



Possible Effects of Beetroot Supplementation on Physical Performance Through Metabolic, Neuroendocrine, and Antioxidant Mechanisms: A Narrative Review of the Literature

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Athletes often seek to use dietary supplements to increase performance during exercise. Among various supplements, much attention has been paid to beetroot in recent years. Beetroot is a source of carbohydrates, fiber, protein, minerals, and vitamins; also, it is a natural source of nitrate and associated with improved sports performance. Nitrates can the modification of skeletal muscle contractile proteins or calcium handling after translation. The time to reach the peak plasma nitrate is between 1 and 3 h after consumption of a single dose of nitrate. Nitrate is metabolized by conversion to nitrite and subsequently nitric oxide. Beetroot can have various effects on athletic performance through nitric oxide. Nitric oxide is an intracellular and extracellular messenger for regulating certain cellular functions and causes vasodilation of blood vessels and increases blood flow. Nitric oxide seems to be effective in improving athletic performance by increasing oxygen, glucose, and other nutrients for better muscle fueling. Nitric oxide plays the main role in anabolic hormones, modulates the release of several neurotransmitters and the major mediators of stress involved in the acute hypothalamic-pituitary-adrenal response to exercise. Beetroot is an important source of compounds such as ascorbic acid, carotenoids, phenolic acids, flavonoids, betaine, and highly active phenolics and has high antioxidant properties. Beetroot supplement provides an important source of dietary polyphenols and due to the many health benefits. Phytochemicals of Beetroot through signaling pathways inhibit inflammatory diseases. In this study, the mechanisms responsible for these effects were examined and the research in this regard was reviewed.

Keywords: beetroot supplement, resistance exercise, skeletal muscle, nitrate, O₂ cost, dietary supplements, endurance exercise

INTRODUCTION

In sports competitions, the winning margin is decreasing and, in some cases the results of competitions may change by a fraction of a second due to the performance of athletes. Therefore, athletes are constantly looking for every benefit to improve sport performance. Some athletes maybe resort to dietary supplements (natural and organic resources) to provide these benefits (1). Dietary supplements are a significant option for the elite and recreational athletes to enhance their performance (2). Athletes are exposed to a variety of food products marketed with the claim of improving health, efficiency, and performance. However, few studies confirm these claims, and the affection and safety of these products are questioned (3).

There are many dietary supplements, however in recent years; special attention has been paid to beetroot (BR) supplements. BR is a source of carbohydrates, fiber, protein, vitamins, and minerals (sodium, potassium, calcium, and iron) (as shown in **Table 1**) (4–8) and among other foods rich in nitrate (NO_3^-) including spinach, celery, lettuce, and carrot juice has high NO_3^- (<250 mg per 100 g of fresh BR) (9). NO_3^- can be converted to nitrite (NO_2^-) by bacteria in the oral cavity and by certain enzymes (e.g., xanthine oxidase) in the tissue (1) and, then the NO_2^- is swallowed, absorbed in the intestine and nitric oxide (NO) and other active nitrogen oxides are metabolized in the blood and tissues (10, 11) (as shown in **Figure 1**). NO_3^- is absorbed through plasma after consumption and its average half-life is 5 h. After absorption into the bloodstream, about 25% return to the salivary glands via active transfer and are concentrated in the saliva, with the remainder excreted by the kidneys (12–15). Daily doses of 4.1–16.8 mmol (~150 mg to 1 g) of NO_3^- consumed in 2–15 days enhance the level of NO_2^- in the blood (12–15). The Jones study showed that the typical mean used in the studies was 5–9 mmol (300–550 mg) (12); NO_3^- is usually taken between 1.5 and 3 h prior to training in a single dose up to 5 times a day (16–20). The time to reach the peak plasma NO_3^- is between 1 and 3 h after consumption of a single dose of NO_3^- (21).

There are several pathways for the metabolism of NO_2^- to NO and other nitrogen oxides biologically (22). NO is a signaling molecule formed by the endothelial enzyme NO synthase in the endothelium, which causes vasodilatation and increased blood flow (23, 24). NO increases blood flow at rest (25) and during training (26). NO seems to be effective in improving athletic performance by increasing oxygen (O_2), glucose and other nutrients for better muscle fuel (1). Based on evidence and research on the effects of NO_3^- , the International Olympic Committee (IOC) classified it as a supplement that may improve performance (alongside Creatine and caffeine) (27). Therefore, in this study, we seek to assess the influence of BR supplement consumption on the various dimensions of athletic performance and effective mechanisms.

METHODS

Based on the purpose of the study, a search was conducted in data bases (MEDLINE, PubMed, Scopus, Directory of open access journals and Science direct databases); the

keywords used included Beetroot supplementation, Nitrate supplementation, physical exercise, resistance exercise, aerobic exercise, endurance training, strength training, oxidative stress, O_2 cost, skeletal muscle, hormonal response, nervous function, and mitochondria. Our focus was on English articles published from 2013 to 2020 (**Figure 2**).

THE INFLUENCE OF BR SUPPLEMENTATION ON THE SKELETAL MUSCLE

BR supplements have received less attention in resistance training (28) (**Table 2**). In this case, we can refer to the research of Mosher et al. who stated that taking BR supplement for 6 days increases muscle endurance and number of repetitions (32). Moreover, recent studies have shown that BR preferentially enhance blood flow (58) and muscle contraction (59) in the type II muscle fibers, but has no effect on the type I fibers. Therefore, BR may be able to increase performance in exercises that use the type 2 muscle fibers (such as resistance training). In addition, a NO_3^- -rich supplement can increase neuromuscular performance during strenuous resistance training (28). Previous evidence suggested that sodium nitrite (NaNO_2) administration probably enhance cytosolic Ca^{2+} without changing force generation at a supraphysiological partial pressure of oxygen (PO_2) (60), or decrease cytosolic Ca^{2+} along with less submaximal, but not maximal, force at a physiological PO_2 (61) (during isometric contractions stimulated in isolated rat muscle fibers). However, during a repetitive and fatigue-stimulating contraction protocol, administration of NaNO_2 increases t exhaustion time by compensating for decreased Ca^{2+} pumping and Ca^{2+} sensitivity (62).

The mechanism by which NO_3^- can enhance contractile performance in skeletal muscle is the adjustment of contractile proteins or Ca^{2+} handling in skeletal muscle after translation (63) (as shown in **Figure 3**). In fact, NO can respond with protein thiols [e.g., groups containing sulfhydryl groups, protein thiol (RSH) or thiolate anion (RS^-)] to form nitrosothiols (RSNO) groups in a reversible process called S-nitrosylation (64). S-nitrosylation and denitrosylation alter the composition of the structure and thus the function of proteins (65). For example, NO reaction with heavy chains of myosin S-nitrosylate has been reported in skeletal muscle, causing heightened contractile force (66). Potential effect of S-nitrosylation on the stimulation-contraction pair is complex given that different contraction-related proteins can post translate into the cysteine residues on the thiols such as myosin (67), troponin (68), sarcoendoplasmic reticulum (SR) calcium transport ATPase (SERCA) (69), and ryanodine receptors (RyRs) (70, 71) to undergo irreversible changes; these post-translational protein changes probably depend on the interactions between NO, the reactive oxygen species (ROS), and the bioavailability of glutathione (72). Furthermore, RyR proteins contain a significant quantity of sulfhydryl groups in comparison with the other contractile proteins, and this supports the hypothesis that modulation of RyR and release of Ca_2^+ mediated NO can help increase muscle contraction following the NO_3^- consumption. The important

TABLE 1 | Nutrient composition of raw Beetroot (per 100 g).

