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Anti-inflammatory Potential of Mangosteen Pericarp Extract (*Garcinia mangostana* L.)

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ABSTRACT

Mangosteen pericarp (*Garcinia mangostana* L.) has been used as an active ingredient in numerous traditional medicine formulations. However, their function as an anti-inflammatory agent has yet to be fully understood. Macrophage migration inhibitory factor (MIF) is a mediator that is essential for the development of pro-inflammatory reactions. Hence, MIF activity is often associated with inflammatory diseases and its inhibition could therefore be used as an approach to assess the potential of a material as anti-inflammatory agent. In this study, MIF was exposed with mangosteen pericarp extracts in order to assess the possible anti-inflammatory effect of the extract. The type of mangosteen pericarp extract that possesses the greatest potential as MIF inhibitor and its IC_{50} value were determined. Based on the results, n-hexane extract of mangosteen pericarp possesses the activity as MIF inhibitor with an IC_{50} of 4.24 mg/L, and therefore could potentially be used as an anti-inflammatory agent.

Keywords: *Garcinia mangostana* (L); Pericarp extract; Anti-inflammation; MIF

INTRODUCTION

Living mammals respond to inflammation as a local body defense mechanism to prevent the spread of injurious agents (Malleshappa et al., 2018). Several soluble molecular messengers and immune cells are involved in the inflammation process, including cytokines, chemokines, and innate and adaptive immune cells (Nahand et al., 2020). Inflammation should be disabled after the triggering stimulus has been eliminated and the injury has been resolved. However, if the body fails to resolve the inflammation, it may lead to several health problems that involves chronic inflammation.

MIF is a pro-inflammatory cytokine that circulates in human plasma as a homotrimeric protein (Sumaiya et al., 2022). MIF is involved in various biological functions, such as leukocyte recruitment, inflammation, immune responses, cell proliferation, tumorigenesis, and the counter-regulation of glucocorticoids. Due to its multifaceted nature, MIF plays a central role in the progression of many chronic diseases that involve chronic inflammation, such as cancer, diabetes mellitus, and autoimmune diseases (Purvis et al., 2019; Sumaiya et al., 2022). Several studies have highlighted MIF's role in enhancing the production of inflammatory molecules (IL-1, IL-6, IL-8, nitric oxide, and TNF-α) as a critical factor in the progression of chronic diseases (Cao et al., 2023; Cardoso et al., 2018; Sumaiya et al., 2022), underlining the importance of finding materials that could be used as anti-inflammatory agents by inhibiting MIF activity.

Several studies have suggested that anti-inflammatory potential of a material could be investigated using MIF tautomerase activity inhibition approach (Kok et al., 2018; Nyotohadi & Kok, 2023). MIF enhances the production of inflammatory molecules by interacting with cluster of differentiation 74 (CD74) (Cheng et al., 2022; Cirillo et al., 2020). It is already known

that the interaction site of MIF-CD74 is situated near the p-hydroxyphenylpyruvate tautomerase active site of MIF and the enzyme active site is located at the interfaces of MIF monomer subunits (Wen et al., 2021). It has been identified that the binding of compounds near the active site could disturb the MIF-CD74 interaction (Cirillo et al., 2020; Zapatero et al., 2016).

According to several epidemiological studies, mangosteen pericarp is often used as an active ingredient in traditional medicines in South East Asia for chronic diseases that involve chronic inflammation (Ansori et al., 2020; Li et al., 2020). Mangosteen (*Garcinia mangostana* L.) is one of commonly grown fruit trees in South East Asia countries, such as Thailand, Indonesia, and Malaysia (Ansori et al., 2020; Failla & Gutiérrez-Orozco, 2017; Syahputra et al., 2021). It is reported that the pericarp of mangosteen fruit contains numerous phytochemicals with various health benefits. Some of the phytochemicals, such as garcinone E, gartanin, γ-mangostin, and smeathxanthone A, have been shown to possess anti-inflammatory properties (Gondokesumo et al., 2019; Xu et al., 2017). However, it is not fully understood how mangosteen pericarp exerts its anti-inflammatory effect. Thus, the mangosteen pericarp anti-inflammatory potential was evaluated in this study by its extract inhibition on MIF tautomerase activity. The extracts were evaluated as a whole without further component separation. From the screening process, n-hexane extract of mangosteen pericarp is identified as the one that possess the greatest potential as MIF inhibitor. The extract gave an IC_{50} of 4.24 mg/L, and could probably disrupt MIF pro-inflammatory activity and be used as an anti-inflammatory agent.

