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Antioxidant and Antiaging Properties of Ethanolic Ripe Sesoot Fruit Extract

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Abstract

Skin aging can be characterized by changes in skin, such as the appearance of wrinkles and loss of skin moisture. Some elements that might lead to cell damages and aging are free radicals through the increase of the activities of hyaluronidase and tyrosinase. Bioactive compounds found in sesoot (*Garcinia picrorhiza* Miq.) are known for their antioxidant properties, which may reduce excessive amounts of free radicals in the body and act as an antiaging agent by inhibiting hyaluronidase and tyrosinase activities. This study aimed to examine the antioxidant, anti-hyaluronidase, and anti-tyrosinase properties found in Ethanolic Extract Ripe Sesoot (EERS). The ethanol extract of ripe sesoot fruit obtained from LIPI, Bogor Botanical Garden was used for the antioxidant and antiaging assays conducted at PT Aretha Medika Utama in December 2016. The activity of antioxidants was measured as the Ferric Reducing Antioxidant Power (FRAP) of the EERS, while the antiaging assays were performed through the inhibition activity of hyaluronidase and tyrosinase. Results indicated that the EERS has a higher FRAP activity (17.58 µM Fe (II)/µg) than xanthone (2.54 µM Fe (II)/µg) at the highest concentration of sample of 5,000 µg/mL. The anti-hyaluronidase of the EERS exhibited lower activity (IC50 of 619.21±12.15 µg/mL) than xanthone (IC50 of 365.55±25.10 µg/mL) and the tyrosinase inhibitory assay demonstrated a lower activity of EERS (IC50 of 1060.68±12.81 µg/mL) compared to xanthone (IC50 of 218.33±9.73 µg/mL). To conclude, EERS shows antioxidant and antiaging properties.

Keywords: Antioxidant**,** *Garcinia picrorhiza***,** hyaluronidase, skin aging, tyrosinase

Introduction

Aging is a progressive physiological change in an organism that causes senescence. It happens naturally in the human body. Aging is defined as the result of genetic programming and accumulation of environmental damage.[1,2] Functional changes associated with aging of the skin can result in rough, dry skin, decreased sweat, sebaceous gland secretions, and increased skin pigmentation, which can then cause hyperpigmentation, hypomelanosis guttate, and other irregular pigmentation.[3]

Skin aging is also highly related to hyaluronidase and tyrosinase. Hyaluronidase is an enzyme known to degrade hyaluronic acid by reducing its viscosity. Loss of hyaluronic acid leads to wrinkles and a decline in skin moisture.[4] The enzyme tyrosinase regulates Mammal skin, eyes, and hair pigmentation. These enzymes are crucial for initial immunological responses, wound healing, and pigmentation.[5]

However, the mechanism of the aging process has yet to be agreed upon unanimously among all gerontologists. The proposal of Denham Harman, which states that "free radicals are related to the chemical reactions at the bases of aging," is beginning to be well accepted.[6]

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Prior research has suggested that accumulating endogenous damage from reactive oxygen species (ROS) accelerates skin senescence. Non-free radical species like hydrogen peroxide (H_2O_2), superoxide anion radicals (O_2^-), and hydroxyl radicals (OH) are only a few examples of the extremely reactive, oxygen-containing species that are classified as ROS.[6]

On the other hand, *Garcinia* is known for its abundant source of phytoconstituents. It has been reported that all species from *Garcinia* contain some amount of garcinol, including Garcinia picrorhiza. Garcinol possesses a molecular weight of 602 and molecular formula represented by $C_{38}H_{50}O_6$. Garcinol is also known as camboginol and is similar to curcumin in structure. This chemical compound has been known to have many biological activity capacities, such as antioxidants and antimicrobials. This compound was also shown to scavenge free radical 1,1-diphenyl-2-picrylhydrazyl better than α-tocopherol, a well-established antioxidant. On top of that, it has been reported that garcinol might repress DNA damage by scavenging hydroxy radicals.[7] Garcinia picrorhiza is a woody plant natural to the islands of Maluku and Sulawesi and raised in equatorial climates [8,9]. Studies examining sesoot (*Garcinia picrorhiza* Miq.)'s bioactivity potential are quite limited, specifically its properties in inhibiting skin aging enzymes. Based on these, Ethanolic Extract Ripe Sesoot (EERS) was evaluated to discover its potential as an antioxidant and antiaging agent.