Nutrients	Beetroot (per 100 g)
Water, g	87.58
Energy, kcal	43
Protein, g	1.61
Total fats, g	0.17
Carbohydrate, g	9.56
Fiber, g	2.8
Sugars, g	6.76
Flavonoid, mg/g	0.41–1.16
Riboflavin, mg	0.04
Betalain, mg	14.20
Carotenoids, mg	1.9
Minerals	
Calcium, mg	16
Iron, mg	0.8
Magnesium, mg	23
Phosphorus, mg	40
Potassium, mg	325
Sodium, mg	78
Zinc, mg	0.35
Vitamins	
C, mg	4.9
B ₁ , mg	0.031
B ₂ , mg	0.057
B ₃ , mg	0.334
E, mg	0.04
K, mg	0.2
Essential and non-essential amino acid	
Tryptophan, g	0.019
Isoleucine, g	0.048
Leucine, g	0.068
Tyrosine, g	0.038
Arginine, g	0.042
Glycine, g	0.031
Alanine, g	0.060
Glutamic acid, g	0.428

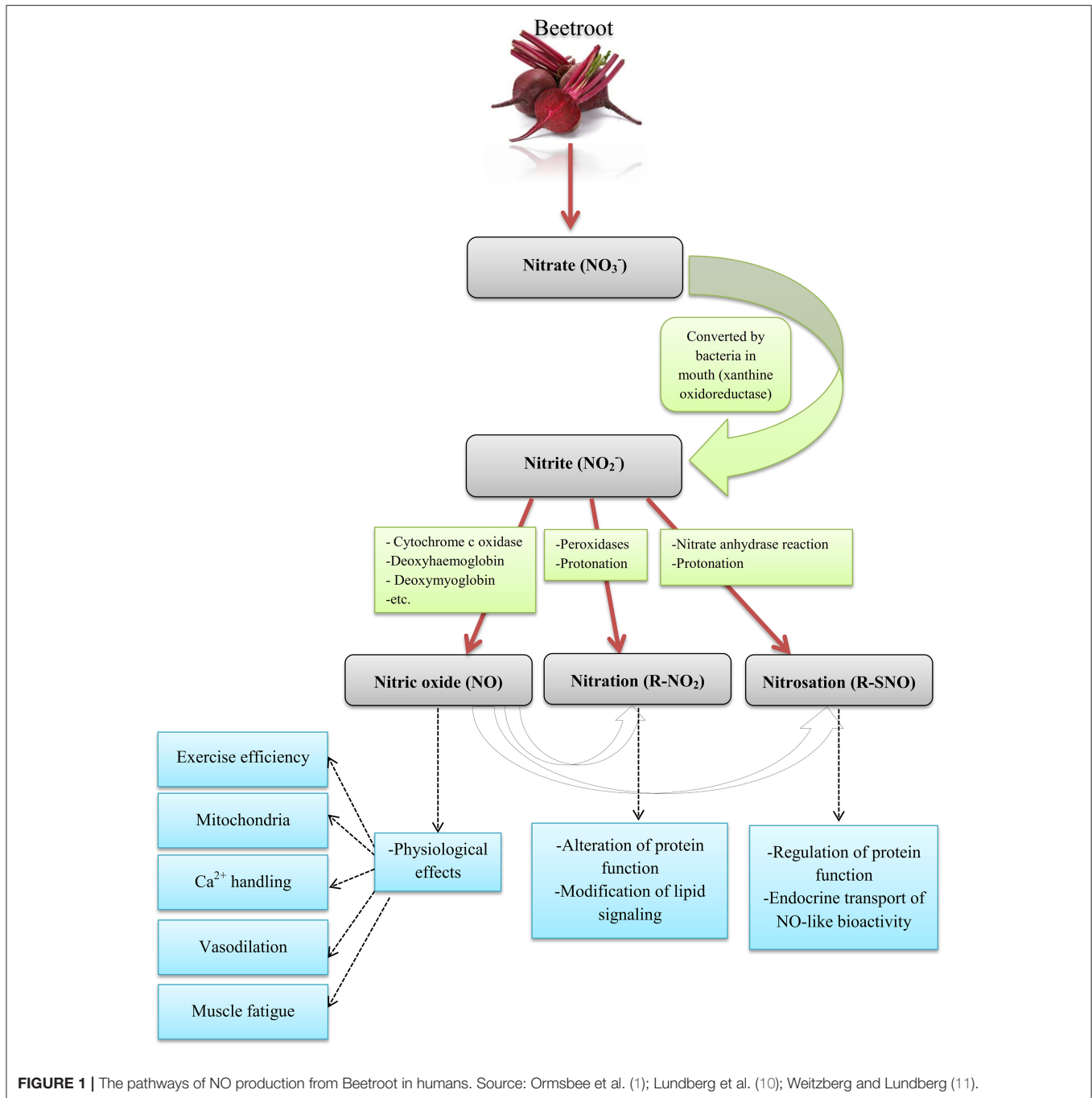
Baiao et al. (4); Chawla et al. (5); Chhikara et al. (6); Kale et al. (7); United States Department of Agriculture Agricultural Research Service. Food Data Central: Food and Nutrient Database for Dietary Studies with Standard Reference Legacy (2019) www.fdc.nal.usda.gov (8).

point is that, these influences can be free of alterations in the substance of Ca₂⁺-handling proteins (73). Further potential alterations in the excitation-contraction coupling proteins, NO₃⁻ supplement consumption has been proposed to change the high-energy phosphate turnover and phosphorus metabolites in the skeletal muscle (20, 29). NO₃⁻ reduces the cost of high-energy phosphates in the generation of skeletal muscle contraction (20, 29) and the intramuscular accumulation of adenosine diphosphate (ADP) and phosphate, factors that are expected to reduce the expansion of fatigue in skeletal muscle (74). Furthermore, NO₃⁻ supplementation increases the muscle blood flow (58) and may help re-synthesize phosphocreatine (PCr)

between the sets (75, 76) and force recovery and performance (77–79). Molecular mechanisms for the oxidative metabolism in skeletal muscle and hypertrophy adaptations due to exercise are diverse and possibly contradictory (80, 81). For example, it has been reported that NO₂⁻ activates the AMP-activated protein kinase (AMPK) (82), while the main regulatory factor is adaptability of the skeletal muscle oxidative metabolism, but interferes with mammalian target of rapamycin complex 1 (mTORC1) signaling, a major regulator of skeletal muscle hypertrophy (83, 84).

