

Review

Health Benefits of (Poly)phenols from Cherries: A Review of Clinical Trials

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Abstract: Cherries are well known to be a rich source of (poly)phenols, especially anthocyanins, with exhibited antioxidant and anti-inflammatory properties. The aim of this review is to describe the effects of cherry extract observed in clinical trials and the respective tolerability indications, highlighting the differences in efficacy depending on the type of extract, cherry, formulation, and dosage used. In particular, the supplementation of standardized tart cherry extracts has been shown to improve different markers of human health, exercise performance, and quality of sleep. Most clinical studies conducted to date have reported the total (poly)phenol and anthocyanin doses administered that were contained in cherry extracts, which ranged from 143 to 2140 mg/day and 15 to 547 mg/day, respectively, as well as the duration of treatments, which ranged from acute supplementation to 84 days. Although cherry extracts are currently prescribed as dietary supplements in several areas of medicine, further investigations of the mechanisms of action and long-term randomized clinical trials (RCTs) are required in order to validate the efficacy and safety of clinical applications. In addition, a real challenge for the next few years is the standardization of cherry's (poly)phenolic fractions. In this context, the optimization of the extraction procedure and downstream processing represents a key point in reliable active guiding principles for the formulation of food supplements. In fact, due to the different extraction methods of cherries, the relative efficacy is closely related to the specific (poly)phenol profile obtained, which cannot be extrapolated from the literature. Future research should include an analysis reporting the total (poly)phenol content and the specific analytical methods used to quantify total and individual anthocyanin contents.

Keywords: tart cherry; anthocyanins; nutraceutical; exercise recovery; cardiovascular prevention; dietary supplement



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1. Introduction

Cherries are part of the *Prunus* species and more than one hundred cherry cultivars in the world are known, despite them being commonly grouped into two main types: the sweet cherries (*Prunus avium* L.) and the tart cherries (*Prunus cerasus* L.). The sweet cherry, belonging to the *Rosaceae* family, a *Prunus* genre, and *Avium* subgenre, is one of the most appreciated fruits worldwide. Its largest producer is Turkey, followed by the United

States of America, Iran, and Italy. The most commonly cultivated sweet cherry cultivar in the United States is Bing, while the one most used for the preparation of desserts is the Montmorency variety [1]. Tart cherries are widely cultivated in the Balkans and in other areas of Central-Western Europe [2]. Both sweet and tart cherries are very nutritious fruits and have numerous health benefits, deriving mainly from high levels of phytochemicals (Table 1). These fruits are particularly rich in numerous phenolic compounds, which have a very positive and beneficial bioactivity as demonstrated by different clinical trials [3,4]. Despite sweet cherries containing 4 g more sugar (per 100 g of product) and half as much folates, as well as being 20 times less rich in vitamin A in comparison with tart cherries, the content of (poly)phenols and, in particular, anthocyanidins, flavan-3-ols, and flavonols is quite similar [5]. Nevertheless, many factors can impact on the final composition of the cherry phytochemical complex, including the stadium of ripening, portion of fruit, storage, and other factors which contribute to the (poly)phenolic concentration and the phytochemical composition of cherries. In particular, dry extracts of cherries may differ from their composition in phenolic compounds, depending on the variability of several aspects from the cultivation of the plant to the extraction and production techniques [6]. In this context, the use of standardized and titrated cherry extracts has made it possible to significantly reduce the physiological variability of the composition of the extract due to the plant (moisture content, plant origin, method and time of harvest), extraction (extraction method, type of solvent, solvent concentration), and production processes (batch size, extraction speed).

Table 1. Comparison of major nutrients, vitamins, and phenolic compounds between tart cherries and sweet cherries (modified from Sabou et al. [5]).

	Per 100 g	Sweet Cherry	Tart Cherry
Energy ^a	Kcal	63	50
Water ^a	g	82	86
Protein ^a	g	1.06	1.00
Total lipid (fat) ^a	g	0.20	0.30
Carbohydrate ^a	g	16.0	12.2
Fiber, total dietary ^a	g	2.10	1.60
Mono and disaccharides ^a	g	12.82	8.49
Fatty acids, total saturated ^a	g	0.04	0.01
Potassium, K ^a	mg	222	173
Vitamin C, total ascorbic acid ^a	mg	7	10
Thiamin, B1 ^a	mg	0.03	0.03
Riboflavin, B2 ^a	mg	0.03	0.04
Niacin, B3 ^a	mg	0.15	0.40
Pantothenic acid, B5 ^a	mg	0.20	0.14
Vitamin B6 ^a	mg	0.05	0.04
Folate ^a	µg	4.0	8.0
Choline ^a	mg	6.1	6.1
Carotene, beta ^a	µg	38	770
Vitamin A ^a	IU	64.0	1283.0
Lutein + zeaxanthin ^a	µg	85.0	85.0
Vitamin E (alpha-tocopherol) ^a	mg	0.07	0.07
Vitamin K (phylloquinone) ^a	µg	2.1	2.1

Table 1. *Cont.*

	Per 100 g	Sweet Cherry	Tart Cherry
Anthocyanidins, cyanidin ^b	mg	30.21	32.57
Anthocyanidins, peonidin ^b	mg	1.50	0.87
Flavan-3-ols, (–)-epicatechin ^b	mg	5.00	3.83
Flavan-3-ols, (+)-catechin ^b	mg	4.36	0.30
Flavonols, isorhamnetin ^b	mg	0.05	0.72
Flavonols, kaempferol ^b	mg	0.24	0.24
Flavonols, myricetin ^b	mg	0.05	0.00
Flavonols, quercetin ^b	mg	2.29	1.47

^a based on 100 g of fresh weight, ^b based on 100 g of edible weight.

