The mechanism of physical exercise increases glutathione peroxidase as an endogenous antioxidant : a systematic review

El mecanismo del ejercicio físico aumenta la glutatión peroxidasa como antioxidante endógeno: una revisión sistemática

Authors

Junian Cahyanto Wibawa [1]
Nendra Febrianto [1]
Muhammad Soleh Fudin [1]
Yovhandra Ockta [2]
Rifqi Festiawan [3]

[1] STKIP PGRI Trenggalek (Indonesia)
[2] Universitas Negeri Padang (Indonesia)
[3] Universitas Jenderal Soedirman (Indonesia)

Corresponding author:
Junian Cahyanto Wibawa
juniancahyanto96@stkippgritrenggalek.ac.id

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Abstract

Study Purpose. This study aims to analyze the effect of physical exercise on increasing glutathione peroxidase as a biomarker for endogenous antioxidants. Materials and methods. This type of systematic review research uses searches from journal databases such as MEDLINE-Pubmed, Web of Science, Scopus and Science Direct. The inclusion criteria in this study were articles published in the last 5 years and articles discussing glutathione peroxidase, physical exercise and antioxidants. A total of 95 articles from the Science Direct, Pubmed, and Web of Science databases were identified. A total of 10 articles that met the inclusion criteria were selected and analyzed for this systematic review. For standard operations, this study followed the Preferred Reporting

Items for Systematic Reviews and Meta-Analyses (PRISMA) assessment. Results. This systematic review reports that physical exercise has been shown to increase levels of glutathione peroxidase as a marker of endogenous antioxidants. Conclusions. Physical exercise has been proven to increase glutathione peroxidase levels as a marker of endogenous antioxidants. This increase is triggered by ROS which is a physiological response to exercise.

Keywords

Glutathione peroxidase; antioxidant; physical exercise.

Resumen

Objetivo del estudio. Este estudio pretende analizar el efecto del ejercicio físico sobre el aumento de glutatión peroxidasa como biomarcador de antioxidantes endógenos. Materiales y métodos. Este tipo de investigación de revisión sistemática utiliza búsquedas en bases de datos de revistas como MEDLINE-Pubmed, Web of Science, Scopus y Science Direct. Los criterios de inclusión en este estudio fueron artículos publicados en los últimos 5 años y artículos que trataran sobre la glutatión peroxi-dasa, el ejercicio físico y los antioxidantes. Se identificaron un total de 95 artículos de las bases de datos Science Direct, Pubmed y Web of Science. Se seleccionaron y analizaron para esta revisión sistemática un total de 10 artículos que cumplían los criterios de inclusión. Para las operaciones estándar, este estudio siguió la evaluación Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). Resultados. Esta revisión sistemática informa de que se ha demostrado que el ejercicio físico aumenta los niveles de glutatión peroxidasa como marcador de antioxidantes endógenos. Conclusiones. Se ha demostrado que el ejercicio físico aumenta los niveles de glutatión peroxidasa como marcador de antioxidantes endógenos. Este aumento está provocado por las ERO, que son una respuesta fisiológica al ejercicio.

Palabras clave

Glutatión peroxidasa; antioxidante; ejercicio físico.

Introduction

Physical exercise triggers oxidative stress which is evidenced by an increase in ROS (reactive oxygen species) (Shamsnia et al., 2023). During physical exercise, the oxygen demand increases 20-100 times from normal so that the oxygen supply cannot fulfill the body (Wang et al., 2021). The body's ROS are hydrogen peroxide (H2O2), hydroxyl radical (OH-), and superoxide anion (O2-) which has an important role in cellular physiological mechanisms during stress triggered by physical exercise (Saberi et al., 2024). Skeletal muscle has an important role during exercise, namely playing a level of ROS formation that has an impact on the continuity of muscle maintenance, increasing muscle strength, cellular signal transduction, and gene expression, whereas if ROS is too excessive it will interfere with muscle contraction and the continuity of muscle performance (Wang et al., 2021). If the level of ROS production is excessive during physical exercise, it will trigger oxidative stress (Wibawa et al., 2021).

