The potential of polyphenol compounds in grapes to reduce oxidative stress and inflammation after exercise: systematic review

El potencial de los compuestos polifenólicos de las uvas para reducir el estrés oxidativo y la inflamación después del ejercicio: revisión sistemática

Authors

Novadri Ayubi [1]
Atika Syafawi [2]
Anton Komaini [3]
Dhea Regita Sastika Putri [2]
Ilham [3]
Deby Tri Mario [3]
Dyah Fitria Padmasari [3]
Junian Cahyanto Wibawa [4]
Procopio B. Dafun Jr. [5]

[1] Universitas Negeri Surabaya (Indonesia)
[2] Universitas Airlangga (Indonesia)
[3] Universitas Negeri Padang (Indonesia)
[4] STKIP PGRI Trenggalek (Indonesia)
[5] Mariano Marcos State University (Philippines)

Corresponding author:
Novadri Ayubi
novadriayubi@unesa.ac.id

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Abstract

Introduction: Mechanical stress and inflammation contribute to exercise-induced muscle damage.
Objective: This research analyzed the potential of polyphenolic compounds in grapes to prevent inflammation and lower oxidative stress after exercise.
Methodology: This research employed a systematic review to guide the researchers in achieving the objectives. It involved a thorough search of global databases, such as Web of Science, Scopus, Embase, and Pubmed. The inclusion criteria were articles investigating grapes, inflammation, oxidative stress, and physical exercise published within the last five years. On the other hand, articles that were not reputable or indexed by these databases were excluded from the search. The initial search process generated 2947 articles. After undertaking several screening processes, 8 articles were finally selected and analyzed.
Results: This research shows that the polyphenol content in grapes has antioxidant and inflammatory properties which can reduce levels of oxidative stress and inflammation.
Discussion: The polyphenol content works by reducing ROS, MDA, and TBARS levels and increasing GSH levels. Furthermore, grapes also have anti-inflammatory properties that reduce uncontrolled inflammation as a result of intense exercise. In this case, grapes work by blocking several inflammatory pathways and decreasing inflammatory markers. In vivo studies also confirmed these anti-inflammatory and antioxidant benefits by stimulating eNOS gene expression and increasing CAT, SOD, and GPx4 levels.
Conclusions: The polyphenol content in grapes can potentially reduce oxidative stress due to its antioxidant properties. Besides, the grapes have anti-inflammatory properties, which are responsible for lowering uncontrolled inflammation and alleviating muscle pain fierceness.

Keywords

Grapes, inflammation, oxidative stress, physical training, healthy lifestyle.

Resumen

Introducción: El estrés mecánico y la inflamación contribuyen al daño muscular inducido por el ejercicio.
Objetivo: Esta investigación analizó el potencial de los compuestos polifenólicos de la uva para prevenir la inflamación y reducir el estrés oxidativo después del ejercicio.
Metodología: Esta investigación empleó una revisión sistemática para guiar a los investigadores en el logro de los objetivos. Implicó una búsqueda exhaustiva en bases de datos globales, como Web of Science, Scopus, Embase y Pubmed. Los criterios de inclusión fueron artículos que investigaran la uva, la inflamación, el estrés oxidativo y el ejercicio físico publicados en los últimos cinco años. Por otro lado, se excluyeron de la búsqueda los artículos que no tenían buena reputación ni estaban indexados en estas bases de datos. El proceso de búsqueda inicial generó 2947 artículos. Tras realizar varios procesos de selección, finalmente se seleccionaron y analizaron 8 artículos.
Resultados: Esta investigación muestra que el contenido de polifenoles en las uvas tiene propiedades antioxidantes e inflamatorias que pueden reducir los niveles de estrés oxidativo e inflamación.
Discusión: El contenido de polifenoles actúa reduciendo los niveles de ROS, MDA y TBARS y aumentando los niveles de GSH. Además, las uvas también tienen propiedades antiinflamatorias que reducen la inflamación descontrolada como consecuencia del ejercicio intenso. En este caso, las uvas actúan bloqueando varias vías inflamatorias y disminuyendo los marcadores inflamatorios. Los estudios in vivo también confirmaron estos beneficios antiinflamatorios y antioxidantes al estimular la expresión del gen eNOS y aumentar los niveles de CAT, SOD y GPx4.
Conclusiones: El contenido de polifenoles en la uva puede potencialmente reducir el estrés oxidativo debido a sus propiedades antioxidantes. Además, las uvas tienen propiedades antiinflamatorias, que se encargan de bajar la inflamación descontrolada y aliviar la intensidad del dolor muscular.

Palabras clave

Uva, Inflamación, Estrés oxidativo, Entrenamiento físico, Estilo de vida saludable

Introduction

The World Health Organization (WHO) describes physical exercise as a movement that skeletal muscles generate using a certain amount of energy. At any age, regular physical activity provides major health benefits, such as reducing the risk of diabetes, heart disease, cancer, dementia, and Alzheimer's. In addition, it prevents non-alcoholic fatty liver disease (NAFLD), reduces oxidative stress, and gradually increases antioxidant defenses while activating mediators that reduce inflammation. Scientific evidence shows that athletes have lower levels of oxidative stress than sedentary individuals (Taherkhani, Suzuki, and Castell, 2020; Elejalde, Villarán, and Alonso, 2021; Daniela *et al.*, 2022; Aghaei *et al.*, 2023). However, acute and heavy physical exercise causes negative effects as it might trigger excessive free radicals. The large amount of free radicals then leads to increasing oxidative stress that might harm muscle cells and cause discomfort and irritation (Canals-Garzón *et al.*, 2022).

