https://doi.org/10.31925/farmacia.2025.2.17 **ORIGINAL ARTICLE**

EXPLORING THE ANTI-FATIGUE EFFECTS OF WATERMELON RIND: A NATURAL BOOST FOR ENDURANCE

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Abstract

Watermelon rind, often discarded as organic waste, contains significant levels of citrulline and arginine, particularly in its inner peel compared to the outer peel. This study aimed to quantify these amino acids in watermelon rind sourced from the Hulu Sungai Tengah region, South Kalimantan Province, and evaluate their potential anti-fatigue effects. High Performance Liquid Chromatography (HPLC) analysis revealed that the rind had higher citrulline (162.8 mg/g) and arginine levels the peel. Male Balb/C mice subjected to swimming tests after oral administration of watermelon rind demonstrated improved endurance, reduced blood lactate levels, and better maintenance of biochemical parameters related to fatigue compared to controls. These findings suggest that watermelon rind, rich in citrulline and arginine, could be a valuable source for supplements or nutraceutical products to enhance physical performance and health. Further research into cultivation and processing methods could unlock its economic potential and promote sustainable utilization.

Rezumat

Coaja de pepene verde, adesea considerată deșeu organic, conține niveluri semnificative de citrulină și arginină, în special în stratul intern. Scopul studiului a fost de a cuantifica acești aminoacizi în coaja de pepene verde provenită din regiunea Hulu Sungai Tengah, provincia Kalimantanul de Sud, și de a evalua potențialele efecte de combatere a oboselii. Analiza prin cromatografie lichidă de înaltă performanță (HPLC) a evidențiat un conținut ridicat de citrulină (162,8 mg/g) și arginină în stratul intern al cojii. Șoarecii masculi din rasa Balb/C, supuși unor teste de rezistență la înot după administrarea orală de extract de coajă de pepene verde, au demonstrat o andurанță îmbunătățită, niveluri reduse de lactat seric și o îmbunătățire a parametrilor biochimici asociați oboselii, comparativ cu lotul de control. Coaja de pepene verde, bogată în citrulină și arginină, ar putea reprezenta o sursă valoroasă pentru suplimente sau produse nutraceutice destinate îmbunătățirii performanței fizice și susținerii sănătății. Cercetări suplimentare privind metodele de cultivare și procesare ar putea evidenția potențialul economic al acestei resurse și ar încuraja valorificarea sa durabilă.

Keywords: watermelon rind, citrulline, arginine, HPLC analysis, anti-fatigue, physical endurance, nutraceuticals

Introduction

Physical fatigue can be experienced by anyone. It is caused by excessive muscle activity [30]. The level of fatigue is highly dependent on many factors, including motivation, intensity, duration, and environment [28]. Physical fatigue can occur briefly or last a long time, thereby reducing recovery time and triggering a decline in performance [14]. This is not desirable, especially for athletes, as it can impact the achievement of performance goals. The decline in muscle function due to physical activity can be influenced by several factors, including metabolic changes, depletion of energy reserves such as glucose, liver glycogen, and muscle glycogen, as well as alterations in muscle fibers [4, 5]. During intense physical activity, muscle fibers undergo significant contraction, resulting in reduced phosphocreatine reserves, lactate accumulation, ion imbalance, and increased oxidative stress [3, 6].

Citrulline and arginine are amino acids that have the potential to delay fatigue, lower blood pressure, and address inflammation in arthritis [3, 11, 17, 31, 34]. Arginine and citrulline compounds work synergistically to enhance the production of nitric oxide (NO) [31]. A decrease in citrulline levels in the body can lead to a reduction in nitric oxide (NO), which may contribute to inflammation and result in blood pressure imbalance, potentially causing fatigue [46]. Pharmacologically, NO can expedite the removal of metabolites produced during intense physical activity, thus delaying fatigue and dilating blood vessels to increase blood flow and optimize nutrient delivery to tissues [13, 14]. Although citrulline is a non-essential amino acid, its benefits to the human body are substantial [5].

Citrulline and arginine compounds are abundantly found in watermelon [16, 25, 37]. Several researchers have explored watermelon as a source of citrulline.

The geographical location of growth affects the citrulline levels in watermelon [18, 19]. Indonesia is a tropical country with year-round sunlight exposure, which is believed to influence the chemical composition of plants, especially fruits. One region in Indonesia known for its high watermelon yield and significant sunlight exposure is the island of Kalimantan. The location of this island on the equator results in greater sunlight exposure compared to other areas.

This study focuses on determining the arginine and citrulline compounds in watermelon rind sourced from the Hulu Sungai Tengah region, South Kalimantan Province. The study further investigates the effects of watermelon rind samples on the physical endurance of male mice subjected to swimming tests.

Materials and Methods

Sampling and Preparation

Watermelons with red flesh and seeds were harvested from Hulu Sungai Tengah in South Kalimantan Province, after 30 - 40 days of cultivation, and collected in July 2023. The chosen watermelons had red flesh and contained seeds. The fruit was divided into peels, rind, and flesh. The rind samples were sliced thinly to increase the cross-sectional area, which make the drying process more efficient. The flesh of the fruit was discarded. The prepared samples were dried in an oven at 50°C for 72 hours. The dried samples were then ground into a fine powder using a blender.