Methods

The *Garcinia picrorhiza* Miq. fruits used in this research were gathered from LIPI, Botanical Garden, Bogor, West Java, Indonesia. By Botanical Garden's herbarium personnel, *G. picrorhiza* Miq. fruits were precisely identified. The sampling method employed in this study is purposive sampling. A total of 500 g of fruits were crushed and then extracted with 70% distilled ethanol by maceration. The ethanol would then be filtered, and waste would be remacerated three times every 24 hours. The extract was then produced by collecting and utilizing a rotary evaporator to condense the filtrate from ethanol maceration. The rotary evaporator was set to 50°C..In preparation for future assays, the paste-formed extract was preserved at -20°C.[10] The standard used for this research was xanthone (Sigma, X0626). Xanthone was used as the standard on account of strong antioxidant value. A previous study reported that xanthone possessed an IC_{50} value of 4.21 µg/mL [11]. The extract and xanthone were then made into several final concentrations for each assay.

Assays of antioxidant and antiaging were conducted at PT Aretha Medika Utama in December 2016. The FRAP assay employed in this study was adapted from Widowati et al.[12] Reagent for FRAP assay was composed by freshly combining 10 mL of acetate buffer 300 mM pH 3.6 with 2.5 mL of 2,4,6-Tris(2-pyridyl)-s-triazine (TPTZ) (Sigma 3682-35-7, USA) 10 mM dissolved in 10% HCl 40 mM. The solution mixture was stored in an incubator at 37°C for 10 minutes. A 96-well microplate, accommodating a maximum of 7.5 µL of samples, was combined with 142.5 µL of the FRAP reagent and subsequently incubated at 37^0C for 30 minutes. The absorbance measurement at 593 nm was done by a microplate reader (Thermo Scientific Multiscan GO). $FeSO_4$ values varying from 0.019 to 95 µg/mL were utilized as the guidelines for standard curve. Results data from the samples were displayed.in µM Fe(II)/µg extract. The FRAP procedure is grounded on an antioxidant's capability to decrease (electron transfer) Fe^{3+} to Fe^{2+} ions in the appearance of TPTZ (2,4,6-tris(2-pyridyl)-s-triazine), resulting in the development of a Fe^{2+}-TPTZ complex with a bright blue color [13].

Hyaluronidase inhibitory activities were assessed using methods from Kolayli et al.,[14] and Sigma Aldrich with modifications from Widowati et al.[15] As much as 25 µL samples with various concentrations (0 to 166.67 µg/mL) were combined with 100 µL hyaluronidase (2 – 4 U/mg) (Sigma H3506, USA), 77 mM sodium chloride, 100 µL buffer phosphate (200 mM, pH 7, 37°C), and 0.01% BSA. The mixture was cultivated for 10 minutes at 37°C. A total 100 µL of hyaluronic acid substrate (Sigma H5542, USA) containing 0.03% in. 300 mM. sodium phosphate (pH 5.35) was.added.to the previous solution and cultivated.at 37°C. for 45 minutes. Hyaluronic decomposition was inhibited using 100 µL acidic albumin acid that contained 24 mM sodium acetate, 0.1% BSA, and 79.mM acetate acid (pH 3.75). After incubating the combined solution for 10 minutes at room conditions, absorbance measurement took place at a wavelength of 600 nm.

Inhibitory.activity :

$$\left(1-\frac{c-s}{c}\right)x\,100\left(1-\frac{c-s}{c}\right)x\,100$$

The formula above calculates the inhibitory activity of hyaluronidase. The C represents the absorbance of solutions without hyaluronidase, and S represents sample solutions.