Oxidative stress is an imbalance between the production and disposal of reactive oxygen/nitrogen species (RONS) through antioxidant mechanisms (Arazi, Eghbali, and Suzuki, 2021). When free radicals and ROS are produced excessively, an inflammatory process can be triggered. The inflammatory process aims to prevent harmful objects, such as irritants, pathogens, and damaged cells, from entering the body through natural defense mechanisms (Fernandes *et al.*, 2023). According to previous research, mechanical stress and inflammation contribute to exercise-induced muscle damage (EIMD). When exercising intensely, inflammation in the muscles will increase inflammatory cytokines, such as inflammatory interleukins (IL-1, IL-6, tumor necrosis factor-alpha (TNF-α)) and leukocyte infiltration (Huang *et al.*, 2019; Seyedsadjadi and Grant, 2021; Canals-Garzón *et al.*, 2022). Cytokines are essential because they function as controllers and regulate inflammatory and immune responses. It increases the body's immunity. The pro-inflammatory cytokines can be released through regular physical activity. In addition, mechanisms that promote anti-inflammatory myokine secretion can reduce muscle cytokines during physical activity (Taherkhani, Suzuki, and Castell, 2020).

When oxidative stress occurs, ROS will increase and activate the NF-κB pathway, making redox prone to changes. It increases the expression of antioxidant enzyme genes in tissues experiencing oxidative stress. Nevertheless, ROS can be lowered by targeting the NF-κB gene. Apart from that, the mechanisms in reducing ROS can be done by involving certain enzymatic antioxidants, such as Glutaredoxins (Grxs), superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx) and non-enzymatic antioxidants such as beta-carotene, flavonoids, vitamin E (Vit E), ascorbic acid (AA), ubiquinone, carotenoids, and lipoic acid. Previous research reported that NF-κB activity using stimulants can be inhibited using antioxidant supplements. These supplements can prevent inflammatory cytokines from being induced, especially TNF- α (Taherkhani, Suzuki, and Castell, 2020; Taherkhani, Valaei, and Arazi, 2021; Valaei, Taherkhani, and Arazi, 2021).

Myriad research has been done to examine nutritional strategies that can improve sports performance and prevent damage. One of them is by giving grapes as a supplement in high-performance training. Grapes and their derivatives have high levels of phenolic compounds. They contain antioxidant, anti-inflammatory, and antimutagenic properties that significantly reduce inflammatory markers and increase antioxidant capacity (Martins *et al.*, 2020).

Grapes have the Latin name Vitis vinifera L. They are annual plants from the Vitaceae family. According to previous research, the plant has rich bioactive compounds comprised of flavonoids (quercetin, anthocyanins, and proanthocyanidins), phenolic acids, and stilbenes. These compounds act as antioxidants, protecting the human body against oxidative damage. Additionally, they have anti-inflammatory effects and are essential in controlling illnesses such as diabetes, cancer, obesity, and cardiovascular (Colombo *et al.*, 2019; Sabra, Netticadan, and Wijekoon, 2021; Fernandes *et al.*, 2023).

Numerous studies have demonstrated the capacity of polyphenols. Some reported that it acts as reactive oxygen species (ROS) scavengers and antioxidants. Other studies argued that it serves as an anti-inflammatory agent by modifying gene expression, such as cyclo-oxygenase (COX), lipoxygenase (LOX), nitric oxide synthase (NOS), and proinflammatory cytokines. The inflammation mainly stems from the formation of ROS as a result of protein oxidation and oxidative stress. Consequently, stopping oxidative processes (such as ROS production) reduces the likelihood of triggering an inflammatory cascade. It is proven that polyphenols exhibit antioxidant properties, scavenging radicals, and chelating metal ions

(quercetin). In addition, quercetin can inhibit NF-κB in human monocytes and epithelial cells. It inhibits the release of growth factors, chemokines, adhesion molecules, and proinflammatory cytokines by releasing (TNF)-α, interleukin (IL)-1β, IL-6, and IL-8. Particularly, the molecular pathways involved in inactivating NF-κB nuclear translocation have been clarified by using quercetin (Magrone *et al.*, 2020).

Therefore, the present research attempts to discuss the effect of grapes as supplementary food in lowering oxidative stress and preventing inflammation after physical activity. In particular, it aims to analyze the potential of grape's polyphenolic compounds in preventing inflammation and reducing free radicals.

Method

Study Design

Using a systematic review method, this research thoroughly searched international journal databases, such as Scopus, Web of Science, Pubmed, and Embase. These databases are considered a primary platform for many global researchers to put their publications with scientific impact and relevance.

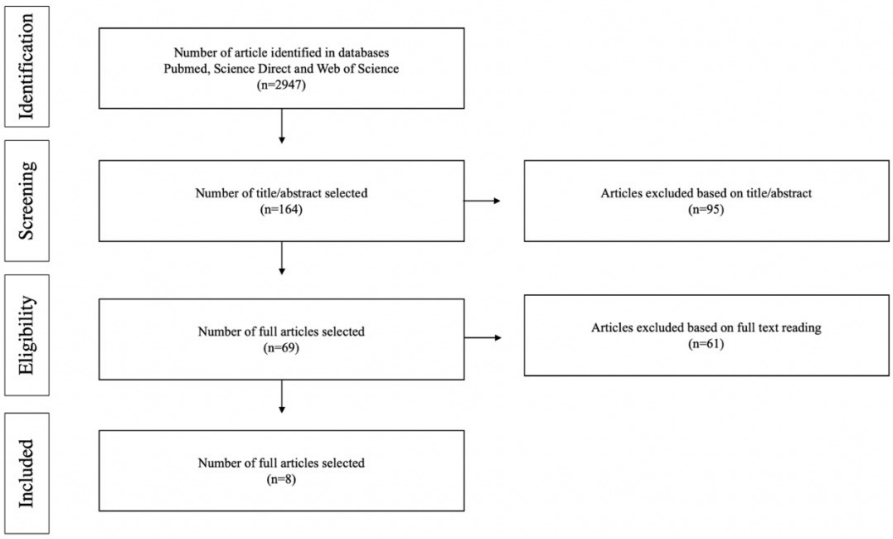
Eligibility criteria

In order to keep data relevant, this research carefully selected articles that could be included in this research by determining several inclusion criteria. For example, this research only included articles investigating grapes, inflammation, oxidative stress, and physical exercise and published within the last five years (2019-2024). On the other hand, the exclusion criteria were set by eliminating non-reputable journals that Scopus and Web of Science did not index.

