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Antihyperuricemia Effectiveness of Ethanol Extract Combination of Bitter Melon (*Momordica charantia*) and Moringa (*Moringa oleifera* L.) in Caffeine-Induced Rats (*Rattus norvegicus*)

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ABSTRACT

***Introduction**: Hyperuricemia is a condition characterized by elevated blood uric acid levels exceeding normal limits. Herbal medicines, such as bitter melon (Momordica charantia) and moringa (Moringa oleifera), have potential efficacy in reducing uric acid levels. This study aims to evaluate the effectiveness of a combination of BME (Bitter Melon Extract) and MLE (Moringa Leaf Extract) as an anti-hyperuricemia treatment. **Aims**: This experimental study assesses the quality standardization of the extracts, including specific and non-specific parameters. The effectiveness of the combined extracts was tested on caffeine-induced hyperuricemic rats, which were divided into six groups: negative control (Na.CMC 0.5%), positive control (Allopurinol), and four treatment groups receiving different doses of BME and MLE (D1, D2, D3, D4). **Result**: The results showed that the combination of BME and MLE met the quality standard parameters. All four dosage variations demonstrated a reduction in uric acid levels. Among them, D3 (1.8 mg/kg BW of BME and 600 mg/kg BW of MLE) was the most effective, with a 41.3% reduction in uric acid levels. Statistical analysis using the Least Significant Difference (LSD) method indicated a significant difference between the negative control group and the treatment groups on the 7th day. **Conclusion**: The combination of BME and MLE has proven to be effective as an anti-hyperuricemia agent. Further research is needed to explore the potential of herbal medicines as alternative treatments for hyperuricemia.*

***KEYWORDS**: Hyperuricemia, bitter melon, moringa, extract, caffeine-induced.*

INTRODUCTION

Gout (hyperuricemia), characterized by joint pain and stiffness, is a common disease in Indonesia and worldwide. This condition is independent of age and gender and is often experienced over the long term. Hyperuricemia is defined by elevated serum uric acid levels exceeding the normal threshold of 7.0 mg/dL in men and 6.0 mg/dL in women. Various factors contribute to hyperuricemia, including environmental, genetic, and anthropometric-metabolic aspects. Additionally, high-purine foods, fructose,

and alcoholic beverages are known dietary factors that elevate uric acid levels (Jumalia, 2021). According to the WHO (2018), the prevalence of gout in 2017 was 34.2%, rising to 1,370 cases (33.3%) in 2018. The Indonesian Basic Health Research (Riskesdas, 2018) reported that 54.8% of individuals aged 75 years suffered from hyperuricemia, with a higher prevalence in women (8.46%) compared to men (6.13%).

Clinically, allopurinol is commonly prescribed to inhibit xanthine oxidase and reduce uric acid production. However, this drug may cause mild to severe allergic reactions, gastrointestinal disturbances, and toxicity to the liver and kidneys. Additionally, allopurinol interacts with medications such as cyclosporine and warfarin, increasing the risk of adverse effects (Fardin et al., 2019). Given these concerns, alternative treatments, particularly those derived from natural sources, are being explored for hyperuricemia management.

One promising approach is the use of herbal medicine, which has long been employed in traditional remedies for gout, a common manifestation of hyperuricemia. In several Asian countries, bitter melon (*Momordica charantia*) is widely used for its potential antihyperuricemic properties. Phytochemical analyses by Kapoor et al. (2017) and Abu Bakar et al. (2018) indicate that bitter melon contains flavonoids, saponins, and polyphenols—compounds known for their bioactive properties. Among these, flavonoids have been identified as potent inhibitors of key enzymes such as xanthine oxidase (XO), cyclooxygenase (COX), lipoxygenase, and phosphoinositide 3-kinase. These inhibitory effects suggest that bitter melon may contribute to lowering blood uric acid levels. Supporting this, a study by Minar et al. (2020) found that administering bitter melon ethanol extract at a dose of 1.8 mg/kg BW effectively reduced uric acid levels in caffeine-induced hyperuricemic male rats (*Rattus norvegicus*).