The tyrosinase inhibitory activity assay was examined employing a modified procedure by Sandhu et al.,[16] Tu et al.,[17] and Widowati et al.[15] The sample was first procured in a 96 well-plate before the addition of 20 µL tyrosinase enzyme from fungal organisms (125 U/mL in potassium phosphate buffer), 140 µL of 20 mM potassium phosphate buffer (pH 6.8), and a 20 µL sample with various concentrations. Following this, the mixture underwent incubation at ambient temperature for a duration of 15 minutes. 20 µL of 1.5 mM L-DOPA was supplemented to the solution after the initial incubation period, and then it was re-incubated at room temperature for 10 minutes. The tyrosinase inhibitory activity was evaluated by determining the amount of DOPA generated and quantified at a wavelength of 470 nm.

Tyrosinase.Inhibitory Activity (%):

$$\frac{A-B}{A} x\ 100 \frac{A-B}{A} x\ 100$$

The formula above represents the Tyrosinase Inhibitory Activity, where A denotes the absorbance of the control sample and B denotes the absorbance of the test sample.

Statistical analyses were performed using One-Way ANOVA followed by the Tukey HSD Post Hoc test, with significance set at P<0.05P <0.05P<0.05. The data are presented as the mean ± standard deviation. All analyses were conducted using IBM SPSS Statistics version 25 (IBM Corp., Armonk, NY, USA).

Results

The basic principle of FRAP is to measure the decreasing concentration of the ferroin analog that occurs within the mixture. Tripyridyltriazine's Fe^{3+} complex Fe $(TPTZ)^{3+}$ is converted to $Fe(TPTZ)^{2+}$ by antioxidants in an acidic environment, and the latter exhibits a vivid blue color, measured at 593 nm.[18] The result of the FRAP assay belonging to EERS and xanthone is shown in Figure 1.

The current study's findings demonstrate that FRAP activity is concentration-dependent, with greater concentrations leading to increased FRAP activity (Figure 1). EERS exhibits stronger FRAP activity than xanthone (17.58 ± 0.48 µM Fe (II)/µg) at the maximum concentration of 5000

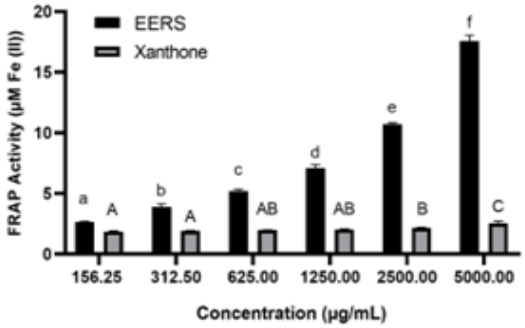

Figure 1 FRAP Activity of EERS and Xanthone

*Note: EERS and xanthone were diluted using DMSO to attain the final concentration of 156.25; 312.50; 625.00; 1250.00; 2500.00; 5000.00 µg/mL. The data is exhibited as means±standard deviations (SD). Varied letters (a, b, c, d, e, f) show significant contrasts among EERS concentrations and (A, AB, B, C) among xanthone concentrations, based on Tukey HSD test

µg/mL. This data indicates that EERS has lesser antioxidant activity in FRAP assay than xanthone (2.54 ± 0.18 µM Fe (II)/µg).

A particularly sensitive spectrophotometric technique was implemented to measure the inhibitory activity of hyaluronidase. The procedure is based on hyaluronidase acid precipitation with cetylpyridinium chloride, which is typically done for large-scale screening

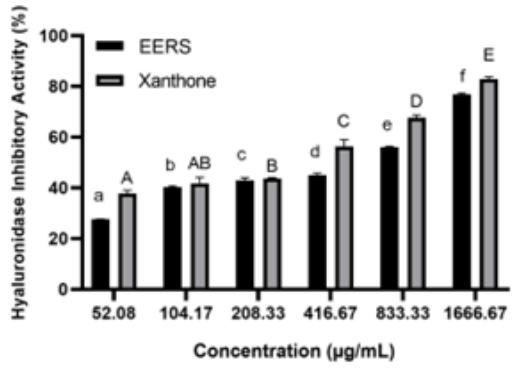

Figure 2 Hyaluronidase Inhibitory Activity of EERS and Xanthone

Note: EERS and xanthone were diluted using DMSO to reach the final concentration of 52.08; 104.17; 208.33; 416.67; 833.33; 1666.67 µg/mL. The data is exhibited as means±standard deviations (SD). Varied letters (a, b, c, d, e, f) show significant contrasts among EERS concentrations and (A, AB, B, C, D, E) among xanthone concentrations, based on Tukey HSD test

