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The use of lime peel as a functional food ingredient for chronic inflammation treatment

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ABSTRACT

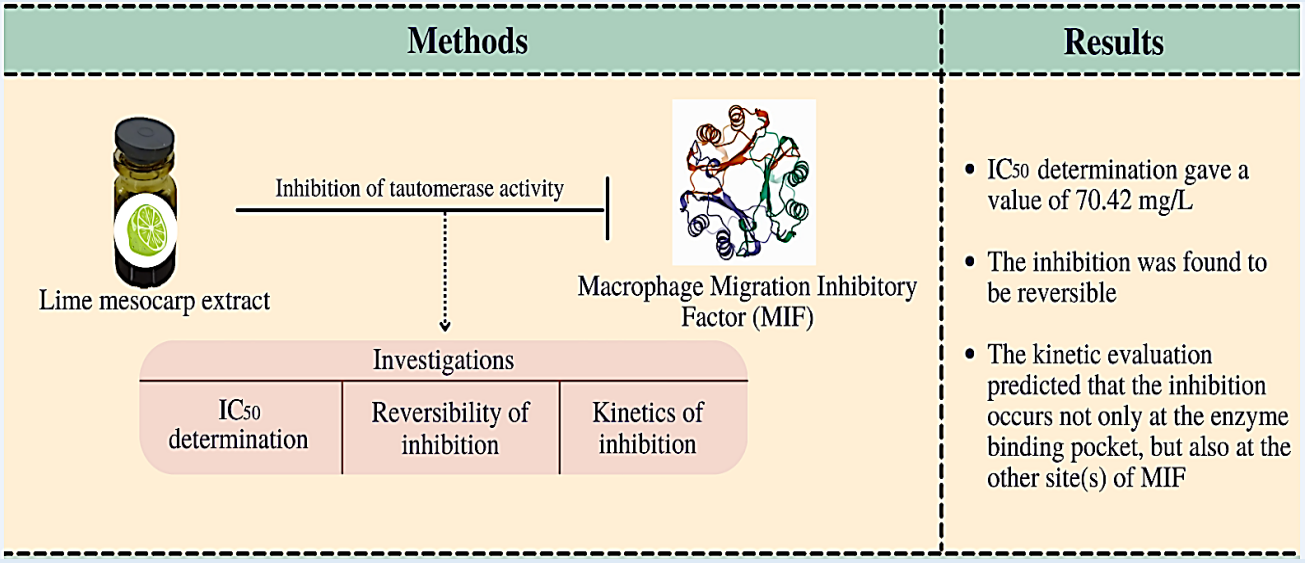
Background: Lime peel, derived from *Citrus aurantifolia* Swingle, is an ingredient that is frequently discarded despite possessing exceptionally high functional food properties. It contains phytochemicals with health-promoting properties, several of which are reported to have anti-inflammatory properties. However, the specific mechanisms underlying their anti-inflammatory properties have not been elaborated. This study aimed to evaluate the potential use of lime peel as a functional food ingredient for chronic inflammation treatment via the inhibition of macrophage migration inhibitory factor (MIF) activity. MIF is a pro-inflammatory mediator that plays a vital role in the progression of inflammation. This activity of MIF is associated with the pathogenesis of chronic inflammation.

Methods: The inhibition of MIF activity could be used as an approach to identify the potential use of a functional food ingredient for chronic inflammation treatment. This study focused on the investigation of the inhibitory potential, reversibility, and kinetics of lime mesocarp extract on MIF tautomerase activity.

Results: The results showed that the lime mesocarp extract can inhibit MIF tautomerase activity with an IC_{50} of 70.42 mg/L in a reversible manner, demonstrating its safe potential for use. The kinetic evaluation predicted that the inhibition occurs not only at the enzyme binding pocket but also at the other site(s) of MIF, speculating the possibility of disruption in MIF pro-inflammatory activity.

Conclusion: The potential safe use of lime peel as a functional food ingredient for chronic inflammation treatment has been identified.

Keywords: Lime peel, functional food ingredient, chronic inflammation, macrophage migration inhibitory factor, reversible inhibitor.



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INTRODUCTION

Bioactive compounds, particularly those derived from sustainable herbal sources, offer promising potential as beneficial active nutrients, serving as potential solutions for chronic conditions [1]. Lime peel is one of the ingredients that has beneficial health-promoting phytochemicals [2-3]. Many scientific studies showed that lime peel contains pharmacologically active phytochemicals [4-6]. Several pharmacologically active phytochemicals in the lime peel are reported to show anti-inflammatory activity, such as hesperidin, luteolin, naringenin, and nobiletin [7-10]. However, it is not fully understood how lime peel exerts its anti-inflammatory properties. Thus, this study was conducted to evaluate the potential use of lime peel as a functional food ingredient for chronic inflammation treatment via the inhibition of MIF activity.