Similar to bitter melon, moringa (*Moringa oleifera*) has also been recognized for its potential in managing hyperuricemia. In Indonesia, moringa is widely used in traditional medicine to treat various ailments, including inflammatory conditions and metabolic disorders. Its leaves possess anti-inflammatory, antioxidant, antitumor, and antiallergic properties, attributed to the presence of bioactive compounds such as tannins, steroids, flavonoids, saponins, anthraquinones, and alkaloids (Putra et al., 2019).

The therapeutic potential of moringa in hyperuricemia management is closely linked to its flavonoid content. Flavonoids have been shown to inhibit uric acid formation by interacting with xanthine

oxidase at its active site, acting as competitive inhibitors. In vitro studies further suggest that specific flavonoids, including luteolin, apigenin, quercetin, and myricetin—found abundantly in moringa leaves—can significantly reduce xanthine oxidase activity (Putra et al., 2019). Reinforcing this, research by Prabadi et al. (2019) demonstrated that administering moringa leaf ethanol extract at a dose of 1200 mg/kg BW significantly reduced uric acid levels in hyperuricemic rats (*Rattus norvegicus*).

These findings highlight the potential of bitter melon and moringa as natural alternatives for hyperuricemia treatment. Their bioactive compounds, particularly flavonoids, play a crucial role in inhibiting xanthine oxidase, thereby reducing uric acid production. Further research is warranted to optimize their therapeutic applications and explore their long-term efficacy and safety in human populations.

Herbal treatments often combine multiple medicinal plants to enhance their therapeutic potential. Research by Mardikawati (2020) demonstrated that a combination of moringa leaf extract and black cumin seed (*Nigella sativa*) extract effectively reduced uric acid levels in test animals. Given that both bitter melon and moringa leaf extracts exhibit antihyperuricemic activity, their combination warrants further investigation to determine their synergistic effects in lowering uric acid levels (Mardikawati, 2020).

METHODS

Materials

The population of this study consists of Moringa leaves (*Moringa oleifera L.*) and Bitter melon fruits (*Momordica charantia*), obtained from PT. Industri Jamu Borobudur Herbal, Semarang, Central Java. The chemicals and reagents used included distilled water, allopurinol 100 mg (*Hexpharm*®), anhydrous acetic acid, sulfuric acid, Dragendorff reagent, ethanol 90%, hydrochloric acid (HCl) 2%, Mayer reagent, ferric chloride (III) 1%, caffeine, sodium carboxymethyl cellulose (Na.CMC), and other analytical-grade reagents.

The instruments used in this study included stirring rods, beakers (*Pyrex*®), funnels, porcelain dishes, Erlenmeyer (*Pyrex*®), scissors, graduated cylinders (*Pyrex*®), filter paper, water baths, dropper pipettes, volumetric pipettes, 1 mL and 5 mL syringes, spatulas, horn spoons, an analytical balance (*Ohaus*®), tubes (*Pyrex*®), and uric acid test strips (*EasyTouch GCU*®).

Phytochemical Screening

Phytochemical screening of BME and MLE was conducted using various methods. First, the preparation of the phytochemical

test solutions involved dissolving 500 mg of extract in 50 mL of 90% ethanol. For the alkaloid test, 2 mL of the test solution were evaporated in a porcelain dish to obtain a residue, which was then dissolved in 5 mL of HCl and divided into three test tubes. The first tube served as a blank with diluted acid, while Dragendorff reagent and Mayer reagent (3 drops each) were added to the second and third tubes, respectively. The formation of orange precipitate in the second tube and yellow precipitate in the third indicated the presence of alkaloids. For the sterol and triterpenoid test, 2 mL of the test solution were mixed with anhydrous acetic acid and concentrated sulfuric acid. A green-blue color indicated steroids, while red-purple or brown suggested triterpenoids. In the saponin test, the test extract was added to a test tube with hot water, cooled, and shaken for 10 seconds. After adding 1 drop of HCl 2N, the presence of sTable foam for 10 minutes confirmed saponins. The flavonoid test involved mixing a small amount of extract with magnesium powder and four drops of HCl 2%, where a change in filtrate color to orange-red indicated flavonoids. Lastly, the tannin test was conducted by mixing a small amount of extract with 1-2 drops of ferric chloride (III) solution, and the development of a green or blue-black color indicated the presence of tannins.