MATERIALS AND METHODS

Instruments

A rotary evaporator (Heidolph, Germany) was used to prepare the mangosteen pericarp extracts. The equipments used to produce and purify the recombinant MIF were incubator shaker (Yihder, Taiwan), refrigerated centrifuge (Thermo Scientific, Germany), and ultra sonicator (Tefic, China). A plate reader (BMG LABTECH, Germany) was used to measure the MIF tautomerase activity.

Chemicals and Reagents

The solvents from Merck (n-hexane, ethyl acetate, and ethanol 99.9%) were used to prepare the mangosteen pericarp extracts. Recombinant MIF was purified using Profinity™ IMAC Ni-charged resin (Biorad). SDS PAGE analysis was conducted with Precision Plus Protein™ dual color standards (Biorad). 4-hydroxyphenylpyruvate (4-HPP) from Difco Laboratories was used as the substrate of MIF. Ampicillin from Sigma Aldrich was used as the antibiotic in the 2YT medium.

Collection of Plant Material

The mangosteen fruits (*Garcinia mangostana* L.) originated in Blitar, East Java, Indonesia. This study used perfectly mature mangosteen fruits with purple and black outer skin. The fruits were authenticated by taxonomist from The Center for Information and Development of Traditional Medicine of the Faculty of Pharmacy, University of Surabaya, Surabaya, East Java, Indonesia.

Mangosteen Pericarp Extracts Preparation

Mangosteen fruits were washed with distilled water and peeled. The pericarp part of the mangosteen fruit was chopped, dried, milled, and sifted. Then the mangosteen pericarp powder was subjected to an extraction procedure using various organic solvents, namely ethanol (99.9%), ethyl acetate, and n-hexane. The extraction was carried out with maceration technique, using 1:10 (w/v) powder:solvent ratio, and incubated for 3 days at 25 °C. The extracts were then evaporated using a rotary evaporator to further eliminate the solvents. Until further use, the concentrated extracts of mangosteen pericarp were stored at 4 °C.

Recombinant MIF Production and Purification

Cultures of *Escherichia coli* BL21 (DE3) pET20b(+)-MIF were prepared by inoculating glycerol stocks into 500 mL of 2YT-ampicillin media (11 g/L yeast extract, 11 g/L NaCl, 22 g/L bacto™ tryptone, 0.1 g/L ampicillin). Then the cultures were incubated at 37 °C until their OD_{600} reached ~ 0.5. The intracellular MIF production by *E. coli* BL21 (DE3) pET20b(+)-MIF was induced by adding isopropyl β-thiogalactopyranoside (IPTG) at a final concentration of 0.05 mM and incubating the cultures overnight (37 °C, 175 rpm).

MIF purification process was started by separating the bacterial cells from the media with centrifugation method (4 °C, 4500 rpm, 15 min). The intracellular MIF was obtained by disrupting the bacterial cells with ultra sonification method (10 cycles at 30% amplitude with 15 s cycle duration and 45 s rest duration) while being cooled in the ice bath. Cell debris was removed by centrifugation and the cell-free extract was incubated overnight with 2 mL of Profinity™ IMAC Ni-charged resin in a gravity flow chromatography column (4 °C, 10 rpm). The chromatography column was then washed with 30 mL of washing buffer (10% glycerol, 50 mM Tris, pH 7.4) to remove the non-bound proteins. MIF was eluted from the chromatography resin with elution buffer (10% glycerol, 50 mM Tris, 500 mM imidazole, pH 7.4). The total protein concentration of each elution fraction was determined using Bradford method. Fractions with high protein concentration were pooled and stored at -80 °C for further use.

SDS PAGE Analysis of Purified Recombinant MIF

SDS PAGE analysis was used to separate and estimate the molecular weight of proteins contained in a solution. It was specifically performed in this study to observe the purity of the obtained recombinant MIF solution. The recombinant MIF solution was first diluted with 1x SDS sample buffer and incubated for 8 min at 60 °C. Together with the protein ladder, sample solution was then loaded onto 18% SDS gel and electrophoresis was performed in SDS-Tris-glycine buffer system (100 V for 60 min). The gel was then stained with Coomassie brilliant blue R-250 to estimate the molecular weight of the proteins.