Another physiological basis may be due to the effects of certain types of muscle fibers on the NO₃⁻ supplement consumption (85). Ferguson et al. stated that the BR consumption elevate blood flow to limbs and skeletal muscle [preferably with fast-twitch fibers (type 2)] (58). Due to the fact that oxygen supply is a limiting factor in the adenosine triphosphate (ATP)-PC regeneration, and lactate clearance perhaps affect the muscle strength generation (86, 87), improving blood flow to type 2 fibers may improve and maintain the muscle strength and ultimately lead to improved performance in the resistance training (28). Moreover, the results of Whitfield et al. showed that BR ingestion enhance force generation at low excitation frequencies and in the human skeletal muscle, this is independent of the change in the redox stress or the expression of protein targets related to calcium operation (33). It has been shown that the amount of ATP turnover in myocyte contraction is largely determined by the activity of actomyosin ATPase and ATPase-Ca₂⁺ (88). Also, NO causes lagging myosin cycling kinetics and increases force production with each power stroke (66), and decreases activity of the ATPase-Ca₂⁺ (69). Increased NO production after the BR supplementation may decrease ATP turnover by declining the activity of actomyosin ATPase or ATPase-Ca₂⁺. Intracellular accumulation of ADP and Pi and PCr degradation are also blunted following the NO₃⁻ supplement consumption (20). Dietary NO₃⁻ supplementation appears to improve the link between the ATP hydrolysis and muscle force generation, and this is a significant determinant of oxygen uptake (VO₂) reduction during the exercise. Alterations in the ADP, Pi, and PCr following the NO₃⁻ consumption were predicted to decrease stimuli for the increased oxidative phosphorylation relying to the existing respiratory control models (89–91).

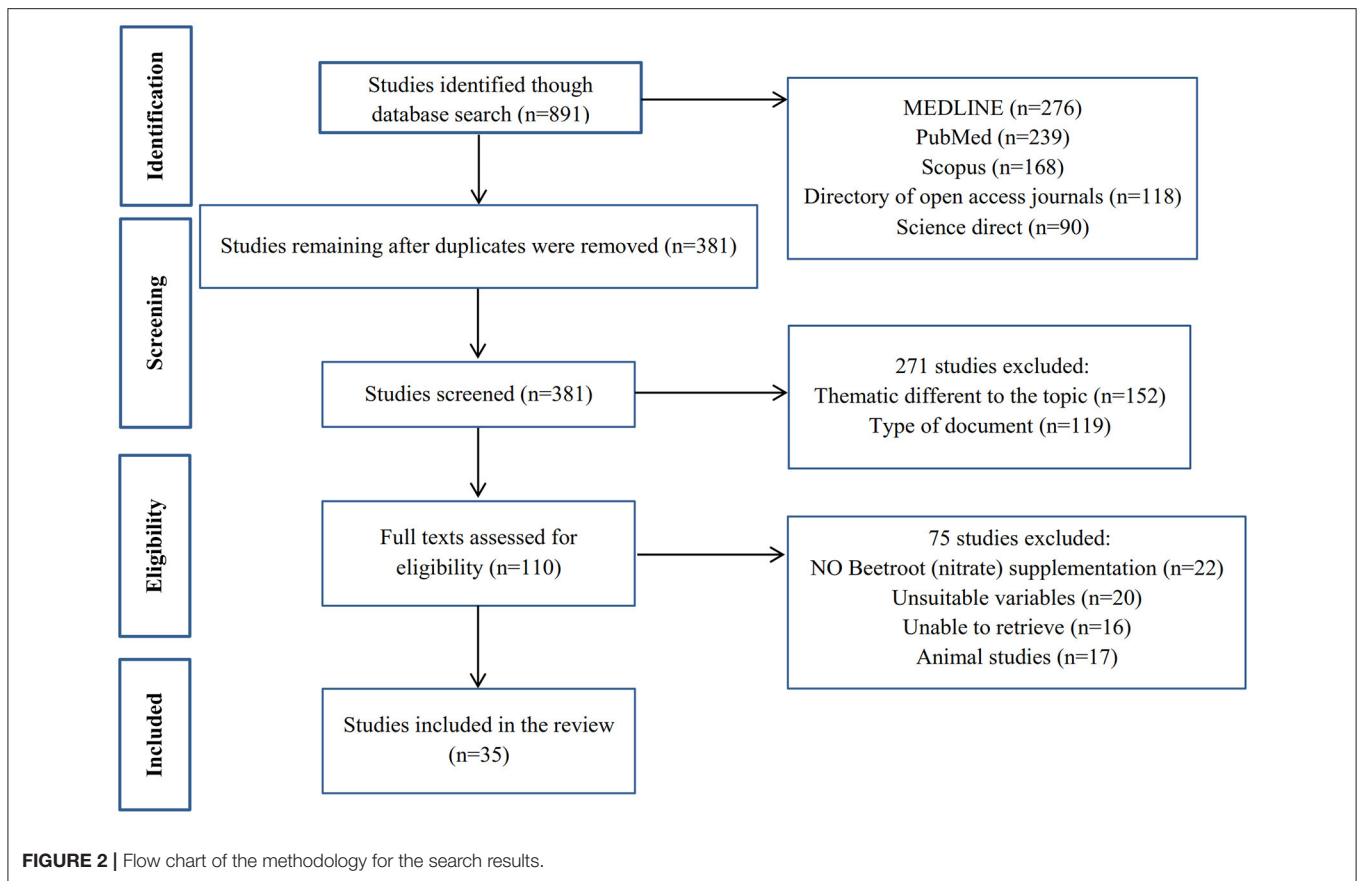
Effective mechanisms for the effects of BR on the performance of resistance training may be the result of increased neuromuscular efficiency (31), decreased ATP-PC cost (92), and alterations in the calcium handling (59). The results of Williams et al. showed that the BR is a sound, natural and efficient ergogenic supplement that has a positive effect on the speed, strength and total repetitions during the chest press exercises with free weights (36). Moreover, the results of research by Flanagan et al. showed that the NO₃⁻ supplementation improves neuromuscular efficiency of force generation and its effects become more pronounced with fatigue. They suggested that the observed improvement in the neuromuscular function may be due to the increased sarcoplasmic reticulum Ca₂⁺ release (31). Hernandez et al. observed that the increase in the contractile force in fast-twitch muscles due to NO₃⁻ supplementation was related to the increase in the tetanic Ca₂⁺ concentrations (59).



Furthermore, analysis of glucose kinetics after the NO₃⁻ intake provides important insights into specifying the impacts of NO₃⁻ on glucose metabolism during the physical activity in humans. In addition, quantitative studies have examined the influence of NO₃⁻/BR consumption on the AMPK signaling during training (AMPK is the skeletal muscle energy sensor that is activated by training) (93, 94). A study by Betteridge et al. on the effect of BR on the glucose kinetics, muscle metabolism, AMPK signaling and oxygen consumption, showed that the acute BR consumption had no significant effects on the glucose disposal, Acetyl-CoA

carboxylase (ACC) phosphorylation, muscle metabolism, oxygen consumption, or RER during the moderate-intensity physical activity in healthy men (50).