Determination of Citrulline and Arginine

High Performance Liquid Chromatography (HPLC) with a Shimadzu LC-10AT instrument and a C18 column (150 x 4.6 mm) was used to determine citrulline and arginine. The sample was prepared by first dissolving 50 mg of the sample in 10 mL of water. The mixture was then sonicated for 30 minutes at room temperature, and centrifuged at 4000 rpm for 15 minutes. The solution was filtered using a 0.45 µm syringe filter and stored in a container. An aliquot of 20 µL of the prepared sample was then injected into the HPLC instrument, with an analysis time of 10 minutes [27].

Evaluation of Anti-Fatigue Activity

Eight-week-old male Balb/C mice were housed in the Animal Laboratory of the School of Pharmacy at Institut Teknologi Bandung. The facility maintained standard conditions (12/12 light-dark cycle, temperature at 22 ± 2°C, and humidity at 50 ± 15%). After two weeks of adaptive feeding, the animals were randomly divided into five groups (n = 6): sedentary control with vehicle treatment (Control); swimming training exercise with vehicle treatment (EC); swimming training exercise with watermelon rind doses of 200 (WR-1), 400 (WR-2), and 600 (WR-3) mg/kg body weight; and a comparative group receiving 42 mg/kg body weight of citrulline. The mice were orally administered the treatments every other day for six weeks [40]. The vehicle group received the same volume of sterile water. Animal experiments were performed and approved by the animal ethics committee of the School of Pharmacy at Institut Teknologi Bandung.

All groups underwent intensive aerobic swim training for 10 minutes over 42 days of treatment [42]. The swim training was conducted 30 minutes after gavage treatment in a square glass tank (30 x 30 x 40 cm) filled with water maintained at 25 ± 2°C. The mice were given an additional weight equal to 10% of their body weight to evaluate endurance. Endurance was recorded at the point of initial fatigue, determined by the loss of coordinated movements and the inability to return to the surface within 8 seconds. The time from the start to the point of fatigue was recorded with a stopwatch. Immediate assessments were performed after swimming to measure glucose (Glu) and blood lactate (BLA) levels using instant test strips. All animals were euthanized at the end of the 42-day treatment period, and blood, tissue, and organ samples were collected immediately after the fatigue test. Serum was prepared by centrifuging the samples at 3500 rpm and 4°C for 15 minutes to determine levels of nitric oxide (NO), creatine kinase (CK), and blood urea nitrogen (BUN).

Chemicals and Reagents

Methanol and hydrochloric acid were purchased from Chem Supply (Gillman, SA). Arginine and citrulline standards, along with all other reagents, were purchased from Sigma Aldrich Australia (Castle Hill, NSW) Ureum reagent test by Meril Diagnostics; Nitric Oxide reagent test by Elabscience Biochemical Assay Reagent Colorimetric Assay Kit catalog number E-BC-K035-S; Creatine kinase reagent test by Biolabo catalog number EC.2.7.3.2.

Statistical Analysis

All data were expressed as mean ± standard sources error mean (SEM). Statistical tests were conducted to determine the differences in swimming duration, lactate, glucose, blood urea nitrogen, creatine kinase, and nitric oxide in serum samples. The data were analysed sources using two-way ANOVA IBM SPPS software version 25. The difference is significant when $p < 0.05$.

Results and Discussion

Table I shows the arginine and citrulline levels in the peel and rind of watermelon, compared to pure citrulline and arginine compounds. Citrulline has the highest amino acid concentration in both parts of the watermelon (Figure 1), with the highest concentration in the rind (162.93 mg/g dw). These findings align with the study conducted by [1,25], which explored the citrulline and arginine content in various taxa of *Cucurbitaceae*. Both studies consistently demonstrate that citrulline is most abundantly found in the rind, further supporting its potential as a valuable source of this amino acid.

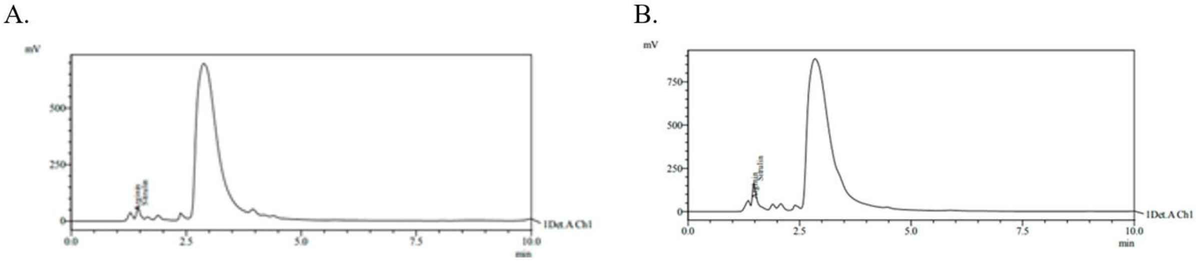

Figure 1.