ROS are involved in many cell reactions when biological conditions are normal, such as signal transduction between organelles, regulation of energy systems and metabolism in mitochondria, and regulation of gene expression. However, excessive levels of ROS in the body can also negatively impact biomacromolecules in cells, causing lipids, proteins, and nucleic acids to break down, aging cells, and muscle cell death—physiological reactions that happen during physical activity (Mendes et al., 2023). Moreover, a variety of cytokines that are stimulated by exercise-induced muscle injury can activate neutrophils and macrophages, which increases the generation of reactive oxygen species (Wang et al., 2021). ROS also affect the release of Ca2+ ions in sarcoplasmic reticulum organelles which can reduce myofibril sensitivity and subsequently affect muscle contraction performance (Magherini et al., 2019). Excessive exhaustive exercise with high intensity can trigger a significant increase in malondialdehyde (MDA) levels as one of the biomarkers of oxidative stress (Joanisse et al., 2021).

Physical exercise in recent decades has provided knowledge as a preventive effort in improving public health and preventing Parkinson's disease (Souza et al., 2022). Patients with diabetes, cardiovascular disease, depression, and metabolic syndrome might benefit from regular exercise as well (Korivi et al., 2023). By exercising, the body will increase antioxidant levels which provide beneficial effects that can reduce the occurrence of oxidative stress (Wibawa et al., 2021). Superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPX) are examples of endogenous antioxidants that are expressed in skeletal muscle. On the other hand, exogenous non-enzymatic antioxidants include vitamin E, vitamin C, polyphenols (flavonoids, tannins), and carotenoids (Wouda et al., 2023). Type, intensity, duration of physical exercise provide redox changes in body homeostasis (Bellafiore et al., 2019). Reactive oxygen species are produced in greater amounts during prolonged, intense aerobic and anaerobic exercise (ROS) (Bellafiore et al., 2021).

Glutathione peroxidase (GPx) belongs to a significant family of selenium-containing endogenous antioxidant enzymes in mammals (Zhao et al., 2019). As part of its operational mechanism, GPx catalyzes the conversion of H2O2 or hydrogen peroxide to H2O or water, collaborating with SOD and CAT and other antioxidants (Zhao et al., 2019). By transforming H2O2 into H2O, the antioxidant response's presence as a catalyst component can aid in the quick reaction (Handy et al., 2021). Although GPx are widely known to be endogenous antioxidants in mammals and have been documented in a wide range of species, their functions in each cell organelle appear to vary (Handy et al., 2021). GPx1 is widely distributed, and it was once known as cytoplasmic GPx in mitochondria and the cytoplasm (Alehagen et al., 2021). By facilitating the reduction of harmful peroxides in the body, such as hydrogen peroxide, cholesterol peroxide, and long-chain fatty acid peroxides, GPx plays a vital function in the body (Alehagen et al., 2021).

GPx reduces reactive oxygen species (ROS) and limits their toxicity in animals by forming an enzymatic antioxidant system with superoxide dismutase (SOD) and catalase (CAT) (Pei et al., 2023). GPx in reducing H2O2 to H2O usually uses glutathione (GSH) (Pei et al., 2023). Our understanding of the significant roles played by this family of proteins has been aided by several research on the structure and function of GPx in mammals. Unfortunately, rigorous studies and scientific reviews on the cellular processes behind GPx's function as an endogenous antioxidant that lowers ROS during exercise are still lacking Research results and reports Rusip & Suhartini, 2020 show that moderate intensity physical exercise by walking 30 minutes per day, 3x a week for 12 weeks of exercise has been proven to increase glutathione peroxidase levels after intervention as a marker of endogenous antioxidants. Few research

have looked at how GPx affects oxidative stress during physical activity. The objective of this comprehensive study is to investigate how the GPx mechanism influences the decrease of oxidative stress in mammals during physical activity and to offer novel strategies for future oxidative stress reduction.

Method

Study Design

This type of systematic review research uses searches from journal databases such as MEDLINE-Pubmed, Web of Science, Scopus and Science Direct. It is considered a premier platform worldwide as it brings together publications that have scientific impact and relevance.