Inflammation is a part of the human body's response against pathogens and injuries. The process is divided into three phases: activation, peak, and resolution [11]. Inflammation is generally a self-limiting process. However, the inflammation can become chronic if the body fails to end the process. Chronic inflammation occurs gradually but lasts for a long time. It is estimated that chronic inflammation may last for several months or years [12]. Various studies state that chronic inflammation is associated with the pathogenesis of various diseases, such as diabetes mellitus, cardiovascular disease, stroke, cancer, chronic kidney disease, neurodegenerative conditions, and autoimmune

disease [12-16]. This emphasizes the importance of investigating compounds that have the potential to alleviate chronic inflammation.

Chronic inflammation stimulates the production of various inflammatory mediators that contribute to the pathogenesis of chronic diseases, one of which is MIF. MIF is a pro-inflammatory cytokine that plays a central role in the development of many chronic diseases, including inflammation and cancer [17]. MIF exists as a homotrimer protein at a plasmid concentration of 0.1-30 ng/mL in healthy subjects [18]. MIF monomeric size is ~13 kDa. In addition to causing macrophages to concentrate at inflammatory areas, a high level of MIF contributes to pathological chronic inflammation [19-21]. Several studies have shown that a MIF-cluster of differentiation 74 (CD74) interaction could trigger the pathogenesis of chronic inflammation by enhancing the production of IL-6, IL-2, IL-1, TNF-α, and IFN-γ [22-23]. Hence, the inhibition of MIF-CD74 interaction has been studied as an approach by many researchers to treat chronic inflammation [24].

Aside from its role as a cytokine, MIF has several enzyme activities, one of which is p-hydroxyphenylpyruvate tautomerase activity [25-26]. The active site of the tautomerase activity has been used as a target for many MIF-CD74 inhibition studies [24, 27] because it is situated near the interaction site of MIF-CD74 [27]. MIF-CD74 interaction is reported to be affected by compounds that bind in the vicinity of the tautomerase active site [28]. Therefore, the inhibition of MIF tautomerase activity can be used as an approach for disrupting MIF-CD74 interaction for the development of potential compounds to treat chronic inflammation.

In this study, the potential use of lime peel as a functional food ingredient for chronic inflammation treatment was evaluated by its mesocarp extract inhibition on MIF tautomerase activity. Investigations were conducted on the extract's functional activity. The IC_{50} of the inhibition was found to be 70.42 mg/L; indicating that the inhibition occurred reversibly, ensuring its safe use. The kinetic evaluation showed a decrease in $V_{max\ app.}$ and an increased tendency in K_{half}, speculating that the inhibition does not occur only at the enzyme binding pocket, but also at the other site(s) of MIF. Hence, the extract could probably disrupt MIF pro-inflammatory activity. Therefore, lime peel was identified as a potential functional food ingredient for chronic inflammation treatment.

MATERIALS AND METHOD

All solvents and reagents were bought from Sigma-Aldrich, Amresco, Merck, RPI, and Difco Laboratories. The modified protocol from Salhi et al. [29] was used to make microbiological media. Recombinant MIF was produced using a glycerol stock of *Escherichia coli* BL21 (DE3) pET20b(+)-MIF. The incubation of bacterial cultures and maceration processes were conducted using the LM450D incubator shaker (Yihder, Taiwan). For centrifugation, a Sorvall Biofuge Stratos refrigerated centrifuge (Thermo Scientific, Germany) was used. Cell disruption was performed with an ultrasonicator (Tefic, China). Evaporation of the maceration solvents was carried out with a Hei-VAP Platinum 5 rotary evaporator (Heidolph, Germany). The FLUOstar® Omega plate reader (BMG LABTECH, Germany) was used to observe the tautomerase reaction of MIF in the assays.

Preparation of Lime Mesocarp Extract: The lime (*C. aurantifolia* Swingle) fruits were obtained from and native to Tinggar Village, Jombang Regency, East Java, Indonesia. The fruits are green or yellowish green in

color, with an average diameter of 4.25 cm, harvested from plants with an average age of 8 months. The identification of the plant was conducted by the Center for Information and Development of Traditional Medicine, Faculty of Pharmacy, University of Surabaya, Surabaya, East Java, Indonesia.

