

Anti-oxidant and anti-inflammatory properties of watermelon (*Citrullus Lanatus*) have the potential to reduce oxidative stress and inflammation after exercise/physical activity: Systematic Review

Las propiedades antioxidantes y antiinflamatorias de la sandía (*Citrullus Lanatus*) tienen el potencial de reducir el estrés oxidativo y la inflamación después del ejercicio/actividad física: Revisión sistemática

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Abstract. This study aims to analyze and highlight the anti-oxidant and anti-inflammatory properties of watermelon (*Citrullus Lanatus*) have the potential to reduce oxidative stress and inflammation after exercise/physical activity: Systematic Review. This research uses a systematic review method by searching various journal databases such as Scopus, Web of Science, and Pubmed. Inclusion criteria in this study were articles published within the last 5 years and articles discussing watermelon, inflammation, oxidative stress, and physical exercise. The exclusion criteria in this study were articles published in non-reputable journals. A total of 2010 articles from the Scopus, Web of Science Pubmed and Embase databases were identified. A total of 7 articles that met the inclusion criteria were selected and analyzed for this systematic review. For standard operations, this study follows the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) assessment. The results of this systematic review research report that the flavonoid content found in *Citrullus lanatus* has anti-oxidant properties which can reduce oxidative stress. Furthermore, the anti-inflammatory properties of watermelon can reduce uncontrolled inflammation due to physical activity and intense exercise. In this case, *Citrullus lanatus* works by inhibiting inflammation through NF-kB signaling and reducing inflammation by suppressing the secretion of pro-inflammatory cytokines such as TNF- α . Reducing inflammation can potentially reduce the intensity of muscle pain. We recommend that *Citrullus lanatus* be used in individuals to reduce oxidative stress and inflammation caused by physical activity and intense exercise. Furthermore, we highly recommend future research to examine the effects of watermelon on other oxidative stress biomarkers such as protein carbonyl, as well as other inflammatory biomarkers such as IL-10, IL-6, and CRP.

Keywords: *Citrullus lanatus*; Inflammation; Free Radicals; Physical training; Healthy Lifestyle

Resumen. Este estudio tiene como objetivo analizar y resaltar las propiedades antioxidantes y antiinflamatorias de la sandía (*Citrullus Lanatus*) que tienen el potencial de reducir el estrés oxidativo y la inflamación después del ejercicio/actividad física: Revisión sistemática. Esta investigación utiliza un método de revisión sistemática mediante la búsqueda en varias bases de datos de revistas como Scopus, Web of Science y Pubmed. Los criterios de inclusión en este estudio fueron artículos publicados en los últimos 5 años y artículos sobre sandía, inflamación, estrés oxidativo y ejercicio físico. Los criterios de exclusión en este estudio fueron artículos publicados en revistas no acreditadas. Se identificaron un total de 2010 artículos de las bases de datos Scopus, Web of Science Pubmed y Embase. Para esta revisión sistemática se seleccionaron y analizaron un total de 7 artículos que cumplieron con los criterios de inclusión. Para operaciones estándar, este estudio sigue la evaluación de Elementos de informes preferidos para revisiones sistemáticas y metanálisis (PRISMA). Los resultados de esta investigación de revisión sistemática informan que el contenido de flavonoides que se encuentra en *Citrullus lanatus* tiene propiedades antioxidantes que pueden reducir el estrés oxidativo. Además, las propiedades antiinflamatorias de la sandía pueden reducir la inflamación incontrolada debida a la actividad física y al ejercicio intenso. En este caso, *Citrullus lanatus* actúa inhibiendo la inflamación a través de la señalización de NF-kB y reduciendo la inflamación al suprimir la secreción de citocinas proinflamatorias como el TNF- α . Reducir la inflamación puede potencialmente reducir la intensidad del dolor muscular. Recomendamos que *Citrullus lanatus* se utilice en individuos para reducir el estrés oxidativo y la inflamación causada por la actividad física y el ejercicio intenso. Además, recomendamos encarecidamente investigaciones futuras para examinar los efectos de la sandía sobre otros biomarcadores de estrés oxidativo como la proteína carbonilo, así como otros biomarcadores inflamatorios como IL-10, IL-6 y CRP.