Determination of arginine and citrulline using HPLC (a) peel; (b) rind

Table I

The results of the examination of arginine and citrulline levels in the peel and rind of watermelon, compared to pure citrulline and arginine compounds

Part	Weight (g)	Volume (L)	Citrulline			Arginine		
			Area	mg/L	mg/g	Area	mg/L	mg/g
Peel	0.05	0.01	543.536	369.3	43.9	257.852	31.1	6.2
Rind	0.05	0.01	1.054.288	814.7	162.9	457.511	109.1	21.8

The oral administration of watermelon (*Citrullus lanatus*) rind did not significantly affect food intake. The study results indicated that the food intake of the negative control group was 7.9 ± 0.7 g/group/day. There were no significant changes in food intake in all groups compared to the negative control group, it means that all test animals are in normal condition (Figure 2A). This indicates that the administered sample is safe and does not cause any adverse effects, as evidenced by the absence of abnormal conditions.

After 42 days of watermelon rind administration, the weight gain was not significant (Figure 2B). The results showed that weight gain after six weeks of training varied from 36.4 ± 2.1 g in the negative control group, 36.8 ± 2.3 g in the positive control group, 38.2 ± 2.1 g in the 200 mg/kg dose group, 38.2 ± 4.2 g in the 400 mg/kg dose group, and 35.4 ± 4.8 g in the 600 mg/kg dose group. When comparing body weight in week 1 and week 6, all groups experienced an increase in body weight.

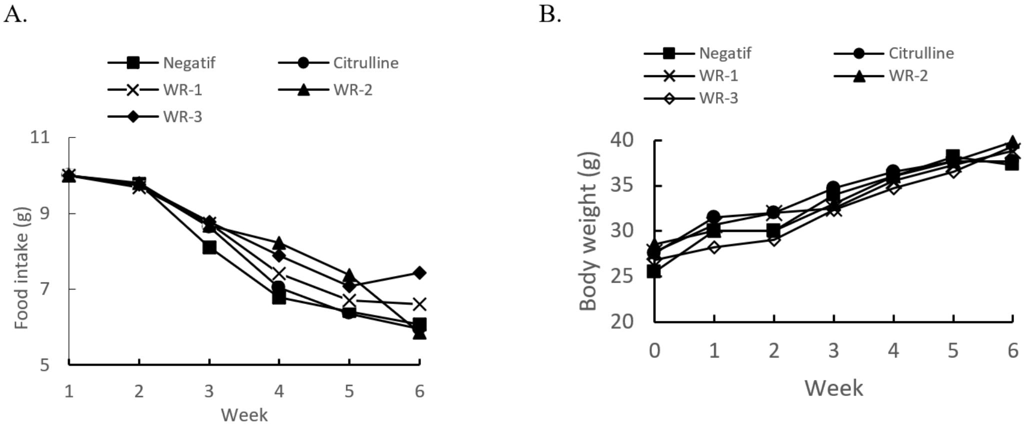

Figure 2.

Food intake (A); Body weight of mice (B)

The results are expressed as mean ± S.E.M. n = 6 animals

The research results indicate a significant difference in fatigue delay after six weeks of swimming tests in different groups of mice (Figure 3A). The swimming duration in mice administered with watermelon rind (*Citrullus lanatus*) significantly increased at a dose of 200 mg/kg, reaching 168.7 ± 7.8 seconds ($p < 0.05$), in the 400 mg/kg dose group to 170.3 ± 7.6 seconds ($p < 0.05$), and in the 600 mg/kg dose group to 188.7 ± 9.0 seconds ($p < 0.05$), compared to the negative control group at 83.3 ± 9.5 seconds ($p < 0.05$). The results in the watermelon rind-treated groups were comparable to the positive control group treated with citrulline, which showed a duration of 188.7 ± 9.0 seconds ($p < 0.05$). The results are expressed as mean ± S.E.M. n = 6 animals. Statistical differences were tested using one-way ANOVA followed by Tukey's multiple comparison test, and differences were considered significant at $p < 0.05$ compared to the negative control group given distilled water and the positive control group treated with citrulline.

Immediately after the swimming test, lactate levels were measured. As shown in Figure 3B, the control group experienced a significant increase in lactate levels, reaching 11.2 ± 0.7 mg/dL ($p < 0.05$), while the WR-1 test group showed levels of 9.9 ± 0.8 mg/dL (P<0.05), the WR-2 test group 9.3 ± 0.9 mg/dL ($p < 0.05$), and the WR-3 test group 9.4 ± 0.2 mg/dL (P<0.05). Blood lactate levels in all test groups where close to the citrulline group, which showed levels of 8.6 ± 0.9 mg/dL ($p < 0.05$). It means that all test groups can decreasing blood lactate level but no one more better than citrulline group.