Quality Standardization of Extracts

Water-Soluble Compound Content

To determine the water-soluble compound content, 5 grams of the extract were macerated with 100 mL of chloroform water in a stoppered flask for 24 hours. The solution was left undisturbed for 18 hours before being filtered. From the filtrate, 20 mL were evaporated and dried at 105°C until a constant weight was obtained. The water-soluble compound content was calculated as a percentage of the initial extract weight.

Ethanol-Soluble Compound Content

For the ethanol-soluble compound content, 5 grams of the extract were macerated with 100 mL of 95% ethanol in a stoppered flask for 24 hours. During the first 6 hours, the flask was intermittently shaken and then allowed to stand for the remaining 18 hours. A 20 mL portion of the filtrate was evaporated and dried at 105°C until a constant weight was achieved. The ethanol-soluble compound content was calculated based on the initial weight of the extract.

Moisture Content

The moisture content was determined by preheating two empty evaporating dishes at 105°C for 30 minutes. The dishes were cooled in a desiccator and weighed. The extract was then placed in the dishes and repeatedly heated, cooled, and weighed until a constant weight was obtained. This

process ensured accurate measurement of moisture content.

Specific Gravity

The specific gravity of the extract was measured using a pycnometer. The pycnometer was first weighed empty, then filled with distilled water, and weighed again. The same procedure was repeated using the extract. The specific gravity was calculated by comparing the weight of the extract to that of the distilled water.

Preparation of Samples and Induction

Preparation of BME and MLE

BME and MLE were prepared separately and mixed with a 0.5% Na.CMC suspension in 10 mL graduated cylinders, then stirred until homogeneous. They were then combined according to the intended formulation, with different dosage variations based on the test groups.

Allopurinol Solution

Allopurinol was weighed (100 mg/kg body weight), ground, and dissolved in 0.5% Na.CMC to a final volume of 100 mL.

Caffeine Solution

Caffeine (5.29 mg/200 g body weight) was dissolved in 20 mL of hot distilled water containing 0.5% Na.CMC and mixed with NaCl to a final volume of 5 mL.

Animal Treatment

Male mice were housed in well-maintained cages and acclimatized for approximately 1 week. The mice were fasted for 8-12 hours prior to treatment. A total of 24 mice were divided into 6 groups, each containing 4 mice:

NC : Negative control (0.5% Na.CMC).

PC : Positive control (allopurinol 100 mg/kg body weight).

D1 : Combinations of BME+MLE (1.8 mg/kg bw + 1200 mg/kg bw).

D2 : Combinations of BME+MLE (0.9 mg/kg bw + 1200 mg/kg bw).

D3 : Combinations of BME+MLE (1.8 mg/kg bw + 600 mg/kg bw).

D4 : Combinations of BME+MLE (0.9 mg/kg bw + 600 mg/kg bw)

Mice were fasted for 8 hours and their normal uric acid levels were measured. Hyperuricemia was induced with caffeine (5.29 mg/200 g body weight) for 6 days, and uric acid levels were checked on days 3 and 6. Mice with uric acid levels above 3 mg/dL received the extract combinations orally for 7 consecutive days. Data were analyzed using one-way ANOVA with LSD testing ($p < 0.05$).

RESULTS AND DISCUSSION

Hyperuricemia is a condition characterized by elevated serum uric acid levels, exceeding 7.0 mg/dL in men and 6.0 mg/dL in women. The normal uric acid range is 2.4–6.0 mg/dL for women and 3.5–7.0 mg/dL for men. Hyperuricemia can result from genetic metabolic disorders that lead to excessive uric acid production or the inability of the body to effectively eliminate

uric acid (Jumalia, 2021). Although hyperuricemia is a fundamental factor in the development of gout, it is often asymptomatic. Gout occurs when excessive uric acid levels in bodily fluids lead to the formation of monosodium urate crystals in synovial fluid, causing pain and inflammation (Ernst et al., 2008).

