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The Effects of Varying Fermentation Durations on Uric Acid Levels in Noni Fruit: An Investigation of Sex-Specific Responses

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KEYWORDS

Fermentation

Noni (Morinda citrifolia L.)

Uric Acid

Xanthine Oxidase

Anti-Inflammatory

ABSTRACT:

Introduction: Pharmacological interventions for managing uric acid levels often have limitations, including long-term side effects and limited accessibility. Exploring natural alternatives has become more popular as a result of this. Inhibiting xanthine oxidase, a crucial enzyme in the metabolism of uric acid, noni (Morinda citrifolia) demonstrates strong antioxidant qualities.

Objectives: This study aimed the impact of fermentation duration (2 and 3 months) on the efficacy of noni fruit in reducing uric acid levels among government employees in South Sulawesi, Indonesia.

Methods: Seventy-two respondents were divided into two intervention groups, each receiving 2-month and 3-month fermented noni products for 30 days. Uric acid levels were assessed at baseline, mid-point, and endpoint. Data analysis was performed using the Kruskal-Wallis test due to non-normal data distribution.

Results: The results showed that fermentation duration affects the outcome, with a more significant difference observed in 3-month fermentation for males and 2-month fermentation for females.

Conclusions: Improved gut microbiota profiles, estrogen influence, xanthine oxidase inhibition, elevated uric acid excretion, and anti-inflammatory actions are the underlying processes. According to these results, fermented noni is a potentially effective natural treatment for hyperuricemia. More investigation is required to fully examine these pathways and identify the precise substances causing these effects.

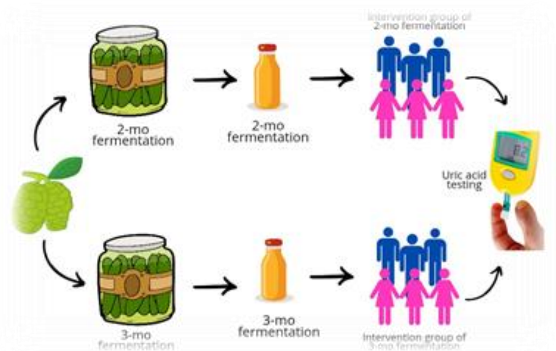

Figure 1. Graphic Abstract of Research Study.

1. Introduction

Gout, a chronic inflammatory arthritis, is primarily caused by the deposition of monosodium urate (MSU) monohydrate crystals in tissues. Recent epidemiological data indicate that gout affects approximately 7.44 million people worldwide, with a prevalence of 41.22 million cases. This translates to an incidence of 0.097% and results in 1.28 million Disability-Adjusted Life Years (DALY) (1–12). In Indonesia, data from the 2018 Basic Health Research (Riskesdas) show that the prevalence of gout disease reached 24.7%, making it the second-highest prevalence after hypertension. In South Sulawesi Province, the prevalence of gout decreased from 10.6% in 2013 to 6.39% in 2018, although this figure remains relatively high compared to the national average (13). Hyperuricemia, a condition characterized by elevated uric acid levels in the plasma, is the primary cause of gout disease. Lifestyle changes, such as increased consumption of animal protein and sedentary

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habits, contribute to the rising burden of this disease (2,4,10,14–20).

Pharmacological interventions for hyperuricemia, while effective in lowering serum uric acid concentrations, are often associated with limitations that impact long-term patient adherence and overall management. These limitations include the potential for significant adverse effects, such as gastrointestinal disturbances, renal dysfunction, and drug interactions, which can necessitate careful monitoring and dose adjustments (1). Furthermore, the chronic nature of hyperuricemia often requires prolonged or lifelong medication, leading to concerns regarding long-term safety and the cumulative impact of side effects (2). Additionally, accessibility to certain pharmacological agents may be restricted due to cost, availability, or patient comorbidities, highlighting the need for complementary or alternative therapeutic strategies that offer comparable efficacy with reduced side effect profiles.

Given the limitations of conventional pharmacological treatments for hyperuricemia, there is a growing interest in exploring natural therapeutic alternatives, among which Morinda citrifolia (noni) has been identified as a potential non-pharmacological therapy for reducing uric acid levels. The fermentation process can alter the chemical composition of noni, increasing the availability of bioactive compounds such as flavonoids and polyphenols. Fermentation of noni fruit not only enhances its nutritional value but also increases the bioactivity of its compounds. Research has shown that fermentation can enhance the antioxidant content and anti-inflammatory compounds in noni, which contribute to the management of uric acid levels and overall health (21–30). Probiotics produced during the fermentation process are beneficial for gut microbiome health. The consumption of fermented noni products can increase the diversity of gut microbiota, which is associated with reduced inflammation and improved metabolic health, including the management of uric acid levels. The bioactive compounds present in noni, such as scopoletin, have anti-inflammatory effects and can assist in the management of uric acid levels. Fermentation can increase the concentration of these compounds, thereby providing better therapeutic effects (31–37). However, despite the promising evidence supporting the use of fermented Morinda citrifolia in managing hyperuricemia, there remains a notable gap in understanding the optimal fermentation duration and its specific impact on uric acid levels across diverse populations. While existing studies have explored the general benefits of fermented noni, there is a paucity of research that systematically compares the effects of varying fermentation periods, particularly in relation to gender-specific responses and temporal changes in uric acid concentrations. This study aims to address this gap by investigating the differential effects of 2-month and 3-month fermented Morinda citrifolia products on uric acid levels, providing a more nuanced understanding of the therapeutic potential of fermented noni in gout management.