Screening of Extracts That Have The Potential as MIF Inhibitor

An assay was carried out in triplicate to screen the extracts with potential as MIF inhibitor. The assay began with the preparation of test and control solutions. Test solutions were made by mixing 45 µL of MIF solution (1.1 µM in boric acid buffer 0.4 M, pH 6.2) with 5 µL of the extract solutions (1346 mg/L for the ethanol extract, 948 mg/L for the ethyl acetate extract, and 257 mg/L for the n-hexane extract; in DMSO). 45 µL of boric acid buffer (0.4 M, pH 6.2) was mixed with 5 µL of DMSO to make the negative control. The inhibitor control was made by mixing 45 µL of MIF solution (1.1 µM in boric acid buffer 0.4 M, pH 6.2) with $CuSO_4$ solution (50 µM). Meanwhile, the positive control was made as the negative control, except that the boric acid buffer was replaced with MIF solution (1.1 µM in boric acid buffer 0.4 M, pH 6.2). To begin the tautomerase reaction, 50 µL of 4-HPP solution (0.5 mM) was added to a UV-Star® half area 96-well microplate containing test and control solutions. The MIF residual tautomerase activity was observed at 306 nm (Nyotohadi & Kok, 2023). The extracts were then screened on the basis of their MIF residual tautomerase activity percentage. Extract with MIF residual tautomerase activity below 20% was chosen to be subjected to IC_{50} assay (protocol modified after Nyotohadi & Kok, 2023).

The IC_{50} Assay

The IC_{50} assay was conducted in triplicate, using the same volume for test and control solutions as the screening assay, but the test solutions were conditioned to have final extract concentrations of 2.15–8.21 mg/L in 5% DMSO (1.25 fold serial dilution). As in the screening assay, 50 µL of test and control solutions were transferred into a UV-Star® half

area 96-well microplate and added with 50 µL of 4-HPP solution (0.5 mM) to start the tautomerase reaction by MIF. The tautomerase activity of MIF was measured at 306 nm.

Data Analysis

The analysis of data was conducted using GraphPad Prism 8.0. Absorbance vs. time graph was first constructed. Calculating the ascending slope of absorbance vs time graph gave the reaction rate of MIF tautomerase activity. The residual tautomerase activity was then obtained by normalizing the reaction rate of MIF activity to the controls. Then, the percentage of residual tautomerase activity vs log [extract concentration] was constructed using the curve fitting feature to get the sigmoidal graph and IC_{50} value of the extract.

RESULTS AND DISCUSSION

Authentication of Plant Material

Center for Information and Development of Traditional Medicine of the University of Surabaya, Surabaya, East Java, Indonesia verified that the collected plant materials were mangosteen (*Garcinia mangostan*a L.) fruits.

Mangosteen Pericarp Extracts Preparation

Ethanol (99.9%), ethyl acetate, and n-hexane extracts were produced after the extraction process of mangosteen pericarp. Each extract gave a different yield: 10% is obtained from extraction with ethanol (99.9%), 9% from extraction with ethyl acetate, and 0.5% from extraction with n-hexane.

SDS PAGE Analysis of Purified Recombinant MIF

Figure 1A indicated that recombinant MIF was successfully purified. From the visualization of SDS gel electrophoresis results, it could be seen that the sample solution (SL) only gave one protein band with ~13 kDa molecular weight. The recombinant MIF has a molecular weight of ~13 kDa, hence this process was considered to yield a relatively pure recombinant MIF solution. MIF was reported to take part in the development of several chronic inflammatory diseases by enhancing the production of inflammatory molecules (Cao et al., 2023). Thus the purified MIF solution was then used in further assays as an approach to evaluate the anti-inflammatory potential of the produced mangosteen extracts.

Screening of Extracts That Have The Potential As MIF Inhibitor

The assay was conducted to measure the MIF residual tautomerase activity by detecting the presence of borate and enzymatic enol product of 4-HPP complexes in the solution (Nyotohadi & Kok, 2023). The extract with MIF residual tautomerase activity below 20% was chosen for further assays. The screening assay showed that all types of mangosteen pericarp extracts can inhibit MIF tautomerase activity (Figure 1B), but only n-hexane extract of mangosteen pericarp that gave residual tautomerase activity below 20% (3.25% ± 0.16%). Thus, the n-hexane extract of mangosteen pericarp (HMP) was chosen for IC_{50} assay. N-hexane extract of mangosteen pericarp was reported to contain various anti-inflammatory phytochemicals, such as gartanin and β-mangostin (Kameng et al., 2020). Thus, it may have the potential as an anti-inflammatory agent (Gondokesumo et al., 2019).

