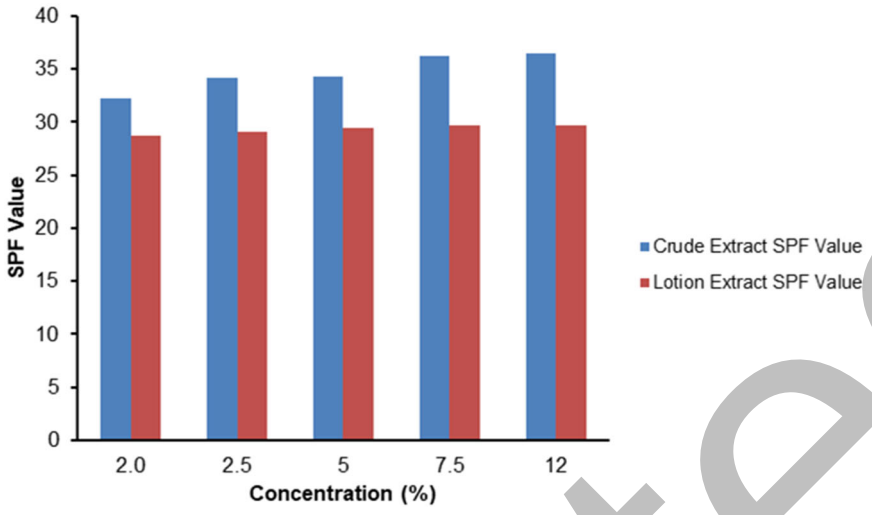


Fig 1. The graph of SPF values of crude extract and lotion containing ethanolic extract of *A. camansi* leaves

double bond has a lower energy to act as a sunscreen [4]. In addition, the SPF value of the extract and lotion of *A. camansi* leaves extract is in the ultra-category, namely > 15 [28], which indicates that *A. camansi* leaf is excellent for use as a sunscreen. The SPF value on the lotion decreased from the SPF on the crude extract. This is due to the addition of chemicals in the manufacture of lotion, which decreases sunscreen activity.

Lotion Physical Properties Testing

The results of the emulsion type test of the lotion are oil in water (o/w) type. The lotion was stored for 4 weeks, and the lotion properties of the ethanol extract of *A. camansi* leaves did not change, which indicated that the lotion was stable. The viscosity value of the lotion that was stored for 4 weeks increased due to the storage process and external environmental factors. External environmental factors that may occur are temperature changes. If the temperature of the storage area is high, the amount of distilled water will decrease, causing the viscosity value to increase. The viscosity value of lotion extract with a concentration of 2–12% is in the range of 3057.1–5001.1 cP, with the highest viscosity being 12% lotion and the lowest viscosity being 2% lotion. Thus the extract lotion has met the standard for semi-solid preparations based on SNI. 16-4399-1996 [29] is in the 2000–50000 cP range.

The acidity or pH test results on the lotion on storage time in each formulation of *A. camansi* leaves extract lotion are as follows. The lowest pH value is owned by lotion extract with a concentration of 12%, and the highest is owned by lotion extract 2%. This indicates that the sample of *A. camansi* leaf extract is acidic, so the more the extract is added to the lotion, the lower the pH of the lotion will be. A decrease in the pH value that is too low from the standard (< 4.5) can cause irritation and itching of the skin, while a pH value higher than the standard (> 8) can cause membrane disruption and disturbance of lipid domains [30]. This may be explained by the ionization of free fatty acids and their influence on lipid–lipid interactions [31]. The results of the measurement of the pH value that had been stored for 4 weeks experienced an insignificant decrease. The overall pH value of the lotion met the pH requirements of skin moisturization, which was in the range of 4.5–833, based on SNI 16-4399-1996.

The power spread of lotion that was stored for 4 weeks decreased. This is due to the evaporation of water contained in the lotion during storage. The spread of the lotion extract was in the range of 4.60–6.90 cm. The spreadability test aims to determine the ability to spread lotion preparations when applied to the skin. Semi-solid preparations that are comfortable to use are formulations that have a dispersion range of 5–7 cm [31]. Thus, lotion formulations with an extract concentration of 2 to 5% are convenient to use because they have dispersion that meets the standards. Lotion

with a concentration of 7.5 and 12% is inconvenient because the dispersion value is too low and does not meet the standards. The stickiness of the lotion that was stored for 4 weeks increased due to environmental and temperature factors that caused the distilled water to evaporate from the lotion, making it thicker. The value of the stickiness of the extract lotion was in the range of 14.55–25.03 s. Lotion preparations can be good if they have an adhesion value of more than 10 s [22].