The fruits were peeled and sorted. The mesocarp parts of the lime peel were taken, separately chopped, dried in an oven (3 days, 55 °C), milled, and sifted with a 60-mesh sifter. The powder was then macerated with ethanol (99.8%) and n-hexane, respectively. The ratio of powder to solvent was 1:10 (w/v) and the incubation period was 3 days (25 °C, 110 rpm). The solvents were then evaporated using a rotary evaporator to obtain dry extracts, which were kept at 4 °C until further use.

Production and Purification of Recombinant MIF: The method used to produce recombinant MIF was based on Kok et al. [30] with some adjustments. Pre-cultures were produced by inoculating glycerol stocks of *Escherichia coli* BL21 (DE3) pET20b(+)-MIF into 5 mL of 2YT-ampicillin medium (11 g/L yeast extract, 11 g/L NaCl, 22 g/L bacto™ tryptone, 0,1 g/L ampicillin), after which the cultures were incubated overnight (37 °C, 175 rpm). Large cultures were produced by inoculating pre-cultures into 500 mL of 2YT-ampicillin medium (11 g/L yeast extract, 11 g/L NaCl, 22 g/L bacto™ tryptone, 0,1 g/L ampicillin). The cultures were incubated at 37°C, 175 rpm until an OD_{600} of 0,4 was reached. Isopropyl β-thiogalactopyranoside (IPTG) was added and the cultures were incubated overnight (37 °C, 175 rpm). Cells were harvested by centrifugation at 4 °C, 4500 rpm, 15 min, after which the collected cell pellet was washed with 0.9% NaCl and kept at -20 °C until further use. The purification process of MIF began with the resuspension of cell pellet with lysis buffer (10% glycerol, 50 mM Tris, pH 7.4) to eliminate non-bound proteins and contaminants. MIF was eluted from chromatography resin with an elution buffer (10% glycerol, 50 mM Tris, 500 mM imidazole, pH 7.4). The protein concentration of each eluted fraction was determined by the Bradford method. The eluted fractions with high protein concentration were pooled and analyzed with SDS-PAGE, aliquoted, and kept at -80 °C until further use.

IC_{50} Determination: The inhibition of MIF tautomerase activity by lime mesocarp extracts was conducted using the procedure of Kok et al. [30] with some modifications. This assay used a 4-hydroxyphenyl pyruvate (4-HPP) substrate to measure the tautomerase activity of MIF. The 10 mM 4-HPP stock solution was prepared in ammonium acetate buffer (50 mM, pH 6) and incubated overnight at room temperature to equilibrate the keto and enol forms of the substance. The stock solution was then kept at 4 °C until further use.

Solutions of MIF, 4-HPP, and lime mesocarp extracts were prepared to give suitable concentrations for the assay. MIF was diluted with boric acid (0.4 M, pH 6.2) to a final concentration of 1.1 µM, and 4-HPP was diluted with ammonium acetate buffer (50 mM, pH 6) to a final concentration of 1 mM. Lime mesocarp extracts were diluted in dimethyl sulfoxide (DMSO) until the desired concentration (2450 mg/L for ethanol extract and 1535 mg/L for n-hexane extract in 5% DMSO). Then, 45 µL of the diluted MIF was mixed with 5 µL of the diluted extract to make test mixtures. The positive control of this assay was made by mixing 45 µL of the diluted MIF and 5 µL of DMSO. The negative control was made as the positive control, except the diluted MIF solution was replaced by boric acid buffer (0.4 M, pH 6.2). Meanwhile,

the inhibitor control was made as the positive control, except the DMSO was replaced by $CuSO_4$ solution (50 µM) as a potent MIF inhibitor. To evaluate the potential inhibition of MIF tautomerase activity by the extracts, the MIF residual activity of test mixtures and the controls were measured using a plate reader in triplicate. The mixtures were put into a UV-Star® half area 96-well microplate. The tautomerase reaction was started by adding 50 µL of diluted 4-HPP (final concentration of 0.5 mM) and was observed with a microplate reader at 306 nm. The extracts giving MIF residual activity below 20% were selected for further assays.

The IC_{50} of MIF tautomerase activity was determined using the selected extract with final concentrations of 303.21–39.93 mg/L in 5% DMSO (1.5-fold serial dilution). The assay was conducted as described previously, in triplicate. The data were analyzed using GraphPad Prism 8.0. The rate of MIF tautomerase reaction was obtained by initially taking the ascending slope of the absorbance vs. time curve. Normalization of the rate of reaction to that of the controls gave the MIF residual activity (%). Plotting the residual activity vs. log [extract concentration] using the software curve fitting would yield a sigmoidal curve along with its IC_{50}.