Palabras clave: *Citrullus lanatus*; Inflamación; Radicales libres; Entrenamiento físico; Estilo de vida saludable

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Introduction

Over time, intense exercise performance has been shown to induce substantial metabolic and circulatory adaptations that can improve health and physical performance as well as function of the musculoskeletal and cardiovascular systems (Ras et al., 2023). On the other hand, exercise can cause oxidative stress due to an imbalance between reactive oxygen species (ROS) and antioxidants (Thirupathi et al., 2021). Recent studies have reported that protein carbonyl (PC) and Malondialdehyde (MDA) are biomarkers of oxidative stress (El Assar et al., 2022). In this regard, ROS can

cause several degenerative diseases such as cell damage, diabetes mellitus and cancer (Darenskaya et al., 2021). The latest survey reports that as many as 17 million people around the world have died from degenerative diseases (Ayubi, Yuniarti, et al., 2022). Apart from that, exercise can also cause inflammation which is characterized by delayed muscle soreness (DOMS) (Sonkodi, 2021). It has been reported that muscle pain is caused by an increase in pro-inflammatory cytokines in the blood such as interleukin 6 (IL-6) and Tumor Necrosis Factor Alpha (TNF- α) (Wu et al., 2019).

Our previous study reported that DOMS peaks within

24-48 hours after exercise and can last for 5-7 days (Ayubi et al., 2024). Currently, pharmacological modalities by consuming non-steroidal anti-inflammatory drugs (NSAIDs) have been used to treat post-exercise muscle pain (Golovacheva & Golovacheva, 2021; Lundberg & Howatson, 2018). It is estimated that NSAID use worldwide reaches 30 million people and the highest prevalence is among athletes and individuals who engage in physical activity (Kafrawi et al., 2023). Mefenamic acid, piroxicam, and diclofenac sodium are some types of NSAIDs (Bindu et al., 2020). In this case, if NSAIDs are misused without a doctor's advice it will certainly have an impact on health (Lucas et al., 2019).

Alternative solutions are needed to overcome this problem. One natural ingredient that can be utilized with potential anti-inflammatory and antioxidant effects is watermelon. Watermelon (*Citrullus lanatus*) is rich in water and nutrients that are beneficial for human health (Lum et al., 2019). The fruit contains sugars (fructose, sucrose, and glucose) and phytochemical compounds such as carotenoids (lycopene and β -carotene) which are utilized because they contain high antioxidant capacity (Manivannan et al., 2020). Watermelon is also rich in non-essential organic compounds such as amino acids (citrulline), has strong antioxidant properties and is an efficient hydroxyl radical scavenger (Mashilo et al., 2022). A study reported that watermelon has a number of phytochemical compounds such as total phenolics, flavonoids and flavanols (Saiharini & Padmaja, 2022). This fruit extract shows significant in vitro antioxidant activity, hypolipidemic activity, and anti-inflammatory activity due to the presence of phenolic and flavonoid compounds (Odo et al., 2021). In medicine, watermelon is used to control diabetes and alcohol poisoning, treat obesity and eating disorders (Michael et al., 2021; Saiharini & Padmaja, 2022). In this case, the many benefits of watermelon provide us with the opportunity to relate and discuss in depth the effects of watermelon in reducing oxidative stress and uncontrolled inflammation after exercise/physical activity through a systematic review.

This study aims to analyze the anti-oxidant and anti-inflammatory properties of watermelon (*Citrullus Lanatus*) in reducing oxidative stress and inflammation after exercise/physical activity: A Systematic Review.