In addition to muscle strength, improving muscle endurance during the resistance training can be due to the role of NO, because it participates in the regulation of blood pressure (95) by vasodilatory, along with the capability to prevent blood coagulation (96). Moreover, to the endogenous production of L-arginine oxidation, there is a metabolic oxidation pathway, NO₃⁻-NO₂⁻-NO, which is independent of the NO synthases



(NOS) (97). Thus, in exercise that involve main components of muscular endurance, helping the NO_3^- through BR supplement is a more effective way to improve the NO generation, in favor of greater blood volume and hence oxygen. This becomes even more important when exercise specifically leads to an acidic and hypoxic body environment, a condition in which a decrease in the NO_3^- metabolism increases the NO precursor supplement activity (97). More oxygen supply causes delay in the onset of muscle fatigue in sportive performance (98) and leads to enhanced energy generation in the form of ATP through the aerobic metabolic pathways. In more intense and longer exercise, delays in the onset of anaerobic metabolic pathways lead to the increased oxygen consumption which is required for ATP production (98). Consequently, the use of NO_3^- can improve sport performance, because of the vasodilatory function and providing more oxygen to the muscles enhances the maximum oxygen consumption of individuals and decreases the oxygen consumption for exercise. All these reduce the cost of ATP and, therefore, alter intramuscular substrates and metabolic generation (PCr, ADP, Pi), increases muscle oxygenation (12) and delays the onset of muscle fatigue. As a result, decreased oxygen consumption and lower ATP costs cause delay in the lactate generation (98). Since lactate is an indicator of cooperation of the glycolysis in the metabolism, after consuming BR with the same concentrations of blood lactate, increasing the total number of repetitions obtained can indicate energy efficiency

(99). Accordingly, Bailey et al. showed that ingestion of BR decreases the cost of oxygen and the rate of PCr degradation during the low and high intensity training without affecting muscle pH and improving training performance (20).

In addition, studies have investigated the influence of BR on the rating of perceived exertion (RPE); some studies have suggested improved performance without a considerable effect on the RPE (32, 100, 101) and other studies have shown a decrease in the RPE values (37, 102). Mosher et al. stated that RPE muscle endurance in resistance training was not affected by 6 days of NO_3^- consumption (32). In contrast, the results of Jodra et al. showed that the BR consumption can reduce muscle RPE (37). Possible mechanisms that may explain the effect of BR on the RPE include higher blood flow to the brain frontal lobe, which regulates motor control and decision-making, contributing to a subjective perception of effort (103), and possibly increasing athletic performance (37). In addition, it should be noted that the maintenance of RPE after the BR supplement consumption can be the result of decreased central motor command due to the contractile operation maintained during the exercise (102), as RPE displays a central feedback process in which a motor order output is dispatched from the motor zones to the sensory brain to allow conscious awareness of the actions relevant to motor yield (103). During strenuous contractions, a gradual enhance in the RPE may indicate an increment in the central motor command required for training-induced deficiencies in

TABLE 2 | Summary of studies investigating the effects of Beetroot supplementation on skeletal muscle, hormonal response, nervous function, O₂ Cost, mitochondria, and oxidative stress.

Studies	Subject	Aim	Intervention	Main outcome
BR supplementation and skeletal muscle				
Fulford et al. (29)	Healthy, physically active (N = 8)	Assess the role of dietary NO ₃ ⁻ in regulating force generation under normal physiological conditions	-Received 0.5 l/day of BRJ for 15 days -Exercise protocol: 50 MVCs at 2.5 h, 5, and 15 days after the beginning of the supplement consumption period	↓PCr cost of force production -Improved muscle efficiency
Hoon et al. (30)	Healthy participants (n = 18)	Assess the effect of NO ₃ ⁻ consumption on muscle contraction	-Days 1–3: 525 mg NO ₃ ⁻ , day 4: 1,050 mg NO ₃ ⁻	=Maximal force, submaximal contractile force -Improved Ca ²⁺ handling in the muscle ↓Muscular fatigue
Flanagan et al. (31)	RT men (n = 14)	The effects of NR supplement consumption on neuromuscular efficiency	-The NR Bar contained 3 g of concentrated BR extract for 3 days	-Provided neuromuscular advantages during metabolically taxing resistance exercise ↑oxygen consumption
Mosher et al. (32)	Recreational active resistance trained males (n = 12)	Examine the effects of NO ₃ ⁻ consumption on performance of bench press resistance exercise till failure	–6 consecutive days of 70 ml of NO ₃ ⁻ shot containing 6.4 mmol/L or 400 mg of NO ₃ ⁻ +resistance exercise session (60%1RM)	↑Total work and repetitions until failure ↓Energy cost = RPE, blood lactate
Whitfield et al. (33)	Recreationally active males (n = 8)	Investigate the influence of 7 d of BRJ ingestion on skeletal muscle contractile characteristics and function	–7 days of BRJ supplement consumption (280 mL.d ⁻¹ , 26 mmol NO ₃ ⁻) - Performed 20 min of cycling (10 min at 50 and 70% VO _{2peak}) 48 h before “Pre” and “Post” 5 day of supplement consumption	=Maximal voluntary force production or electrically induced tetanic contractions ↑Force production, maximal rates of force development -Change in calcium handling, the content of associated proteins (SERCA1a, SERCA2a, dihydropyridine receptor, ryanodine receptor, and calsequestrin)
de Oliveira et al. (34)	Adult male Brazilian jiu-jitsu trained athletes (n = 12)	Investigate the effect of BR-based gel (BG) consumption on MVC, exercise time until fatigue, muscle O ₂ saturation (SmO ₂), blood volume (tHb), and plasma NO ₃ ⁻ and lactate in response to handgrip isotonic exercise	–100 g of BR-based nutritional gel containing 12.2 ± 0.2 mmol of NO ₃ ⁻ , 8 days, 120 min previous exercise	- Prevented force decrease after the handgrip exercise -Improved forearm muscle O ₂ saturation and delayed the accumulation of blood lactate. = Exercise time until fatigue
Papadopoulos et al. (35)	Young males (n = 16)	Investigate the effects of BRJ on <i>in vivo</i> skeletal muscle VO ₂ and microvascular reactivity at rest and muscle performance, muscle oxygenation during sustained isometric handgrip exercise	-NO ₃ ⁻ -rich BRJ (500 mg/8.1 mmol NO ₃ ⁻ , BRJ NO ₃ ⁻), After 2.5 h of BRJ consumption participants performed the tests	= Skeletal muscle microvascular reactivity and basal oxidative efficiency ↑Muscle oxygenation -Provided ergogenic benefits
Ranchal-Sanchez et al. (28)	Healthy men (n = 12)	Examine the acute influence of BRJ on muscular endurance and movement concentric velocity during RT	-Incremental RT test with three sets, at 60, 70, and 80% 1RM. -One of the drinks, 70 mL of BRJ, 120 min before each visit	-Ergogenic effect on the muscular endurance ↑Total repetitions performed =RPE
Williams et al. (36)	RT male subjects (n = 11)	Assess the effects of acute BRJ ingestion on power, velocity, and repetitions to failure (RTF) during bench press exercise	–70 ml of BRJ, 2 h before exercise	↑Mean velocity and mean power, total RTF. -Positively impacts velocity, power, and total repetitions
Jodra et al. (37)	Resistance trained male (n = 15)	Examine the effects of 6 NO ₃ ⁻ rich BJ consumption on POMS, RPE, and performance in a 30 s Wingate cycle test	–3 h before initiating Wingate test participant consumed 70 ml of BRJ	↑Peak power output (W _{peak}) ↓ Time taken to reach W _{peak} ↑POMS prior to the Wingate test ↓RPE _{muscular} immediately follows the Wingate test
Jonvik et al. (38)	Recreational active males (n = 14)	Examine the effect of BRJ ingestion on maximal isometric strength and isokinetic power, workload achieved during 30 reciprocal voluntary isokinetic contractions and CMJ performance	–140 mL/d NO ₃ ⁻ -rich (BR; 985 mg/d), 6-d supplementation periods -Three h following the last supplement, assessed indicators	= Maximal strength, CMJ performance and muscular endurance