Ethanol Extract Fractionation Results

The ethanol extract was separated by column chromatography, as much as 17.00 g, with the eluent using an elution gradient, namely: 100% *n*-hexane; 9.5:5 (*n*-hexane:ethyl acetate), and 100% ethyl acetate, 70 g of silica gel stationary phase, and obtained 126 fractions, after grouping by thin-layer chromatography, then obtained 5 subfractions, (A, B, C, D, and E), each weighing: 0.469, 0.433, 0.226, 0.918, and 2.203 g. Each subfraction group produced was tested for SPF value and made into lotion. The SPF value for the subfraction of ethanol extract and *A. camansi* leaf lotion presented in Fig. 2.

The highest SPF value in subfraction E with an average SPF of 32.110 ± 0.2410, and the lowest SPF value is owned by subfraction B with an average SPF of 29.864 ± 0.3003. The highest SPF value in subfraction E is suspected because it has the highest active compound as sunscreen compared to other subfractions.

The lotion of subfraction has the highest SPF value of 29.333 ± 0.1926, and the lowest SPF value is owned by lotion subfraction D, which is 28.234 ± 0.0876. Due to the addition of chemicals, the SPF subfraction value is higher than the SPF lotion subfraction value. The SPF subfraction and lotion subfraction values are in the ultra-category, namely > 15 [28], indicating the subfraction has good sunscreen activity.

Isolation of Pure Compounds from Subfraction E

Pure *A. camansi* leaf compound was isolated using gravity column chromatography. The subfraction E was studied further because it had the highest SPF value and the most significant number. Separation was conducted using 8:2 (*n*-hexane:ethyl acetate) eluent and obtained pure isolates, which showed one stain with 3 eluent systems, namely 100% (chloroform), 9:1 (*n*-hexane:ethyl acetate) and 5:5 (*n*-hexane:ethyl acetate), with respective R_f values of 0.4, 0.3 and 0.8. The test results of the pure isolate SPF value were 28.483 ± 0.1422, including a high SPF value, and were in the ultra-category and declared active as a sunscreen.

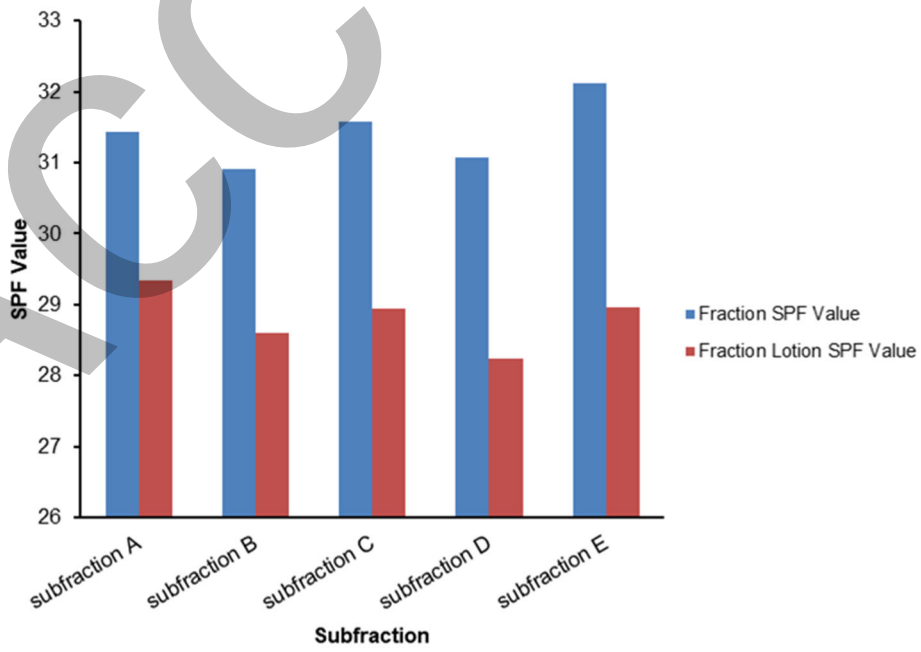


Fig 2. The comparison of the SPF value of the ethanol subfraction and the SPF value of *A. camansi* leaves lotion

The fragmentation pattern of the GC-MS results of the ethanolic extract of *A. camansi* leaves indicated the presence of chemical compounds including steroid secondary metabolites, whose retention times were very close together, so they seemed to combine. The study's results estimated the presence of β-sitosterol compounds, which may be combined with the epimer, namely γ-sitosterol. The MS spectrum of the GC-MS ethanol extract of *A. camansi* leaves, with several steroid compounds having very close retention times, as shown in Fig. 3.