Among the (poly)phenols present in cherries, at least 24 anthocyanins, 12 phenolic acids, 17 flavanols, and 18 flavones have been identified, which collectively represent approximately 352 mg of total (poly)phenols per 100 g of fresh weight (fw) [7]. Despite the fact that anthocyanins from cherries have received the highest interest from research groups to date (especially cyanidin-3-glucoside, cyanidin-3-glucosylrutinoside, cyanidin-3-rhamnoglucoside, cyanidin-3-sophorose, peonidin-3-glucoside, and peonidin-3-rutinoside), it is possible that the entire phytochemical complex and the various (poly)phenols present in this fruit may act synergistically in modulating various molecular pathways [8]. Several randomized clinical trials (RCTs) have suggested the beneficial properties of (poly)phenol extracts of cherries, demonstrating a reduction in muscle damage commonly associated with prolonged physical effort [9,10] and improving sleep quality [11]. Moreover, cherry extracts proved to be potentially useful in cardiovascular prevention, improving arterial stiffness, and reducing the serum levels of uric acid and biomarkers of inflammation and oxidative stress [12,13].

However, the Achilles' heel regarding most of the (poly)phenols is its reduced bioavailability caused by extensive first-pass gut microbiota metabolism. In fact, the collection of microbes living in the intestine modifies and/or degrades (poly)phenols into metabolites, which exhibit a different bioaccessibility and may become available (or not) to the host [14]. In this regard, there is still little knowledge on how the gut microbiota influence the bioavailability of cherry (poly)phenols and vice versa. Further, the strong individuality in human gut microbiota profiles and microbiome functions arguably leads to different metabolome profiles [15,16].

The aim of this review is to describe the effects of cherry extract observed in clinical studies and the respective tolerability notes, highlighting the differences in effectiveness relating to the type of extract, cherry, formulation, and dosages used.

2. Materials and Methods

A systematic search strategy was conducted for this review in order to identify trials in both the Cochrane Register of Controlled Trials (The Cochrane Collaboration, Oxford, UK) and MEDLINE (National Library of Medicine, Bethesda, Maryland, MD, USA; January 1970 to February 2025). The terms 'tart cherries', 'sweet cherries', 'cherry concentrate', 'dietary supplement', 'functional food', 'clinical trial', and 'human' were incorporated into an electronic search strategy.

Eligibility criteria for article inclusion were determined as follows: (1) all studies underwent initial screening based on their title and abstract, and (2) articles that passed this initial step were further evaluated through a thorough review of the full manuscript. Only

articles published in English were included in the review. No restriction concerning the publication year of the articles was applied. No exclusions were made based on ethnicity.

After a general introduction with an overview on the composition of cherries, a specific paragraph regarding the pharmacodynamic and pharmacokinetic profile of (poly)phenols from cherries was included, followed by specific sections for each potential therapeutic indication reporting a short description of the mechanism of action, the clinically observed effects, and the most relevant tolerability notes. The authors of the writing and reviewing panels completed Declaration of Interest forms where real or potential sources of conflicts of interest might be perceived.

3. Pharmacokinetics and Pharmacodynamics of (Poly)phenols from Cherries

The phytochemical complex of cherries is particularly rich in anthocyanins and other phenolic compounds (chlorogenic acid, protocatechuic acid, and vanillic acid). In addition, cherries contain kaempferol, quercetin, melatonin, hydroxycinnamic acids, vitamins C, A, and E, alpha-linolenic acid, beta-carotene, folic acid, thiamine, potassium, phosphorus, and calcium, which may contribute to health effects [17]. As highlighted in the introduction section, the concentration of the secondary metabolites in cherry extract can differ considerably depending on several factors such as the cherry variety (e.g., despite the fact that Balaton and Montmorency tart cherries contain the same anthocyanins, its concentration is approximately 6 times higher in the Balaton variety; however, Montmorency tart cherries contain about 13 ng/g of melatonin compared with 2 ng/g for the Balaton variety [18,19]), pedo-geo-climatic conditions, harvesting methods, collection times, and extraction and production techniques [6].

Despite (poly)phenol supplementation from cherries demonstrating the prevention of the risk of developing different diseases and risk factors, it is well known that this category of molecules may present problems of bioaccessibility and bioavailability caused by its high molecular size and gut microbiota metabolism [20]. In particular, after oral administration, (poly)phenols from cherries are subject to fermentation, modification, and degradation by the microbiota [21]. Several studies with distinct methodological approaches have been performed to assess the bioaccessibility and bioavailability of sweet cherry compounds, demonstrating that they circulate in the human blood as intact or metabolized conjugates [22]. Martini et al. showed a remarkable reduction in gut bioaccessibility of total and individual phenolic compounds after the digestion process (only 39.7% and 29.9% of total phenolic compounds were bioaccessible) [23]. Clinical pharmacokinetic studies with foods rich in anthocyanins are typically limited in its time course, with plasma and urine collected within six hours of consumption. Some preliminary investigation shows that protocatechuic acid and vanillic acid reach peak levels in the plasma 1–2 h after ingestion of tart cherries, with trace amounts detectable 8 h after ingestion [24]. The maximum serum concentration for cyanidin metabolites is between 2 and 4 h [25]. (Poly)phenols from tart cherry not initially absorbed in the first tract of the intestine will reach the colon and may be further metabolized by gut microbiota. The secondary metabolites generated by this microbial metabolism may then be absorbed by colon enterocytes and taken into systemic circulation. In addition, phytochemicals absorbed in the small intestine are metabolized by the liver and then released back into the small intestine through biliary excretion, making a second pass through the gastrointestinal tract [25]. Enterohepatic metabolism therefore predicts that the absorption of phytochemicals and their metabolites are not limited to a few hours after intake. Both unmodified anthocyanins and anthocyanin metabolites are found in the urine after consumption of whole tart cherries.