(Continued)

TABLE 2 | Continued

Studies	Subject	Aim	Intervention	Main outcome
Rodríguez-Fernández et al. (39)	Adult males ($n = 18$)	Examine the impact of BRJ consumption on power output during concentric and eccentric muscle contractions during a half-squat	–140 mL dose of 2×70 mL concentrated NO_3^- rich BR shots providing 400 mg $\text{NO}_3^-/70$ mL. Acute ingestion BR 2.5 h before test	↑ Mean and peak lower limb power output in the concentric and eccentric movement phases of a half-squat
BR supplementation and hormonal response				
Singh et al. (40)	Infantry soldiers ($n = 30$)	Examined the effects of 15 days dietary NO_3^- supplementation on High Density Lipoprotein-Cholesterol and Oxidative Stress in Physically Active Individuals	–400 ml BRJ (consumed twice daily) for 15 days	↓ Cortisol levels
Roberts et al. (41)	Healthy non-obese volunteers ($n = 19$)	Assess the impact of inorganic nitrate on markers of the adaptive response to exercise in skeletal muscle	– 2×70 mL/day BRJ (12 mmol nitrate) for 7 days	↑ Circulating growth hormone levels
Garnacho-Castaño et al. (42)	Well-trained CF ($n = 12$)	Asses the causal physiological association between hormonal, metabolic and mechanical responses, and CF workouts performance after acute BJ consumption	-Ingestion 140 mL of BRJ (~ 12.8 mmol NO_3^-), 3 h before the start of each test (CF workout)	↑ Cortisol and testosterone levels
BR supplementation and nervous function				
de Vries and DeLorey (43)	Men ($N = 12$)	Investigate the hypothesis that acute dietary NO_3^- ingestion would attenuate sympathetic vasoconstrictor responsiveness at rest and during exercise	-Consumption of NO_3^- rich BRJ (~ 12.9 mmol NO_3^-), Exercise: 2.5 h after consumption	= Plasma catecholamines, and sympathetic vasoconstrictor at rest or during exercise
Kozłowska et al. (44)	Elite fencers ($n = 20$)	Investigate of the long-term metabolic effect of a diet with and without BRJ supplement consumption	–4 weeks with 26 g/d of freeze-dried BRJ consumption	-Significant changes in tyrosine and tryptophan metabolism, mainly associated with such neurotransmitter's metabolism as: serotonin, noradrenaline, and adrenaline
BR supplementation and O₂ Cost and mitochondria				
Kelly et al. (45)	Healthy subjects ($n = 12$)	Examine the influence of dietary NO_3^- ingestion on the concentration of plasma NO_2^- , VO_2 kinetics, and exercise tolerance in normoxia and hypoxia	–140 ml/day of NO_3^- rich BRJ (8.4 mmol NO_3^- ; BR) for 3 days prior to moderate-intensity and severe-intensity exercise tests	↑ VO_2 kinetics - Improving exercise economy and exercise tolerance in hypoxia
Pinna et al. (46)	Trained male master swimmers ($n = 15$)	Investigate whether BRJ supplementation can also improve performance	-Swimming test after 6 days of BRJ (0.5 l/day organic BRJ containing about 5.5 mmol of NO_3^-)	↓ Energy cost ↑ Workload at anaerobic threshold
Muggeridge et al. (18)	Competitive amateur male cyclists ($n = 9$)	Assess the influence of a single dose of BR ingestion on the physiological responses to submaximal exercise and TT performance	-Consumption of either 70 mL of BR, 3 h before exercise	↓ VO_2 during submaximal exercise ↑ TT performance of trained cyclists in normobaric hypoxia
Arnold et al. (47)	Male runners ($n = 10$)	Investigated the effect of NO_3^- ingestion upon endurance running performance at altitude in well-trained runners	–7 mmol NO_3^- at 2.5 h before exercise	= Oxygen cost, arterial oxygen saturation, heart rate, and RPE
MacLeod et al. (48)	Trained male cyclists ($n = 11$)	Assess the influence of BR supplementation on steady-state exercise economy and 10-km TT performance in normoxia and moderate hypoxia (simulated altitude: $\sim 2,500$ m)	-Two h before exercise, subjects consumed 70 mL BR (~ 6 mmol NO_3^-) - $\text{VO}_{2\text{peak}} \geq 60$ ml·kg ⁻¹ ·min ⁻¹	= Oxygen cost of steady-state exercise = Economy, mean power output, or 10-km TT completion time
Whitfield et al. (49)	Young active males ($n = 10$)	Determine if BRJ altered various indices of mitochondrial bioenergetics	–7 day supplement consumption with BRJ (280 ml day ⁻¹ , 26 mmol NO_3^-) -Performed 20 min of cycling (10 min at 50 and 70% $\text{VO}_{2\text{peak}}$) 48 h before “Pre” and “Post” 5 day of supplement consumption	↓ Oxygen cost ↑ H_2O_2 = Mitochondrial coupling and respiratory efficiency

(Continued)