This study aimed to evaluate the effect of 2-month and 3-month fermented Morinda citrifolia products on serum uric acid concentrations in male and female participants, compare the efficacy of 2-month versus 3-month fermentation durations in reducing uric acid concentrations across gender and measurement time points, and assess the subjective health benefits reported by participants following consumption of fermented Morinda citrifolia products; by comprehensively examining the impact of varying fermentation durations on uric acid levels and subjective health outcomes, this research contributes valuable insights into the potential of fermented Morinda citrifolia as a natural, non-pharmacological intervention for hyperuricemia and gout management, with the findings anticipated to inform future research and clinical practices, potentially leading to optimized fermentation protocols and personalized therapeutic strategies for individuals with hyperuricemia and gout.

2. Objectives

Generally, this study aimed the impact of fermentation duration (2 and 3 months) on the efficacy of noni fruit in reducing uric acid levels among government employees in South Sulawesi, Indonesia.

The study has several specific objectives. It seeks to conduct biochemical parameter tests to determine the nutritional content and active compounds in fermented noni products. Additionally, sensory tests will be conducted to determine the organoleptic characteristics of fermented noni products. The study also aims to compare the results of biochemical parameter tests and sensory tests between noni products fermented for 2 months and 3 months to determine differences in product quality and characteristics. Furthermore, it will investigate the effect of Morinda citrifolia (noni) beverage consumption on serum uric acid concentrations.

3. Method

1. Research Design

This study used a quasi-experimental pre-posttest design without a control group, with two intervention groups: one receiving 2 months of fermented noni drinks and the other receiving 3 months of fermented noni drinks. This design was chosen to observe changes in uric acid levels in each group based on gender and measurement time (Day 1, Day 15, and Day 30).

2. Materials

Noni fruit; granulated sugar; and drinking water, sterilized fermenting container, straining cloth, packaging bottles, and measuring cup.

3. Research participants

The sample size in this study for each intervention group is 36 individuals, resulting in a total sample size of 72 individuals. This number is adjusted according to the inclusion, exclusion, and dropout criteria established to ensure the selection of appropriate participants.

The inclusion criteria were designed to identify individuals most relevant to the research objectives. Participants must be active government employees at the South Sulawesi Provincial Secretariat, demonstrating a direct connection to the study's context. Furthermore, individuals must be willing to participate in the research and provide informed consent, ensuring that they understand the nature of the study and their role within it. Additionally, participants were required to have uric acid levels at the upper limit of normal or exhibit hyperuricemia, defined by established medical criteria as greater than 6.0 mg/dL for females and greater than 7.0 mg/dL for males. This criterion is crucial for assessing the impact of the intervention on uric acid levels.

Conversely, the exclusion criteria were implemented to eliminate potential confounding factors that could compromise the integrity of the study results. Individuals with a history of allergy or hypersensitivity to noni fruit were excluded to prevent adverse reactions that could skew the findings. Moreover, participants suffering from chronic diseases, such as uncontrolled diabetes, advanced kidney disease, or severe heart disease, were also excluded, as these conditions could significantly affect uric acid metabolism and overall health. Additionally, individuals currently undergoing treatment with medications that influence uric acid levels, such as anti-hyperuricemia drugs like allopurinol, were not eligible for participation. Pregnant or breastfeeding women were excluded to safeguard the health of both the mother and child. Lastly, individuals who could not commit to following all research procedures for a one-month period were also excluded, ensuring that the study maintained a consistent participant pool.

To address participant retention and the integrity of the study, specific dropout criteria were established. Participants who exhibited non-compliance with the research protocol would be withdrawn from the study to maintain the validity of the data collected. Significant side effects experienced during the study would also necessitate withdrawal to protect participant safety. Additionally, any deterioration in health conditions that could arise during the study period would lead to exclusion to ensure participant well-being. Instances of pregnancy occurring during the study would also result in withdrawal, as would the use of unauthorized medications or interventions that could interfere with the study's outcomes. Participants who chose to withdraw voluntarily or who were absent during key measurements would also be considered dropouts, ensuring that the study's data remained robust and reliable.

In summary, the careful delineation of sample size, inclusion, exclusion, and dropout criteria was essential for maintaining the study's scientific rigor and ensuring the safety and relevance of the participant population.

4. Materials And Methods

The study was conducted in several stages, as illustrated in Figure 2.

a) *Fermentation of Noni Fruits.*

Ripen Noni fruits (Morinda citrifolia) were subjected to a rigorous washing procedure prior to fermentation, which was conducted for two distinct durations: 2 and 3 months. Each fermentation batch was prepared with the addition of 6.98% (w/w) sucrose and 46.51% (v/w) distilled water. The resulting mixtures were incubated and stored under anaerobic conditions at ambient temperature, without the introduction of a starter culture.

