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Major relationships among polyphenols, gut microbiota and sports performance: a systematic review

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Abstract

Introduction: Among the various phytochemicals, polyphenols represent a heterogeneous class of compounds with marked antioxidant and anti-inflammatory properties. One of the biggest challenges is to understand the mechanisms of the interrelationship between polyphenols and the human body, also considering the fundamental role played by the gut microbiota in their absorption and bioavailability to improve sports performance. **Objective:** It was to present the main relationships between polyphenols, gut microbiota, and sports performance. **Methods:** The PRISMA Platform systematic review rules were followed. The search was carried out from September to October 2024 in the Scopus, PubMed, Science Direct, Scielo, and Google Scholar databases. The quality of the studies was based on the GRADE instrument and the risk of bias was analyzed according to the Cochrane instrument. **Results and Conclusion:** A total of 126 articles were found, and 72 articles were evaluated in full, and 61 were included and developed in the present systematic review study. Considering the Cochrane tool for risk of bias, the overall assessment resulted in 08 studies with a high risk of bias and 26 studies that did not meet GRADE and AMSTAR-2. Most studies showed homogeneity in their results, with X^2=75.7%>50%. The Funnel Plot graph showed symmetrical behavior, not suggesting a significant risk of bias in studies with smaller sample sizes. Dietary polyphenols exert several beneficial effects on sports performance, demonstrated in vivo and in human studies. The health-related mechanisms of polyphenols mainly concern the modulation of mitochondrial biogenesis and the stimulation of stress-related enzymes or transcription factors, as well as a nutritional deficiency, which regulates gene expression of essential antioxidant proteins (SOD, Catalase, Glutathione system, etc.). Overall, these mechanisms promote athletic performance by improving cardiometabolic functions, reducing recovery times and post-exercise pain, maintaining a low degree of oxidative stress, and preventing dysregulated inflammatory processes. Therefore, polyphenols are able, through their interaction with the gut microbiota, to favor the proliferation of bacterial genera of great importance for metabolic and cognitive functions, such as Akkermansia, Lactobacilli, and Bifidobacteria. The microbiota, on the other hand, metabolizes polyphenols in the colon to produce small bioactive molecules that exert epigenetic mechanisms on biochemical pathways modulating gene expression.

Keywords: Nutritional Genomics. Polyphenols. Gut microbiota. Sports Performance.

Introduction

Interest in a personalized approach is increasing in sports to maximize the athletic capacity of each individual in endurance and strength sports [1,2]. Research has increasingly focused on the genetic aspects that characterize elite athletes [3], as well as on their precise nutrition, and recently great interest has been directed towards plants and their phytocomplexes, which provide valuable molecules of interest for sports performance [2].

Among the various phytochemicals, polyphenols represent a heterogeneous class of compounds with marked antioxidant and anti-inflammatory properties [4]. Polyphenols can act as key signal molecules when introduced into an organism. This can be achieved through a multitude of mechanisms, both direct on receptor proteins and indirect through modulation of the transcription of factors or enzymes critical in survival and bioenergetic signaling pathways [5-8]. In this regard, one of the greatest challenges is to understand the mechanisms of the interrelationship between polyphenols and the human body, also considering the fundamental role played by the gut microbiota in their absorption and bioavailability [8].

In this sense, the impact of the gut microbiota on the bioavailability and activity of polyphenols is fundamental. The use of polyphenols in sports performance also presents a holistic approach, considering all relevant biological layers, so that the effects of polyphenols in sports present epigenetic and genetic aspects [9].

In this sense, dietary recommendations for individuals who exercise should emphasize consuming a well-balanced diet and/or natural foods rich in antioxidants, such as cocoa and chocolate, rather than taking antioxidant supplements. This strategy has been increasingly proposed as a potentially suitable tool to prevent or reduce oxidative stress and related inflammation during intensive physical training. In addition to being highenergy-density foods, cocoa and cocoa products, including chocolate, are a rich source of antioxidant polyphenols that have been shown to have health-promoting effects through their antioxidant, anti-inflammatory, and metabolic properties [10]. In addition, flavonoids such as quercetin, catechins, and other polyphenols such as resveratrol have been shown to improve athletic performance [11].