Procedure

After deciding the inclusion and exclusion criteria, this research was ready to collect the data. First, the articles' titles, abstracts, and full texts were screened from the aforementioned databases. They were verified and stored in Mendeley software. This process generated 2947 articles, yet only 164 articles were selected. Next, these articles were screened again. If the title and abstract were not suitable, the articles were discarded. This screening yielded 69 articles that advanced to the subsequent screening process. We filtered the articles based on their overall suitability. Finally, we analyzed 8 articles because they matched the inclusion criteria required beforehand. The process of this data collection and analysis is illustrated in a flowchart to make it easy to understand. The flowchart refers to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). For this research, the flowchart is documented in Figure 1.

Figure 1. Process flowchart for selecting articles using PRISMA



Results

This section summarizes the key findings of 8 articles included in this research. The findings discuss whether grapes affect oxidative stress and inflammation in the human body. The details of the findings are provided in Table 1.

Table 1. Research findings on the effects of grape on oxidative stress and inflammation after exercise

Author	Sample Characteristics	Study Design	Intervention	Results
(Martins et al., 2020)	The research invited 12 young volleyball athletes aged 16-17 years. They were requested to participate in match simulations within three different situations. The first situation was a control with no drink provided. Second, the participants were given grape juice. The last situation gave them a placebo drink. The subjects performed daily high-intensity exercise for 3 hours. It was done five times a week. Then, they were evaluated to test their muscle strength and subjective perception of the effort scale. 20 mL of their blood was also taken as a sample.	Experimental	The subjects were given 400 mL of grape juice diluted from the species Vitis labrusca Bordeaux every day for two weeks. This species contained 66 g of carbohydrate. The same amount of polyphenol-free drink was given to 12 athletes in the placebo group. This treatment was also conducted for two weeks. Both groups were then analyzed to find out the composition of both supplemental drinks.	Grape juice supplementation was found to lower oxidative stress and DNA damage. The placebo group experienced increased inflammation in IL-4 levels and muscle damage, which was measured by keratin kinase levels. The potential causes of this increase are the antioxidant and anti-inflammatory content that come from polyphenolic compounds in the grape supplement.
(de Lima Tavares Toscano et al., 2020)	Fourteen male runners carried out a running test with 2 procedures: one experimental and the other control. Then, the subjects were randomly given grape juice supplements or placebo drinks.	Experimental	A total of 10 ml/kg/day of grape juice and placebo drinks were given orally to subjects after aerobic exercise for 2 weeks. The biomarkers of oxidative stress, inflammation, and muscle injury were then tested and analyzed.	Grape juice supplementation was reported to have higher antioxidant activity than placebo due to the polyphenolic compounds in grapes. Apart from that, the compound also has anti-inflammatory properties.
(Annunziata et al., 2020)	Two groups of 16 male Sprague Dawley (SD) rats were created. The first comprised a group of rats given Taurisolo (a grape polyphenol-based supplement). Another group was given a placebo and maltodextrin.	Experimental	Subjects were given Taurisolo supplements (a grape polyphenol-based supplement) and maltodextrin orally with the prescribed dosage for 30 days. Then, the subjects performed 5 training sessions on the rotarod to examine endurance and anti-fatigue performance. Gastrocnemius muscle organ samples were taken to determine antioxidant activity, MDA, N-Tyrosine tests, and gene expression related to oxidative stress and inflammation.	The grape polyphenol-based supplement in this research significantly increased antioxidant capacity. The supplement could also counteract increased levels of MDA and N-Tyr, which are associated with oxidative stress and inflammation. Polyphenols present in grapes could also inhibit the NF-κB pathway, which is associated with pro-inflammation and pro-oxidation through decreasing IL-6.
(Bobadilla et al., 2021)	This research employed 6-week-old mice. The mice were put into randomized groups of 5 (n=5/group).	Experimental	Subjects were given 200 µL of grape juice supplement orally, either with or without natural extract (red grape) for 5 days in a row. Additionally, 2.8 mg of natural extract was administered in each session. Then, the subject was given restraint pressure for 6 hours, and brain samples were analyzed to determine antioxidant enzymes.	Grape juice supplements could significantly reduce IL-6 and TNF-alpha because of the presence of po compounds lifenol. Apart from that, this supplement can also significantly increase Nrf-2 expression as protection against oxidative stress. Other results show that these grape polyphenols can increase the activity of the SOD enzyme indicating its strong antioxidant effect. Additionally, grape polyphenols decrease MDA levels.
(Goulart et al., 2020)	Twenty judo athletes aged 17-21 were divided randomly into 2 groups: the grape juice group and the placebo group. Subjects were instructed to	Experimental	Grape juice supplements or placebo, as much as 400 mL, were given to subjects for 14 days. After the washout period, the judo athlete performed 2 fight	It was reported that the grape juice group had a high total antioxidant capacity post-exercise. Athletes' muscle strength also increased after

Table 1. Research findings on the effects of grape on oxidative stress and inflammation after exercise