The gut microbiota is able to degrade anthocyanins (cyanidin-glycosylrutinoside), flavonoids (quercetin-rutinoside), and chlorogenic and neochlorogenic acids contained in

cherries mainly to 4-hydroxyphenylpropionic acids, epicatechin, and 4-hydroxybenzoic acids. Moreover, cherry (poly)phenols showed a prebiotic action by the modulation of levels of *Bacteroides*, *Lactobacillus*, and *Bifidobacterium* spp. [26]. In particular, a metabolomic study revealed two different responses after tart cherry consumption: high-*Bacteroides* people responded with a decrease in *Bacteroides* and *Bifidobacterium*, and an increase in *Lachnospiraceae*, *Ruminococcus*, and *Collinsella*, while low-*Bacteroides* individuals responded with an increase in *Bacteroides* or *Prevotella* and *Bifidobacterium*, and a decrease in *Lachnospiraceae*, *Ruminococcus*, and *Collinsella* [26]. The potential existence of different kinds of metabotypes may suggest the use of cherry extracts in the specific modulation of microbial populations of the gut.

The phenolic compounds in both sweet and tart cherries exhibit a range of biological activities with promising therapeutic potential. These compounds, including anthocyanins and non-colored phenolics, contribute significantly to the cherry's anti-inflammatory and antioxidant properties, which may be utilized for treating various conditions and diseases [27]. In particular, cherry phenolics may significantly reduce inflammation, primarily by inhibiting the expression of pro-inflammatory enzymes such as inducible nitric oxide synthase (iNOS) and cyclooxygenase-2 (COX-2). The phenolic extracts, when tested on RAW 264.7 macrophages stimulated with lipopolysaccharide (LPS), displayed concentration-dependent reductions in nitric oxide (NO) production [28]. This reduction occurs due to the ability of the phenolic compounds to scavenge NO radicals and modulate inflammatory pathways like nuclear factor-kappa B (NF- κ B), which plays a central role in the production of pro-inflammatory cytokines and enzymes. The phenolic compounds in cherries provide significant protection against oxidative stress, a major contributor to cardiovascular and neurodegenerative diseases. In various cell models, including AGS and SH-SY5Y cells, cherry extracts protected against oxidative damage induced by agents like tert-butyl hydroperoxide (t-BHP), hydrogen peroxide (H₂O₂), and glutamate. Moreover, the antioxidant activity seems to be linked to the ability of the phenolic compounds to scavenge reactive oxygen species (ROS) and mitigate cellular damage [28].

4. Results

This review focuses on the main potential evidence-based uses of cherry extracts in the treatment of cardiovascular prevention, sleep disorders, and sport activities.

4.1. Cherry Extracts and Cardiovascular Risk Factors

As stated above, cherry extracts may find a role in the management of some highly prevalent cardiovascular and cerebrovascular risk factors, such as hyperuricemia, high blood pressure, insulin resistance, and dyslipidemia.

4.1.1. High Blood Pressure

Hypertension is one of the major causes of morbidity and mortality worldwide, with a global prevalence of 31% of all adults (about 1.39 billion people) in 2010 [29]. Cherry (poly)phenols seem to exert a direct effect on the endothelium, determining vasodilation and lowering blood pressure [30]; this effect is bound to its ability to improve the bioavailability of nitric oxides and to induce vasodilatation, especially in patients with hypertension [31,32]. In a single-blind, randomized, placebo-controlled study, supplementation with 200 mL of cherry drink (juice supplemented with dark sweet cherry powder) or a placebo drink twice/day for 30 days, in 40 obese participants (>18 years, male and female), was demonstrated to decrease systolic blood pressure (SBP) ($p = 0.05$) and diastolic blood pressure (DBP) compared to placebo ($p = 0.04$), with a greater ($p = 0.008$) SBP reduction in subjects with body mass index (BMI) > 35. Moreover, the nutraceutical group lowered

pro-inflammatory interferon-gamma (IFN γ) ($p = 0.001$) [31]. This result is in agreement with the one obtained by Kent and colleagues, which performed a pilot cross-over study that demonstrated a significant reduction in blood pressure and heart rate acutely, after 2 h of consumption of anthocyanin-rich cherry juice (300 mL) in young (mean age, 21.8 ± 0.97 ; BMI, 26.3 ± 4.2) and older adults (mean age, 77.5 ± 6.2 ; BMI, 28.6 ± 3.8) [33]. Similar results were obtained in an RCT in which fifteen men (age 31 ± 9) with early hypertension received either a 60 mL dose of tart cherry concentrate or placebo. Tart cherry concentrate was demonstrated to reduce SBP (peak reductions in mean of -7 ± 3 mmHg, 2 h after cherry consumption; $p < 0.05$) and improve the arterial stiffness ($p < 0.05$) [30].

Other studies demonstrated that cherry extracts (280 g/day) supplemented for 28 days lowered circulating concentrations of pro-inflammatory markers such as C-reactive protein (CRP) and interleukin (IL)-18 in healthy individuals (45–61 years older) [34,35].

Finally, Chai et al. reported a reduction in SBP of 4 mmHg in older subjects (17 men and 20 women, age: 65–80 years) who consumed tart cherry juice (480 mL/day, with a content of 450 mg gallic acid equivalent/mL) for 12 weeks [13].

4.1.2. High Serum Uric Acid

Hyperuricemia is a highly prevalent condition affecting approximately 3.9% of the US population, causing gouty arthritis, where uric acid crystallizes in the joints and results in pain and stiffness in the affected areas [36]. Individuals with gout have a higher risk of metabolic syndrome, because both conditions have underlying oxidative stress and inflammation [37,38].