Based on the fragmentation pattern, the above spectrum is estimated to be the fragmentation of the γ-sitosterol compound with a relative molecular mass (*m/z*) of 414 obtained from the molecular formula of $C_{29}H_{50}O$. The breakdown of 396 *m/z* resulted from the release of H_2O from the $C_{29}H_{49}^+$ ion, while the breakdown of the 43 *m/z* base peak was the release of $C_3H_7^+$ molecular ions from the 8-molecule ion peak. The splitting of *m/z*, i.e.,55, 69, 255, 273, 329, and others, is a fragmentation pattern of the breakdown of the C–C bond [32]. The results of the melting point measurement of the pure isolate were 147 °C. A literature search showed that the pure isolate was suspected of γ-sitosterol, which is a steroid compound [33]. The fragmentation pattern of the γ-sitosterol can be seen in Fig. 4 [34].

The discovery of γ-sitosterol in the ethanolic extract of *A. camansi* leaves adds to the variety of chemical compounds in *A. camansi* plants included in the steroid secondary metabolite group. Previous studies have found β-sitosterol propionate in the ethyl acetate

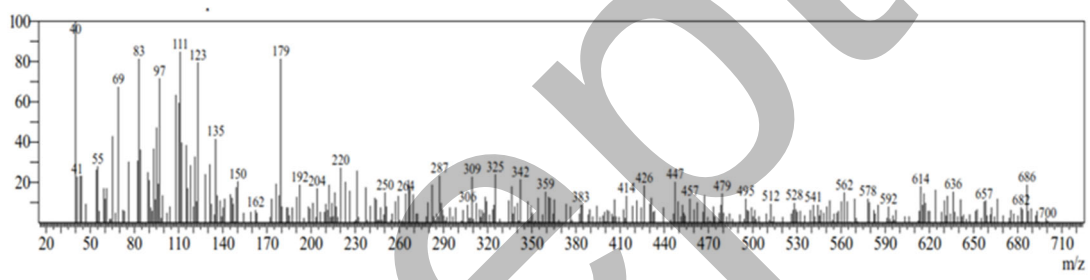


Fig 3. Mass spectrum of ethanol extract of leaves of *A. camansi*

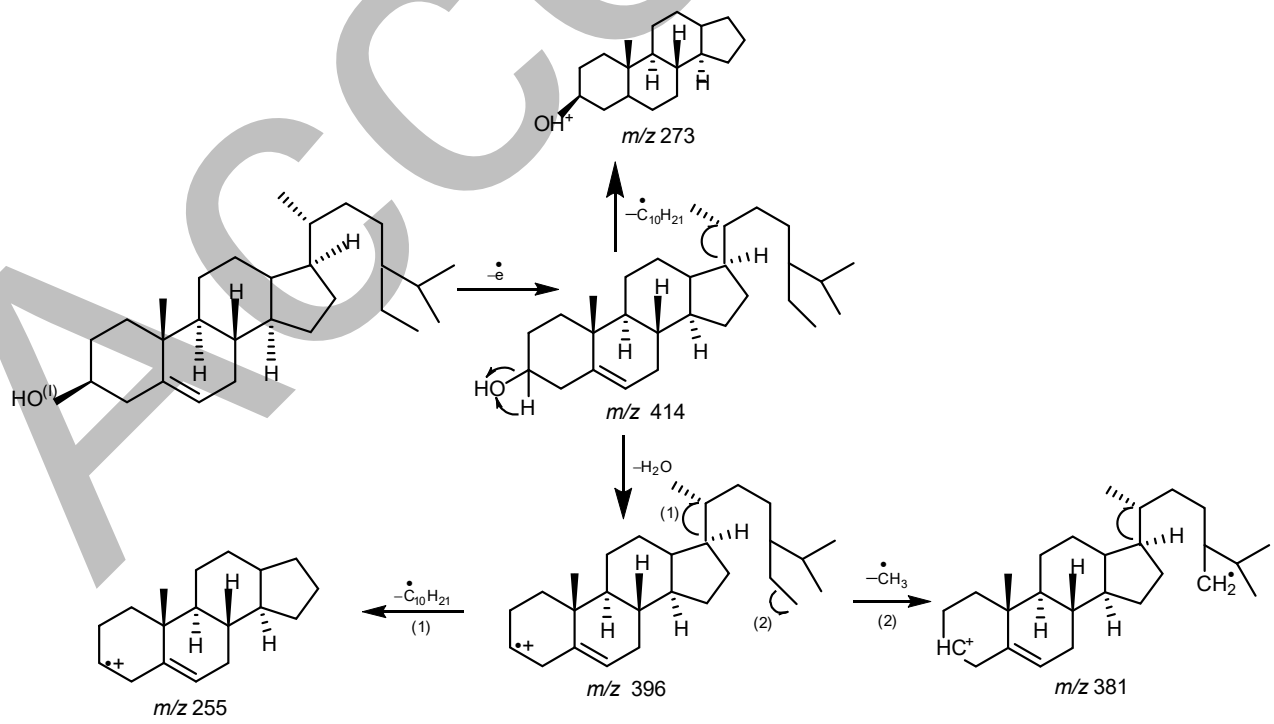


Fig 4. Fragmentation pattern of γ-sitosterol molecular ion

extract of the leaves of *A. camansi* [5] and β-sitosterol in the bark of *A. camansi* [6]. Steroid compounds β-sitosterol and γ-sitosterol have the same mainframe. The difference is in the position of the C-C24 atom, namely in the β-sitosterol position at the top or front, while the γ-sitosterol is in the