TABLE 2 | Continued

Studies	Subject	Aim	Intervention	Main outcome
Betteridge et al. (50)	Healthy recreationally active males ($n = 8$)	Assess the influence of BRJ supplementation on oxygen consumption, glucose kinetics, or skeletal muscle metabolism during submaximal exercise	-BRJ; 8 mmol NO_3^- 2.5 h later, participants cycled for 60 min on an ergometer at 65% of $\text{VO}_{2\text{peak}}$	= Oxygen consumption ↑ Muscle creatine, lactate, and phosphorylated acetyl CoA carboxylase during exercise
Thompson et al. (51)	Recreationally-active subjects ($n = 36$)	Investigated the independent and combined performance and physiological effects of SIT and NO_3^- ingestion	-BRJ; ~6.4 mmol of NO_3^- per 70 ml for 28 days -Subjects consumed 2 × 70 ml of their allocated supplement 2.5 h before the exercise tests	↓ O_2 cost ↑ Peak work rate - SIT and BR ingestion provided greater improvements in incremental exercise performance compared to either intervention alone and led to greater improvements in some indices of muscle metabolic adaptation
Santana et al. (52)	Healthy participants ($n = 16$)	Influence of inorganic NO_3^- ingestion combined to a short training program on 10-km running TT performance, maximum and average power on a Wingate test, and $[\text{La}^-]$ in recreational runners	-Consumed 750 mg/day (~12 mmol) of NO_3^- plus 5 g of resistant starch, for 30 days	- Improved 10-km TT performance and kept blood $[\text{La}^-]$ steady
Pawlak-Chaouch et al. (53)	Elite endurance athletes ($n = 17$)	Investigated the effects of BR consumption on enhances the tolerance to SIE	-3day BR supplementation (340 mg/day) -Exercise test: 15-s cycling exercise bouts at 170% of the maximal aerobic power interspersed with 30-s passive recovery period	= Tolerance to SIE = VO_2 and local muscle O_2 delivery and extraction
Wickham et al. (54)	Recreational active females ($n = 12$)	Determine the influence of acute and chronic BRJ ingestion on submaximal exercise VO_2 , TT performance	-Supplementation acutely (2.5 h) and chronically (8 days) with 280 mL BRJ/d (~26 mmoles NO_3^-) -Cycled for 10 min at 50 and 70% $\text{VO}_{2\text{peak}}$	= MVC, voluntary activation, peak twitch torque, time to peak torque, or half relaxation time. - Not reduce O_2 cost of submaximal exercise
Behrens et al. (55)	Adults with obesity (body mass index >30 kg/m^2) ($n = 16$)	Investigate the effect of BRJ on ET, EE, and cardiometabolic health	- NO_3^- rich BRJ (BRJ; ~6.4 mmol of NO_3^- per 70 ml), 2.5 h before exercise	-Improved exercise efficiency during submaximal exercise by 7%, and time to exhaustion by 15% compared to other conditions
BR supplementation and antioxidant				
Roth (56)	Recreationally active ($n = 30$)	Examine the influence of acute versus chronic BR supplement consumption on oxidative stress, and antioxidant capacity (SOD)	- Consuming BR for 7 days, 140 ml or 0.8 g of NO_3^-	↑ Antioxidant capacity (SOD)
Singh et al. (40)	Infantry soldiers ($n = 30$)	Investigated the influence of 15 days dietary NO_3^- supplement consumption on high density lipoprotein-cholesterol and oxidative Stress	- 400 ml BRJ (consumed twice daily) for 15 days	↑ Plasma total antioxidant capacity ↓ Stress markers plasma hydroperoxides
Whitfield et al. (33)	Recreationally active males ($n = 8$)	Investigate the influence of 7 d of BRJ ingestion on skeletal muscle contractile characteristics and function	- 7 days of BRJ ingestion (280 mL·d ⁻¹ , 26 mmol NO_3^-) - Performed 20 min of cycling (10 min at 50 and 70% $\text{VO}_{2\text{peak}}$) 48 h before "Pre" and "Post" 5 day of supplement consumption	= GSH:GSSG ratio
Kozłowska et al. (57)	Elite fencers ($n = 20$)	Examine the effects of diet and active substances in BRJ supplementation on the oxidative stress, inflammation, and muscle damage in elite fencers	- Received freeze-dried BRJ in the amount of 26 g per day, which corresponded to one glass of juice (200 ml), 4 weeks	↑ Lipid peroxidation, GPx1 activity ↑ $\text{VO}_{2\text{max}}$ and changes of this parameter were negatively related to changes of LDH serum activity, as well as to the concentrations of β-carotene and MDA.

=, No significant difference; ↓, significantly decreased responses; ↑, significantly increased responses; BRJ, Beetroot juice; TT, Time trial; VO_2 , Oxygen uptake; NO_3^- , Nitrate, NO_2^- Nitrite; MVS, Maximum voluntary strength; EE, Exercise efficiency; O_2 , Oxygen; IO, Individuals with obesity; ET, Exercise tolerance; CF, CrossFit; ROS, Reactive oxygen species; RT, Resistance training; RPE, Rating of perceived exertion; H_2O_2 , Hydrogen peroxide; POMS, Profile of mood states; NR, Nitrate-Rich; La^- , Lactate concentration; SIE, Supramaximal intensity intermittent exercise; CMJ, Countermovement jump; BR, Beetroot; SIT, Sprint interval training; GPx1, Glutathione peroxidase 1; TAC, Total antioxidant capacity; TP, Total polyphenol; SOD, Superoxide dismutase; DNA, Deoxyribonucleic acid; GSH:GSSG, The ratio of reduced/oxidized glutathione; GST, Glutathione S-transferase; NQO1, NAD(P)H:quinone oxidoreductase 1; NP-SH, Non-protein sulfhydryl; GSH, Glutathione; LDH, Lactic acid dehydrogenase; MDA, Malondialdehyde.

the contractile muscle function to ensure that there is sufficient output power to maintain work (104). In fact, decreased blood flow to the brain during training is known to be a major cause of fatigue (105). Therefore, increased cerebral blood flow can play a role in reducing the muscle RPE and improving function after the BR supplementation (37). Based on studies (Table 2), acute (2–3 h) (28, 35–37, 39), short-term (<15 day) (30–34, 38), and long-term (≥ 15 day) (29) BR supplementation is effective for building muscle adaptations.

The results of Wylie et al. showed that the skeletal muscle NO_3^- stores are sensitive to NO_3^- ingestion and probably help to NO production during training. They reported that skeletal muscle contains sialin (NO_3^- transporter) and xanthine oxidoreductase and stated that skeletal muscle also plays a main role in the transport, storage, and metabolism of the NO_3^- . They also stated that baseline NO_3^- levels and NO_2^- concentrations in muscle are much higher than plasma, and NO_3^- intake increases plasma and muscle NO_3^- concentrations (106). Also, Srihirun et al. concluded that muscle cells rely on the transport of NO_3^- from external sources for achieving sufficient NO_3^- stores in order to convert sufficiently to NO_2^- and NO, and that muscle cells normally cannot raise endogenous NO_3^- levels to high levels for supporting all routine and emergency procedures. They also stated that sialin and chloride channel 1 (CLC1) (NO_3^- transporters) play an important role (107). During skeletal muscle contraction, increased NO storage supports increased mitochondrial respiration, glucose uptake, and other functions (64).

THE IMPACT OF BR SUPPLEMENTATION ON THE HORMONAL RESPONSE

NO is an intracellular and extracellular messenger for the adjustment of several cellular functions, such as changes in the hormone secretion (108, 109) for anabolic and catabolic aim. It is one of the major mediators of stress involved in the acute hypothalamic-pituitary-adrenal (HPA) response to training. The effects of NO on the pituitary and adrenal cortex have been confirmed (110) and it has been suggested that the cortisol secretion can be stimulated directly by the NO concentration after tadalafil administration (111). Activation of the HPA axis during the training greatly increases the cortisol levels (112), which acts as a metabolic and catabolic hormone (113) by mobilizing the glucose (114), endogenous stores of amino acids (115), and fatty acids (116), enhances the availability of all fuel substrates; as a result, BR improves performance (42).