In a meta-analysis of six studies and 945 subjects, a positive correlation between tart cherry consumption and a decrease in uric acid concentrations was observed [39]. Zhang et al. reported that after the ingestion of cherry extracts for a period of two days, there was a significant decrease in the risk of gout attacks, even in combination with allopurinol [40]. This result was in agreement with the one obtained by Martin and Coles who reported significant reductions in plasma urate levels following the ingestion of tart cherry juice for 4 weeks in overweight and obese participants (18 women and 8 men, age: 41 ± 11 years) [41]. Even Schlesinger et al. observed a slightly but not significant decrease in plasma urate levels after the administration of cherry juice, despite being considered less pronounced compared with the consumption of pomegranate juice [42]. In general, the reduction in urate levels was even observed acutely, already after 2–5 h of treatment with cherry juice, highlighting the rapid intestinal absorption of cherry (poly)phenols [43,44]. Jacob et al. showed a reduction in plasma urate levels from 214 micromol/L at baseline to 183 micromol/L at 5 h post consumption; in addition, urinary urate levels increased from 202 at baseline to a peak excretion of 350 micromol/mmol of creatinine 3 h post consumption of cherry (poly)phenols [44].

Data produced to date indicate that a single dose of tart cherry juice may be not enough to avoid the rise in uric acid levels at 24 and 48 h, suggesting that the twice-per-day approach is more appropriate and highlighting the importance of chronic supplementation for mildly or moderately hyperuricemic people [43]. In addition, powdered tart cherry supplements (containing at least 480 mg of cherry dry extract per day) seem to be equally effective for lowering uric acid compared with 30–60 mL of cherry juice concentrate and therefore may be used by those who do not enjoy the taste of tart cherry juices [39,45]. However, there was no significant change over time in hsCRP or plasma oxygen radical absorbance capacity (ORAC) after cherry extract supplementation [45].

Contrary to what was reported by the aforementioned studies, Schumacher et al. performed a randomized clinical study including 58 nondiabetic patients (56.7 ± 11.3 years, 44 men, 14 women) with Kellgren grade 2–3 knee osteoarthritis treated with cherry juice

(237 mL b.i.d. for six weeks) or placebo, which did not find improvements in uric acid levels despite there being a significant reduction in the Western Ontario McMaster Osteoarthritis Index (WOMAC) ($p < 0.01$) compared with baseline [46].

An ongoing long-term RCT, performed in adults aged 18 to 80 years with an existing clinical diagnosis of gout, with a duration of 12 months, will investigate the effects of cherry (poly)phenols on the frequency of gout flares from baseline to 12 months, gout flare pain, serum urate concentration, the fractional excretion of uric acid, blood lipids and recognized markers of inflammation (CRP, interleukin-6, TNF- α), oxidative stress, and vascular function (BP, arterial stiffness). The intervention group will receive a daily supplement of tart cherry juice (870 mg of phenolics and 14 mg of anthocyanins) and the placebo group will receive a cherry-flavored drink [47].

4.1.3. Insulin Resistance and Overweight

Overweight and obesity are spreading around the world and are strictly related to insulin resistance [48]. Data regarding the effects of cherry (poly)phenols on the glycometabolic profile are still unclear and, in part, contrasting. In a meta-analysis of ten RCTs (272 people), tart cherry juice consumption led to a significant reduction in fasting blood sugar levels (WMD = -0.51 mg/dL [95% CI: -0.98 , -0.06]). This lowering effect of fasting plasma glucose (FPG) was robust in subgroups with cross-over studies, participants with age range ≥ 40 , duration of follow-up ≤ 4 weeks, and baseline BMI ≥ 30 [49]. However, tart cherry consumption showed no significant effects on body weight (BW), body mass index (BMI), waist circumference (WC), fat mass (FM), fat-free mass (FFM), and percentage body fat (PBF), as highlighted by a recent meta-analysis of six trials that enrolled 126 subjects [50].

In general, 480 mL of tart cherry juice provides approximately 181 kcal of energy and 34 g of sugar. Despite these amounts of energy and sugar being lower when compared with other consumed fruit juices and soft drinks in the United States and Europe [51], the use of sugar-free dry extracts should be preferable in these cohorts of subjects.

4.1.4. Systemic Inflammation and Oxidative Stress

Nuclear factor- κ B (NF- κ B) is a family of transcription factors that are involved with inflammation, proliferation, differentiation, and cell survival [52]. Inflammation is considered a main process involved in atherosclerosis development and vascular lesions [53,54].

Cyanidin-3-glucoside and quercetin from cherries were shown to act by reducing the formation of ROS, inhibiting the activity of nicotinamide adenine dinucleotide phosphate (NADPH) oxidase (NOX), xanthine oxidase, cyclooxygenase (COX), and lipoxygenase (LOX). Moreover, it was demonstrated to reduce levels of IL-1 β , IL-6, and TNF- α , which are inflammatory mediators produced in response to pathogenic stimuli that affect the transcription of the NF- κ B gene [55].

Jung and colleagues showed that cyanidin-3-glucoside and cyanidin-3-rutinoside downregulate NF- κ B expressions against H₂O₂-induced oxidative stress and LPS-induced inflammation using RAW 264.7 murine macrophage cells [56]. In addition, cyanidin-3-glucoside may also reduce the lipopolysaccharide (LPS)-induced pro-inflammatory cytokines in fibroblast-like synoviocytes, and could inhibit MAPK activation, which could induce a significant reduction in the production of TNF- α , IL-1 β , and IL-6 [57]. This reduction in pro-inflammatory cytokines might also be due to the effects of cherries on the intestinal microbiota as reported in a single-blind, placebo-controlled study that primarily aimed to examine the effects of dark sweet cherry (DSC) consumption on obesity-related dysbiosis. Participants (N = 40, aged >18 years, BMI: 30–40 kg/m²) consumed either 200 mL of DSC juice supplemented with 3 g of DSC powder or placebo beverage twice daily for 30 days. At the end of the treatment, the results indicated that DSC supplemen-

tation reduced the abundance of *Anaerostipes hadrus* ($p = 0.02$) and *Blautia* ($p = 0.04$), with these changes being particularly significant in participants with a BMI ≥ 35 ($p = 0.004$ and $p = 0.006$, respectively). Additionally, DSC intake prevented an increase in *Alistipes shahii* ($p = 0.005$) and *Bilophila* ($p = 0.01$) compared to the placebo group. Notably, DSC consumption promoted the growth of beneficial gut bacteria, including *Roseburia intestinalis* ($p = 0.01$), *Turicibacter* ($p = 0.01$), and *Bacteroides vulgatus* ($p = 0.003$), as well as *Clostridium leptum* ($p = 0.03$), compared with placebo [58].