Table 1 IC_{50} Value Hyaluronidase Inhibitory Activity by EERS and Xanthone

Sample	Linear Equation	R^2	IC_{50} (µg/mL)
EERS	y = 0.0263x + 33.693	0.94	619.21 ± 12.15
Xanthone	y = 0.0277x + 39.856	0.95	365.55±25.10

Note: Linear equations, coefficient of regression (R^2) and IC_{50} of each sample were calculated. IC_{50} of each sample was calculated

Table 2 IC_{50} Value of Tyrosinase Inhibitory Activity by EERS and Xanthone

Sample	Linear Equation	r^2	IC_{50} (µg/mL)
EERS	y = 0.0449x + 2.4182	0.94	1060.68 ± 12.81
Xanthone	y = 0.1518x + 16.845	0.95	218.33 ± 9.73

Note: Linear equations, coefficient of regression (R^2) and IC_{50} of each sample were calculated. IC_{50} of each sample was calculated

of hyaluronidase inhibitors.[19] The result of this assay can be applied to assess antiaging activity of EERS and xanthone. The hyaluronidase inhibitory action of EERS and xanthone is depicted in Figure 2, whereas IC_{50} values are shown in Table 1.

Figure 2 proves the concentration dependence of hyaluronidase inhibitory action. At the. uppermost concentration of 1666.67 µg/mL, the hyaluronidase inhibitory activity of EERS (76.83±0.53%) is lower than that of xanthone (82.97±0.73%). In addition to that, the IC_{50} value of EERS (619.21±12.15 µg/mL) was also shown to be upper than that of xanthone (365.55±25.10 µg/mL) (Table 1). These two findings imply that, compared to xanthone, EERS has less hyaluronidase inhibitory action.

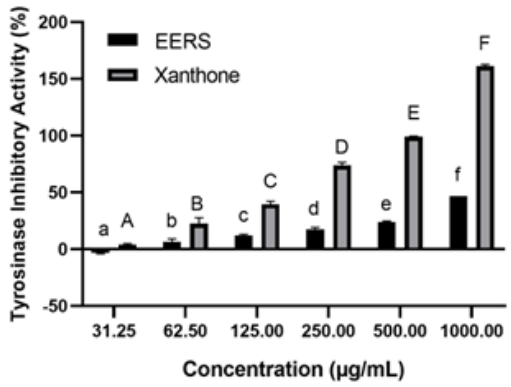

Figure 3 Tyrosinase Inhibitory Activity of EERS and Xanthone

Note: EERS and Xanthone were diluted with DMSO to reach the final concentration of 31.25; 62.50; 125.00; 250.00; 500.00; 1000.00 µg/mL. The data is exhibited as means±standard deviations (SD). Varied letters (a, b, c, d, e, f) show significant contrasts among EERS concentrations, and (A, B, C, D, E, F) between xanthone concentrations, based on Tukey HSD test

Tyrosinase inhibitory.activity was quantified to help determine EERS ability to detail the formation of melanin during melanogenesis. L-tyrosine (mono-phenol) has the potential to undergo hydrolysis into L-DOPA (di-phenol) catalyzed by tyrosinase, and subsequently, L-DOPA can be oxidized to form a dopaquinone (a quinone compound). Dopachrome is created when dopaquinone spontaneously reacts.[20]

The outcome of the assay has shown that tyrosinase inhibitory activity is concentration-dependent (Figure 3). At 1000 µg/mL, the highest concentration, EERS has lower inhibitory activity than xanthone, with a value of 46.55±0.09% as opposed to 161.20±1.36% from the latter. The IC_{50} value of EERS (1060.68±12.81 µg/mL) is higher than that of xanthone (218.33±9.73 µg/mL) (Table 2). This suggests that compared to xanthone, EERS has less antiaging action through tyrosinase inhibition.