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Upon completion of fermentation, the products were stored at 4°C until further analysis.

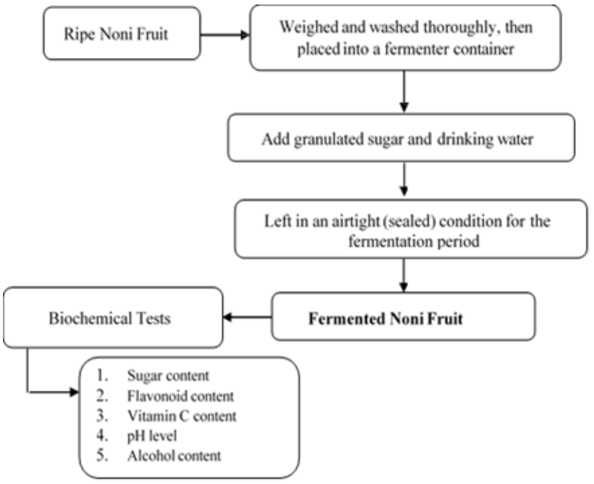

Figure 2. Noni fermentation flowchart of Noni Fruit (Morinda citrifolia L.) Fermentation and Biochemical Tests.

b) ***Recruitment of Participants***

Participants were enrolled in the study based on the following inclusion criteria: age range of 25 to 55 years, baseline uric acid concentrations exceeding the upper normal limits (greater than 6 mg/dL for females and 7 mg/dL for males), absence of current anti-hyperuricemic medication use, and provision of written informed consent. Following enrollment, participants were randomly assigned to one of two intervention groups.

c) ***Intervention***

Participants were instructed to consume 30 mL of the fermented Morinda citrifolia beverage twice daily, in the morning and evening, for a period of 30 days. Adherence to the intervention protocol was monitored daily through direct participant communication and facilitated online group interactions

d) ***Data Measurement***

Biochemical analyses of the fermented Morinda citrifolia products were conducted at the Public Health Laboratory (*Labkesmas*) in Makassar, South Sulawesi Province, Indonesia. These analyses, which included the quantification of ethanol, glucose, pH, ascorbic acid, and total flavonoids, were performed using reference methods detailed in Table 1. Additionally, a sensory evaluation, involving 25 untrained panelists, was performed to assess the products' taste, color, texture, aroma, and overall acceptability.

Table 1. Specifications of the Testing Method for biochemical Parameters

Parameter	Unit	Testing Method Specification
Alcohol	%	Density Measurement (Pycnometer)
Glucose	%	Spectrophotometric
pH		pH meter (SNI 6989, 11-2019)
Vitamin C	µg/mL	Spectrophotometric
Flavonoid	µg/mL	Spectrophotometric

Serum uric acid concentrations were determined using the Easy Touch 6-in-1 point-of-care testing device. Measurements were obtained at baseline (pre-intervention), mid-intervention (Day 15), and post-intervention (Day 30). All data were meticulously recorded on pre-designed data collection forms.

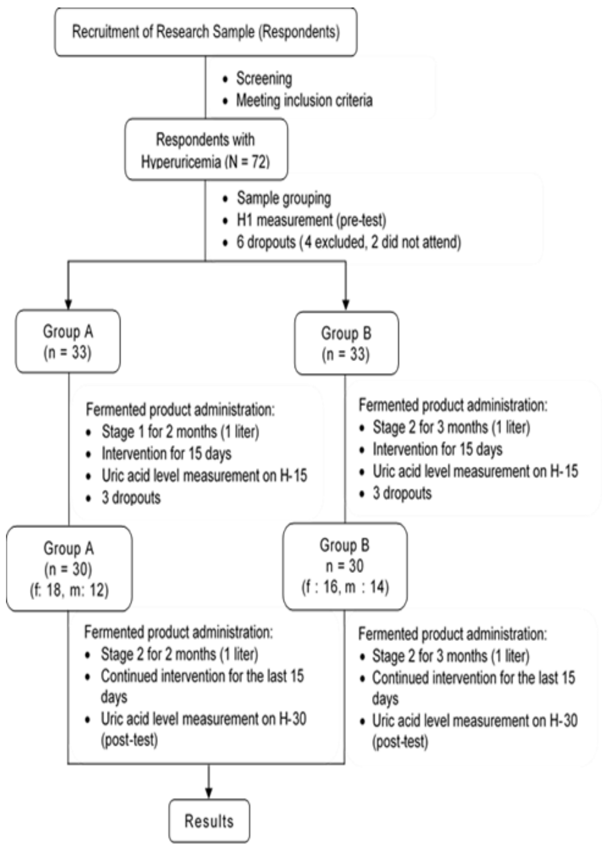

Figure 3. Flowchart of sample recruitment and intervention.

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e) *Data Analysis*

Initial descriptive univariate analysis was performed to examine the distribution and patterns of uric acid concentrations across gender and measurement time points. Mean uric acid concentration changes, stratified by gender and time, are depicted in Figure 4. Subsequently, the non-parametric Kruskal-Wallis test was used to assess for statistically significant differences in uric acid concentrations across measurement time points (pre-intervention, mid-intervention, post-intervention) and between gender-specific intervention groups (2-month and 3-month fermented *Morinda citrifolia*). Where the Kruskal-Wallis test indicated significant differences ($p < 0.05$), post-hoc Dunn's tests were conducted to identify specific pairwise comparisons contributing to these differences, thereby identifying intervention groups exhibiting significant variations.