Therefore, the present study aimed to present the main relationships between polyphenols, gut microbiota, and sports performance under the management of nutritional genomics.

Methods

Study Design

The present study followed an international systematic review model, following the PRISMA (preferred reporting items for systematic reviews and meta-analysis) rules. Available at: http://www.prisma-statement.org/?AspxAutoDetectCookieSupport=1. Accessed on: 09/19/2024. The AMSTAR-2 (Assessing the methodological quality of systematic reviews) methodological quality standards were also followed. Available at: https://amstar.ca/. Accessed on: 09/19/2024.

Research Strategy and Search Sources

The literature search process was carried out from September to October 2024 and developed based on Web of Science, Scopus, PubMed, Science Direct, Scielo and Google Scholar, using scientific articles from 2019 to 2023, using the descriptors (MeSH Terms): Nutritional Genomics. Polyphenols. Gut microbiota. Sports Performance, and using the Boolean "and" between the MeSH terms and "or" between the historical discoveries.

Study Quality and Risk of Bias

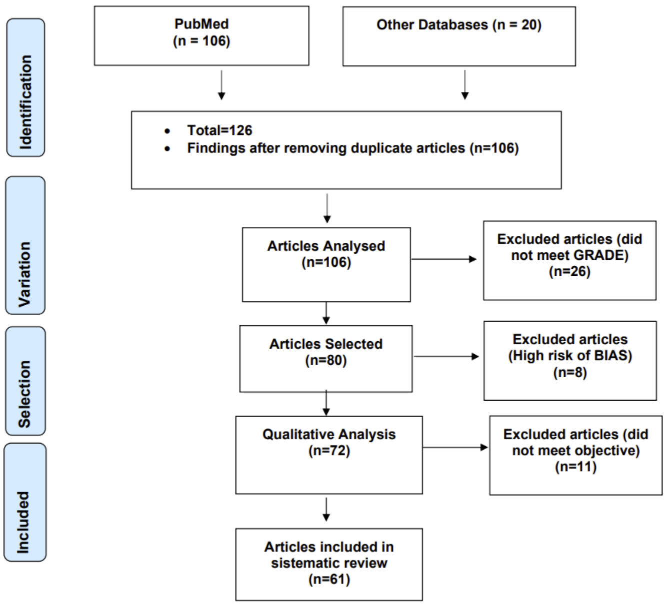
Quality was classified as high, moderate, low, or very low regarding the risk of bias, clarity of comparisons, precision, and consistency of analyses. The most evident emphasis was on systematic review articles or meta-analyses of randomized clinical trials, followed by randomized clinical trials. Low quality of evidence was attributed to case reports, editorials, and brief communications, according to the GRADE instrument. The risk of bias was analyzed according to the Cochrane instrument through analysis of the Funnel Plot graph (Cohen's test (d)).

Results of the Literary Review

Summary of Findings

A total of 126 studies were found and submitted to eligibility analysis, and then 61 of the 72 total studies were selected for this systematic review (Figure 1), considering firstly the level of scientific evidence of studies in study types such as meta-analysis, consensus, randomized clinical, prospective and observational. Biases did not compromise the scientific basis of the studies. According to the GRADE instrument, most studies presented homogeneity in their results, with X^2=75.7%>50%. Considering the Cochrane tool for risk of bias, the overall assessment resulted in 08 studies with a high risk of bias and 26 studies that did not meet GRADE and AMSTAR-2.

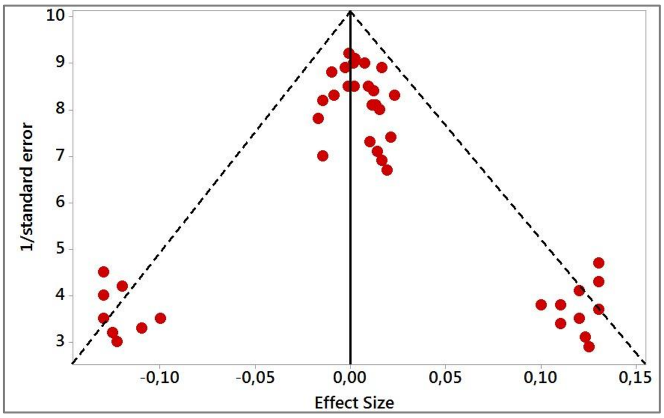
Figure 1. Flowchart showing the article selection process.