Discussion

Sesoot is a species that belongs to the genus Garcinia, a well-known genus that possesses various pharmacological properties. According to reports, sesoot contains many bioactive compounds, such as xanthones, biflavonoidsa, and benzophenons.[21] *Garcinia* is usually used as a dietary supplement because of its antioxidant and antiaging activities.[22] In this study, EERS was examined for its potential as an antioxidant

through the FRAP assay and as an antiaging agent through the assays of the inhibitory activity of hyaluronidase and tyrosinase.

A FRAP assay was undertaken to measure antioxidant activities in reducing Fe^{3+} ions at low pH and causing the formation of the ferric-colored tripidilltriazin complex.[23] This finding. is consistent.with prior studies indicating that EERS has stronger antioxidant activity through H_2O_2 scavenging action when compared to xanthone. The current study found that EERS had higher antioxidant activity through FRAP inhibitory activity when compared to xanthone.[24] While α-mangostin had minimal activity, the extract and all fractions of *G. mangostana* had solid 2,2-diphenyl-1-picrylhydrazyl (DPPH) scavenging activity.[23] In another study, EERS showed antioxidant activity by reducing ABTS free radicals.[24] Because of its capacity for scavenging, xanthone can also reduce the levels of DPPH and Fe^{3+}.[25]

Hyaluronan (HA, also known as hyaluronic acid) is a matrix-substantial tissue component and possesses a role in skin growth and development. Hyaluronic acid possesses the ability to keep the skin moisturized and well-hydrated. In the process of aging, the skin loses this critical component as a result of hyaluronidase activity. Hyaluronidase (Haases) can specifically degrade Hyaluronic Acid (HA), a large structural polysaccharide found exclusively within the Extracellular Matrix (ECM).[10] From this study, hyaluronidase inhibitory activity of EERS is lower than xanthone. However, other studies have shown that *G. indica* methanolic extract has a notable hyaluronidase inhibitory activity of 88.83%.

The tyrosinase enzyme is dependable for catalyzing the oxidation of L-DOPA to *o*-quinone with the help of L-tyrosine's (monophenol activity) hydroxylation. Both of these reactions help induce the production of the pigment melanin.[26] Microbial melanin is typically synthesized through either the DOPA (3,4-dihydroxyphenylalanine) pathway or the DHN (1,8-hihydroxynaphtalene) pathway. In the DOPA pathway, tyrosine is converted into levodopa, then dopaquinone, facilitated by enzymes like tyrosinase and laccase. Dopaquinone spontaneously polymerizes to form melanin.[27] In addition, many inhibitors of tyrosinase, such as kojic acid and arbutin, have been reported and evaluated as cosmetics and medicals to detain melanin production.[28,29] Based on research, the tyrosinase inhibitory activity of EERS is lower than that of xanthone. This study showed that EERS had more significant antioxidant activity than xanthone in the FRAP assay but less than xanthone in the hyaluronidase and tyrosinase inhibitory activity assay. However, this study is constrained by its limitations, as we have yet to characterize EERS with LC-MS/MS to discover its specific compounds that might be responsible for antioxidant and antiaging activity.

Previous research indicated that the methanol extract of *G. indica* exhibited hyaluronidase inhibitory activity within the concentration range of 500 to 750 µg/mL. Specifically, the methanol extract at a concentration of 1000 µg/mL demonstrated a hyaluronidase inhibitory activity of 90.5±0.01%. In contrast, the water fraction of *G. indica* did not show any significant hyaluronidase inhibition, even at very low concentrations.[30]

Based on the collected data, the EERS extract demonstrated superior activity in the FRAP antioxidant, anti-tyrosinase, and anti-hyaluronidase assays at the highest concentrations tested. The IC50 values for anti-hyaluronidase and anti-tyrosinase activities were 619.21±12.15 µg/mL and 1060.68±12.81 µg/mL, respectively. Additionally, the FRAP antioxidant test recorded a measurement of 17.58±0.48 µM Fe(II), surpassing the value observed for xanthone. These findings indicate that the EERS extract possesses notable antioxidant properties and exhibits effective inhibitory effects on enzymes associated with anti-aging mechanisms.

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