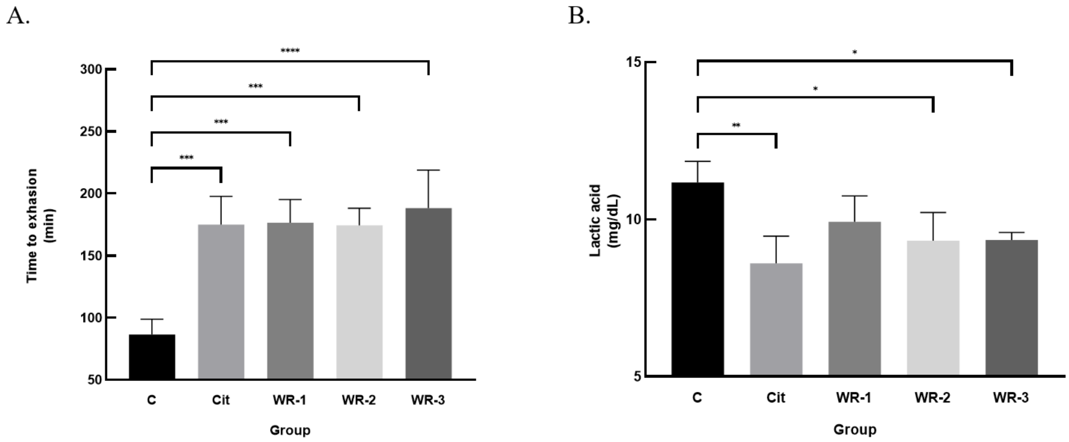

Figure 3.

Time swimming test (A); Blood lactic acid (B); The results are expressed as mean ± S.E.M. n = 6 animals

Biomarkers associated with fatigue such as, lactate, glucose (Glu), blood urea nitrogen (BUN), creatine kinase (Ck), and nitric oxide (NO) levels in the kidney and serum (Table II). All test groups and the citrulline group exhibited better blood glucose maintenance than the negative control group, which had 143.8 ± 4.8 mg/dL. Although not statistically significant, the citrulline and test groups showed promise in maintaining blood glucose levels.

The citrulline group significantly reduced blood urea levels to 1.9 ± 0.2 mg/dL ($p < 0.05$) compared to the control group at 7.1 ± 0.9 mg/dL ($p < 0.05$). Blood urea levels in the test groups were lower than those in the control group. The increase in Ck level following intense exercise is a normal response to muscle fiber damage and the accompanying repair process. Citrulline significantly lowered Ck to 78.5 ± 2.0 U/L ($p < 0.05$), as did the WR-1 test group to 54.5 ± 5.5 U/L ($p < 0.05$), the WR-2 test group to 51.9 ± 4.5 U/L ($p < 0.05$), and the WR-3 test group to 50.2 ± 4.9 U/L ($p < 0.05$). This indicates the potential to reduce muscle damage or cellular stress [7].

NO is a multifunctional molecule that plays a crucial role in enhancing athletic performance and physiological adaptation to exercise[7]. Its primary functions include vasodilation, increased blood flow, blood pressure regulation, reduction of oxidative stress, and improved muscle function and performance [29]. Citrulline increases renal NO levels to 24.2 ± 3.0 μM and serum NO levels to 8.1 ± 0.3 μM. Meanwhile, all test groups, particularly the WR-3 group, experienced a significant increase in NO similar to the Citrulline group, with renal NO levels measuring 29.8 ± 3.3 μM and serum NO levels measuring 7.73 ± 0.4 μM.

Overall, citrulline administration and the WR test groups showed varying effects on organ weight (Table III). A reduction in liver weight was observed in all treatment groups compared to the control, with most significant decrease in the WR-2 group (1.8 ± 0.4 g). This reduction may indicate a positive effect of citrulline and WR in reducing liver stress or inflammation, or in enhancing liver function, potentially leading to a decrease in liver mass. In different study, citrulline can decrease liver fat accumulation [43]. The intestines showed a reduction in weight in the citrulline group, which may suggest improved organ health or reduced stress/inflammation. Other organs, such as the kidneys, lungs, heart, and testes, did not show significant weight changes, indicating that the treatment might not substantially affect these organ weights. The differences in organ responses may depend on the specific characteristics of citrulline and WR treatment and their mechanisms of action on different organs.

Table II

Effect of test group and citrulline group on biochemical parameters

Parameter	Group				
	Control	Citrulline	WR-1	WR-2	WR-3
Glucose (mg/dL)	143.8 ± 4.8	150.3 ± 3.1	148.8 ± 3.7	146.8 ± 4.5	149.8 ± 4.4
BUN (mg/dL)	7.1 ± 0.9	1.9 ± 0.2	3.8 ± 0.4	4.0 ± 0.3	3.6 ± 0.4
Ck (U/L)	110.2 ± 1.8	78.5 ± 2.0	54.5 ± 5.5	51.9 ± 4.5	50.2 ± 4.9
NO Renal (µM.)	12.2 ± 1.5	24.2 ± 3.0	19.7 ± 0.3	21.2 ± 0.4	29.8 ± 3.3
NO Serum (µM.)	4.9 ± 0.3	8.1 ± 0.3	6.7 ± 0.1	6.2 ± 0.9	7.7 ± 0.4