4. Results And Discussion

4.1 Results

4.1.1 Biochemical Parameter Test of Fermented Noni Product

The fermentation process of noni fruit conducted in this study produced two types of products, namely 2-month fermentation product and 3-month fermentation product. Both types of fermented noni fruit products were then administered to the study participants/samples for 30 days of intervention. The results of laboratory tests with five measurement parameters are shown in Figure 4.

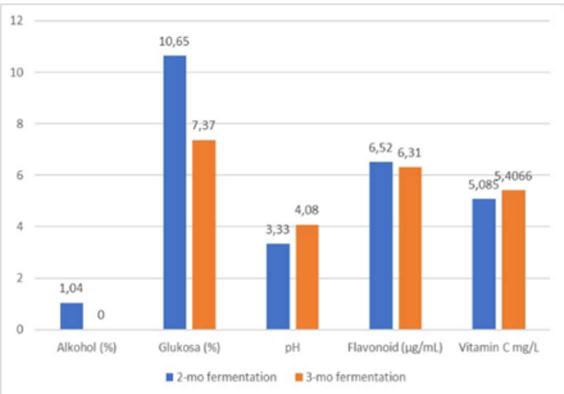

Figure 4. The comparison of biochemical parameters of two feremeted noni drinks. Blue bar indicates the 2-month fermentation, whereas orange bars indicate the 3-month fermentation.

The graph (Figure 4) shows that the 2-month fermented noni product still contains an alcohol content of 1.04%, whereas the 3-month fermented product does not contain any alcohol. The 2-month fermented product still contains a glucose content of 10.65%, whereas the 3-month fermented product contains 7.37%. The acidity level of the 2-month fermented product is higher (low pH, 3.33) compared to the 3-month fermented product (high pH, 4.08). The flavonoid content in the 2-month fermented product is 6.52 µg/mL, whereas the 3-month fermented product contains slightly lower levels of 6.31 µg/mL. However, the 3- month fermented product contains higher levels of Vitamin C, at 5.4066 mg/L, compared to the 2-month fermented product, which contains 5.085 mg/L.

4.1.2 Sensory test

A spider chart in Figure 5 illustrates the hedonic test results. Comparing the 2-month and 3-month fermented noni drink groups, minimal variations were noted in all attributes.

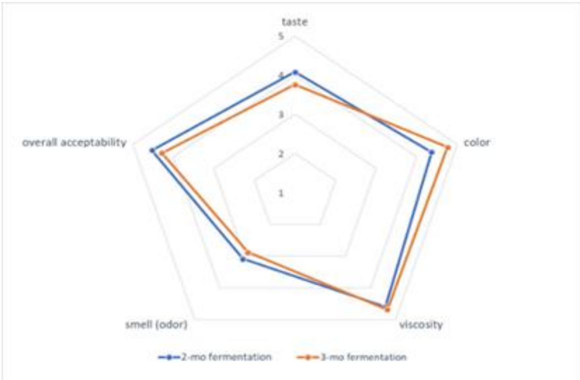

Figure 5. The comparison of sensory test between 2-mo (blue line) vs 3-mo fermentation noni drinks (orange line).

Sensory evaluation revealed that the 2-month fermented product exhibited a significantly higher taste score (4.08) compared to the 3-month fermented product (3.76), indicating a stronger preference among panelists. Conversely, the 3-month fermented product was rated higher for color (4.76 vs. 4.36), suggesting a more appealing visual attribute. Texture scores were comparable between the two groups, with the 3-month fermented product showing a marginally higher score (4.68 vs. 4.6). Despite relatively low scores, the 2-month fermented product was perceived as having a more desirable aroma (3.08 vs. 2.88). Overall acceptability

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was also higher for the 2-month fermented product (4.52 vs. 4.28). These findings suggest that the 2-month fermented product was preferred for taste, aroma, and overall acceptability, while the 3-month fermented product excelled in color and exhibited a slightly better texture. Therefore, if the primary objective is to maximize taste and overall consumer acceptance, the 2-month fermentation period appears optimal.

4.1.3 Effect of Morinda citrifolia Beverage Consumption on Serum Uric Acid Concentrations

Prior to inferential statistical analysis, a descriptive univariate analysis was performed to characterize the research data and provide an initial overview of uric acid levels. This preliminary analysis aimed to elucidate the fundamental distribution and central tendencies of the data, thereby facilitating a comprehensive understanding of the observed uric acid level variations. Specifically, the mean changes in uric acid concentrations were calculated and stratified by gender and measurement time. These descriptive statistics, which offer a foundational insight into the data's structure, are visually represented in Figure 6.