Results

Table 1.
Results of a review of the effects of watermelon on oxidative stress and inflammation

Author	Sample Characteristics	Study Design	Intervention	Results
(Michael et al., 2021)	30 male Wistar rats weighing 180-200 g were grouped into 5 groups, namely the control group, the group exposed to the heavy metal lead, the group receiving watermelon extract with pre-treatment + lead, the group receiving post-treatment watermelon extract + lead, the watermelon - lead group (simultaneous).	Experimental	Watermelon extract supplementation at a dose of 400 mg/kg and 5 mg/kg lead. Interventions were given to groups that were given pre-treatment and post-treatment every day for the first 15 days for watermelon extract and every day for the next 15 days for lead. Meanwhile, the simultaneous group received watermelon and lead together every day for 30 days.	Watermelon extract supplementation is able to protect against oxidative stress caused by lead acetate and tissue damage by enhancing antioxidant defenses through uric acid/nitric oxide-dependent pathways.
(Bazabang et al., 2023)	30 male Wistar rats weighing 145-160 g were grouped into 5 groups, each	Experimental	Supplementation with citrullus lanatus seed flavonoids (FCL) at a dose of 100 mg/kg	Flavonoid extracts found in watermelon are reported to increase

Methods

Study Design

This research uses a systematic review method by searching various journal databases such as Scopus, Web of Science, and Pubmed. Database It is considered a major platform worldwide because it brings together publications that have scientific impact and relevance.

Eligibility criteria

Inclusion criteria in this study were articles published within the last 5 years and articles discussing watermelon, inflammation, oxidative stress, and physical exercise. The exclusion criteria in this study were articles published in non-reputable journals..

Procedure

Titles, abstracts and full texts of articles were screened then verified and stored in Mendeley software. In the first stage, 2010 articles from the Scopus, Web of Science, and Pubmed databases were identified. Next, in the second stage, 1680 articles were obtained based on the suitability of the title and abstract. In the third stage, 24 articles were obtained for further processing. At this stage, we filter based on the overall suitability of the article. Then in the final stage 7 articles were selected that met the inclusion criteria and analyzed for this systematic observation. For standard operations, this study followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses assessment (PRISMA).

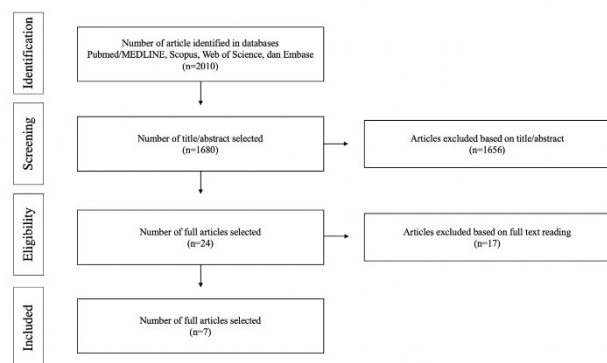


Figure 1. PRISMA flowchart of the article selection process

Table 1.
Results of a review of the effects of watermelon on oxidative stress and inflammation