Reversibility of Inhibition: Preincubation and dilution assays were used to evaluate the reversibility of inhibition by the n-hexane extract on MIF tautomerase activity. The preincubation assay was started by preparing two batches of extract-MIF mixture 1.5-fold dilution series (final extract concentration of 303.21–39.93 mg/L, in 5% DMSO). Before starting the assay, the first batch was pre-incubated for 2 min (the regular preincubation time in IC_{50} assay), and the second batch was pre-incubated for 30 min. The assay was conducted as described previously. Both sigmoidal curves and IC_{50} values were compared.

For dilution assay, initial solutions, i.e., an extract mixture containing a high concentration of MIF (47.8 µM) and extract (10-fold of IC_{50}, in 5% DMSO) along with its positive control (MIF of 47.8 µM) were prepared. The test mixture was prepared by adding 7.5 µL of extract (7042 mg/L) into 67.5 µL of MIF (53.13 µM). The positive control was prepared by diluting 67.5 µL of MIF (53.13 µM) with 7.5 µL of DMSO. Each mixture was diluted 100-fold with a solution containing 1 mM 4-HPP and 0.4 M boric acid (pH 6.2), and then the assay was conducted as described previously, in triplicate. The absorbance was plotted against time.

Kinetics of Inhibition: A kinetic evaluation was carried out to identify the inhibition mechanism of the extract on MIF tautomerase activity. As part of the assay, three types of extract solutions were prepared: the first containing no extract, the second containing extract at a concentration of the IC_{50}, and the third containing extract at a concentration of 2-fold of the IC_{50}. Each 5 µL of extract solution was mixed with 45 µL of MIF (1.1 µM). 4-HPP with concentrations of 0.21, 0.33, 0.51, 0.64, and 1.00 mM in ammonium acetate buffer (50 mM, pH 6) were added using a multichannel pipette to each mixture, and the reaction was started. The assay was performed in triplicate. The reaction rate (absorbance/min) was plotted against the concentration of 4-HPP using enzyme kinetic-allosteric sigmoidal analysis in GraphPad Prism 8.0. The analysis yielded an allosteric sigmoidal curve, $V_{max\ app.}$, Hill slope, and $K_{prime\ app}$ for each mixture. The K_{half} value was calculated using the

equation from Kok et al. [30]. The inhibition mechanism was deduced from the curve profiles and the $V_{max\ app.}$ and K_{half} values.

RESULTS AND DISCUSSION

Preparation of MIF: Recombinant His-tag MIF was successfully produced in a BL21 (DE3) bacterial system and purified using immobilized metal affinity chromatography (IMAC) resin in a gravity flow column. Sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE) analysis indicated that the obtained MIF has ~13 kDa size as expected (Figure 1A).

Evaluating IC_{50}: The inhibition potential of lime mesocarp on MIF tautomerase activity was first determined by preliminary assays using concentrated mesocarp extracts in ethanol and n-hexane. The results showed that all concentrated extracts can inhibit MIF tautomerase activity, with residual activity of ~72% for the ethanol extract and much lower, i.e., 19% (below our 20% cut-off) for n-hexane extract (Figure 1B). Hence, the n-hexane extract was chosen for further assays. The IC_{50} determination of the n-hexane extract gave a value of 70.42 mg/L (Figure 1C).