Several factors influence uric acid levels, including genetics, lifestyle, and physical activity. A diet rich in fats, carbohydrates, and proteins, along with excessive coffee consumption without adequate water intake, can contribute to increased uric acid levels. Additionally, physical activity impacts uric acid metabolism, as intense exercise reduces uric acid excretion and increases lactic acid production. The greater the physical exertion, the higher the lactic acid accumulation, which can further influence uric acid levels (Tantri, 2019).

This study evaluates the antihyperuricemic efficacy of a combination of MLE and BME in caffeine-induced hyperuricemic rats. Both extracts have been previously studied for their antihyperuricemic properties, either individually or in combination with other medicinal plants. BME contains flavonoids, saponins, and polyphenols, with flavonoids being potent inhibitors of key enzymes involved in uric acid metabolism (Bakar et al., 2018). Similarly, MLE contains flavonoids that effectively inhibit uric acid formation while exhibiting anti-inflammatory and analgesic properties.

BME and MLE used in this study were obtained from PT. Industri Jamu Borobudur, Semarang, Indonesia. The samples consisted of dry extracts produced via maceration using 70% ethanol as a solvent. The extracts underwent heavy metal content analysis and microbiological testing for bacteria and fungi, as detailed in the appendix. These tests were conducted by PT. Borobudur, the extract manufacturer, to ensure product safety and quality. Phytochemical screening was conducted to identify the bioactive compounds present in BME and MLE. This screening utilized specific chemical reagents to detect various compound groups, including flavonoids, alkaloids, tannins, saponins, and terpenoids (Putri et al., 2013).

The results of the phytochemical screening, as shown in Table 1, confirm the presence of secondary metabolites in both extracts. The presence of alkaloids was confirmed by the formation of an orange precipitate with Dragendorff's reagent, a yellow precipitate with Mayer's reagent, and a brownish-red precipitate with wagner reagent. According to Svehla (1990), alkaloid compounds react with tetraiodomercurate (II) ions, forming a complex that precipitates. This occurs because mercury ions, as heavy metal ions,

Table 1. Phytochemical Screening of BME and MLE

Compound	Reagent	Parameter	Results (+/-)	
			BME	MLE
Alkaloid	Dragendorff	Orange precipitate	+	+
	Mayer	Yellow precipitate	+	+
	Wagner	Brown precipitate	+	+
Flavonoid	2N HCl	Yellow color change	+	+
Saponin	2N HCl	STable foam remains for 10 minutes and does not disappear after adding 2N HCl	+	+
Tannin	$FeCl_3$	Greenish-black color change	+	+
Steroid	Liebermann-Burchard	The color changes to reddish-brown	+	-
Triterpenoid	Liebermann-Burchard	Brown color change	+	+

can precipitate basic alkaloids, facilitating their identification. The flavonoid test was conducted by adding magnesium (Mg) and hydrochloric acid (HCl) to both extracts, resulting in a yellow coloration, indicating the presence of flavonoids. According to Harborne (1987), flavonoids undergo reduction reactions with Mg and HCl, producing colors ranging from red to yellow or orange, depending on the specific flavonoid compounds present. Saponins are surface-active compounds that are easily detected by their ability to form sTable foam. The glycosidic components within saponins contribute to their polar nature (Harborne, 1987). In this test, the foam produced remained sTable, and the addition of HCl further enhanced foam stability. According to Harborne (1987), when shaken, the hydrophilic groups bind to water, while the hydrophobic groups bind to air, forming persistent foam. The tannin test, performed using ferric chloride ($FeCl_3$), resulted in a greenish-black color change, indicating the presence of condensed tannins. According to Soamole et al. (2018), tannins react with $FeCl_3$, binding to hydroxyl groups, leading to a distinct color change. The presence of steroids and terpenoids was confirmed using the Liebermann-Burchard test, where a red or purple coloration indicated the presence of triterpenoids. These findings align with previous research conducted by Gandung Prakoso et al. (2016). Among the identified compounds, flavonoids are particularly significant due to their antihyperuricemic properties. Several studies suggest that flavonoids effectively inhibit uric acid formation, exhibit anti-inflammatory activity, and provide analgesic effects. This mechanism is attributed to flavonoids' ability to inhibit xanthine oxidase (XO) activity through competitive inhibition and interactions with enzyme side chains. Additionally, in vitro studies have demonstrated that specific flavonoids, including luteolin, apigenin, quercetin, and myricetin, can suppress xanthine oxidase activity, thereby reducing uric acid