Source: Own authorship.

Figure 2 presents the results of the risk of bias of the studies using the Funnel Plot, showing the calculation of the Effect Size (Magnitude of the difference) using Cohen's Test (d). Precision (sample size) was determined indirectly by the inverse of the standard error (1/Standard Error). This graph had a symmetrical behavior, not suggesting a significant risk of bias, both among studies with small sample sizes (lower precision) that are shown at the base of the graph and in studies with large sample sizes that are presented in the upper region.

Figure 2. The symmetrical funnel plot does not suggest a risk of bias among the studies with small sample sizes that are shown at the bottom of the graph. High confidence and high recommendation studies are shown above the graph (N_{Total}=61 studies evaluated in full in the systematic review).



Source: Own authorship.

Nutritional Genomics, Gut microbiota, and Sports Performance

The gut microbiota is composed of about 100 trillion bacteria, viruses, fungi, and protozoa that live in perfect symbiosis with our organism [12]. About 90% of the bacteria that live in the human gastrointestinal tract belong to 5 main phyla: Bacteroidetes characterized by some well-known genera, such as Prevotella and Bacteroides [13]; Firmicutes to which the genera Ruminococcus, Lactobacillus and Streptococcus belong [14]. Actinobacteria belong to the genus Bifidobacterium; Proteobacteria (Gramnegative) and possibly pathogenic; and Verrucomicrobia, known mainly by the genus Akkermansia [12,15-17].

The individual response to nutrients and non-nutritive molecules can be largely affected by three important biological layers. The intestinal microbiome can alter the bioavailability of nutrients and other substances, the genome can influence the kinetics and dynamics of molecules, while the epigenome can modulate or amplify the properties of the genome. The use of omics and bioinformatics techniques allows the construction of individual multilayer networks and, thus, the identification of personalized strategies that have recently been considered in all medical fields, including sports medicine [9].

In this sense, the composition of each athlete's microbiome influences sports performance both directly by acting on energy metabolism and indirectly by modulating the availability of nutrients or non-nutritive molecules that, ultimately, affect the individual epigenome and genome. Among non-nutritive molecules, polyphenols can enhance physical performance through different epigenetic mechanisms [9].

In this way, polyphenols interact with the gut microbiota, undergoing extensive metabolism to produce bioactive molecules that act on transcription factors involved in mitochondrial biogenesis, antioxidant systems, glucose and lipid homeostasis, and DNA repair [9].

Thus, omics disciplines, including epigenomics (the study of the complete set of epigenetic modifications in a cell's genetic material, known as the epigenome), aim to fully characterize and quantify pools of biological molecules that affect the structure, function, and dynamics of an organism. In nutrition, omics technologies are useful for customizing dietary strategies for each individual, providing personalized dietary approaches [18,19]. In this regard, the standardized nutritional approach, preferably related to guidelines for healthy nutrition, such as those established by the World Health Organization (WHO), should be reviewed and updated, considering the influence that genetic, environmental, and microbiota factors have on each individual, to optimize nutritional and nutraceutical choices and promote the health of individuals according to their characteristics [20].

At the genetic level, two nutritional fields analyze the intricate relationships between nutrients, genes, and biological systems: nutrigenetics and nutrigenomics. Nutrigenetics aims to understand how our genetic background can modulate the absorption, distribution, metabolism, and elimination of nutrients, affecting the response to diet. Nutrigenomics focuses on individual sensitivity to nutrients in terms of influence on gene and protein expression and, subsequently, metabolite production, thus providing actionable information on the effects of diets and allowing effective personalization of dietary intervention strategies to prevent diet-related diseases [21,22].