In an RCT including 37 people between the ages of 65 and 80, supplementation with 480 mL of tart cherry juice, for 12 weeks, significantly increased the plasma levels of DNA repair activity of 8-oxoguanine glycosylase ($p < 0.0001$) and lowered ($p = 0.03$) the mean C-reactive protein (CRP) level compared with the placebo group. Moreover, there was a significant effect observed for malondialdehyde (MDA) ($p = 0.03$), and a borderline effect observed for plasma-oxidized low-density lipoprotein (OxLDL) ($p = 0.07$) [59]. Similar results were obtained after consuming 480 mL of tart cherry juice for 6 weeks in people with mild to moderate osteoarthritis [46]. In another study, the consumption of 240 mL of tart cherry or placebo juice twice daily for 14 days, in older adults with ischemic reperfusion, lowered the urinary levels of 8-hydroxy-2'-deoxyguanosine and 8-hydroxyguanosine, biomarkers of oxidative stress (in comparison with the placebo group) [60]. Finally, the pilot study by Martin and colleagues showed that 240 mL of tart cherry juice consumption, for 4 weeks, in 10 overweight and obese adults, significantly decreased pro-inflammatory monocyte chemoattractant protein 1 (MCP-1) compared with the placebo group, without affecting CRP levels [51]. Despite some evidence suggesting that tart cherry supplementation may moderate the glycemic response to a meal and impact certain inflammatory cytokines [61], larger and longer research studies are needed to confirm these preliminary findings.

4.2. Sports

Tart cherry extracts have been shown to improve muscle function and reduce muscle damage, oxidative stress/inflammation, and muscle soreness in athletes (Figure 1). The effects of cherry extracts in strength training, aerobic exercise, marathon running, cycling, and water sports are described below.

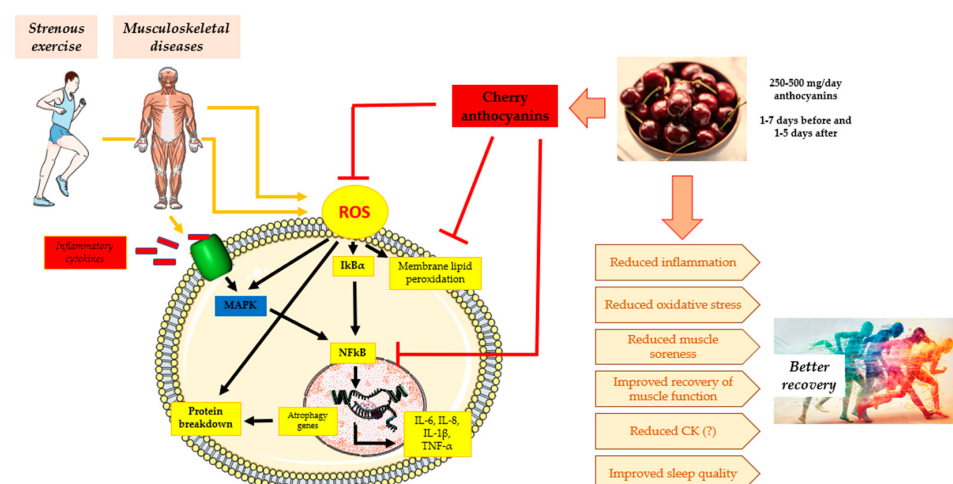


Figure 1. The impact of strenuous exercise and skeletal muscle diseases on the increase in ROS, IκBα, and MAPK signaling. ROS and both IκBα and MAPK activate the expression of NF-κB, which stimulate several pro-inflammatory cytokines and atrophy genes. This phenomenon results in protein breakdown, which may have a negative impact on the health of skeletal muscle and sport performance/recovery. In this regard, the anthocyanins from cherry extracts can attenuate the negative

inflammatory consequences by decreasing the production of ROS, decreasing lipid peroxidation, and inhibiting NF- κ B. Abbreviations: I κ B α , protein kappa B alpha; IL, interleukin; MAPK, mitogen-activated protein kinase; NF- κ B, nuclear expression of factor nuclear kappa B; ROS, reactive oxygen species; TNF- α , tumor necrosis factor alpha. (Red lines means inhibition).

4.2.1. Strength Training

Skeletal muscle hypertrophy is generally hampered by inflammation and oxidative stress phenomena. Moreover, the senescence and aging process may alter the function of skeletal muscle and contribute to anabolic resistance to protein consumption [62]. In this context, the study conducted in 2006 by Connolly et al. was the first investigation on humans regarding the effect of cherry juice on physical exercise. This RCT included 14 male college students which were treated with 350 mL of cherry juice or placebo for 8 days. On the fourth day of supplementation, subjects performed muscle-damaging eccentric elbow flexion exercises (2×20 maximum contractions); the group treated with cherry juice benefited from a strength loss of 4% compared to 22% for the placebo. In addition, the perception of pain was significantly lower in the active group ($p = 0.017$) [9].

Several studies were subsequently conducted to investigate the potential benefit of cherry extracts on strength training. In 2011, Bowtell and colleagues investigated the effects of tart cherry juice consumption (30 mL b.i.d. for 10 days) on exercise-induced muscle damage after intensive unilateral leg exercises through an experimental cross-over fashion, showing that the consumption of the cherry juice produced a faster recovery of strength 24 h and 48 h post exercise ($p = 0.04$ compared with placebo) [63]. However, data regarding the influence of cherry supplementation on the muscular adaptations and post-exercise inflammatory response are still partially contrasting. Jackman et al., in an RCT which included 16 older men, reported that the consumption of cherry juice did not promote an added benefit compared with the placebo group in terms of an increased rate of myofibrillar protein synthesis [64]. Nevertheless, the total amount of intramuscular nuclear factor kappa light-chain-enhancer of activated B cells (NF κ B: a transcription factor that encodes the expression of genes related to atrophy and apoptosis) protein was decreased with cherry supplementation compared with placebo [64].