Author	Sample Characteristics	Study Design	Intervention	Results
	take the supplement for 14 days.		simulations consisting of 3 7-minute fight rounds with 14-minute intervals.	grape juice supplementation through the action of polyphenols in grapes. Thus, it can minimize oxidative stress. Grape juice supplementation can also reduce lipid and DNA damage before exercise.
(Dani et al., 2021)	The research invited 29 volunteers who were divided into 3 groups. 9 First, 9 volunteers were assigned to grape juice group (GJG). Meanwhile, 10 were put into the placebo and exercise group (PLEG). Last, 10 others were placed into grape juice and exercise group (GJEG)	Experimental	Subjects per group were given a supplement of 400 mL grape juice or placebo biweekly at the intervention location for 1 month by undergoing physical exercise protocols such as resistance and aerobics simultaneously (twice a week, an hour per session). The intervention yielded a total of 8 sessions. Blood samples were taken both at the start and conclusion of the 30-day experiment. Then, the samples were analyzed for IL-6 levels and oxidative stress analysis.	The experimental results showed that physical exercise had an effect on IL-6 levels. In particular, a significant decrease was discovered in IL-6 levels due to PLEG & GJEG (effect of exercise training & grape supplements and placebo). In addition, grape juice supplements after intervention could significantly increase the retention of non-enzymatic antioxidants.
(Zuanazzi et al., 2019)	This research recruited 25 women, ages 50–67, to serve as volunteers. Depending on how much time and how often they spent exercising, they were divided into three groups: no physical activity, 1-2 times per week, and more than 3 times per week.	Experimental	Subjects were instructed to consume grape juice at 7 mL/kg/day WJG for 30 days. Grape juice supplements were given in 2-3 portions at breakfast, lunch, and dinner. Then, blood samples were taken to analyze antioxidant activity, lipid profile, serum glucose and insulin levels, SOD activity, and oxidase damage to lipids.	Grape juice supplements showed high total phenolic content, indicating a high antioxidant capacity. However, this study discovered no effect of grape juice supplements on oxidative damage to lipids and SOD activity.
(Choleva et al., 2023)	Eighteen healthy women aged 22 and 35 years were divided into 2 groups: women who had a body mass index (BMI) of 25 kg/m2 and one with a BMI>25 kg/m2. Subjects were given 2 interventions, namely capsules containing grape pomace extract powder and placebo capsules. A long-term study in which 4 healthy women with a BMI>25 kg/m2 were tested.	Experimental	Subjects were given 2 different interventions depending on the group. One group received grape pomace (GP) extract powder capsules, while another took placebo capsules. After 6 hours, their blood samples were collected. Then, tests were conducted to measure markers of oxidative stress, superoxide dismutase (SOD) activity, and glutathione peroxidase (GPx).	This research noted that endogenous antioxidant (UA) levels in the BMI>25 kg/m2 group in the extract group were higher than in the placebo intervention. SOD activity decreased in the extract intervention, while the placebo intervention did not affect SOD activity.

Discussion

This research aims to analyze the effect of grapes on preventing inflammation and lowering free radicals after physical exercise. It has been proven that exercise generally improves health in several ways, including improving immunity and lowering the risk of various degenerative and cardiovascular diseases. However, it is vital to remember that the exercise should be performed in a proper intensity and manner. Excessive exercise can rapidly trigger reactive oxygen species (ROS) and reactive nitrogen species (RNS), molecules that have long been considered the main causes of oxidative stress in muscles, which can damage cells and impair exercise capacity (Mason *et al.*, 2020; Rojano-Ortega, 2021).

Although a rapid formation of ROS and RNS might be harmful, they are necessary for optimal muscle adaptation during the inflammatory process. When this inflammatory process is not treated properly, it can cause muscle pain during physical activity, hindering an athlete's recovery. Therefore, a proper recovery strategy after exercise is urgently needed in that muscle fibers produce and release pro-inflammatory myokines during physical activity. Myokines are also expressed in inflammatory conditions, such as TNF-α and IL-10 (Porto *et al.*, 2023; Volpe-Fix *et al.*, 2023). TNF-α is a pro-inflammatory cytokine that triggers discomfort in the muscle (Fernández-Lázaro *et al.*, 2020; Ayubi *et al.*, 2022; Nanavati *et al.*, 2022). The signaling system regulated by nuclear factor E2 (NRF2) regulates

the suppression of oxidative damage. It regulates many antioxidant enzymes, strengthening the body's defenses against free radicals. (Wang *et al.*, 2021).

Chemicals containing phenolic compounds have the potential to prevent or treat oxidative stress-related diseases, including diabetes mellitus, cancer, heart disease, neurological disorders, and uncontrolled inflammatory processes caused by vigorous exercise. It is believed that this substance inhibits free radicals and acts as an anti-inflammatory and antioxidant, reducing oxidative stress and helping athletes post-workout recovery (Mason *et al.*, 2020; Rojano-Ortega, 2021). It inhibits enzymes that make ROS highly oxidized. In this way, the amount of ROS can be minimized (Aatab *et al.*, 2023).

In addition, quercetin and anthocyanin compounds can inhibit IL-6 production by regulating p38-mitogen-activated protein kinase (p38-MAPK). This compound can also suppress the expression of TNF-α by reducing the NF-kβ gene and decreasing Iκβα and Iκββ phosphorylation. Consequently, the NF-κβ activation can be halted by quercetin. Similarly, it has been observed that the reactive oxygen species can be minimized by anthocyanins. This reduction prevents MAPK activation and inflammatory cytokines. Anthocyanins inhibit NF-κβ translocation from the cytosol to the nucleus and halt Iκβ phosphorylation, which decreases the formation of proinflammatory mediators, including IL-6 and TNF-α. (Santoso *et al.*, 2019). Grapes are one naturally occurring product that contains these bioactives. Because of their anti-inflammatory and antioxidant qualities, grapes can be used as an intervention strategy to manage uncontrollably high levels of inflammation brought on by vigorous exercise.

Grapes is a common grape species belonging to the genus Vitis and family Vitaceae. This species dominates by 90% compared to other species. Thus, it is easier to find them. They have seedless varieties, such as red, black, and white (Zhou *et al.*, 2022). Because of its abundance, grapes are widely cultivated. They can be consumed fresh and even processed into drinks, juice, or jam. Various parts of grapes, such as the flesh, leaves, seeds, and grape pomace, can be used because they contain important bioactive compounds, namely high polyphenol content. These compounds can be seen in Figure 2 and Table 1.