levels (Putra et al., 2019).

The standardization process was conducted to refine and enhance previous standardization efforts undertaken by PT. Jamu Industri Borobudur, the producer of the extracts. This standardization included both specific parameters (identity, organoleptic properties, and soluble compounds) and non-specific parameters (moisture content and specific gravity). According to the Indonesian Ministry of Health (2000), extracts intended for pharmaceutical use as raw materials must comply with the requirements outlined in official monographs, such as the Materia Medika Indonesia (1980).

The determination of water-soluble compounds aimed to quantify the polar compounds present in the extract, given their affinity with water. The results indicated that the water-soluble compound content in bitter melon (*Momordica charantia*) extract was 20%, meeting the standard of ≥16% as stated in the Indonesian Herbal Pharmacopoeia (2017). Meanwhile, the water-soluble compound content in moringa leaf (*Moringa oleifera*) extract was 2.4%, aligning with the standard of ≤4.9%. Furthermore, the determination of ethanol-soluble compounds was conducted to assess the content of semi-polar compounds, which exhibit similar polarity to ethanol (Saefudin et al., 2011). The ethanol-soluble compound content in bitter melon extract was 5.2%, surpassing the required standard of ≥3.30%, while in moringa leaf extract, it was 3.2%, complying with the standard of ≤5.0%. These results confirm that both extracts meet the established quality standards based on the Indonesian Herbal Pharmacopoeia (Ministry of Health Republic of Indonesia, 2017).

For non-specific parameters, the moisture content determination was conducted to evaluate the amount of volatile compounds lost during the drying process. Moisture content is a critical parameter in extract quality control, as excessive moisture can promote fungal growth (Safitri, 2008). The study found that the moisture content in bitter melon extract was 11.6%, while in moringa leaf extract, it was 17.4%. These values comply with the Ministry of Health Republic of Indonesia (2017) standards, which require moisture content levels of ≤10% for both extracts (Indonesian Ministry of Health, 2008).

The specific gravity determination was performed to provide insight into the concentration of dissolved chemical constituents within the extracts. The results revealed that the specific gravity of bitter melon extract was 1.01 g/mL, while that of

Table 2. The standardization of BME and MLE

Parameters	BME	MLE
The water-soluble compounds	20%± 0.057	2.4%±0.005
The ethanol-soluble compound	5.2%±0.006	3.2%±0.006
Loss of drying (%)	11.6%±0.042	17.4% ±0.053
Moisture content % (g/mL)	1.02±0.02	1.01% ±0.01

moringa leaf extract was 1.02 g/mL, further supporting their adherence to quality standards. In conclusion, the standardization of bitter melon and moringa leaf extracts produced by PT. Jamu Industri Borobudur successfully met the required specifications outlined in the Indonesian Herbal Pharmacopoeia (2017). These findings reinforce the importance of rigorous quality control in ensuring the consistency and efficacy of herbal medicinal extracts.

This study used 24 male white rats (*Rattus norvegicus*) divided into six treatment groups to evaluate the effects of BME and MLE extracts on uric acid levels. After a one-week acclimatization, hyperuricemia was induced using caffeine, followed by a seven-day treatment with different extract combinations. Uric acid levels were measured at multiple time points, and the results indicated that the combination of BME and MLE effectively reduced uric acid levels.