In another study, 13 healthy participants completed an incremental cycle exercise test to exhaustion (TTE) under two conditions: hypoxia (13% O₂) with placebo and hypoxia with tart cherries (200 mg of anthocyanin per day for 4 days and 100 mg on day 5). At the end of the treatment, anthocyanins from cherry were demonstrated to improve the hypoxic exercise tolerance probably through the reduction in deoxygenated hemoglobin (HHb) and increase in the tissue oxygen saturation (StO₂) [65].

The study by Levers et al., which involved strength-trained men treated with 480 mg/day of powdered cherry and placebo, for ten days prior to 48 h after performing high-volume lower limb exercises (squats of 10 sets of 10 repetitions at 70% of one-repetition maximum with a recovery of 3 min between sets), found that the levels of creatine kinase (CK) were attenuated over time even if the cherry group did not reach statistical significance compared to placebo ($p = 0.10$) [66]. Similar results were obtained in triathletes [67]. It is important to emphasize that, despite CK levels being traditionally used as a marker of muscle damage, post-exercise CK variability correlates poorly with measures of muscle soreness [68]. For this reason, the practical implications regarding the supplementation of cherry extracts on the regulation of CK levels must be interpreted cautiously. Further and larger clinical trials are urgently needed in order to better understand the efficacy of cherry extract supplementation on the post-exercise inflammatory response as well as on exercise-induced muscle damage.

4.2.2. Aerobic Exercises and Marathons

Cherries' (poly)phenols have been proposed as a dietary approach to reduce the aerobic exercise-induced oxidative stress which may generate excessive amounts of reactive oxygen species and the oxidation of proteins and lipids, leading to mitochondrial damage and a reduced hypertrophic response [69]. According to this concept, the supplementation of 237 mL of cherry juice 5 days before, on the day of, and 2 days after a marathon race in 20 marathon runners (37 ± 13 years) was shown to significantly increase the total antioxidant status, reduce the lipid peroxidation (evaluated through the concentration of thiobarbituric acid reactive species (TBARS)), attenuate the IL-6 levels and CRP, and improve the isometric knee extensor strength compared with placebo [70]. However, cherry juice did not significantly reduce biomarkers of muscle damage expressed as creatine kinase and lactate dehydrogenase. Similar results were also obtained using 480 mg/day of powdered tart cherry extract from 10 days before the competition. In this regard, 27 endurance-trained runners and triathletes, with scheduled half-marathon runs, benefited from a general improvement in race finish times (-13% , $p < 0.001$ compared to placebo); a general attenuation of the levels of creatinine, urea/blood urea nitrogen, and cortisol; and an improvement in soreness perception in comparison with the placebo group ($p = 0.035$) [67]. In addition, consumption of 236 mL b.i.d. of freshly pressed cherry juice attenuated the levels of CRP 24 and 48 h post marathon ($p < 0.01$ and $p < 0.01$, respectively, compared with control) and significantly reduced the risk of upper respiratory tract symptoms ($p < 0.05$ versus placebo) [71]. In a study which included people with scheduled London Marathon runs, the consumption of 237 mL five days prior to the competition was shown to attenuate the increase in CK levels (immediately post race, 590 U/L cherry group vs. 910 U/L placebo group; one day after the run, 2230 U/L vs. 2810 U/L) [70]. Preliminary data are available on the efficacy of cherry juice in reducing post-aerobic exercise muscle pain. A total of 54 people who ran for 26.3 km were randomly predisposed to consume 335 mL b.i.d. of cherry juice or placebo for the 7 days before the competition. After the competition, the cherry juice group reported a significantly smaller sensation of pain and a greater satisfaction in pain reduction in comparison with placebo ($p < 0.001$ for all) [72].

4.2.3. Water Sports

McCormick et al. conducted an RCT including nine water polo athletes treated with 90 mL/day of cherry juice concentrate or placebo for 6 days. No differences in performance, recovery, and inflammatory serum markers (IL-6, CRP, uric acid, and F2-Isoprostan) were observed between the two groups [73]. This result may be partially explained because there is a mismatch between the exercise-induced muscle damage by water in comparison with land-based sports; in fact, aquatic protocols can attenuate the degradation of myocytes [74].

4.2.4. Cycling

Cherry extracts might also be used to enhance cycling performance. The acute consumption of 30 mL of tart cherry juice in 10 cyclists which performed, 1.5 h after the ingestion of the supplement, 6 minutes of moderate- and severe-intensity cycling was shown to improve the performance measured as the total work completed during the 60 s all-out sprint (21 vs. 19 kJ) and the peak power over the first 20 s (363 vs. 330 W) ($p < 0.05$ for both), even if no differences were reported in terms of time to exhaustion ($p > 0.05$ compared with control) [32]. Morgan et al. reported that the consumption of cherry powder (257 mg/d of anthocyanin), in eight cyclists, for 1 week, resulted in a significant ergogenic effect, improving the completion of the faster time trial (-4.6%) compared with the control (physical exercise: 10 min of steady-state cycling at $65\% \text{VO}_{2\text{peak}}$ followed by a 15 km time trial) [75]. In 16 cyclists, 30 mL/day of tart cherry juice may also contribute

to attenuating levels of IL-6, high-sensitivity C-reactive protein (hs-CRP), and lipid hydroperoxide (LOOH) [76]. However, the study by Gao et al. enrolled 12 recreational cyclists treated with cherry juice or sports drink twice a day (300 mL/d) for 4 days before and 2 days after exercise, and reported no differences in performance improvement, substrate oxidation during exercise, and recovery from exercise, compared to a high-glycemic-index sports drink [77].