One of the most useful applications of nutritional genomics is certainly in sports performance. Genetic factors account for approximately 50% to 80% of interindividual variation in body mass, and this has an essential impact on the muscle growth response [23]. In addition, endocrine functions, muscle fiber composition, psychological aspects, and nutrition may have differences associated with genotype and influence athletic performance [24].

Polyphenols in Sports Performance

Polyphenols represent a considerable heterogeneous class of compounds with common phenolic structural units present in nature in a wide variety of foods, such as fruits, vegetables, cereals, tea, and chocolate, among others [25]. The various polyphenol groups are distributed according to the number of phenolic rings in flavonoids (> 10,000 natural compounds) that can be further subclassified into many flavones, flavonols (Capparis spinosa), flavones or flavan-3-oils or catechins (Theobroma cacao, Camellia sinensis), anthocyanins or anthocyanidins (Vaccinium myrtillus), isoflavones and chalcones (Glycine max); and non-flavonoid polyphenols, such as tannins, diferuloylmethanes (Turmeric Longa), coumarins, benzophenones, secoiridoids, stilbenes (Polygonum cuspidatum), phenolic acids, etc. [4,26,27].

In general, various health properties have been attributed to polyphenols, including antioxidant, anti-inflammatory, antibacterial, antiviral, antipruritic, antiparasitic, and cytotoxic [5,7,28–31]. In athletic performance, several studies have investigated the antioxidant and anti-inflammatory potential of various polyphenols [32,33]. In this sense, individuals carrying specific genetic mutations (e.g., N-acetyltransferase (NAT) 1/2, SOD1/2, glutathione peroxidase (GPX) 1, paraoxonase (PON) 1, X-ray repair cross-complementation family (XRCC) 1) may have lower efficiency to modulate oxidative stress and inflammation during exercise and therefore require a significant increase in antioxidants with epigenetic mechanisms such as polyphenols [34-38]. One of the most innovative areas to understand the mechanisms of polyphenols related to health in sports performance is the study of bidirectional interactions with the gut microbiota [8,25].

In plants, polyphenols are generally found in their glycosylated form, although esterified or polymerized forms may also be present [39]. Once ingested, polyphenols are recognized by the human body as xenobiotics, so their absorption rate is notably lower than that of nutrients introduced with the diet and varies greatly depending on the degree of polymerization or the complexity of their chemical structure. Only 5-10% of polyphenols are absorbed in the small intestine, while the remaining 90–95% reach the colon, where they undergo fermentation processes by the gut microbiota and subsequently generate metabolites with different physiological implications. After oral ingestion of 10500 mg of polyphenols, the maximum plasma concentration does not usually exceed 1 μM, mainly due to poor absorption and metabolism by gastrointestinal tissues and microbiota [39].

In addition, polyphenols are also substrates for ATP-binding transporters, which are mainly efflux transporters and which eliminate their substrates outside the cell. These proteins may influence the oral availability and tissue distribution of polyphenols, limiting their beneficial effects [40,41]. Genetic mutations affecting these transporters, such as those affecting hepatic and intestinal cytochromes, should be taken into account to determine the dosage of polyphenols based on the genotypic characteristics of the subject (poor, intermediate, or extensive metabolizers) [42-44].

Once in the large intestine, polyphenols can modulate the proliferation of specific bacteria and act as prebiotics for some other microorganisms [45,46]. A meta-analysis showed that polyphenol supplementation increases the abundance of Lactobacillus and

Bifidobacterium and reduces the abundance of some pathogenic Clostridium in the human gut microbiota [47,48].

In practice, polyphenol supplementation should be provided before or after physical exercise and not immediately after, mainly because post-exercise inflammatory processes are essential for muscle hypertrophy and learning of muscle actions (Table 1). With the advent of omics technologies, it has become possible to analyze the individual genome, epigenome and other classes of biologically relevant molecules, as well as the genetic composition of the gut microbiota (microbiome). The biological data contained in the genetic/epigenetic fingerprint and the composition of the individual microbiota, together, provide valuable information to understand a subject's own sensitivity and response to external/internal stimuli and dietary xenobiotics. This, in turn, may allow personalized interventions in all medical fields, including sports medicine, where personalized nutritional and nutraceutical regimens can be implemented to maximize athletic performance.