behind or below position. This position shows that β-sitosterol is a mirror image of γ-sitosterol (epimer). This causes differences in the melting points of the two compounds, where β-sitosterol melts in the temperature range 140–143 °C, while γ-sitosterol is 147–148 °C. However, these two compounds have antihyperglycemic and anticancer activity for γ-sitosterol [6,34-35]. The structure of β-sitosterol and the structure of γ-sitosterol are in Fig. 5 [6].

The activity of sunscreens on γ-sitosterol compounds is related to the structure, namely the presence of a double bond and the presence of 4 cyclic cyclohexane C atoms, which is also considered a double bond [4]. Compounds with double bonds can function as sunscreens by reducing the energy of UV rays exposed to objects coated with these compounds or the presence of phenolic compounds that can neutralize free radicals [4].

The *in silico* method used human neutrophile collagenase receptors and fibroblast collagenase-1. These receptors were obtained from the RCSB PDB database. Interaction of γ-sitosterol with human neutrophile collagenase receptors has a binding affinity value of −7.4 kcal/mol and fibroblast collagenase-1 −8.2 kcal/mol. The interaction involved in the β-sitosterol bond with the receptor is hydrophobic, namely pi-sigma and alkyl. This interaction can be seen in Fig. 6(a) and 6(b).

The γ-sitosterol has chemical characteristics of lipophilicity with a log P value of 4.79, which exhibits high solubility in lipid. log K_p is approximated with a value

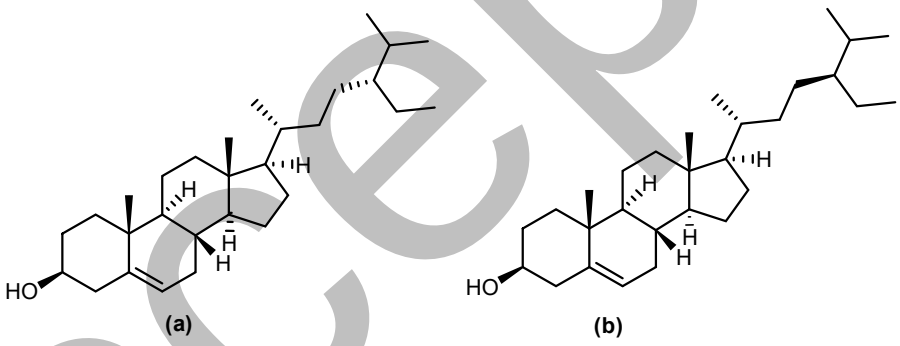
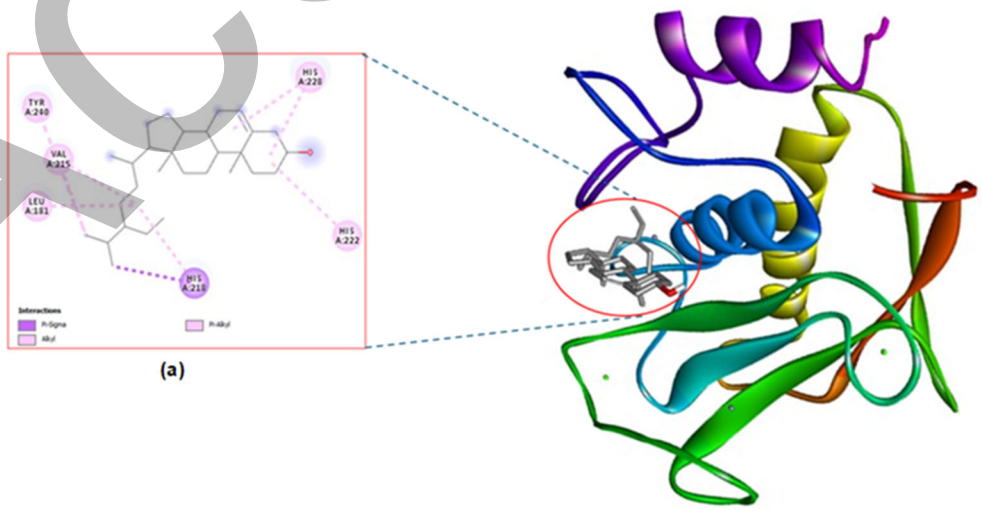