BUN: blood urea nitrogen; Ck: creatine kinase; NO: nitric oxide; The results are expressed as mean ± S.E.M. n = 6 animals

Table III

Comparison of organ weights for each group

Organ (g)	Group				
	Control	Citrulline	WR-1	WR-2	WR-3
Liver	2.1 ± 0.3	1.9 ± 0.2	1.9 ± 0.2	1.8 ± 0.4	1.8 ± 0.3
Right renal	0.3 ± 0.04	0.3 ± 0.01	0.3 ± 0.05	0.3 ± 0.09	0.3 ± 0.03
Left renal	0.3 ± 0.03	0.3 ± 0.02	0.3 ± 0.03	0.3 ± 0.06	0.3 ± 0.02
Lung	0.2 ± 0.03	0.2 ± 0.02	0.2 ± 0.03	0.2 ± 0.02	0.2 ± 0.02
Heart	0.2 ± 0.02	0.2 ± 0.01	0.2 ± 0.02	0.2 ± 0.02	0.1 ± 0.02
Intestint	5.8 ± 1.7	4.8 ± 0.5	5.2 ± 0.1	5.1 ± 0.9	5,31 ± 0.7
Stomach	0.3 ± 0.03	0.3 ± 0.02	0.3 ± 0.04	0.3 ± 0.04	0.3 ± 0.05
Testis	0.3 ± 0.03	0.3 ± 0.02	0.3 ± 0.03	0.3 ± 0.05	0.3 ± 0.03

The results are expressed as mean ± S.E.M. n = 6 animals

This study examines the citrulline and arginine content in two parts of the sample: the peel (outer skin) and the rind (inner skin) from watermelon (*Citrullus lanatus*). The potential of these amino acids is particularly promising for addressing several issues in cardiovascular disease patients [15, 26]. Citrulline does not act directly but undergoes metabolism in the kidneys to become arginine and subsequently a precursor for NO [27, 28]. However, the administration of citrulline alone is still more effective than arginine [4].

The analysis results show that the rind has significantly higher citrulline and arginine content compared to the peel. However, the ratio of citrulline to arginine in both parts remains relatively constant, around 7.05 in the peel and 7.47 in the rind. This indicates that despite the significant difference in the absolute amounts of these amino acids, the ratio between citrulline and arginine remains similar in both parts.

These findings suggest that the rind is richer in citrulline and arginine than the peel and, could be a potential source for supplements or products that utilize these two amino acids. Nonetheless, the potential to use both parts of the watermelon rind as a source of citrulline and arginine is quite promising, considering that the rind constitutes 40-50% of the total weight. The rind also contains many other essential nutrients such as vitamins C, B, and E, minerals, flavonoids, β-sitosterol, and several volatile compounds [2, 21]. Citrulline and arginine, two key amino acids, tend to accumulate in the rind due to their role in the metabolism and growth of the watermelon [25].

In a study on mice subjected to a swimming test, it was observed that high lactic acid concentrations correlated with relatively short swimming times in the control group. Accumulated lactic acid in the blood during intensive exercise due to the lack of supplementation results in a decrease in the pH of muscles, which can cause acidosis. Acidosis damages muscles and other vital organs and cause fatigue [19]. Meanwhile, the group given citrulline showed a significant reduction in lactic acid levels compared to the control group, with almost double the swimming time. Citrulline helps improve physical performance by reducing lactic acid production through increased blood flow and oxygen availability to muscles [33-35]. These results confirm that citrulline effectively enhances physical endurance by delaying fatigue.

In the WR-1, WR-2, and WR-3 groups, lactic acid concentrations were slightly higher than in the citrulline group but still lower than in the control group. The extended swimming times indicate that even though lactic acid levels were higher than in the citrulline group, endurance significantly improved. This suggests that WR-1, WR-2, and WR-3 treatments support better physical performance than the control. The citrulline and WR-3 groups demonstrated the most significant increase in swimming time and lower lactic acid concentrations, indicating that these treatments effectively enhance physical performance and endurance in mice during intensive activity. This study correlate with research by [42].

The reduction in lactic acid levels reflects better metabolic efficiency and more effective handling of metabolic by-products, contributing to the mice ability to swim longer without experiencing rapid fatigue [44]. These findings support the potential use of citrulline and WR treatments in enhancing endurance through better lactic acid management, which can be applied to nutritional and training strategies in sports and rehabilitation.

This study evaluates the effects of treatments on swimming duration, lactic acid levels, and biochemical parameters, including glucose, Blood Urea Nitrogen (BUN), Creatine Kinase (CK), and Nitric Oxide (NO) in mice, and how these relate to fatigue, physical performance, and potential recovery. The biochemical parameters also reflect improved performance and reduced fatigue. Mice receiving treatments showed higher glucose levels, providing a stable and sufficient energy source during prolonged physical activity, and supporting better physical endurance. Previous research indicates that citrulline contributes to the energy formation process for aerobic activity [13].