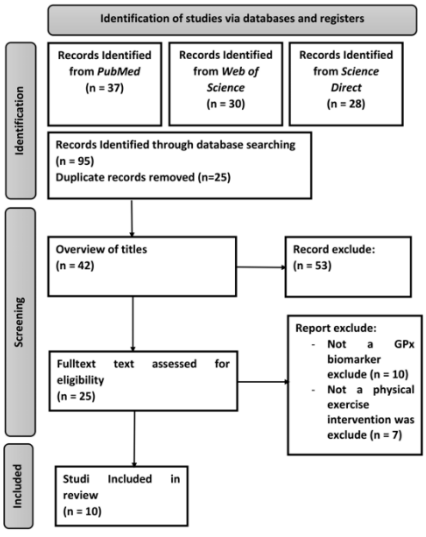
Eligibility Criteria

The inclusion criteria in this study were articles published in the last 5 years and articles discussing glutathione peroxidase (GPx), physical exercise and antioxidant. Furthermore, the exclusion criteria in this research are journals that are not reputable or are not indexed by Scopus and Web of Science.

Procedure

Titles, abstracts and full texts of articles were screened then verified and stored in Mendeley software. In the first stage, 95 articles from the Science direct, Pubmed and web of science databases were identified. Next, in the second stage, 42 articles were screened based on the suitability of the title and abstract. In the third stage, 25 articles were ordered for further processing. At this stage we filter based on the overall suitability of the article. Then in the final stage 10 articles were selected that met the inclusion criteria and analyzed for this systematic observation. For operational standards, this study followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) assessment.

Figure 1. PRISMA flowchart of the article selection process



Results

Table 1. Results of Physical Exercise in Increasing Glutathione Peroxidase (GPx)

Author	Sample Characteristics	Study Design	Intervention	Results
(Delrieu et al., 2021)	49 women aged 18 - 78 years who were diagnosed with breast cancer participated in	Experimental	Home physical activity program for 6 months. Step targets were increased from a	There was an increase in GPx levels after the physical exercise intervention.

Table 1. Results of Physical Exercise in Increasing Glutathione Peroxidase (GPx)

Author	Sample Characteristics	Study Design	Intervention	Results
	this study to carry out pre and post tests.		maximum of 1000 steps per week to 10,000 steps.	
(Rusip & Suhartini, 2020)	73 sedentary women participated in this study and were divided into 2 groups. Control group and physical exercise intervention group.	Experimental	Moderate intensity physical exercise by walking 30 minutes per day, 3x a week for 12 weeks of training.	In the group that received physical activity intervention, there was a rise in GPx levels.
(Reza salehi et al., 2020)	45 rats were randomly assigned to 5 treatment groups, which included an estrogen solvent (sesame oil) group, an aerobic training group, an estrogen group, and an aerobic training plus estrogen group.	Experimental	Aerobic physical exercise was carried out 5 sessions per week for 8 weeks of training.	The group that underwent aerobic exercise had an increase in GPx levels.
(Bunpo et al., 2021)	19 young healthy women aged 22-25 years participated in this study and carried out pre and post test research.	Experimental	Physical exercise cycling for 30 minutes after taking vitamin c 1000 mg or placebo.	When consuming placebo, there was an increase in GPx shortly after post exercise. And there was an increase in GPx levels after consumption of ascorbic acid at 30 minutes after physical exercise intervention.
(Mohammadjafari et al., 2019)	45 bodybuilders participated in this study and were divided into 3 groups. Group 1 physical exercise + growth hormone, group 2 physical exercise + IGF-1, control group physical exercise without hormone peptide.	Experimental	Resistance training consists of 6 types of exercises namely back squats, knee extension, knee flexion, lat rowing, bench press, and arm curl which are carried out in 5 sets with a load of 80% maximum repetitions.	There was an increase in GPx in all groups after the physical exercise intervention.
(Macarro et al., 2021)	In this study, 43 healthy males between the ages of 18 and 45 were split into two groups. Probiotic Group 1.	Experimental	Long-term, high-intensity physical activity using a roll bike.	After six weeks of physical activity intervention, there was an increase in GPx levels in the placebo group.
(Börzsei et al., 2024)	Three sets of twenty-four male rats each were used in this investigation. Isoproterenol (ISO) therapy, fixed-control, and pre-swim training combined.	Experimental	Swimming training for 3 weeks. On the first day, the duration is 5 minutes in the first week. And increased for 5 minutes for the next day.	In the group receiving physical activity therapy, GPx increased.
(Kazem & Abboud, 2024)	Thirty female college basketball players were split up into three groups for the study. The players in the exploratory experiment were female, control, and experimental.	Experimental	Aerobic basketball training 2x a week for 8 weeks.	In the group that received physical activity intervention, there was a rise in GPX levels.
(Kwon et al., 2024)	For this investigation, 40 six-month-old female rats were split into four groups: a control group, one that received 125 mg/kg of hemoHIM supplementation, one that received 500 mg/kg of hemoHIM supplementation, and one that received 625 mg/kg of creatine supplementation.	Experimental	Physical exercise grip strength test and swimming exercise.	The group that received 500 mg/kg of HemoHIM supplementation in addition to physical activity had a substantial rise in GPx levels.
(Saberi et al., 2024)	For this investigation, a total of twenty-eight male rats were randomly assigned to four groups. There are four types of control groups: healthy, diabetes, physical activity, and diabetic plus physical exercise.	Experimental	High-intensity physical exercise for 8 weeks.	Both the physical activity + diabetes group and the standard physical exercise group had higher GPx levels.