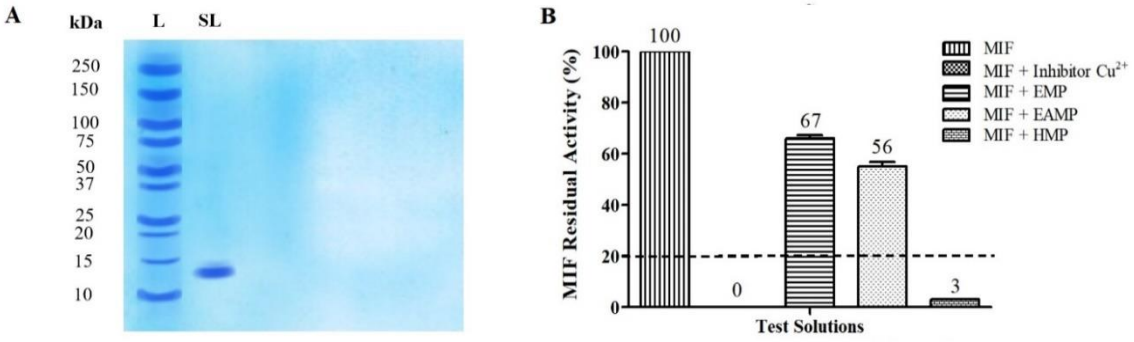

Figure 1. A is the visualization of SDS-PAGE gel electrophoresis (18% acrylamide), containing protein ladder (L) and sample solution (SL). One protein band (~13 kDa) was formed at SL lane. B is screening assay results of the positive control (MIF), inhibitor control (MIF + inhibitor Cu^{2+}), and the test solutions (MIF + EMP (ethanol extract of mangosteen pericarp), MIF + EAMP (ethyl acetate extract of mangosteen pericarp), and MIF + HMP (n-hexane extract of mangosteen pericarp).

IC_{50} Assay

In this assay, the MIF residual tautomerase activity was measured for the construction of the sigmoidal graph and determination of IC_{50} value of HMP extract. The result of the assay could be seen in Figure 2, in which the HMP inhibits MIF tautomerase activity with an IC_{50} of 4.24 mg/L. The IC_{50} is an important parameter that is often measured in many pharmaceutical studies (Bag, 2020; Chtita et al., 2021). The IC_{50} is described as the required concentration of an inhibitor to achieve 50% inhibition of an enzyme (Lei et al., 2020; Liu et al., 2020; Wang et al., 2019). In previous work with multi-strain probiotics extract, an IC_{50} of 7.80 mg/L was obtained for MIF tautomerase activity inhibition. Meanwhile, in other study, acetaminophen was reported to inhibit MIF tautomerase activity, with an IC_{50} of 10 mM (Senter et al., 2002). Hence, it was indicated that HMP has the potential as MIF tautomerase activity inhibitor and could possibly be developed as an anti-inflammatory agent.

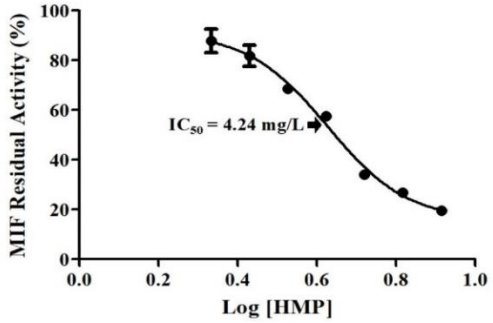

Figure 2. Sigmoidal graph of the percentage of MIF residual activity vs log [extract concentration] for MIF + HMP. It was shown that HMP gives an IC_{50} of 4.24 mg/L.

CONCLUSIONS

Mangosteen pericarp has been used as active ingredient in numerous traditional medicines in South East Asia, to treat chronic diseases that involve chronic inflammation. The results of this study indicated the possible anti-inflammatory effect of the mangosteen pericarp extract. It was shown that n-hexane extract of mangosteen pericarp has the potential as MIF tautomerase activity inhibitor, with an IC_{50} of 4.24 mg/L. Hence, mangosteen pericarp could possibly be developed as an anti-inflammatory agent.

List of Abbreviations: MIF: macrophage migration inhibitory factor, CD74: cluster of differentiation 74, SDS-PAGE: sodium dodecyl sulfate-polyacrylamide gel electrophoresis, 4-HPP: 4-hydroxyphenyl pyruvate, DMSO: dimethyl sulfoxide, EMP: ethanol extract of mangosteen pericarp, EAMP: ethyl acetate extract of mangosteen pericarp, HMP: n-hexane extract of mangosteen pericarp.

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and wrote the manuscript. All authors have read and agreed to the published version of the manuscript.

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