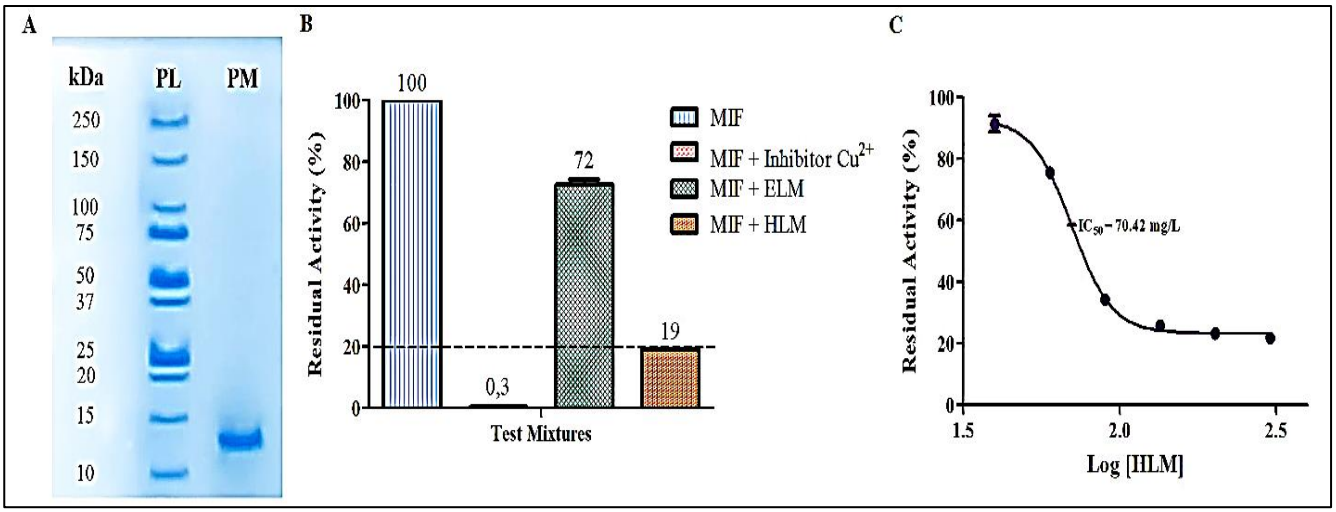

Figure 1 (A, B, C): SDS-PAGE (18% acrylamide) result of PL (protein ladder) and PM (purified MIF): (**A**). Residual activity (%) of MIF (the positive control), MIF + Inhibitor Cu^{2+} (the inhibitor control), MIF + ELM (ethanol extract of lime mesocarp), and MIF + HLM (n-hexane extract of lime mesocarp) (**B**). IC_{50} curve of MIF + HLM (**C**). The assays were performed in triplicate.

Reversibility of Inhibition: The reversibility of inhibition for n-hexane extract of lime mesocarp (HLM) on MIF tautomerase activity was analyzed with preincubation and dilution assays. Based on the sigmoidal curves and IC_{50} values of the preincubation assay, no difference was observed between the 2 and 30-minute preincubation (Figure 2A). This indicates that the inhibition of the extract on MIF tautomerase activity does not change over a period. A dilution assay was conducted to further investigate the reversibility of MIF tautomerase inhibition by the extract. In the assay, no apparent difference was observed between the positive control

(MIF) and test mixture (MIF +HLM) curve. This means that the activity of MIF is recovered after dilution (Figure 2B). Diluting the mixture of MIF and irreversible inhibitors will not restore MIF activity [30], hence the curve of the MIF-extract mixture will be flat. These results confirmed that the inhibition is reversible.

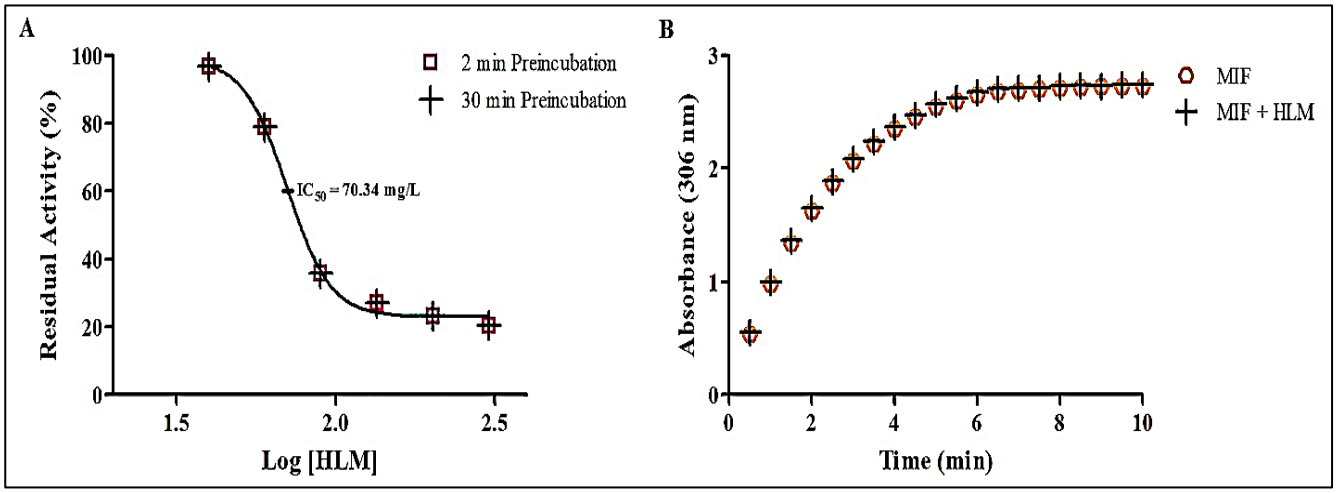

Figure 2 (A, B): Preincubation assay resulted in identical sigmoidal graphs and IC_{50} values between 2 min and 30 min preincubation: (**A**). Dilution assay resulted in similar absorbance vs. time graph between MIF and MIF + HLM (n-hexane extract of lime mesocarp) (**B**). The assays were performed in triplicate.