Author	Sample Characteristics	Study Design	Intervention	Results
	consisting of 5 rats with different treatments.		and 10 mg/kg ethanol (ET) 50%. All treatments (FCL and ET extracts) were given orally for 28 days.	antioxidant properties in kidney tissue while reducing indicators of oxidative stress. Administration of flavonoid extract in watermelon causes a decrease in inflammatory cytokines (TNF- α and IL-1) in kidney tissue thereby preventing the onset and development of inflammatory disorders.
(Sabar et al., 2019)	A total of 28 adult <i>Musculus</i> mice weighing 14-18 g were grouped into 4 groups with different treatments, namely the control group (S), the cholesterol group (B), the cholesterol + <i>Citrullus lanatus</i> extract group (E), and the <i>Citrullus lanatus</i> extract group (R).	Laboratory experiment	Control group (S) subjects were fed white flour (100 mg/mouse), group (B) were fed cholesterol (400 mg/kg/day) + <i>Citrullus lanatus</i> extract (120 mg/kg/day), and group (R) given <i>citrullus lanatus</i> extract (120mg/kg/day) which lasted for 3 weeks.	In group (R), there was a significant decrease in LDL-c levels because <i>citrullus lanatus</i> extract contained citrulline which was converted into arginine, thereby avoiding an increase in oxidative stress. In group (E), it is known that <i>Citrullus lanatus</i> extract reduces plasma CRP levels due to its anti-inflammatory effect caused by the presence of polyphenolic compounds such as tannins and flavonoids. The results of this study also show that pretreatment with lycopene, which is abundant in watermelon, greatly improves oxidant/antioxidant status and reduces oxidative stress.
(Shanely et al., 2018)	20 male cyclists went on a moderate carbohydrate diet and watermelon drinks that lasted for 2 weeks to keep their body weight stable and avoid using large doses of vitamin/mineral supplements.	Experimental	Subjects consumed 980 mL of watermelon puree drink per day before the WM (watermelon) trial. On the morning of the 75 km time trial, the subject consumed WM porridge (980 mL) and in the afternoon consumed 0.4 g/kg carbohydrates from WM/ from a standard 6% CHO drink. Subjects cycled 75 km and then had their heart rate, RPE monitored, and post-exercise blood samples were taken.	Data show that consuming watermelon pulp is as effective as consuming a 6% carbohydrate drink in supporting endurance exercise performance and is effective in increasing antioxidant capacity through increasing lycopene, L-citrulline, and vitamins A and C, but without the acute effects seen on post-exercise inflammation.
(Sulistyaning et al., 2022)	35 male Sprague Dawley mice, 8 weeks old, weighing 230 g were divided into 5 different groups that received different treatments, namely positive control group (without juice supplement and exercise), negative control (without juice supplement but exercise), group with single sausage supplement, double dose supplement, and single dose supplement group + addition of 0.27 granulated sugar.	Experimental	Subjects were given yellow watermelon + plantain juice weighing 1.8 g and 3.6 g respectively. After 30 minutes, the subject did anaerobic exercise, namely a swimming test for 3 minutes and then a blood sample was taken after exercise.	Watermelon juice in this study was effective in supplying energy during anaerobic exercise, as well as suppressing serum MDA levels after exercise. This is caused by the powerful antioxidants contained in yellow watermelon, such as carotenoids, lycopene, phenols, flavonoids and ascorbic acid.
(Saiharini & Padmaja, 2022)	Watermelon skin and flesh were analyzed for nutritional composition, phytochemical content and anti-nutrients.	Laboratory experiment	The rind and flesh of the watermelon were prepared and then analyzed for their nutritional composition and phytochemical content using solvent extracts.	The flavonoid, phenol and flavanol content of watermelon shows significant results on antioxidant activity and the methanol extract of watermelon peel and fruit shows efficient anti-inflammatory activity by inhibiting enzymes.
(Ajiboye et al., 2020)	40 adult female Wistar albino rats weighing 120-130 g were divided randomly into 5 groups and given watermelon juice orally to subjects with different treatments, namely the normal control rat group, the untreated diabetic rat group, the diabetic + metformin rat group, the diabetic mice + watermelon juice (500 mg/kg), and diabetic mice + watermelon juice (1000 mg/kg).	Experimental	Subjects were given 500-1000 mg/kg watermelon juice for 14 days. Then blood samples are collected for biochemical analysis.	Watermelon juice shows antioxidant, anti-inflammatory, anti-hyperglycemic activity.

Discussions

The main research objective of this systematic review is to analyze and highlight the potential of watermelon in reducing inflammation and free radicals after physical exercise. Watermelon is a creeping flowering plant originating from South Africa (Sorokina et al., 2021). Potential

phytochemicals and antioxidants found in watermelon such as alkaloids, saponins, total phenolics, flavonoids, lycopene, vitamins A and C (Manivannan et al., 2020). Meanwhile, the seeds contain alkaloids, flavonoids, tannins, amino acids (citrulline and arginine), carotenoids (lycopene and β -carotene), terpenoids and saponins. Meanwhile, watermelon rind contains flavonoids, saponins, steroids, glycosides and

proteins (Gbolahan & Clara, 2021; Mashilo et al., 2022).