Additionally, the low BUN values in the treatment groups suggest reduced protein breakdown, which typically occurs under high physical stress conditions. This indicates that the mice bodies can utilize energy more efficiently and maintain optimal physiological function during activity. Moreover, since BUN is a clinical indicator of kidney function [39], the normal and reduced BUN levels also suggest that the watermelon rind treatment does not impair renal function and may help maintain kidney health. Heavy physical activity causes a significant spike in CK [12]. CK is released shortly after muscle tissue damage, making it an essential marker for assessing muscle tissue damage [10]. The reduction in CK suggests that these treatments can reduce muscle damage during intense physical activity, helping maintain muscle integrity and reducing muscle fatigue.

The increase in NO, both in the kidneys and serum, indicates the deposition of citrulline and arginine metabolites. In the body, citrulline is metabolized in the kidneys to be converted into arginine through the arginine-ornithine pathway [45]. The resulting arginine then serves as the precursor for NO production in various tissues, including skeletal muscle [38]. NO enhances blood vessel vasodilation, improving blood flow and oxygenation of muscle tissue [18]. This increased circulation accelerates the removal of metabolic waste products, such as lactic acid, from muscles and supports adequate oxygen and nutrient supply, which is essential for rapid recovery [15]. With sufficient citrulline reserves in the body due to WR consumption, there is an increase in NO bioavailability, which can regulate blood pressure [6]. These biochemical parameter changes indicate improved physical performance and faster recovery after physical activity, allowing mice to return to an optimal state more quickly. These results highlight how the treatments improve physical performance, reduce fatigue, and accelerate recovery in mice, with important implications for sports and rehabilitation contexts. Watermelon rind is often overlooked as an organic waste product, but holds economic value potential. This discovery invites further research into how various factors such as environment, growth stage, and metabolic processes contribute to the higher accumulation of citrulline and arginine in the rind. A better understanding of these mechanisms could enhance the utilization of nutritional benefits from the rind and create opportunities for innovation in processing and producing nutrition-based products from plants.

Conclusions

The findings of this study indicate that watermelon rind, particularly its inner peel, contains significantly higher levels of citrulline and arginine compared to the outer peel or rind. Despite notable differences in the absolute amounts of these amino acids between the two sample parts, the citrulline-to-arginine ratio remains relatively stable. This suggests that watermelon rind has the potential to be utilized as a raw material for the production of supplements or nutraceutical products enriched with these amino acids. Beyond its health benefits, this study also highlights the economic potential of utilizing watermelon rind, which is often overlooked or discarded as organic waste. Due to its high citrulline and arginine content, watermelon rind could be further developed for various industrial applications, including its use as a raw material for dietary supplements, functional beverages, and nutrient-enriched food products. Utilizing this byproduct not only contributes to waste reduction but also adds economic value to the agricultural and food industries.

However, several limitations of this study must be acknowledged. Factors such as the influence of watermelon cultivar, growing conditions, and processing methods on citrulline and arginine content have not been fully explored. Additionally, while the results indicate that the consumption of watermelon rind does not cause observable adverse effects, further research - including toxicological analysis and clinical trials - is necessary to confirm its long-term safety. Therefore, future studies are essential to optimize the utilization of watermelon rind as a potential nutritional source and to evaluate its safety before widespread application in the health and food industries.

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Conflict of interest

The authors declare no conflict of interest.