Kinetics of Inhibition: The kinetics of extract inhibition on MIF tautomerase activity was evaluated. The rate of MIF tautomerase reaction (absorbance/min) was determined at increasing substrate (4-HPP) concentrations in the presence of several extract concentrations. The rate was plotted against the concentrations of 4-HPP (Figure 3). The apparent maximum rate ($V_{max\ app.}$), Hill slope, and the concentration of 4-HPP that gave half of $V_{max\ app.}$ ($K_{prime\ app.}$) from each curve were determined (Table 1). The results showed that sigmoidal curves with a Hill slope greater than 1 were formed, indicating that the enzyme reaction does not follow Michaelis-Menten kinetics [30]. This happens because the binding is affected by factors that the equation does not consider. In this study, the reaction rate of each sigmoidal curve increased as the substrate concentration increased, and the tendency of K_{half}. An increase in reaction rate and K_{half} resemble a competitive-like type of inhibition. In a competitive-like type of inhibition, there is direct competition between the inhibitor and substrate to bind at the enzyme binding pocket. The increase of reaction rate in the presence of the extract does not reach the maximum (V_{max}). In this case, the V_{max} decreases with the increasing extract concentration, confirming the inhibition by the extract does not take place only at the enzyme binding pocket but also at other(s) sites of MIF. This phenomenon was expected to occur because the extract may contain several varieties of metabolites. This type of inhibition had the potential to change MIF conformation, disrupting its pro-inflammatory activity [31].

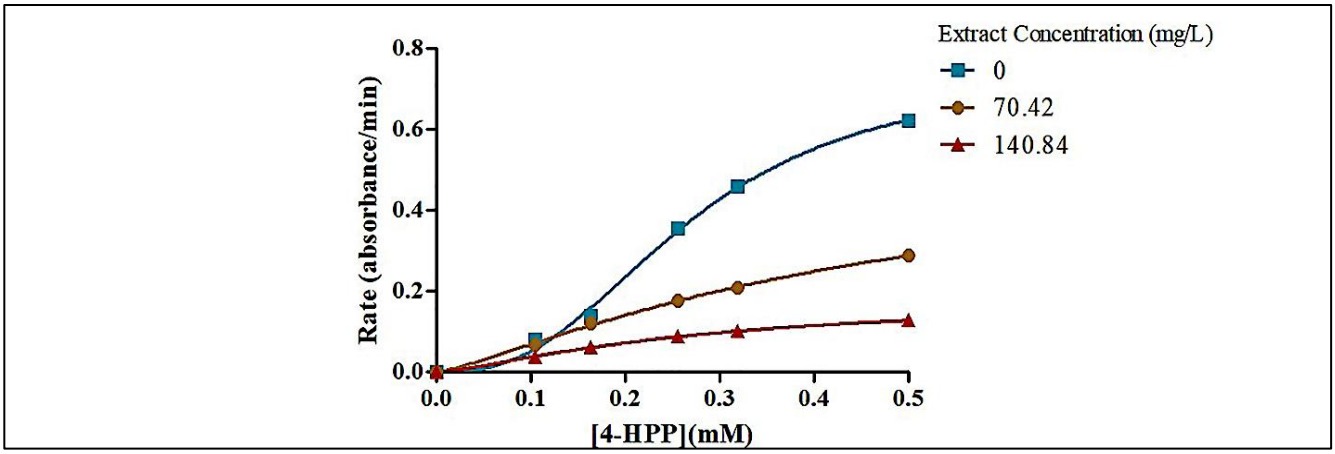

Figure 3. Kinetic evaluation of HLM (n-hexane extract of lime mesocarp) inhibition on MIF tautomerase activity. The assays were performed in triplicate.

Table 1. The $V_{max\ app.}$, Hill slope, and $K_{prime\ app.}$ from kinetic evaluation assay of HLM (n-hexane extract of lime mesocarp)

Parameters	[HLM](mg/L)		
	0	70.42	140.84
$V_{max\ app.}$ (absorbance/min)	0.74 ± 0.06	0.54 ± 0.10	0.18 ± 0.01
Hill slope	2.65 ± 0.32	1.29 ± 0.14	1.37 ± 0.06
K_{half} (mM)	0.27 ± 0.00	0.45 ± 0.00	0.28 ± 0.00

The values of $V_{max\ app.}$, Hill slope, and K_{half} (mM) were expressed as mean ± SE of 3 replicates.