The results of this study showed that the baseline uric acid levels in all rats were within the normal range before induction. However, after caffeine administration, uric acid levels increased to above 5.0 mg/dL, confirming the successful induction of hyperuricemia. This increase was attributed to the oxidation of caffeine's methyl group by xanthine oxidase, leading to elevated uric acid production. The administration of 0.5% Na.CMC was chosen as a negative control because it is a neutral carrier that does not affect uric acid reduction (Jangga, 2016). The positive control, allopurinol at a dose of 100 mg/kg BW, was included as it is a well-established xanthine oxidase inhibitor commonly used to reduce uric acid production. Allopurinol works by inhibiting the activity of xanthine oxidase, and its metabolite, allopurinol-1-ribonucleotide, provides additional inhibition of de novo synthesis. Allopurinol has a plasma half-life of approximately 40 minutes and is metabolized into oxypurinol, which has a prolonged half-life of around 14 hours, contributing to its sustained uric acid-lowering effect (Frastyowati, 2012).

The uric acid level data obtained in this study were analyzed using SPSS software, applying the *Least Significant Difference* (LSD) method, with a significance threshold of $p < 0.05$. The results showed a significant decrease in uric acid levels on day 7.

Table 3. Measurement of average uric acid levels in mice. BI (Before Induction), AI (After Induction), * (significant difference p<0.05 against NC, *post hoc* LSD)

Observation	Groups					
	NC	PC	D1	D2	D3	D4
BI (mg/dL)	3.6±0.39	3.97±0.77	3.5±0.61	3.52±0.26	3.42±0.51	3.62±0.68
AI (mg/dL)	12.07±4.66	11.45±4.46	10.9±0.78	10.9±3.18	10.97±4.06	11.37±3.74
H1 (mg/dL)	12.07±4.68	9.25±2.21	9.72±0.55	9.82±2.71	10.02±3.78	10.5±3.78
H3 (mg/dL)	12.10±4.66*	7.42±1.58*	7.95±0.77	7.77±1.40	8.72±3.54	9.60±3.96
H5 (mg/dL)	12.07±4.61*	5.55±0.64*	5.80±0.58*	6.95±1.32*	7.07±3.32*	8.80±4.08
H7 (mg/dL)	12.12±4.59*	3.42±0.39*	3.77±0.33*	5.07±1.38*	4.15±0.68*	7.82±4.02*

Table 4. Percentage of average uric acid levels in mice

Observation	Groups					
	NC	PC	D1	D2	D3	D4
H1 (%)	0	19.21	10.83	9.91	8.66	7.65
H3 (%)	-0.25	19.78	18.21	20.88	12.97	8.57
H5 (%)	0.25	25.2	27.04	10.55	18.92	8.33
H7 (%)	-0.41	38.38	35.86	29.21	41.3	11.14

Statistical analysis indicated that the negative control group exhibited a significant difference ($p < 0.05$) compared to all treatment groups (Table 7 and Figure 6), with varying degrees of reduction (Figure 7). These findings suggest that the combination of MLE and BME effectively lowered uric acid levels in all tested doses. According to Table 8 and Graph 2, the most effective uric acid-lowering effect was observed in the group receiving BME 1.8 mg/kg BW and MLE 600 mg/kg BW. While both extracts demonstrated uric acid-lowering effects when administered individually, their combination enhanced their potency, enabling a reduction in the required dose of Moringa leaf extract (MLE) from 1200 mg/kg BW to 600 mg/kg BW while maintaining efficacy.

The results of this study confirm that the combination of BME and MLE effectively reduces uric acid levels in rats. These findings align with previous studies on the synergistic effects of medicinal plant combinations in reducing uric acid levels. The combined administration of these extracts not only enhances their therapeutic potential but also allows for a reduction in individual dosages while maintaining their efficacy. This approach may provide a more effective and natural alternative therapy for managing hyperuricemia.

CONCLUSION

This research's statistically analysed results indicate that BME and MLE effectively reduce uric acid levels in rats. Among the administered doses, Dose 3 (BME 1.8 mg/kg BW and MLE 600 mg/kg BW) demonstrated the highest efficacy. It reduced uric acid levels by 41.3%.

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