References

1. Abudayeh ZH, Karpiuk U, Kyslychenko V, Abualassal Q, Sirhan AY, Talhouni A, Robinson DK, *Bryonia Alba* L. - A Prospective Medicinal Plant of The *Cucurbitaceae* Family. *Farmacia*, 2024; 72(1): 10-27.
2. Abu-Hiamed HA, Chemical Composition, Flavonoids and β-sitosterol Contents of Pulp and Rind of Watermelon (*Citrullus lanatus*) Fruit. *Pak J Nutr.*, 2017; 16(7): 502-507.
3. Adnyana IK, Arlinda ND, Safitri D, Efek Antilelah Ekstrak Air Mesokarp Semangka Kuning (*Citrullus lanatus* Thunb.) Tanpa Biji. *Kartika Jurnal Ilmiah Farmasi.*, 2017; 2(2): 27.
4. Agarwal U, Didelija IC, Yuan Y, Wang X, Marini JC, Supplemental Citrulline Is More Efficient Than Arginine in Increasing Systemic Arginine Availability in Mice. *J Nutr.*, 2017; 147(4): 596-602.
5. Aguayo E, Martínez-Sánchez A, Fernández-Lobato B, Alacid F, L-Citrulline: A Non-Essential Amino Acid with Important Roles in Human Health. *Applied Sci.*, 2021; 11(7): 3293.
6. Allerton T, Proctor D, Stephens J, Dugas T, Spielmann G, Irving B, L-Citrulline Supplementation: Impact on Cardiometabolic Health. *Nutrients*, 2018; 10(7): 921.
7. Anghel L, Gurau TV, Gurau G, Mușat CL, Voinescu DC, Onu I, Cordun M, Codreanu CM, Iordan DA, The Role of Biomarkers in Elite Sports. *Balneo and PRM Research Journal*, 2023; 14(3): 581.
8. Assefa AD, Hur OS, Ro NY, Lee JE, Hwang AJ, Kim BS, Rhee JH, Yi JY, Kim JH, Lee HS, Sung JS, Kim MK, Noh JJ, Fruit Morphology, Citrulline, and Arginine Levels in Diverse Watermelon (*Citrullus lanatus*) Germplasm Collections. *Plants*, 2020; 9(9): 1054.
9. Bahri S, Zerrouk N, Aussel C, Moinard C, Crenn P, Curis E, Chaumeil JC, Cynober L, Sfar S, Citrulline: From metabolism to therapeutic use. *Nutrition*, 2013; 29(3): 479-484.
10. Baird MF, Graham SM, Baker JS, Bickerstaff GF, Creatine-Kinase- and Exercise-Related Muscle Damage Implications for Muscle Performance and Recovery. *J Nutr and Metabolism*, 2012; 2012: 1-13.
11. Barkhidarian B, Khorshidi M, Shab-Bidar S, Hashemi B, Effects of L-citrulline supplementation on blood pressure: A systematic review and meta-analysis. *Avicenna J Phytomed*, 2019; 9(1): 10-20.
12. Bekkelund SI, Leisure physical exercise and creatine kinase activity. The Tromsø study. *Scand J Med Sci Sports*, 2020; 30(12): 2437-2444.
13. Bendahan D, Mattei JP, Ghattas B, Confort-Gouny S, Le Guern ME, Cozzone PJ, Citrulline/malate promotes aerobic energy production in human exercising muscle. *Br J Sports Med.*, 2002; 36(4): 282-289.
14. Bogdanis GC, Effects of Physical Activity and Inactivity on Muscle Fatigue. *Front Physiol.*, 2012; 3(142): 1-15
15. Borne R, Hausswirth C, Bieuzen F, Relationship Between Blood Flow and Performance Recovery: A Randomized, Placebo-Controlled Study. *Intr J Sports Physio and Performance*, 2017; 12(2) : 152-160.
16. Casacchia T, Sofo A, Crinatoma C, Draganescu D, Tita B, Statti GA, Nutraceutical Properties and Health-Promoting Biological Activities of Fruits of Watermelon Cultivars With Different Origins. *Farmacia*, 2020; 68(4): 679-686.
17. Casonatto J, Góes RC, Grandolfi K, Cavalari JV, Effects of L-citrulline malate oral supplementation on post-exercise hypotension. *Manual Therapy, Posturology & Rehabilitation J.*, 2018; 16(562): 1-5.
18. Chen K, Pittman RN, Popel AS, Nitric Oxide in the Vasculature: Where Does It Come From and Where Does It Go? A Quantitative Perspective. *Antioxidants & Redox Signaling.*, 2008; 10(7): 1185-1198.
19. Chen YJ, Baskaran R, Shibu MA, Lin WT, Anti-Fatigue and Exercise Performance Improvement Effect of Glossogyne tenuifolia Extract in Mice. *Nutrients*, 2022; 14(5): 1011.
20. Davis AR, Webber CL, Fish WW, Wehner TC, King S, Perkins-Veazie P, L-Citrulline Levels in Watermelon Cultigens Tested in Two Environments. *HortScience*, 2011; 46(12): 1572-1575.
21. Du X, Davila M, Ramirez J, Williams C, Free Amino Acids and Volatile Aroma Compounds in Watermelon Rind, Flesh, and Three Rind-Flesh Juices. *Molecules*, 2022; 27(8): 2536.
22. Furrer R, Hawley JA, Handschin C, The molecular athlete: exercise physiology from mechanisms to medals. *Physio Reviews*, 2023; 103(3): 1693-1787.
23. Gonzales JU, Fischer SM, Maharaj A, Vellers H, Anderson T, Karnjanapiboonwong A, Subbiah S, Kellawan JM, Figueroa A, Response of exercise-onset vasodilator kinetics to L-citrulline supplementation during different phases of the menstrual cycle. *Physio Rep.*, 2020; 8(15): 1-11
24. Gonzalez AM, Pinzone AG, Lipes SE, Mangine GT, Townsend JR, Allerton TD, Sell KM, Ghigiarelli JJ, Effect of watermelon supplementation on exercise performance, muscle oxygenation, and vessel diameter in resistance-trained men. *Europ J App Physio.*, 2022; 122(7): 1627-1638.
25. Hartman J, Wehner T, Ma G, Perkins-Veazie P, Citrulline and Arginine Content of Taxa of Cucurbitaceae. *Horticulturae*, 2019; 5(1): 22.
26. Hearris M, Hammond K, Fell J, Morton J, Regulation of Muscle Glycogen Metabolism during Exercise: Implications for Endurance Performance and Training Adaptations. *Nutrients*, 2018; 10(3): 298.
27. Johnson JB, Ohri B, Walsh KB, Naiker M, A Simple Isocratic HPLC-UV Method for the Simultaneous Determination of Citrulline and Arginine in Australian Cucurbits and Other Fruits. *Food Analytical Methods*, 2022; 15(1): 104-114.
28. Junaidi, Apriyanto T, Decreased Level of Fatigue in Aerobic Sports in the Use of Vitamin C. *Proceedings of the 1st South Borneo Inter Conf on Sport Sci and Edu.*, 2020; 407: 93-95.