CONCLUSION

In this study, we identified the potential use of lime peel as a functional food ingredient for chronic inflammation treatment via inhibition of MIF activity. The results showed that the IC_{50} value of the lime mesocarp extract on MIF tautomerase activity is 70.42 mg/L, the inhibition is reversible and occurs not only at the enzyme binding pocket but also at other sites of MIF. This suggests that the extract has the potential to disrupt MIF's pro-inflammatory activity, making lime peel a promising candidate for the development of functional foods.

List of Abbreviations: MIF: macrophage migration inhibitory factor, CD74: a cluster of differentiation 74, IC_{50}: inhibitory concentration of 50%, IMAC: immobilized metal affinity chromatography, SDS-PAGE: sodium dodecyl sulfate-polyacrylamide gel electrophoresis, 4-HPP: 4-hydroxyphenyl pyruvate, ELM: ethanol extract of lime mesocarp, HLM: n-hexane extract of lime mesocarp, DMSO: dimethyl sulfoxide.

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Conflict of Interest: There is no conflict of interest to declare.

Authors' Contributions: TK conceived the project, designed, and supervised the work, and critically reviewed the manuscript; ANFK conducted the experiments and did data analysis and manuscript writing; MTG and RPA critically reviewed the manuscript. All authors have read and agreed to publish the article in BCHD.

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Ethical Statement: Not applicable.

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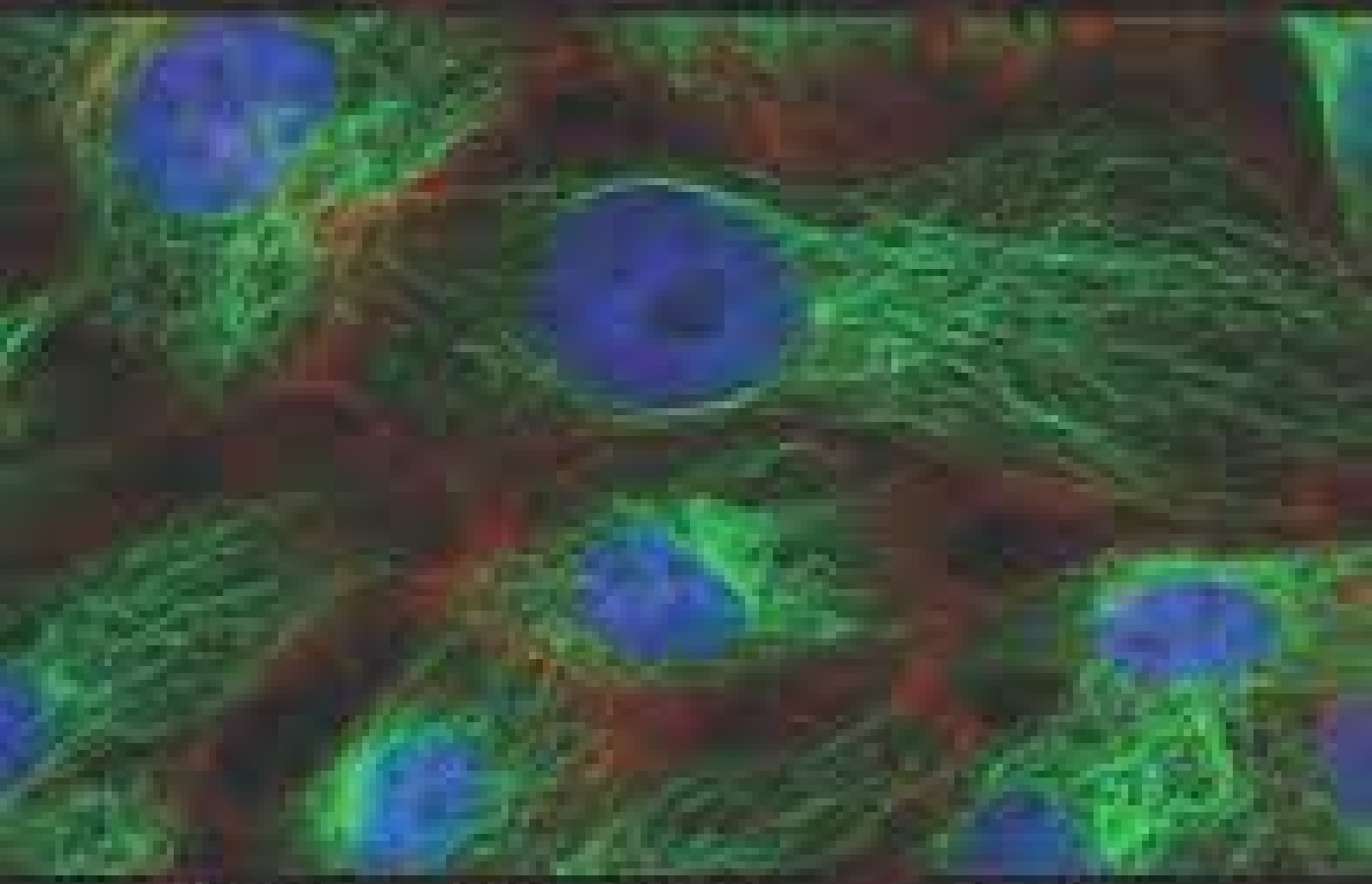