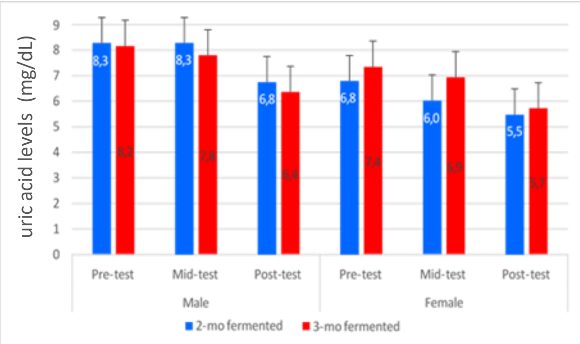

Figure 6. The mean changes in uric acid concentrations during the intervention period, delineated by gender and fermentation duration (2-month: blue bars; 3-month: red bars), are depicted in Figure 5, illustrating pre-intervention (Day 1), mid-intervention (Day 15), and post-intervention (Day 30) measurements.

Figure 6 illustrates the mean changes in uric acid levels observed over a one-month measurement period across different intervention groups. In the female cohort, the 2-month fermented product intervention resulted in a progressive decrease in uric acid levels, from a pre-test mean of 6.8 mg/dL to 6.0 mg/dL at mid-test, and further to 5.5 mg/dL at post-test. Similarly, the 3-month fermented product intervention in females demonstrated a reduction in uric acid levels, with mean values decreasing from 7.4 mg/dL at pre-test to 6.9 mg/dL at mid-test, and 5.7 mg/dL at post-test.

In the male cohort subjected to the 2-month fermented product intervention, a sustained mean uric acid concentration of 8.3 mg/dL was observed between the baseline and mid-intervention time points, subsequently followed by a significant reduction to 6.8 mg/dL at the post-intervention assessment. Similarly, the 3-month fermented product intervention in males resulted in a gradual decrease in mean uric acid concentrations, from an initial 8.2 mg/dL to 7.8 mg/dL at mid-intervention and ultimately reaching 6.4 mg/dL at the study's conclusion. These findings indicate a potential modulatory effect of both 2-month and 3-month fermented product interventions on uric acid levels across both male and female participants, with discernible variations in the temporal dynamics and extent of the observed changes. Collectively, these data suggest that both the 2-month and 3-month fermented product interventions were efficacious in lowering uric acid concentrations within the studied population.

4.1.4 The Effect of Fermented Noni Administration on Uric Acid Levels

The effect of fermented noni drink administration on uric acid levels, stratified by sex and measurement time, was assessed using the Kruskal-Wallis's test, with results presented in Table 2.

Table 2. The Bivariate Analysis Using the Kruskal-Wallis Test to Assess the Effect of Fermented Noni Administration on Uric Acid Levels (Mean ± SD) Based on Gender and Measurement Time.

Duration of fermentation*	2-Month			3-Month		
Measurement Time	Pre intervention	Mid-intervention	Post-intervention	Pre intervention	Mid-intervention	Post-interventio
Male	8.28±1,41^{Aa}	8.28 ±2,29^{Aa}	6.75±0,78^{Bb}	8.16±1.01^{Aa}	7,8 ± 1.62^{Ba}	6,36±0,87^{C}
Female	6.79±0,85^{Ba}	6.03±0,83^{Bb}	5.48±0,83^{Bc}	7.35± 0.99^{Ba}	6,94±1.23^{Ba}	5,73±0,58^{B}

Statistically significant differences ((p<0.05)) between fermentation indicated by the Asterix, Statistically significant differences ((p<0.05)) sex groups are indicated by uppercase superscripts (Kruskal-Wallis test),, and statistically significant differences (p<0.05) in uric acid levels among measurement time points are

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denoted by lowercase superscripts (Post-Hoc Dunn's Test).

The Kruskal-Wallis test (Table 2) demonstrated a statistically significant effect of fermented Morinda citrifolia on uric acid concentrations ($p < 0.05$). In the male cohort, the 3-month fermented product resulted in a greater reduction of uric acid concentrations compared to the 2-month product ($p = 0.000$ vs. $p = 0.007$). Both fermented beverages significantly lowered uric acid concentrations in the female cohort ($p = 0.000$). Subsequent stratified Kruskal-Wallis analysis further confirmed the superior efficacy of the 3-month product ($p < 0.01$). Therefore, the 3-month product exhibited greater overall effectiveness. To delineate specific inter-group differences, a post-hoc Dunn's test was performed, identifying the intervention groups that demonstrated the most substantial variations in uric acid concentrations. The Dunn's test (indicated by differing lowercase superscripts) revealed significant reductions in uric acid concentrations between pre-test and post-test for both 2-month and 3-month products within the male cohort. The 3-month product demonstrated a significantly larger mean difference (19.286, $p = 0.000$) compared to the 2-month product (12.875, $p = 0.002$). In the female cohort, both products significantly reduced uric acid concentrations across all measurement time points. While the 2-month product exhibited a slightly greater mean reduction (24.972 vs. 24.125), both interventions demonstrated equally high statistical significance ($p = 0.000$). In summary, the 3-month fermented product was more effective in males. In females, the 2-month product showed earlier effectiveness, with a significant reduction at mid-test ($p = 0.004$ vs. $p = 0.151$ for the 3-month product.