4.2.5. Sleep Disorders

Poor sleep and/or sleep deprivation are certainly associated with a worsening of physical performance [78]. In this context, an arsenal of supplements has been proposed to improve sleep in athletes [79], and cherries are well known to physiologically contain melatonin, which physiologically regulates sleep and the sleep–wake rhythm [79]. Different studies showed that a cherry-enriched diet ameliorates sleep quality, increasing the concentrations of pro-somnogenic cytokines (IL-1 β , tumor necrosis factor- α (TNF- α), and IL-8), urinary 6 sulfatoxymelatonin (aMT6-s), and the antioxidant status in humans [80]. Moreover, cherry juice supplemented with procyanidin B-2 increased sleep time and sleep efficiency (measured with polysomnography and the Pittsburgh Sleep Quality Index), probably through the inhibition of indoleamine 2,3-dioxygenase (IDO), the increase in tryptophan availability, and the reduction in inflammation (prostaglandin E-2) [81].

In an RCT where 20 volunteers consumed either a placebo or tart cherry juice concentrate for 7 days, the total melatonin content was significantly elevated ($p < 0.05$) in the cherry juice group, whilst no differences were shown between baseline and placebo trials. In addition, there were significant increases in time in bed, total sleep time, and total sleep efficiency ($p < 0.05$) with cherry juice supplementation [82]. Similar results were observed by Pigeon et al. and Losso et al., which highlighted sleep improvements after the consumption of 235 mL and 240 mL (taken twice daily) of cherry juice, respectively [81,83]. These effects were also observed in elderly populations, which are often affected by sleep disorders [84,85].

5. Discussion

Evidence from the scientific literature is quite promising and suggests that cherry extract ingestion reduces markers of inflammation, exercise-induced muscle soreness, oxidative stress, loss of strength, and blood pressure. Few studies also report the beneficial effects of cherry extract/juice supplementation on arthritis, diabetes, sleep, cognitive functions, and possibly mood (Tables 2 and 3) [17]. In general, 30 mL of Montmorency tart cherry juice concentrate corresponds to 102 kcal, 24/26 g of carbohydrates, and 9.117 mg/mL of anthocyanins, equivalent to 90–110 tart cherries [73]. Despite the fact that juice concentrate can be diluted in water to improve the palatability of the functional beverage, and its sugar content helps increase muscle glycogen storage in aerobic sports, contributing to the improvement in exercise performance [17], this aspect may represent a limiting factor for people with altered glucometabolic profiles or in clinical populations. In addition, the use of non-standardized juices may not guarantee the repeatability of the desired effects, due to the variability in the (poly)phenolic active ingredients contained within. Only with the use of titrated and standardized cherry extracts is it possible to always make the same qualitative–quantitative formula. Standardizing means defining the specifications of the extract to make it as repeatable as possible (plant species, part of the plant used, place and period of collection, extraction solvent used, form of the extract (solid, semi-solid, liquid), extraction method, DER (drug/extract ratio), markers for titration). In this context, the use of powdered tart cherries, deprived of sugars, particularly in clinical populations, may be interesting in order to standardize the effects and potentially

modulate the glucometabolic profile [45]. In general, the health benefits obtained with powdered cherry extracts included a total (poly)phenol content of 300–600 mg/day and a total anthocyanin content of 250–500 mg/day [75], which is equivalent to an intake of 200/300 g of tart cherries and sweet cherries, respectively [86]. On the other hand, cherry juice supplementation may be implemented as a nutritional pattern to load muscle glycogen stores within the pre-/post-window during prolonged exercise. Cherry juice contains both glucose and fructose in percentages of 59% and 41%, respectively [87], avoiding the saturation of carbohydrate transporters and thus enhancing carbohydrate utilization during exercise [88].

Table 2. Cherry extracts: clinical applications beyond sports.

Condition	Level of Evidence	Duration of Treatments	Active Daily Doses	Effects on Symptoms and/or Grade of Disease	Effects on Lab or Instrumental Parameters
Hypertension	RCTs (adults, elderly)	1 day–12 weeks	60–480 mL of concentrated cherry juices or 280 g/day of lyophilized cherry extract	Not investigated	↓ SBP, DBP (?), low-grade inflammation (IFN-gamma, TNF-alpha, IL-6, IL-18, hsCRP), ↑ arterial stiffness (FMD and PWV)
High serum uric acid	Meta-analysis of RCTs (adults, elderly)	1 day–1 year	60–480 mL of concentrated cherry juices or 800–1000 mg of total (poly)phenols from cherry extracts	Not investigated	↓ serum urate concentration, frequency of gout flares, low-grade inflammation (IFN-gamma, TNF-alpha, IL-6, IL-18, hsCRP), ↑ arterial stiffness (FMD and PWV) and urinary excretion of uric acid, ↓ malondialdehyde and oxidative stress
Insulin resistance, metabolic syndrome (MetS)	RCTs (adults, elderly)	4–12 weeks	60–480 mL of concentrated cherry juices	Not investigated	↓ lipid peroxidation, FPG, and low-grade inflammation (TNF-alpha, IL-6, hsCRP), ↑ insulin sensitivity
Chronic inflammatory conditions (osteoarthritis)	RCTs (adults, elderly)	7 days–4 weeks	240–480 mL of concentrated cherry juices	Not investigated	↑ exercise capacity and arterial stiffness, ↓ lipid peroxidation, formation of ROS, and low-grade inflammation (TNF-alpha, IL-6, hsCRP), ↓ malondialdehyde and oxidative stress
Sleep disorders	RCTs (adults, elderly)	4–8 weeks	240–480 mL of concentrated cherry juices	Improvement in total sleep time, sleep efficiency, time in bed	↑ pro-somnogenic cytokines, urinary 6-sulfatoxymelatonin, and antioxidant status

DBP = diastolic blood pressure, FMD = flow-mediated dilatation, FPG = fasting plasma glucose, hsCRP = high-sensitivity C-reactive protein, IFN-gamma = interferon gamma, IL-6 = interleukin 6, PWV = pulse wave velocity, RCTs = randomized clinical trials, SBP = systolic blood pressure, TNF-alpha = tumor necrosis factor-alpha. (Down arrow means reduction, Arrow up means increase).