Fig 5. Structure of (a) β-sitosterol and (b) γ-sitosterol



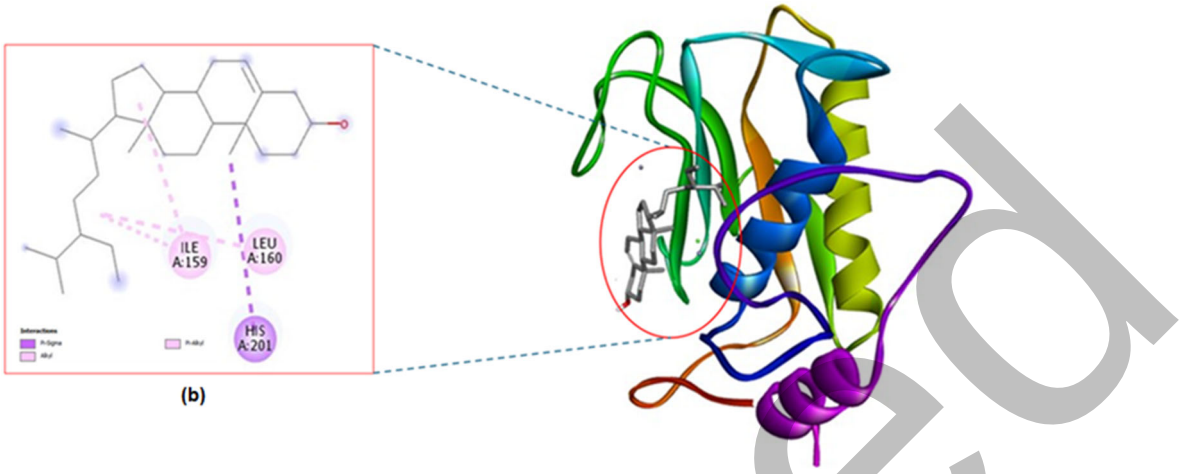


Fig 6. Visualization of non-covalent interactions on (a) receptor fibroblast collagenase-1 and (b) human neutrophile collagenase with γ-sitosterol

of −2.20 cm/s. The more negative the log K_p (with K_p in cm/s), the less skin permeant the molecule, indicating a lower ability to pass through the skin barrier and reach systemic circulation. A more negative log K_p value suggests slower diffusion or absorption through the skin, making the molecule less likely to be absorbed transdermally. The permeability of γ-sitosterol is estimated to be significant because it is firmly bound in the lipid bilayer of human skin. It has a molecular weight of 414.71 g/mol and a log P value 4.79. The presence of active compounds in the ethanolic extract of *A. camansi* lotion can support the activity of the SPF so that it can be used as a sunscreen.

■ CONCLUSION

Lotion of ethanol extract, subfraction, and pure compound of *A. camansi* leaf has a value of SPF in the ultra-category. The highest is owned by lotion with a concentration of 12% (29.740 ± 0.1360), and the lowest SPF value is owned by lotion with a concentration of 2% (28.716 ± 0.1557). The lotion meets the requirements according to SNI 16-4399-1996. Isolation of the pure compound had a melting point of 147 °C, which was thought to be γ-sitosterol. From molecular docking data, γ-sitosterol has the highest binding affinity value of −7.4 and −8.2 kcal/mol to human neutrophile collagenase and fibroblast collagenase-1. Its presence in the ethanolic extract of *A. camansi* lotion can support the SPF activity to be used as a sunscreen formula.

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■ CONFLICT OF INTEREST

All authors declare no conflicts of interest.

■ AUTHOR CONTRIBUTIONS

Conceptualization, methodology: Rosnani Nasution, Rafna Azura, and Muhammad Bahi. Analysis: Muhammad Bahi, Rosnani Nasution, and Marianne. Investigation and supervision: Rosnani Nasution, Rafna Azura, Nur Balqis Maulydia, and Muhammad Bahi. Writing draft preparation: Rosnani Nasution, Reza Akbar Bastian, and Michelia Mutiara Hilda. Review and editing: Muhammad Bahi and Marianne. All authors have approved this article for publication.

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