4.2 Discussion

Figure 4 illustrates that the 2-month fermented Morinda citrifolia product exhibited an ethanol concentration of 1.04%, while the 3-month fermented product demonstrated undetectable levels. Furthermore, the 2-month product contained a glucose concentration of 10.65%, compared to 7.37% in the 3-month product. These data indicate an inverse relationship between fermentation duration and both ethanol and glucose concentrations. Consistent with previous studies, noni fruit fermentation results in a reduction of both alcohol and sugar content, attributed to microbial metabolism. Specifically, microorganisms consume sugars, initially producing ethanol, which is subsequently degraded. Nur Hafiza et al. (2013) demonstrated a decrease in sugar and ethanol content during Morinda citrifolia extract fermentation using Saccharomyces, employing chemical analysis to track compositional changes (38). Similarly, Wang et al. (2021) observed a decrease in ethanol and sugar levels during 63 days of noni juice fermentation, correlating with alterations in aroma and taste profiles (39). Qomariyah et al. (2021), using gas chromatography, also reported a reduction in ethanol content with extended fermentation periods in noni herbal products (40). Furthermore, Konsue et al. (2018) found that increased fermentation duration significantly decreased both ethanol and sugar concentrations in noni juice (41). In the present study, ethanol content was determined using a pycnometer, yielding results expressed as % weight/weight (w/w). To comply with Indonesian National Standard (SNI) 3839:2015, which specifies a maximum ethanol content of 1% volume/volume (v/v) for non-alcoholic fermented beverages, a conversion from % w/w to % v/v was performed. The converted ethanol content of the 2-month fermented product was 0.82% v/v, thus meeting the SNI standard and indicating safety for consumption. Sugar content, while not explicitly regulated by SNI 3839:2015, was assessed in relation to the Indonesian Ministry of Health's recommended daily sugar intake (50 grams or 4 tablespoons). The observed sugar content of 10.65% in the 2-month and 7.37% in the 3-month fermented products was deemed safe. The reduction in sugar content from 10.65% to 7.37% suggests effective microbial activity during the extended fermentation.

Figure 2 indicates that the 2-month fermented Morinda citrifolia product contained a flavonoid concentration of 6.52 μg/mL (6.52 mg/L), while the 3-month product exhibited a slightly lower concentration of 6.31 μg/mL (6.31 mg/L). Literature reports flavonoid concentrations in fresh noni fruit ranging from 0.5 to 1.5 mg/g. Ali et al. (2018) reported a flavonoid concentration of approximately 1.5 mg/g (1500 mg/L) in fresh noni fruit. Meilawati et al. (2021) quantified the total flavonoid content in 7-day fermented noni juice, reporting 5.9 ± 0.008 mg quercetin equivalents/g extract (42). These studies highlight the presence of significant bioactive compounds, including flavonoids and scopoletin, in noni products, which contribute to antioxidant activity. The

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flavonoid concentration reported by Meilawati et al. (2021), when converted, is equivalent to 5900 mg/L, suggesting that fermentation processes influence flavonoid content.

Conversely, the 3-month fermented product demonstrated a higher ascorbic acid concentration (5.4066 mg/L) compared to the 2-month product (5.085 mg/L). These results suggest that fermentation duration influences and potentially enhances ascorbic acid content. Similar findings were reported in red dragon fruit kombucha fermentation, where ascorbic acid concentrations increased after 14 days (43). Adetuyi & Ibrahim (2014) also observed significantly higher ($p < 0.05$) phenolic, ascorbic acid, total flavonoid, and non-flavonoid content, along with enhanced antioxidant activity, in fermented okra seeds compared to unfermented seeds (44). Furthermore, studies on kombucha tea fermentation have documented increases in ascorbic acid levels (45). Ascorbic acid and flavonoids play a crucial role in uric acid management through mechanisms that reduce uric acid concentrations and inflammation. Clinical studies have shown that ascorbic acid supplementation can lower serum uric acid concentrations, thereby reducing the risk of gout. For instance, Choi et al. (2009) demonstrated that higher ascorbic acid intake is associated with lower serum uric acid concentrations, attributing this effect to its antioxidant properties that mitigate oxidative damage and subsequent joint inflammation associated with hyperuricemia. Similarly, flavonoids, abundant in fruits and vegetables, possess anti-inflammatory properties that can alleviate gout-related inflammation. Research indicates that flavonoids can inhibit pro-inflammatory cytokine production and reduce the activity of enzymes involved in inflammatory pathways. Additionally, flavonoids, such as quercetin, have been suggested to inhibit renal uric acid reabsorption, contributing to lower serum uric acid concentrations (27,46–49).

Throughout the intervention period, participants from both the 2-month and 3-month intervention groups reported subjective improvements in health. A majority of participants described a sensation of increased physical lightness and reported a significant reduction or complete resolution of joint paresthesia, particularly in the hands and extremities. Participants further reported subjective improvements in stamina and physical fitness, noting a reduction in dyspnea and fatigue during stair climbing, and an overall enhanced sense of physical well-being. Furthermore, participants with pre-existing back pain reported a decrease in pain intensity, with some reporting complete resolution following regular consumption of the fermented Morinda citrifolia beverage. These subjective observations align with findings from previous research, such as the study by Wang et al. (50), which demonstrated that Morinda citrifolia juice consumption significantly improved quality of life in adults with chronic diseases. Specifically, the aforementioned study, utilizing validated questionnaires, reported significant enhancements in various domains of physical and mental health following Morinda citrifolia consumption.