The antioxidant activity of medicinal plants can be attributed to their flavonoid content. Flavonoids act as scavengers of various oxidizing species namely superoxide anions, hydroxyl radicals or peroxy radicals, they also act as singlet oxygen scavengers (Ajiboye et al., 2020). Flavonoids are a group of polyphenolic compounds that are found in many plants, one of which is watermelon. The flavonoids contained in watermelon have strong antioxidant, anti-inflammatory and free radical scavenging activities (Gbolahan & Clara, 2021; Sabar et al., 2019). In addition, phytochemical compounds such as lycopene, carotenoids, and non-essential amino acids (citrulline) also have strong antioxidant and hydroxyl radical scavenging activities (Saiharini & Padmaja, 2022). Flavonoids act as anti-inflammatory agents by inhibiting transcription factors (Nf-kB) and regulatory enzymes involved in inflammation and its development. Flavonoids can inhibit the activity of phosphodiesterase (PDE), which is responsible for controlling pro-inflammatory and anti-inflammatory mediators, thereby reducing LPS-induced TNF- α and nitrate content. So if NF-kB signaling is inhibited, it will also affect the secretion of TNF- α and reduce muscle pain. In addition, flavonoids can capture free radicals (ROS) produced during inflammation due to the unique chemical structure of flavonoids, namely specific substitution patterns and phenolic hydrogen which act as contributing molecules in the reaction (Rakha et al., 2022).

Lycopene is a group of carotenoids which is the main producer of the red pigment in watermelon. This compound is a very strong antioxidant, has the molecular formula C₄₀H₅₆, and is an open, unsaturated acyclic carotenoid with 11 double bonds, 11 of which are linear conjugated double bonds and has no provitamin A activity which can be seen in Figure 1. The typical structure of lycopene shows antioxidant properties. which is able to bind single oxygen and capture peroxide (Monica & Rollando, 2019).

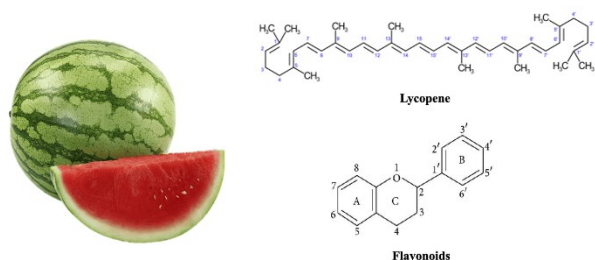


Figure 2. Chemical structure of *Citrullus lanatus*

Regular physical activity is recognized as an important factor for maintaining health. However, intense physical exercise can cause athletes to experience muscle injuries and chronic fatigue, which is directly linked to the toxic effects of free radicals (FR) (Souissi et al., 2020). The occurrence of an imbalance between the formation of free radicals and the ability of cells to neutralize/repair the damage caused by these reactive products is called oxidative stress (Michael et al., 2021). Oxidative stress can be identified by

examining biomarkers such as examining Malondialdehyde (MDA) levels in the blood (Cherian et al., 2019).

One of the main sources of oxidative stress is the immune system, and inflammation is the main reaction of the immune system to restore cells damaged by intense exercise back to normal (Simioni et al., 2018). Indeed, when the cells of an organ are damaged, the immune system becomes active (Marshall et al., 2018). The cells will stimulate macrophages to increase the production of pro-inflammatory and anti-inflammatory cytokines (Ayubi, Purwanto Bambang, et al., 2022). It has been reported that TNF- α is one of the pro-inflammatory cytokines that trigger muscle pain (Ayubi, Purwanto Bambang, et al., 2022; Fernández-Lázaro et al., 2020; Nanavati et al., 2022). In this regard, watermelon which has anti-inflammatory properties can be an intervention strategy in controlling uncontrolled inflammatory processes due to intense exercise.