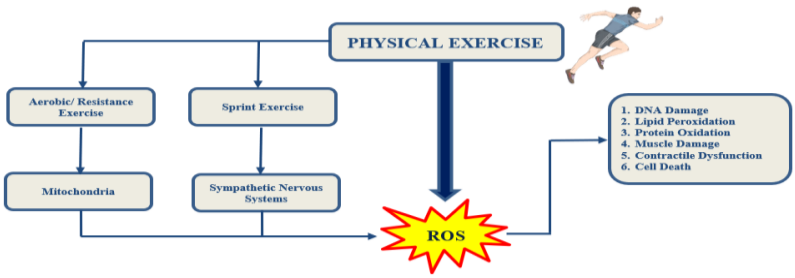
Discussion

Research results from Delrieu et al., 2021 proved that there was an increase in GPx levels in women who were given physical activity interventions for 6 months. Another study's findings on women who exercised for 30 minutes a day, three times a week for a period of 12 weeks likewise showed a substantial rise in GPx levels (Rusip & Suhartini, 2020). An increase in GPx levels also occurred in mice that were given aerobic physical exercise 5 sessions per week for 8 weeks (Reza salehi et al., 2020). Healthy young women participated in research involving physical exercise by cycling for 30 minutes. The results of the study also proved that there was an increase in GPx levels after physical exercise (Bunpo et al., 2021). The red blood cell enzyme glutathione peroxidase 1 (GPx1) was initially discovered in 1957 and is responsible for shielding hemoglobin from oxidative stress (Pei et al., 2023). It is possible to speculate that physical exercise-induced increases in GPx activity might help reduce cellular ROS (Delrieu et al., 2021). Bodybuilders who are given resistance training also have a positive effect on increasing GPx levels (Mohammadjafari et al., 2019).

Physical activity is referred to be a "miracle drug" by the Academy of Medical Sciences as it has been shown to enhance human health (Gomez-cabrera et al., 2021). Strong scientific evidence backs up the academy's claim that physical exercise helps prevent and treat a number of illnesses, including mental, neurological, metabolic, cardiovascular, pulmonary, musculoskeletal, and even cancer (Gomez-cabrera et al., 2021). Engaging in physical exercise offers several noteworthy health advantages. Physical strength, endurance, bone mineral density, and neuromusculoskeletal fitness are just a few of the traits that can improve with regular exercise due to mechanical stress and repeated exposure to gravitational forces. These traits are all necessary for an autonomous and functional life (Mahindru et al., 2023).