Figure 2. Grape derivatives (Singh *et al.*, 2023)

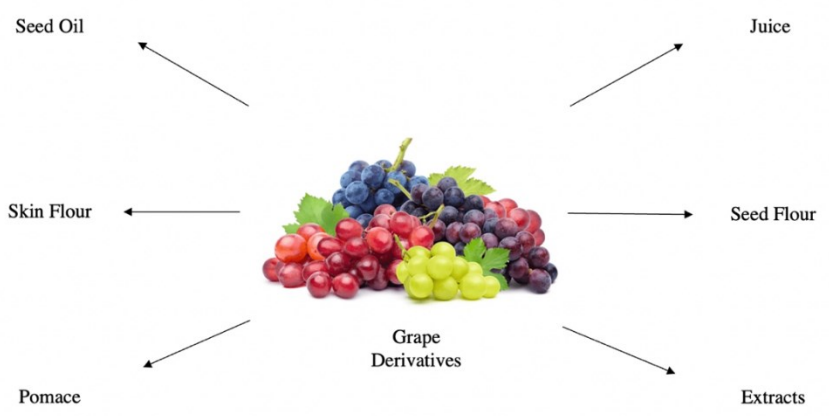


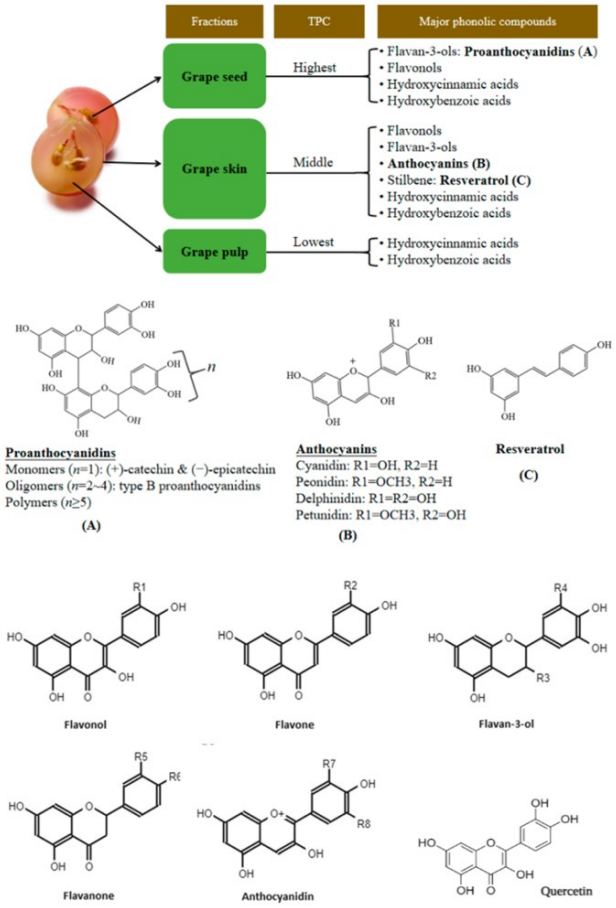
Table 2. Various parts of the plant (Vitis vinifera L.) contain bioactive substances (Singh *et al.*, 2023)

Part of grapevine	Bioactive compounds present	Potential Health Benefit
Grape seeds	Flavan-3-ols (catechin and epicatechin), procyanidins, tannins, and gallic acid	Anti-platelet, anti-coagulant, antioxidant, hypoglycemic, and anti-cancer activity
Grape stem	Gallic acid, catechin, quercetin, quercetin-3-glucoside, malvidin-3-glucoside, malvidin-3-glucoside, resveratrol, and viniferin	Antimicrobial activity, anti-inflammatory, anti-aging, antioxidant, and anti-cancer properties
Grape skin	Flavan-3-ols, phenolic acids, (+) -catechins, proanthocyanidins, flavonols, and anthocyanins	-
Grape leaves	Glycosylated forms of Myricetin, quercetin, kaempferol, and isorhamnetin	Useful for managing hypertension caused by chronic venous insufficiency, diarrhea, hemorrhage, inflammatory disorders, and hypoglycemia.

Grapes have diverse nutritional content. For example, the main mixture of grapes contains phenolic compounds, flavonoids, proanthocyanidins, stilbenoids, epicatechin, catechin, anthocyanin, protein, fat,

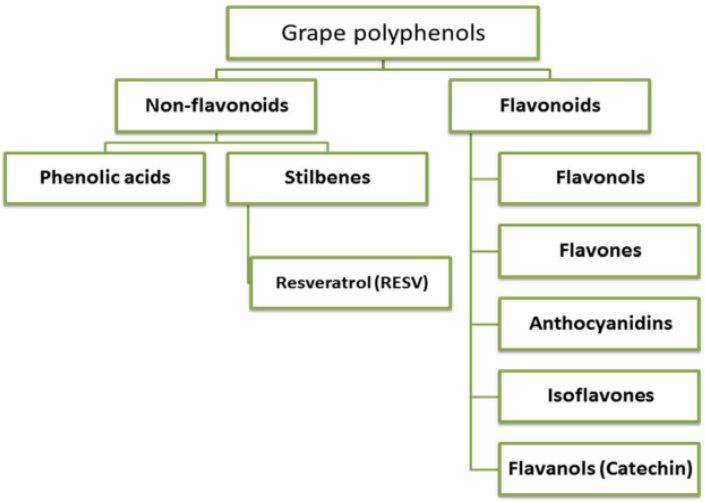
and vitamin C. Meanwhile, grape leaves contain hydroxycinnamic acids (caftaric acid, caffeic acid, and fertaric acid), coumarin, dihydrochalcone, stilbene monomer, stilbene dimer, catechin, procyanidins, quercetin, anthocyanin, and coumarin. Grape root extract contains stilbenoid compounds, while grape seeds contain procyanidin, gallic acid, epicatechin, catechin, and quercetin. The grape skins are also useful as they contain resveratrol, flavonols, anthocyanins, flavan-3-ols, and phenolic acids. Meanwhile, quercetin, vanillic acid, kaempferol, syringic acid, and gallic acid were found in grape pomace extract. The chemical structures of all these bioactive compounds can be seen in Figure 3 and Figure 4. (Di Lorenzo *et al.*, 2019; Ibrahim Fouad and Zaki Rizk, 2019; Insanu *et al.*, 2021; Zhou *et al.*, 2022; Singh *et al.*, 2023).