The idea that watermelon contains antioxidant properties and reduces oxidative stress is supported by a study conducted on male Wistar mice reporting that giving an oral intervention of watermelon extract at a dose of 400 mg/kg against tissue damage caused by lead acetate was able to increase the antioxidant defense system due to the presence of the molecule. bioactives in watermelon such as β -carotene, lycopene, vitamin C, and flavonoids can reduce serum MDA levels. Watermelon rind which is rich in citrulline in this study also causes an increase in nitric oxide thereby reducing oxidative stress which acts as a hydroxyl radical scavenger (Michael et al., 2021). The results of this research were strengthened by a study conducted on mice reporting that administration of flavonoid extract contained in watermelon was able to increase antioxidant properties in kidney tissue while reducing oxidative stress. Administration of flavonoid extracts causes a decrease in inflammatory cytokines (TNF- α and IL-1 β) in kidney tissue. So it was concluded that flavonoids prevent the onset and development of inflammatory disorders and reduce muscle pain after exercise (Bazabang et al., 2023). Next, research (Sabar et al., 2019) reported that the potential of watermelon extract given to mice caused a significant reduction in LDL-c levels because the citrulline content in watermelon was used to make arginine produce nitric oxide, thereby avoiding an increase in oxidative stress. In addition, the results obtained in this study show that the compound lycopene which is abundant in watermelon greatly improves oxidant/antioxidant status and reduces oxidative stress. The results of this study are also strengthened by other research which reports that watermelon intervention consumed by athletes who do cycling exercise can support endurance training performance in the form of increasing antioxidant capacity through increasing intake of lycopene, L-citrulline, vitamins A and C. So it is able to prevent and reduces pain intensity, and prevents a decrease in muscle strength due to muscle damage and post-exercise inflammatory processes (Shanely et al., 2018).

This research is also strengthened by a laboratory study which reported that watermelon peel and fruit extracts showed significant results in vitro regarding their

antioxidant activity and anti-inflammatory activity. This observation is supported by the high levels of total phenolics, flavonoids and flavanols contained in watermelon (Saiharini & Padmaja, 2022). Physiologically, another interesting thing is that the flavonoids contained in watermelon work by increasing mitochondrial calcium ions (Ca²⁺) in cells, causing hyperpolarization of cell membranes. So increasing mitochondrial Ca²⁺ has the potential to reduce oxidative stress (Overdevest et al., 2018). Research by (Sulistyaning et al., 2022) and (Ajiboye et al., 2020) reported that watermelon juice contains flavonoids, carotenoids, lycopene, phenols which are strong antioxidants that can suppress the formation of serum MDA, thereby reducing oxidative stress. In addition, antioxidants also act as inhibitors of nitric oxide (NO) production which is strongly related to the treatment of inflammatory diseases. Watermelon juice shows the ability to donate protons and can function as a significant scavenger of NO free radicals and acts as a primary antioxidant.

So, the flavonoids and citrulline contained in watermelon have antioxidant and anti-inflammatory properties, so they have the potential to reduce oxidative stress and uncontrolled inflammation after exercise/physical activity. Furthermore, for more details regarding the benefits of watermelon in reducing oxidative stress and inflammation, see Figure 3.

On the other hand, the lack of research regarding the effects of water melon after exercise is a limitation in this research. We highly recommend future research to examine the effects of watermelon on other oxidative stress biomarkers such as protein carbonyl, as well as other inflammatory biomarkers such as IL-10, IL-6, and CRP.

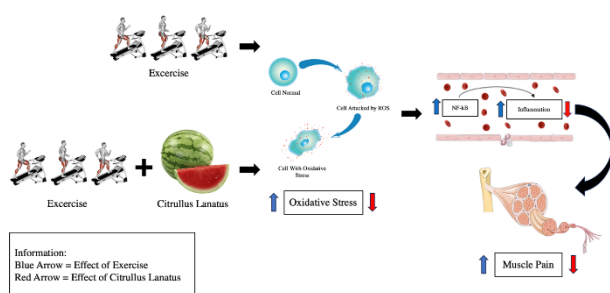


Figure 3. Mechanism of Action of Citrullus Lanatus in Reducing Oxidative Stress and Inflammation

Conclusions

The flavonoid content in watermelon has anti-oxidant properties which can reduce oxidative stress. In addition, the anti-inflammatory properties of watermelon can reduce uncontrolled inflammation caused by intense physical activity and exercise. In this case, watermelon works by inhibiting inflammation through NF-kB signals and reducing inflammation by suppressing the secretion of pro-inflammatory cytokines such as TNF- α . Reducing inflammation can potentially reduce the intensity of muscle pain. We recommend using watermelon individually to reduce oxidative

stress and inflammation caused by physical activity and intense exercise. Furthermore, we highly recommend future research to examine the effects of watermelon on other oxidative stress biomarkers such as protein carbonyl, as well as other inflammatory biomarkers such as IL-10, IL-6, and CRP.

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Conflicts of Interest

The authors declare no conflict of interest.

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