Apart from increasing antioxidants and health status, acute physical exercise can also increase ROS, but this is a physiological response to physical exercise (Wibawa et al., 2021). Mitochondria are organelles that act as energy stores that increase the formation of ATP in muscles, so that in the mechanism there is also ion leakage which has an impact on increasing oxidative stress (Olaso-gonzalez et al., 2020). As explained above, a massive increase in ROS caused by exercise will occur in skeletal muscle which has an influence on muscle fibers experiencing an increase in ROS. (Wyckelsma et al., 2020). Roh et al., 2020 also reported that 12 weeks of resistance physical training significantly reduced inflammatory markers in people with obesity. Skeletal muscles not only function to produce force and movement, but now also as signal transducers acting as endocrine organs that secrete cytokines and transcription factors into the bloodstream, thereby regulating the function of other organs (Vargas-Ortiz et al., 2019). The sole health practice linked to a decrease in all-cause mortality in adults is regular exercise, therefore it appears strange that physical activity of the skeletal muscle boosts ROS generation (Powers et al., 2020a). Numerous investigations conducted on

Figure 2. Physical Exercise Increase ROS (reactive oxygen species)



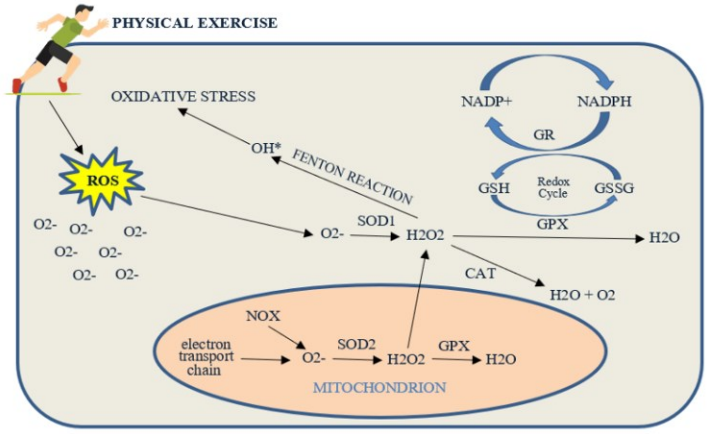
both people and animals have demonstrated that aerobic exercise raises the body's levels of non-enzymatic antioxidants, which will improve human health, as well as the activity of antioxidant enzymes like CAT, SOD, and GPX (Ye et al., 2021).

Numerous studies have demonstrated that regular aerobic exercise at a 75–80% intensity for four to six weeks can raise young students' and male soccer players' total antioxidant capacity (Yol et al., 2020). The results of this research show that consistent aerobic exercise training significantly increases the

effectiveness of the body's enzymatic and nonenzymatic antioxidant defense mechanisms, fortifying its capacity to get rid of pro-oxidants (Yol et al., 2020). Excessive levels of MDA and ROS, together with a reduction in antioxidant enzyme levels, have been linked to persistent weariness during physical activity (Kwon et al., 2024). Regular aerobic exercise has also been shown to lower levels of LDL (low density lipoprotein) and MDA, two pro-oxidants, in line with the findings of other studies (Rytz et al., 2024). ROS will have a negative impact if it accumulates and its production exceeds the neutrality of human tissue and antioxidants (Zhou et al., 2022).

Biologically, the definition of antioxidant is a compound that is able to counteract or reduce the negative impact of oxidants in the body. Exercise-induced protein oxidation results in the generation of MDA and ROS as well as an increase in the concentrations of main antioxidant enzymes such GPx and CAT (Kwon et al., 2024). While GPx is in charge of converting H2O2 into water and alcohol, CAT is able to break down H2O2 into H2O and O2, which helps alleviate tiredness and other physiological ailments (Kwon et al., 2024). Frequent exercise is linked to positive benefits on the central nervous system as well (Souza et al., 2022). Exercise is good for building skeletal muscle mass and improving physical fitness, but it can also have negative side effects and increase inflammation, oxidative stress, or muscle injury when done repeatedly at a high intensity (Korivi et al., 2023). Furthermore, increased energy consumption during exercise results in an excess of reactive oxygen species (ROS) being produced in fatigued skeletal muscle cells, which in turn causes lipids, proteins, and DNA to peroxide (Wang et al., 2021).