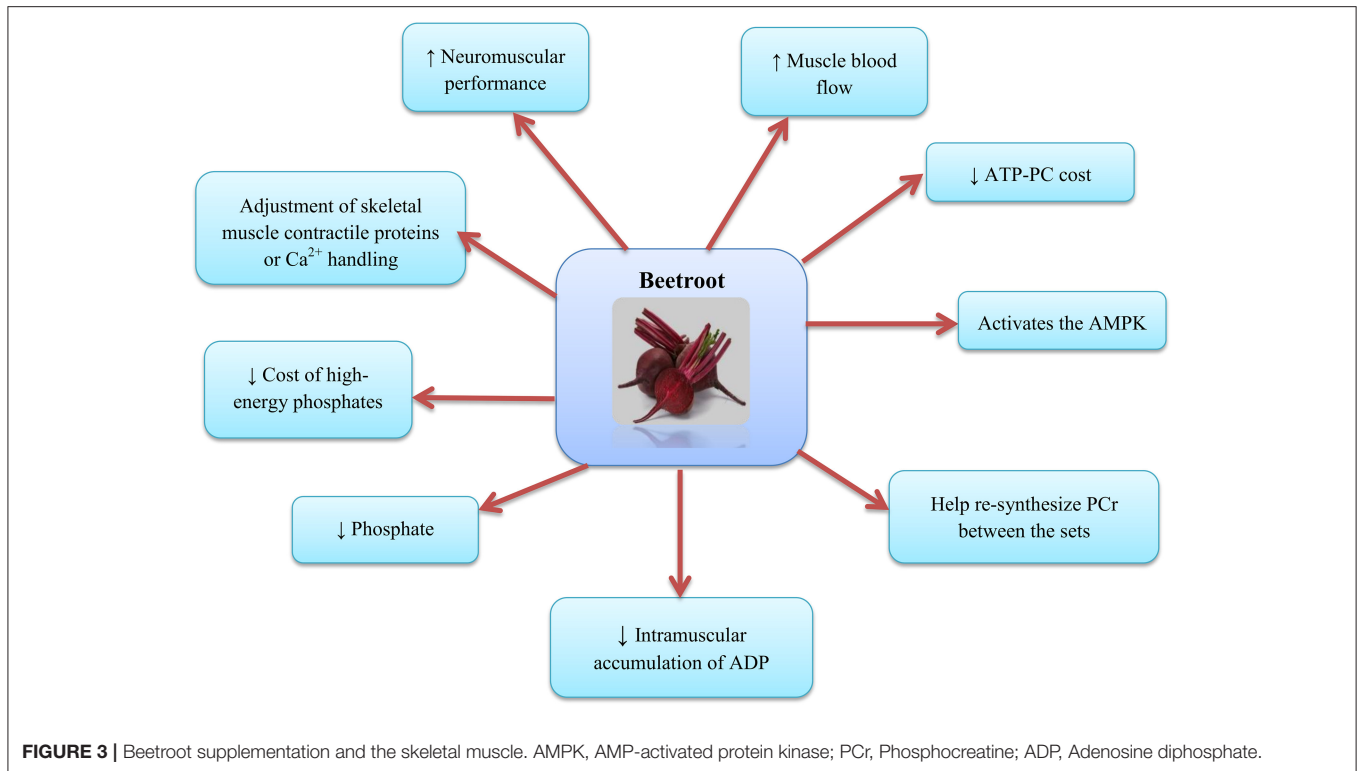
In addition, NO plays the main role in anabolic hormones; Valenti et al. reported that the NO has a biphasic effect on testosterone secretion, NO inhibits testosterone secretion at higher levels and stimulant at low concentrations; the stimulant effect of NO is mediated by cGMP (117). Like NO, testosterone perhaps stimulates the vasodilator effect (118, 119). However, testosterone appears to cause vasodilatation at concentrations above $10 \mu\text{mol/L}$, but at low physiological concentrations, NO appears to be involved in the vasodilatory effects of this hormone

(120). It appears that different concentrations of NO can alter the hormonal response of cortisol and testosterone (42). Garnacho-Castaño et al. concluded that cortisol and testosterone levels were markedly increased in the BR juice and placebo intake groups. They stated that most alterations observed in the cortisol levels after the BR consumption maybe associated with the NO_3^- - NO_2^- -NO pathway and more studies are needed to confirm this hypothesis (42). Also, the results of Roberts et al. Show an increase in growth hormone (GH) concentration in rats and humans due to NO_3^- consumption. They state that peroxisome proliferator-activated receptor gamma coactivator-1 (PGC-1) and NO, by secreting muscle gamma-aminobutyric acid (GABA) and peripheral GABA concentrations, may help release exercise-stimulated GH (41).

THE INFLUENCE OF BR SUPPLEMENTATION ON THE NERVOUS FUNCTION

The NO is produced endogenously in a variety of cells In a mammalian organism, such as nerve cells, endothelial cells, and macrophages, by a category of three isozymes called NOS, and uses L-arginine as a substrate (121). Endogenously synthesized NO has been shown to not only act as an intercellular messenger, but also to spread rapidly and affect NO target cells. Thus, the released NO may affect nerve cells over a wide area (122). The NO is a messenger molecule with numerous molecular targets among other servo-regulatory control functions including neurotransmission (123). Considering the modulation of nerve cell function by the NO *in vivo* and *in vitro* studies, it has been shown that in all brain structures, NO modulates the release of several neurotransmitters. Regarding *in vitro* and *in vivo*, NO donors enhance the release of noradrenaline from the hippocampus (124). In the medial preoptic area (125) and the striatum (126), serotonin release is increased by the L-arginine and NO donors, respectively. NO donors have been shown to increase serotonin secretion in the hypothalamus and in the locus coeruleus. In addition, NO has a moderating role; high levels of NO enhance serotonin values in the hypothalamus, while slight concentrations of NO appear to decrease it (127). Increased serotonin modulates fatigue in long-term activity (128). Serotonin has metabolic and developmental effects on the skeletal and cardiac muscles; it regulates energy balance and glucose uptake by the skeletal muscle and prevents insulin resistance (129). In a study conducted by Kozłowska et al. significant changes in the signal intensity induced by the tyrosine and tryptophan metabolites were observed, especially from the noradrenaline, adrenaline pathways, and serotonin metabolism as well as lipid peroxidation (44).

In the pathway of tyrosine metabolism, most of the experimental metabolites identified come from the adrenaline and noradrenaline degradation subpathway. L-tyrosine is changed to L-dopa and further to dopamine with pyridoxal phosphate as a cofactor (130). Dopamine may modulate skeletal muscle activity (131) and affect mitochondrial activity. Improper regulation of the dopamine stimulates oxidative mechanisms



(132). Moreover, dopamine contributes in the synthesis of noradrenaline and adrenaline as a precursor (130). In nerve cells that use the dopamine as a transmitter, no enzymatic changes occur, but neurons applying noradrenaline as a transmitter, contain other enzymes that convert dopamine to noradrenaline and oxygen, also ascorbic acid is the cofactor of this process. Neurons that use adrenaline as a transmitter contain an another enzyme that catalyzes the conversion of noradrenaline to adrenaline (133).