Figure 3. The chemical structures of numerous typical bioactive chemicals and the phenolic compounds found in various grape fractions. (A) Proanthocyanidins; (B) anthocyanins; (C) resveratrol. Total phenolic content (TPC) (Zhou *et al.*, 2022)



Phytochemical compounds are bioactive compounds found in plants that have many benefits for humans. One of them is polyphenols, which are divided into two categories. The first is "simple phenols" consist of a single aromatic ring with one or more hydroxyl groups, while "polyphenol compounds" are more prevalent and comprise multiple phenol rings. The classification of polyphenols depends on the number of phenol rings and the chemical groups attached to these rings. Phenols can be classified as non-flavonoids or flavonoids based on the number of rings and their affinity to bind certain substances (Figure 4). The classification of flavonoids is divided into five groups, namely anthocyanins, flavanones, isoflavones, flavones, and flavonols. The main constituent of flavonoids consists of two aromatic rings connected by a three-carbon bridge to form C6-C3-C6 as the structural backbone (Ibrahim Fouad and Zaki Rizk, 2019; Chedea et al., 2022).

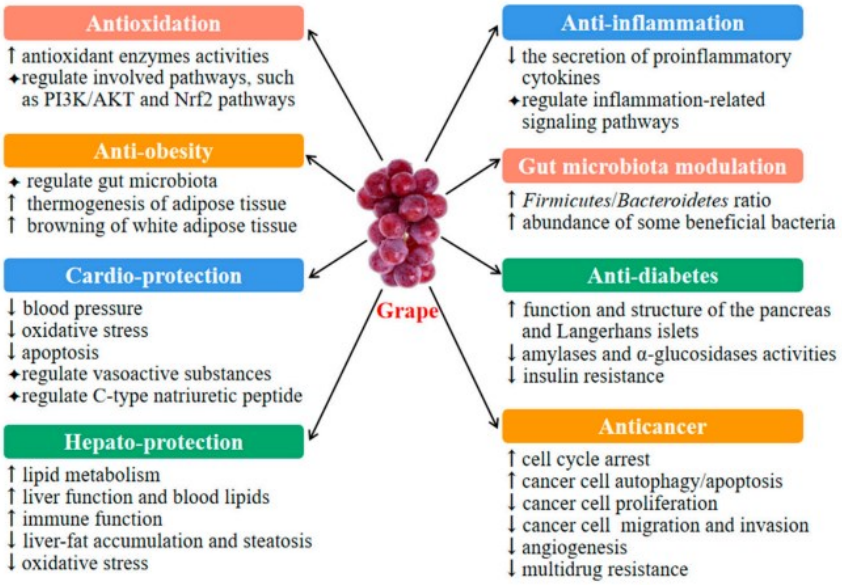
Figure 4. Classification of grape polyphenols (Ibrahim Fouad and Zaki Rizk, 2019)



The bioactive content in grapes provides various biological and pharmacological functions, such as antioxidant, anti-inflammatory, anti-cancer, anti-fungal, antibacterial, antihypertensive, anti-diabetic, and cardioprotective activities (Figure 5). It has a strong antioxidant capacity because it increases the activity of antioxidant enzymes and regulates the nuclear factor Nrf2 pathway. This increase is caused by the phenol group present in the chemical structure of polyphenols, which can reduce the production of reactive oxygen species (ROS) and chelated metal ions by NADPH-oxidase. Consequently, it reduces the regulation and activity of NADPH oxidase (Insanu *et al.*, 2021; Zhou *et al.*, 2022). By increasing the activity of glutathione peroxidase and superoxide dismutase, two antioxidant enzymes associated with increased oxidative stress, resveratrol (as an antioxidant agent in grapes) has been shown to protect against a number of diseases, including inflammatory and degenerative conditions. The grape seed extract is able to remove radical intermediates because the polyphenols in grapes have an iron-chelating effect, which breaks down the chain reaction and prevents the oxidation process.

The polyphenols in grapes also contribute to anti-inflammatory activity by inhibiting the body from producing pro-inflammatory cytokines. In addition, the compounds regulate related signaling pathways. Research findings report that resveratrol (stilbenes class) in grapes mediated by NF-κB activity can reduce oxidative stress and prevent inflammation (Zhou *et al.*, 2022; Singh *et al.*, 2023). Other studies also show that grape extract suppresses the release of IL-8 induced by TNF-α and LPS. This was associated with the suppression of NF-κB-induced transcription, indicating that the grape extract has anti-inflammatory characteristics (Sharafan *et al.*, 2023). Earlier research (Insanu *et al.*, 2021; Zhou *et al.*, 2022) reported that grapes can cure various types of cancer activities, such as liver, bladder, prostate, and cervical cancer. These plants have bioactive compounds, such as proanthocyanidins. By preventing the activation of the MAPK/Akt pathway, grape seed proanthocyanidin extract dramatically triggers apoptosis in cancer cells and prevents the expression of cancer-promoting genes. In addition, high concentrations of grape seed extract can inhibit the growth of cancer cells by producing cytotoxicity followed by a decrease in reactive oxygen species (ROS). On the other hand, grapes also have hepatoprotective activity, which can protect the liver because polyphenolic compounds such as anthocyanins and procyanidins contained in grapes are capable of inhibiting the secretion of lactate dehydrogenase and reducing ROS levels. In addition, grapes can treat liver damage by activating the Nrf2 pathway in vivo. Liver damage can also be prevented through alcohol-induced grape seed extract, thus reducing AST and LDH.