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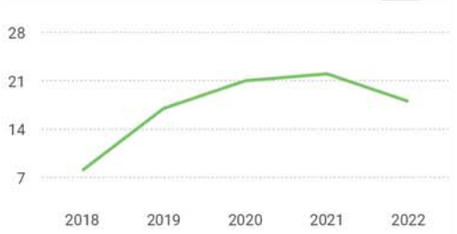

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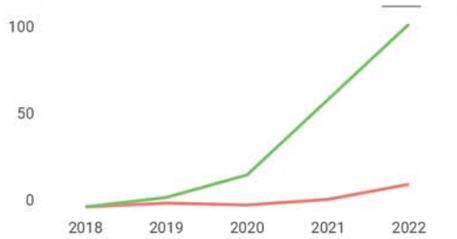

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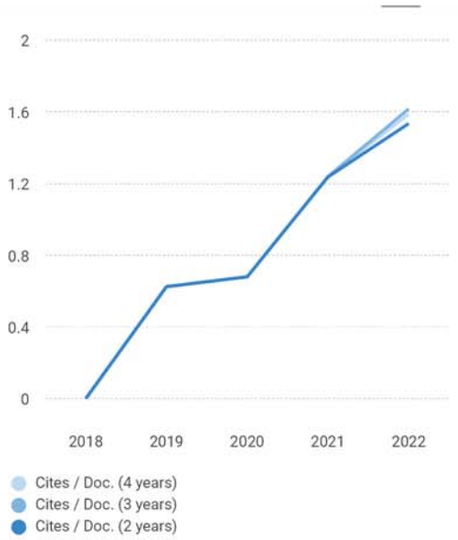

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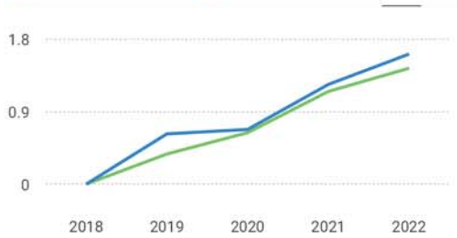

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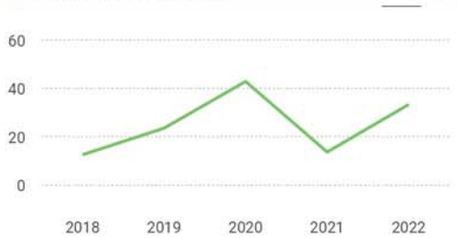

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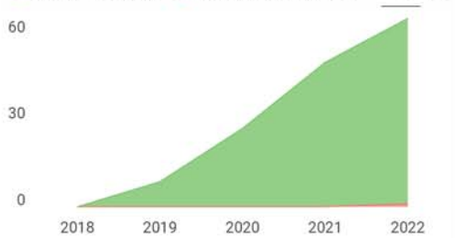

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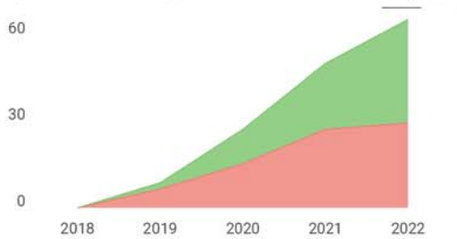

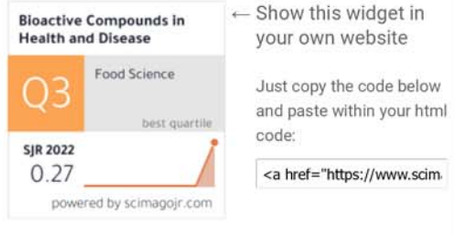

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