Table 1. Average daily dose and overall benefits in humans of polyphenol supplementation on athletic performance.

Polyphenols	*Average Daily Dose*	*Benefits*	*References*
Curcumin	80–200 mg	✓ reduces muscle fatigue, muscle wasting, muscle soreness and post-exercise recovery; ✓ improves redox homeostasis and insulin sensitivity.	[44,49,50]
Resveratrol	100–500 mg	✓ improves muscle strength and fatigue tolerance and muscle regeneration after disuse; ✓ increases the mitochondrial capacity of skeletal muscle; ✓ exerts ergogenic and anti-obesity properties; increases beta-oxidation of fatty acids and glucose metabolism; ✓ improves glucose control and insulin sensitivity in diabetic or pre-diabetic individuals, without altering glycemic measurements in non-diabetic individuals; ✓ induces vasodilation, improves endothelial function and reduces blood pressure; ✓ increases cerebral blood flow;	[51-54]
Cocoa Flavanols	200–500 mg	✓ improves vascular function; ✓ reduces exercise-induced oxidative stress; ✓ alters fat and carbohydrate utilization during exercise without affecting athletic performance;	[55,56]
Quercetin	200–1000 mg	✓ increases athletic performance and energy expenditure; ✓ increases physical and mental performance; ✓ improves neuromuscular performance during and after resistance training sessions; ✓ attenuates the severity of muscle weakness caused by eccentric-induced myofibrillar rupture and sarcolemmal action potential ✓ propagation impairment; ✓ reduces post-stroke muscle soreness, localized pain, oxidative stress, cramps, and post-exercise recovery time;	[57-60]
Green tea	250–1000 mg	✓ reduces muscle damage and oxidative stress with positive effects on neuromuscular parameters of muscle fatigue; ✓ improves recovery after exercise;	[61-63]
Blueberry	75–150 g	✓ improves vascular functions and vasodilation;	[64,65]
Pycnogenol®	100–800 mg	✓ improves physical performance and protects against post-exercise oxidative stress; improves training and performance in both normal individuals and semi-professional athletes with high performance in difficult and high-stress sports, such as triathlon.	[66]
Montmorency cherry juice	30 mL	✓ increases muscle recovery and reduces post-exercise pain, especially in strength sports;	[67,68]
Ecklonia cava polyphenols	40 mg	✓ increases glucose oxidation; ✓ reduces lactate production during intense exercise;	[69]

In recent years, the consumption of chocolate and, in particular, dark chocolate has been "rehabilitated" due to its high content of antioxidant cocoa polyphenols. Although it is recognized that regular exercise improves energy metabolism and muscle performance, excessive or unusual exercise can induce cellular damage and impair muscle function, triggering oxidative stress and tissue inflammation. The interpretation of the available results on the antioxidant and anti-inflammatory activities of cocoa polyphenols remains questionable, probably due to the variety of physiological networks involved. Further experimental studies are mandatory to clarify the role of cocoa polyphenol supplementation in exercise-mediated inflammation [10].

A study investigated the effects of polyphenol supplementation on the composition of the gut microbiota in humans. The study followed a randomized, doubleblind, placebo-controlled (PLA) design, 37 overweight and obese men and women (18 men/19 women, 37.8 ± 1.6 years, body mass index: 29.6 ± 0.5 kg/m^2) received epigallocatechin-3-gallate and resveratrol (EGCG+RES, 282 and 80 mg/day, respectively) or PLA for 12 weeks. Fecal abundance of Bacteroidetes was higher in men than in women, while other bacterial taxa assessed were comparable. EGCG+RES supplementation significantly decreased Bacteroidetes and tended to reduce *Faecalibacterium prausnitzii* in men ($p=0.05$ and $p=0.10$, respectively), but not in women ($p=0.15$ and $p=0.77$, respectively). Other bacterial genera and species were not affected by EGCG + RES supplementation [70].