Figure 5. Pharmacological properties of grape. The up arrow ↑ represents an increase, while the down arrow↓ represents a decrease, and the regulates (Zhou *et al.*, 2022)



Earlier studies support the notion that grapes contain antioxidant properties and reduce oxidative stress. For example, one study examined athletes with high-intensity training. The study reported that oral administration of grape juice intervention has the potential to generate high antioxidant and anti-inflammatory activity so that it can reduce oxidative stress (Martins *et al.*, 2020). According to them, adding grape supplementation after exercise significantly decreases the MDA levels by 50%. The presence of polyphenolic compounds in grapes contributes to this decrease. It can protect important components, such as DNA and proteins, from oxidation by quickly donating hydrogen atoms contained in their structure to free radicals. Apart from that, the polyphenols from this supplement also reduce MDA and carbonyl levels without the need to increase endogenous defenses. This grape supplementation caused a decrease in IFN-γ concentrations as a marker of controlling the inflammatory response and an inhibitory effect on increasing IL-4. The contribution of polyphenolic compounds can lower oxidative stress and prevent inflammation (Martins *et al.*, 2020).

The present research is strengthened by the earlier study conducted on male runners. The research examined the supplementation with purple grape juice. The results indicated that the juice content affected the runners' physical performance, especially after physical exercise. One of the potential reasons is due to the polyphenol content in grapes. This compound contributes to antioxidant and anti-inflammatory activity. It can also correct oxidative imbalances and minimize the protective activity of antioxidant enzymes such as glutathione (de Lima Tavares Toscano *et al.*, 2020).

Another study (Annunziata *et al.*, 2020) reported that grapes have the potential to improve biomarkers related to oxidative stress and inflammation in mouse skeletal muscle. In particular, Taurisolo supplements containing polyphenolic compounds in grapes can increase antioxidant activity through direct capture of reactive oxygen species (ROS) and modulate the body's natural antioxidant defenses. The chemical properties of polyphenols can stabilize reactive species through electron transfer to ROS molecules. Polyphenols are also able to ward off the formation of free radicals and ROS-producing enzymes by inhibiting the production of ROS-chelating metal ions (mainly iron and copper). In addition, polyphenols are responsible for increasing the expression of pro-inflammatory and pro-oxidant genes, including IL-6, by inhibiting the NF-κB pathway. Moreover, Taurisolo-containing polyphenols can reduce MDA and N-Tyr levels by efficiently preventing protein oxidation mediated by ROS/RNS, thereby potentially reducing oxidative damage.

The efficacy of grape juice supplements was also shown by Bobadilla *et al.* (2021). They reported the grapes' high antioxidant potential due to polyphenols' protective properties against oxidative stress, inflammation, and oxidation. When restraint stress is applied to a subject, it might trigger the increasing production of ROS. The release of this ROS can, in turn, increase the production of pro-inflammatory cytokines and significantly decrease the expression of Nrf-2 (as a protective mechanism against

oxidative stress). However, the administration of grape polyphenols was found to reduce the expression of TNF-α, IL-6, and NOX-2. Additionally, it increases Nrf2 levels, thereby providing a protective effect against oxidative stress. In addition, grape polyphenols are also responsible for increasing the activity of catalase and SOD enzymes which show strong antioxidant effects.

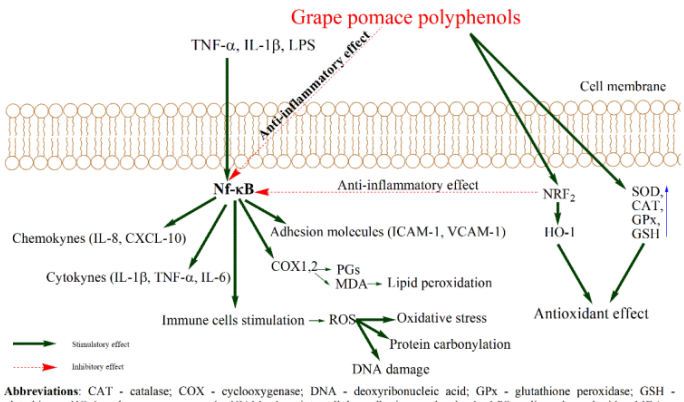
On the other hand, oxidative stress is characterized by increased MDA levels. In fact, giving grape supplements containing polyphenols can efficiently reduce MDA levels, thereby reducing oxidative stress. Furthermore, research was conducted on judo athletes to see the effect of grape juice consumption on oxidative stress and antioxidant activity. The results showed that this grapes contains bioactive compounds, namely polyphenolic compounds. The compounds have a high total antioxidant capacity after physical exercise to minimize the occurrence of oxidative stress and muscle fatigue and significantly improve physical performance (Goulart *et al.*, 2020).

This research finding is also in line with an experimental study by Dani *et al.* (2021). The study reported that grape juice supplements and physical exercise can simultaneously reduce inflammation by modulating inflammatory markers, such as IL-6 levels. The results showed a decrease in IL-6 biomarker levels due to physical exercise and consumption of grape juice. In addition, physical exercise and grape juice supplements also contribute to reducing oxidative stress by increasing antioxidant defenses. These increasing antioxidant levels were found due to the presence of polyphenolic compounds in grapes, which are responsible for increasing the activity of the catalase and SOD enzymes. Thus, they provide a strong antioxidant effect (Dani *et al.*, 2021).

Another study reported that white grape juice supplements have a high natural antioxidant capacity due to the total phenolic content present in grapes. This antioxidant capacity can reduce free radicals so that it can reduce the occurrence of oxidative stress. Antioxidant activity is also closely related to lipid peroxidation and SOD activity, where an increase in antioxidants can be seen from an increase in SOD. However, in this study, no differences were found in SOD activity and oxidative damage in individuals given grape juice supplements. The emergence of these differences may be due to the different composition of grape juice, quantity, and duration of supplementation. However, it is that this white grape juice supplement has high antioxidant activity, so it can potentially reduce oxidative stress (Zuanazzi *et al.*, 2019. Choleva *et al.*, 2023).