29. Kumar S, Singh RK, Bhardwaj TR, Therapeutic role of nitric oxide as emerging molecule. *Biomedicine & Pharmacotherapy*, 2017; 85: 182-201.
30. Listiarini D, Kushartanti BW, Ali MA, Nugroho DPA, Rahayu S, Kongchulagul N, Fatigue and Physical Performance in Recreational Sports. *Proceedings of the 4th Inter Conf on Sports Sci and Health*, 2021; 36: 19-22.
31. Nyawose S, Naidoo R, Naumovski N, McKune AJ, The Effects of Consuming Amino Acids L-Arginine, L-Citrulline (and Their Combination) as a Beverage or Powder, on Athletic and Physical Performance: A Systematic Review. *Beverages*, 2022; 8(3): 48.
32. Osowska S, Neveux N, Nakib S, Lasserre V, Cynober L, Moinard C, Impairment of arginine metabolism in rats after massive intestinal resection: effect of parenteral nutrition supplemented with citrulline compared with arginine. *Clin Sci.*, 2008; 115(5): 159-166.
33. Papadia C, Osowska S, Cynober L, Forbes A, Citrulline in health and disease. Review on human studies. *Clin Nutr*., 2018; 37(6): 1823-1828.
34. Park HY, Kim SW, Seo J, Jung YP, Kim H, Kim AJ, Kim S, Lim K, Dietary Arginine and Citrulline Supplements for Cardiovascular Health and Athletic Performance: A Narrative Review. *Nutrients*, 2023; 15(5): 1268.
35. Pi A, Villivalam SD, Kang S, The Molecular Mechanisms of Fuel Utilization during Exercise. *Biology*, 2023; 12(11): 1450.
36. Rhim HC, Kim S., Park J, Jang KM, Effect of citrulline on post-exercise rating of perceived exertion, muscle soreness, and blood lactate levels: A systematic review and meta-analysis. *J Sport and Health Sci.*, 2020; 9(6): 553-561.
37. Rimando AM, Perkins-Veazie PM, Determination of citrulline in watermelon rind. *J Chromatography A.*, 2005; 1078: 196-200.
38. Speer H, D'Cunha NM, Davies MJ, McKune AJ, Naumovski N, The Physiological Effects of Amino Acids Arginine and Citrulline: Is There a Basis for Development of a Beverage to Promote Endurance Performance? A Narrative Review of Orally Administered Supplements. *Beverages*, 2020; 6(1): 11.
39. Sun L, Li S, Zhou F, Liang J, Yan L, Li H, Effect of Hyperoside On Klotho Protein in Rats With Chronic Renal Failure. *Farmacia*, 2024; 72(1): 193-199.
40. Sun Y, Liang C, Zheng L, Liu L, Li Z, Yang G, Li Y, Anti-fatigue effect of hypericin in a chronic forced exercise mouse model. *J Ethnopharmacology*, 2022; 284: 114767.
41. Supruniuk E, Górski J, Chabowski A, Endogenous and Exogenous Antioxidants in Skeletal Muscle Fatigue Development during Exercise. *Antioxidants*, 2023; 12(2): 501.
42. Takeda K, Machida M, Kohara A, Omi N, Takemasa T, Effects of Citrulline Supplementation on Fatigue and Exercise Performance in Mice. *J Nutr Sci and Vitaminol.*, 2011; 57(3): 246-250.
43. Tovar-Villegas VI, Kang Y, Ibarra-Reynoso LDR, Olvera-Juárez M, Gomez-Ojeda A, Bosquez-Mendoza VM, Maldonado-Ríos ML, Garay-Sevilla MaE, Figueroa A, Oral L-Citrulline Supplementation Improves Fatty Liver and Dyslipidemia in Adolescents with Abdominal Obesity: A Parallel, Double-Blind, Randomized Clinical Trial. *Gastroenterology Insights*, 2024; 15(2) : 354-365.
44. Wang P, Zeng H, Lin S, Zhang Z, Zhang Y, Hu J, Anti-fatigue activities of hairtail (*Trichiurus lepturus*) hydrolysate in an endurance swimming mice model. *J Functional Foods*, 2020; 74: 104207.
45. Wu G, Bazer FW, Davis TA, Kim SW, Li P, Marc Rhoads J, Carey Satterfield M, Smith SB, Spencer TE, Yin Y, Arginine metabolism and nutrition in growth, health and disease. *Amino Acids*., 2009; 37(1): 153-168.
46. Zălar DM, Pop C, Buzdugan E, Todea D, Mogosan CI, The Atherosclerosis-Inflammation Relationship - A Pathophysiological Appoach. *Farmacia*, 2019; 67(6): 941-947.