A notable observation was the transient elevation of uric acid concentrations in some participants at the mid-intervention time point (Day 15). Despite this temporary increase, participants reported a significant reduction or complete resolution of pre-existing joint pain. At the post-intervention assessment (Day 30), uric acid concentrations demonstrated a consistent decrease, suggesting a sustained beneficial effect of fermented Morinda citrifolia on uric acid regulation. While fluctuations were observed at mid-intervention, the overall data indicate that Morinda citrifolia consumption contributes to long-term uric acid management. This aligns with the understanding that compounds within Morinda citrifolia may mitigate inflammation associated with hyperuricemia. However, it is important to acknowledge that individual dietary and lifestyle factors may also influence uric acid levels. Furthermore, several participants reported improved bowel regularity during the intervention, suggesting a potential role for fermented Morinda citrifolia in supporting gastrointestinal function. This is consistent with findings from a review of previous clinical studies (51), which highlighted that Morinda citrifolia juice, containing fiber and bioactive compounds, can enhance gut microbiota balance, alleviate constipation symptoms, and improve overall gastrointestinal health. These cumulative findings, including improvements in quality of life, management of prediabetes and hypertension symptoms, and reduction of joint pain, suggest that fermented Morinda citrifolia products provide a range of significant health benefits. Although transient fluctuations in uric acid concentrations may occur, the overall therapeutic

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potential of Morinda citrifolia consumption remains evident.

The Kruskal-Wallis test was used to assess significant differences in uric acid levels across measurement time points and between intervention groups (2-month and 3-month fermented products) for both male and female participants. The Kruskal-Wallis test (Table 2) revealed significant differences in uric acid levels across intervention groups for both male and female participants ($p < 0.05$). Specifically, the 2-month fermented product resulted in significant changes in uric acid levels in males ($p = 0.007$) and females ($p = 0.000$). Similarly, the 3-month fermented product also resulted in highly significant changes in both males and females ($p = 0.000$). These low p-values indicate a statistically significant effect of the fermented products on uric acid levels during the intervention period, with fermentation duration influencing the observed outcomes. The comparative analysis of pre-intervention and post-intervention uric acid concentrations revealed that the 3-month fermented product intervention resulted in a significantly greater change compared to the 2-month intervention, as evidenced by both the mean difference (19.286 vs. 12.875) and the associated p-value (0.000 vs. 0.002). These data suggest that the 2-month fermented Morinda citrifolia product is more effective in reducing uric acid concentrations in females, whereas the 3-month fermentation demonstrates superior efficacy in males.

The underlying mechanisms of the reduction of uric acid levels post intervention involve increased uric acid excretion, inhibition of the enzyme xanthine oxidase, the influence of estrogen, anti-inflammatory effects, and improvement of gut microbiota profiles. Fermented products, such as noni, contain bioactive compounds that enhance uric acid excretion through the kidneys. The fermentation process can alter the chemical components in noni, thereby increasing the availability of bioactive compounds such as flavonoids and polyphenols. Fermentation of noni fruit not only enhances its nutritional value but also increases the bioactivity of the compounds within the fruit. Research has shown that fermentation can enhance the antioxidant content and anti-inflammatory compounds in noni, which contribute to the management of uric acid levels and overall health. Additionally, the fermentation process is known to produce probiotics that are beneficial for gut microbiome health (51–54). Probiotics are live microorganisms that provide health benefits when consumed in adequate amounts. Research has shown that fermented noni juice with lactic acid bacteria can increase the population of beneficial microbes in the gut, contributing to digestive health and the regulation of uric acid levels. Fermentation of noni can modulate gut microbiota, which plays a crucial role in digestive health and metabolism. Research has shown that the consumption of fermented noni products can increase the diversity of gut microbiota, which is associated with reduced inflammation and improved metabolic health, including the management of uric acid levels (32,34–36,55).

Bioactive compounds in noni, such as scopoletin, have been shown to have anti- inflammatory effects and can assist in the management of uric acid levels. Fermentation can increase the concentration of these compounds, thereby providing better therapeutic effects in addressing uric acid issues (42,56–59). The fermentation process of noni fruit not only enhances the nutritional value and bioactivity of the compounds within the fruit but also produces probiotics that are beneficial for gut microbiome health. Thus, the fermentation process can contribute to the management of uric acid levels and overall digestive health.

Additionally, the physiological differences between males and females also serve as a basis for the differences observed in this study's results. An epidemiological study by Choi et al. (2004) indicates that men tend to have higher uric acid levels compared to women. This is attributed to physiological differences, including purine metabolism and uric acid excretion by the kidneys. Neogi, T. (2011) in his study found that men have a higher risk of developing gout compared to women. Data also indicate that men have a higher incidence of gout (uric acid), particularly at a younger age (20,48). Other studies have also reported that males and females may have different physiological responses to fermented products. This may be due to differences in metabolism, nutritional needs, and hormonal responses, which can affect the outcomes of fermented product consumption (60–62).