Figure 3. Mechanism of Physical Exercise Increase GPx (glutathion peroxidase)



The mechanism of physical exercise in increasing GPx levels as part of endogenous antioxidants in an effort to ward off free radicals is as follows. During physical exercise, the body will activate the sympathetic nervous system in response to exercise (Daniela et al., 2022). The activation of the sympathetic nervous system will trigger a large increase in skeletal muscle contractions which will also have an impact on increasing ROS (Xia et al., 2024). This physical exercise will also increase biogenesis in mitochondria in an effort to provide energy to meet cell needs (Heyne et al., 2024). Exercise capacity is regulated by mitochondria, which are significant adenosine triphosphate (ATP) generators. There is a direct link between increased exercise capacity and mitochondrial activity (Heyne et al., 2024). The metabolic system in the mitochondria will create an electron transport mechanism starting from complex 1 to complex 4 which will also occur and trigger an increase in ROS and superoxide anions O2- (Li et al., 2023). This ROS is very reactive if it is not immediately neutralized by antioxidants, it will have a negative impact on cell damage (Wibawa et al., 2021).

The emergence of ROS during physical exercise will also make antioxidant enzymes automatically appear to help neutralize existing free radicals such as superoxide dismutase, glutathione peroxidase, and catalase (Powers et al., 2023). In the mechanism process, O2- is neutralized by SOD to become H2O2 and the next process is the role of glutathione peroxidase to help convert H2O2 into a neutral reaction, namely H2O (Powers et al., 2020b). Catalase also helps convert H2O2 into H2O (Powers et al., 2020b). If this hydrogen peroxide is left continuously, it will also be very reactive, it will enter the Fenton reaction to be converted into hydroxyl radicals which will trigger oxidative stress which will have an

impact on lipid damage, DNA damage, cell damage, and trigger disease (Powers et al., 2020b). The results of research on men aged 18 - 45 years who participated in research with high intensity physical exercise intervention proved that there was an increase in GPx levels after physical exercise (Macarro et al., 2021).

The results of other research on mice that were given swimming physical training intervention for 3 weeks also proved that there was an increase in GPx levels after the training intervention (Börzsei et al., 2024). 30 female basketball players who were given basketball resistance training intervention 2x a week for 8 weeks also proved that GPx levels had increased (Kazem & Abboud, 2024). Rats conditioned in diabetes mellitus who were given high intensity physical exercise intervention for 8 weeks also proved that there was a significant increase in GPx levels (Saberi et al., 2024). In the end, physical exercise is a physiological response in such a way that it can make the body healthier and fitter by increasing GPx as an antioxidant in the body. In this systematic review, of course there are still many limitations in writing and reviewing the analysis. Researchers only examine the role of GPx as an endogenous antioxidant during physical exercise. Inside the cell it is very complex. During physical exercise there will be many reactions that occur there. Studying the dynamics that occur in cells is an interesting thing that is associated with physical exercise. The latest discoveries related to antioxidant mechanisms will continue to develop in line with the results of the latest research. Of course, there is also a need for writings and studies on the topic of antioxidants and exercise to be able to increase the body of human knowledge, especially in the field of exercise physiology. Researchers hope that in the future further research can be carried out regarding the expression of genes that influence antioxidants and their mechanisms.

Conclusions

In short, physical exercise is proven to improve people's health. Physical exercise can also increase total endogenous antioxidants such as superoxide dismutase, glutathione peroxidase, and catalase. GPx is an antioxidant that is very important in warding off free radicals triggered by physical exercise. GPx in its role wards off free radicals, namely by reducing H2O2 to H2O so that it is neutral and non-reactive. If H2O2 is allowed to continue continuously it will have an impact on increasing oxidative stress through the Fenton reaction. The role of GPx is very important in neutralizing the body and reducing free radicals that occur due to physical exercise. So, this is a natural physiological response that occurs during physical exercise. Further scientific reviews can examine how gene expression increases antioxidants during physical exercise which will provide knowledge to the general public and academics about the importance of exercise for health.

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Authors' and translators' details:

Junian Cahyanto Wibawa	juniancahyanto96@stkippgritrenggalek.ac.id	Author
Nendra Febrianto	nendrafebrianto@stkippgritrenggalek.ac.id	Author
Muhammad Soleh Fudin	fudinbanimustaram@stkippgritrenggalek.ac.id	Author
Yovhandra Ockta	Yovhandra1999@gmail.com	Author
Rifqi Festiawan	rifqi.festiawan@unsoed.ac.id	Translator / Author