For those reasons, the polyphenol content (phenolic acids and flavonoids) in grapes has antioxidant and anti-inflammatory properties that are not controlled by intense exercise. In terms of antioxidant action, polyphenols can change the natural processes of fighting oxidative stress. The ability of polyphenols to scavenge and chelate reactive oxygen species involved in ROS production or to activate nuclear factor E2 and regulate antioxidant enzymes may both produce these effects, as shown in Figure 6. Polyphenols have been shown to downregulate cytokines and chemokines in inflammation and block the Nf-kB pathway, which is a mitogen-activated kinase pathway. Polyphenols also inhibit lipoxygenase and cyclooxygenase found in the arachidonic acid signaling pathway, responsible for the synthesis of prostaglandins, thromboxane A2, and leukotrienes, which ultimately increase the inflammatory response, as described in Figure 5 (Chedea *et al.*, 2022).

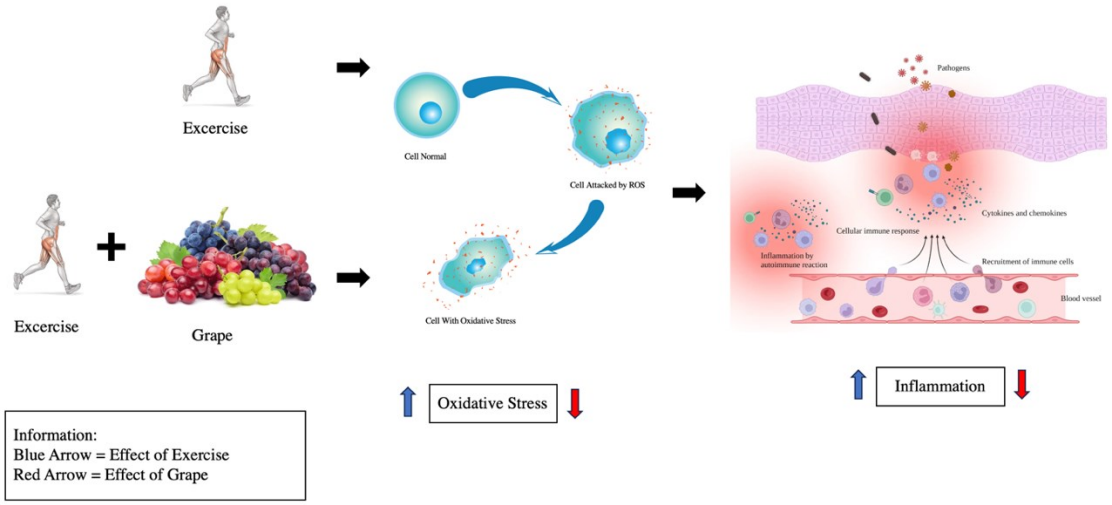
Figure 6. Potential anti-inflammatory and antioxidant properties of polyphenols derived from grape pomace (Chedea *et al.*, 2022)



Abbreviations: CAT - catalase; COX - cyclooxygenase; DNA - deoxyribonucleic acid; GPx - glutathione peroxidase; GSH - glutathione; HO-1 - heme oxygenase 1; ICAM -1 - intercellular adhesion molecule 1; LPS - lipopolysaccharide; MDA - malondyaldehide; Nf-κB - nuclear factor kappa-light-chain-enhancer of activated B cells; NRF_2 - nuclear factor erythroid 2-related factor 2; PGs - prostaglandins; ROS -reactive oxygen species; SOD - superoxyde dismutase; TNF-α - tumor nevrosis factor α; VCAM - 1 - vascular cell adhesion protein 1;

Furthermore, the polyphenols (phenolic acids) in grapes have antioxidant and anti-inflammatory properties. They may thereby lessen oxidative damage and excessive inflammation brought on by exercise. The detailed benefits of grapes in reducing oxidative stress and inflammation are shown in Figure 7.

Figure 7. The process by which grapes decrease inflammation and oxidative stress



Conclusions

In conclusion, this research confirms the efficacy of polyphenol content in grapes to reduce oxidative stress. The compounds have antioxidant properties, effectively reducing ROS, MDA, and TBARS levels and increasing GSH levels. Moreover, the anti-inflammatory qualities of grapes might lessen excessive inflammation brought on by intense exercise and physical activity. In this case, grapes work by blocking several inflammatory pathways and decreasing inflammatory markers. In vivo studies also confirm these anti-inflammatory and antioxidant benefits. In terms of antioxidant activity, eNOS gene expression was stimulated, CAT, SOD, and GPx4 levels were increased, and these effects were added to those already seen in in vitro experiments. Further information regarding its anti-inflammatory potential was also obtained from in vivo investigations, which showed suppression of the release of some inflammatory markers, including TNF-α, CRP, IL-1α, IL-1β, IL-6, and IFN-γ. Muscle pain may become less intense if inflammation is reduced. Therefore, we recommend using grapes to help people reduce inflammation and oxidative stress brought on by excessive exercise and physical activity.

Conflicts of Interest

The authors declare no conflict of interest.

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Authors' and translators' details:

Novadri Ayubi	novadriayubi@unesa.ac.id	Author
Atika Syafawi	atikasyafawi@gmail.com	Author
Anton Komaini	antonkomaini@fik.unp.ac.id	Author
Dhea Regita Sastika Putri	sastikaputri@gmail.com	Author
Ilham	ilhamf@fik.unp.ac.id	Author
Deby Tri Mario	debytrimario@unp.ac.id	Author
Dyah Fitria Padmasari	dyahpadmasari81@gmail.com	Author
Junian Cahyanto Wibawa	juniancahyanto96@stkippgritrenggalek.ac.id	Author
Procopio B. Dafun Jr.	pbdafun@mmsu.edu.ph	Translator