Estrogen is known to influence uric acid excretion through the kidneys. Research indicates that estrogen can enhance uric acid excretion, meaning that women with higher estrogen levels (such as during their fertile period) may have lower uric acid levels compared to men.

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Women, with higher estrogen levels, are more responsive to shorter fermentation products (2 months), while men require a longer fermentation period (3 months) to achieve the same effects. This suggests that the hormone estrogen plays a role in accelerating or enhancing the effects of fermented products in women (8,17,63).

The influence of estrogen on uric acid metabolism in women plays a crucial role in the quicker and more significant response to the 2-month fermented products. Based on the analysis conducted, it can be concluded that the 2-month fermented noni product shows significant results in females. In contrast, the 3-month fermented product provides more significant and consistent results in males.

Based on Table 3, for males in the 2-month fermentation group, there is a significant decrease from pre-test to post-test and from mid-test to post-test, but no significant difference is observed between pre-test and mid-test. However, in the 3-month fermentation group, there is a very significant decrease from pre-test to post-test and also from mid-test to post-test, but no significant difference is found between pre-test and mid-test. These results indicate that fermentation duration affects the outcomes, with a more pronounced decrease observed in the post-test compared to the pre-test and mid-test. For females in the 2-month fermentation group, there are significant differences among all groups (pre-test, mid-test, and post-test). In the 3-month fermentation group, significant differences are only found between pre-test and post-test, as well as mid-test and post-test, but no significant difference is observed between pre-test and mid-test. These results indicate that fermentation duration affects the outcomes, with more pronounced differences observed in the 2-month fermentation compared to the 3-month fermentation.

The 2-month fermentation shows significant differences for females in all comparisons, while males show significant differences only between pre-test and post-test and mid-test and post-test. The 3-month fermentation shows more consistent differences for males, while females do not show significant differences between pre-test and mid-test. These results indicate that fermentation duration affects the outcomes, with more pronounced differences observed in the 3-month fermentation for males and in the 2-month fermentation for females. Analysis of the data revealed that a two-month fermentation period demonstrated significant improvements across all evaluation points (pre-test, mid-test, and post-test) for female subjects. Conversely, a three-month fermentation period yielded more consistent and superior outcomes for male subjects.

The present findings are supported by two key theoretical frameworks. Firstly, the well-established principle that fermentation duration significantly impacts product quality. Extended fermentation periods typically allow microorganisms sufficient time for substrate degradation, thereby enhancing the bioconversion of precursor compounds into bioactive metabolites. This phenomenon is consistent with findings reported in previous studies (30,41,64,65); Secondly, the observed sex-specific responses to fermented products may be attributed to inherent physiological dimorphisms between males and females. These variations, encompassing differences in metabolic pathways, nutrient requirements, and hormonal regulation, can modulate the biotransformation of compounds during fermentation, ultimately influencing the composition and efficacy of the final product (60–62).

4.3 Limitations of the Study

This study presents several limitations that warrant consideration. Firstly, the participant cohort was not stratified based on the duration of hyperuricemia, precluding the differentiation between individuals with chronic hyperuricemia and those with recent onset. This lack of stratification may have introduced heterogeneity within the study population, as chronic and new hyperuricemia patients may exhibit distinct physiological responses to the intervention due to differences in disease progression and underlying pathophysiology. As demonstrated by Khan et al. (2018), individuals with a longer history of hyperuricemia often display differential treatment responses compared to newly diagnosed cases. Furthermore, as shown by Choi et al. (2016), chronic hyperuricemia can be associated with higher levels of systemic inflammation, potentially impacting the efficacy of the intervention. Consequently, the absence of stratification may have compromised the internal validity of the study by limiting the comparability of homogeneous subgroups, and may have also impacted external validity by reducing the generalizability of findings to specific patient

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populations. Stratification, as suggested by Zhang et al. (2019), would have enabled a more nuanced analysis, potentially revealing distinct intervention efficacies for different hyperuricemia durations. This would have facilitated the development of more personalized management strategies, aligning with the principles of individualized care emphasized by Kumar et al. (2020).

5. Conclusion

The research findings unequivocally demonstrate the significant impact of fermentation duration on the observed outcomes. Notably, a more pronounced effect was observed in the 3-month fermentation period for male subjects, whereas a 2-month fermentation period proved most efficacious for female subjects in reducing uric acid levels. These findings provide compelling evidence for the potential of fermented noni as a natural therapeutic agent for hyperuricemia. Future research endeavors should be directed towards elucidating the underlying biochemical mechanisms of noni fermentation and exploring its broader clinical applicability across diverse populations.

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Conflict Of Interest Statement

Authors state no conflict of interest.

Informed Consent

We have obtained informed consent from all individuals included in this study.

Ethical Approval

The research related to human use has been complied with all the relevant national regulations and institutional policies in accordance with the tenets of the Helsinki Declaration and has been approved by the authors' institutional review board or equivalent committee.

Data Availability

The data that support the findings of this study are available on request from the author, [Fitri Isriyani]. The data, which contain information that could compromise the privacy of research participants, are not publicly available due to certain restrictions.

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