Finally, polyphenols have been shown to modulate inflammatory processes and the immune system response (Th1/Th2 balance). Furthermore, some polyphenols favor vascular regulation and endothelial function in humans, increasing endothelial nitric oxide synthesis [71]. Polyphenols have multiple biological effects, and future exercise studies should be designed appropriately and specifically to determine the physiological interactions between exercise and the selected supplement, rather than considering only performance [72].

Conclusion

Dietary polyphenols exert several beneficial effects on sports performance, demonstrated in vivo and in human studies. The health-related mechanisms of polyphenols mainly concern the modulation of mitochondrial biogenesis and the stimulation of enzymes or transcription factors related to stress, as well as nutritional deficiency, which regulate the gene expression of essential antioxidant proteins (SOD, Catalase, Glutathione system, etc.). Overall, these mechanisms promote athletic performance by improving cardiometabolic functions, reducing recovery times and post-exercise pain, maintaining a low degree of oxidative stress, and avoiding dysregulated inflammatory processes. Thus, polyphenols are able, through their interaction with the gut microbiota, to favor the proliferation of bacterial genera of great importance for metabolic and cognitive functions, such as *Akkermansia, Lactobacilli*, and Bifidobacteria. The microbiota, on the other hand, metabolizes polyphenols in the colon to produce small bioactive molecules that exert epigenetic mechanisms on biochemical pathways modulating gene expression.

CRediT

Author contributions: **Conceptualization -** Diego Pereira Netto, Jeffeson Alexandre Azevedo de Araujo, Kennya Medeiros Lopes de Barros Lima, Ana Gabriela de Magalhães, Laís Martins Borges, Karlla Gabrielly Claudino Santos, Leonardo Honório de Andrade Mélo Neto, Vitor Bezerra de Medeiros, Hugo Menezes Lopes, Brysa Freitas Dall'orto, Nicole Velasco Campos; **Data curation -** Diego Pereira Netto, Brysa Freitas Dall'orto, Nicole Velasco Campos; **Formal Analysis -**Diego Pereira Netto, Jeffeson Alexandre Azevedo de Araujo, Kennya Medeiros Lopes de Barros Lima, Ana Gabriela de Magalhães, Laís Martins Borges, Karlla Gabrielly Claudino Santos, Leonardo Honório de Andrade Mélo Neto; **Investigation-**Diego Pereira Netto, Jeffeson Alexandre Azevedo de Araujo, Kennya Medeiros Lopes de Barros Lima; **Methodology-** Diego Pereira Netto, Jeffeson Alexandre Azevedo de Araujo, Kennya Medeiros Lopes de Barros Lima, Ana Gabriela de Magalhães, Laís Martins Borges, Karlla Gabrielly Claudino Santos, Leonardo Honório de Andrade Mélo Neto, Vitor Bezerra de Medeiros, Hugo Menezes Lopes, Brysa Freitas Dall'orto, Nicole Velasco Campos; **Project administration -**Diego Pereira Netto, Vitor Bezerra de Medeiros, Hugo Menezes Lopes, Brysa Freitas Dall'orto, Nicole Velasco Campos; **Writing - original draft -**Diego Pereira Netto, Jeffeson Alexandre Azevedo de Araujo, Kennya Medeiros Lopes de Barros Lima, Ana Gabriela de Magalhães, Laís Martins Borges, Karlla Gabrielly Claudino Santos, Leonardo Honório de Andrade Mélo Neto, Vitor Bezerra de Medeiros, Hugo Menezes Lopes, Brysa Freitas Dall'orto, Nicole Velasco Campos; **Writing-review & editing-** Diego Pereira Netto, Jeffeson Alexandre Azevedo de Araujo, Kennya Medeiros Lopes de Barros Lima, Ana Gabriela de Magalhães, Laís Martins Borges, Karlla Gabrielly Claudino Santos, Leonardo Honório de Andrade Mélo Neto, Vitor Bezerra de Medeiros, Hugo Menezes Lopes, Brysa Freitas Dall'orto, Nicole Velasco Campos.

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No additional data are available.

Conflict of Interest

The authors declare no conflict of interest.

Similarity Check

It was applied by Ithenticate@.

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It was performed.

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