Table 3. Cherry extracts: clinical applications in sports.

Type of Sport	Level of Evidence	Duration of Treatments	Active Daily Doses	Effects on Recovery and/or Performance	Effects on Lab or Instrumental Parameters
Strength training	RCTs (adults)	4–8 days	60–480 mL of concentrated cherry juices or 200 mg/day of cherry anthocyanins	↑ recovery from eccentric contractions of the elbow flexors, single-leg knee extensions, lower body strength exercises, isokinetic concentric/eccentric contractions of the quadriceps	↓ low-grade inflammation (IFN-gamma, TNF-alpha, IL-6, IL-18, hsCRP) and CK (?)
Aerobic exercise	Meta-analysis of RCTs (adult marathon runners)	5 days before–2/4 days after	60–480 mL of concentrated cherry juices or 480 mg/day of cherry dry extract	↑ recovery from pain following long-distance/marathon running, intermittent running, intermittent sprinting protocol, professional rugby match, professional football match, endurance exercise performance, 15 km time-trial performance, muscle protein synthesis	↓ low-grade inflammation (IL-6, IL-18, hsCRP), ↓ malondialdehyde and oxidative stress, cortisol, creatinine

Table 3. Cont.

Type of Sport	Level of Evidence	Duration of Treatments	Active Daily Doses	Effects on Recovery and/or Performance	Effects on Lab or Instrumental Parameters
Cycling	RCTs (adult cyclist athletes)	1–6 days	30–480 mL of concentrated cherry juices or 257 mg/day of anthocyanins	↑ repeated days of high-intensity stochastic cycling, high-intensity cycling, faster time trial (VO _{2 peak})	↓ lipid peroxidation and low-grade inflammation (TNF-alpha, IL-6, hsCRP)
Water sports	RCTs (adult water polo athletes)	6 days	90 mL of concentrated cherry juices	↑ water polo-specific training	Unclear

CK = creatine kinase, hsCRP = high-sensitivity C-reactive protein, IFN-gamma = interferon gamma, IL-6 = interleukin 6, PWV = pulse wave velocity, RCTs = randomized clinical trials, TNF-alpha = tumor necrosis factor-alpha. (Down arrow means reduction, Arrow up means increase).

Regarding the type of cherry, the most studied is tart cherry; nevertheless, a similar phytochemical complex is present in sweet cherries. Despite the fact that sour cherry seems to contain a greater number of total (poly)phenols, the phytonutrients of sweet cherries might be considered quite similar to that of tart cherries and both types should be included and considered in a correct healthy plan [86].

Cherry extract supplementation benefits may be attributed not only to its (poly)phenolic content but also to the broader phytochemical complex, which includes bioactive compounds such as carotenoids, organic acids, and vitamins. For instance, cherries are rich in vitamins (such as vitamin C), carotenoids (such as beta-carotene), and essential fatty acids, which are not part of the (poly)phenol family but play significant roles in the overall health benefits of the fruit. Furthermore, the presence of organic acids like citric and malic acids, as well as various minerals, also adds to the complexity of the cherry's phytochemical complex [89]. These components likely work together synergistically, and more studies are necessary to determine how each of these molecules contributes to the extract's effects.

To date, larger and longer RCTs are needed in order to evaluate the effectiveness of cherry powder supplementation in different fields including cardiovascular prevention, skeletal muscle disorders, and exercise tests. The results derived from clinical trials testing the efficacy of cherry juices or extracts in different settings are often contrasting and make it difficult to derive definitive conclusions on its efficacy in several conditions. This could be summarized by a series of causes: the studies are often underpowered, the duration is too short to test effect on hard outcomes, the methodology applied is sometimes of low quality with a scarce standardization of patient characteristics at the baseline, the tested dosage is not always titrated in anthocyanins and/or total (poly)phenols, and there is usually no quantification of (poly)phenol intake with diet. Moreover, one of the most important problems about cherry (poly)phenols is their oral bioavailability/bioaccessibility, which is extremely variable in relation to many aspects: the type of formulation and the release method, the dosage of (poly)phenols, the mode of administration, and the impact of gut microbiota on its metabolism [21]. In this context, new pharmacokinetic studies and the evaluation of both the inter- and intra-variability of gut microbiota composition should be considered to analyze the final impact on the absorption, distribution, metabolism, and excretion of cherry (poly)phenols. Furthermore, cherry extracts exert many mild positive effects on different tissues and metabolism. They could be individually not so relevant from a quantitative point of view, but it is very difficult to quantify their impact as a whole on human health. In fact, the long-term contemporary reduction in systemic inflammation and oxidative stress, a mild reduction in blood pressure, and insulin resistance might have a positive impact on cardiovascular disease risk.

6. Conclusions

Clinical evidence supports the supplementation with cherry extracts rich in anthocyanins, which may be useful in adjuvating recovery in athletes and promoting short-term

ergogenic effects in different sport activities such as strength training, marathon running, and cycling. Moreover, the consumption of cherry extracts may attenuate pain and reduce levels of inflammatory biomarkers related to skeletal muscle breakdown. Finally, this nutraceutical could be useful in cardiovascular prevention, and, associated with conventional therapies, may contribute to the control of gout and arthritis.

Long-term RCTs with large numbers of patients are still needed to confirm and better understand the efficacy of cherry extracts in sports and whether cherries can play a role in alleviating human disorders.

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