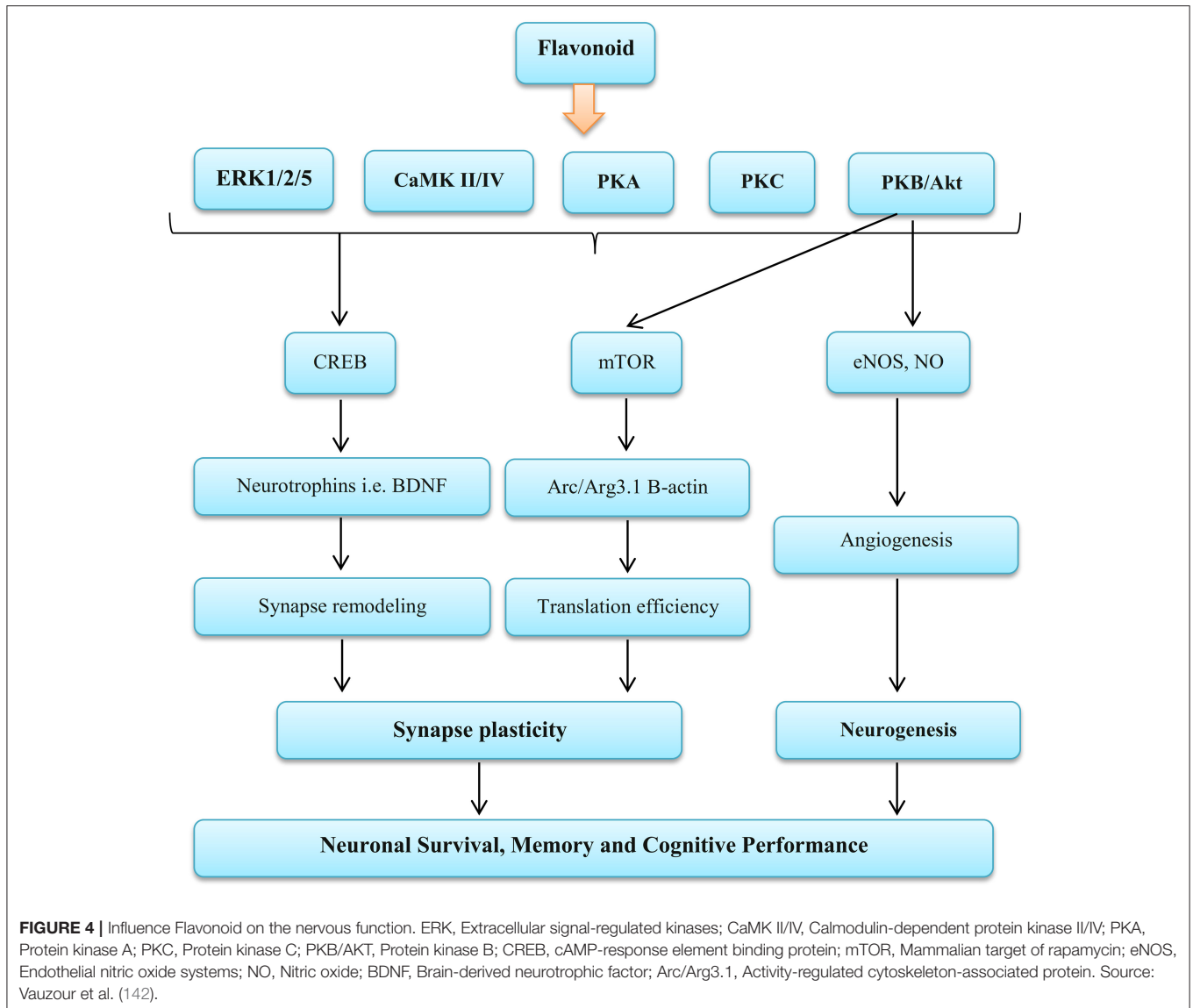
Studies have reported that the brain stem NO bioavailability maybe inhibit sympathetic nerve activity (134–136). In addition, it has been shown that the NO derived from both endothelial NO synthase and neuronal NO synthase inhibits sympathetic vasoconstriction in human and animal specimens (37, 102, 137). Reduction muscle sympathetic activity causes an increase in vasodilation and skeletal muscle blood flow (138). Enhance vasodilation is an important factor in regulating cardiac output, and this is largely related to oxygen delivery (139). In general, evidence has shown that inhibition of the NO generation prevents inhibition of sympathetic vasoconstriction in the skeletal muscle in contracted or rested forms in humans and rodents (103). In contrast, findings of de Vries and DeLorey showed that increasing the NO bioavailability through acute (2.5 h) the BR supplement consumption does not change the sympathetic vasoconstrictor responsiveness to sympathoexcitation at rest or during training (43). In addition, other components of BR can affect nerve function, including flavonoids. Flavonoids exert complex functions on NO synthesis and bioavailability that may increase or decrease NO levels

(140). Flavonoids activate the extracellular signal-regulated kinase (ERK)—cAMP response element binding protein (CREB) pathway and the phosphoinositide 3 (PI3) kinase mTOR cascade, leading to changes in synaptic flexibility. Also they are able to affect neurogenesis by activating PI3 kinase—protein kinase B (Akt)—endothelial NOS (eNOS) (141, 142) (as shown in Figure 4).

THE INFLUENCE OF BR SUPPLEMENTATION ON THE O₂ COST AND MITOCHONDRIA

Dietary NO₃⁻, which is studied as a supplement to the BR, can increase adaptation to endurance exercise due to its ability to enhance NO₂⁻ and NO in plasma (15). By increasing mitochondrial efficiency (22), decreasing the cost of oxygen to muscle contraction (20) and enhancement the contractile force in the fast-twitch muscles (111), it can increase the intensity of exercise (therefore the total work done in a training session) (143). Increased mitochondrial biogenesis (stimulates PGC-1 activation through stimulation of NO by guanylate cyclase) (144) and changes the muscle fiber type to a more oxidative phenotype when combined with the SIT [through the role of nuclear factor activated T cells (NFAT)—calcineurin] (51, 145–147). This is possibly related to the increased mitochondrial hydrogen peroxide (49).

Last evidence indicates that the dietary NO₃⁻ supplement consumption perhaps decreases the cost of O₂ exercise by



reducing the cost of ATP skeletal muscle contraction (20, 33, 59, 148). The major costs of ATP during the skeletal muscle contraction are via myosin ATPase and SERCA (88). One of the main regulatory impacts of the NO is its capability to competitively and reversibly bind to *c* oxidase (COX) and therefore prevent mitochondrial respiration. This was first shown by adding NO donors to the isolated mitochondria (149, 150) and later by showing that NOS inhibition was associated with enhancement of oxygen consumption in the resting muscles of dogs and other organs (151, 152). Even if it is shown that the NO prevents COX, this can automatically lead to a decrease in the mitochondrial respiration. In human mitochondria, COX has a capacity of more than 8 times the maximum flux of the ETS (electron transport system). Therefore, respiration may not be affected to the extent that the COX limits speed. Although the causes for this extra capacity are unclear, it has been proposed that it may be needful to stop intense inhibition of the COX

by NO under natural physiological conditions. Additional COX capacity is significant to maintain a sufficient increase in oxygen affinity to the mitochondria (153).

COX must be severely inhibited before reducing oxygen consumption throughout the body, because peripheral mitochondrial respiratory capacity exceeds systemic oxygen delivery. Actually, even when isolated mitochondria are motivated by the ADP for full respiration at saturating oxygen tension, only part of the total COX capacity is utilized (154). It has been shown that when endogenous NO synthesis is blocked, the body's oxygen consumption increases frequently. This indicates that the physiological level of NO around 20 nM actually has an impact on the tissue oxygen consumption (151, 152). Studies have shown that NO indirectly improves oxidative phosphorylation efficiency by inhibiting COX (155). COX transfers electrons to oxygen and eventually water is formed, and, at the same time, protons are pumped through the

inner membrane of the mitochondria. Although, electrons can move via the COX protein free of pumping protons (156). At the time of COX inhibition by the respiration and the NO is somewhat diminished, documents show that ATP production is sustained to a higher degree compared to the oxygen utilization, resulting in an elevation in the amount of ATP produced per oxygen consumption (P/O ratio) (155). This is supported by the fact that inhibition of endogenous NO generation enhances oxygen consumption without altering ATP production (157). Binding of the NO to the COX can also cause intracellular signaling events, including oxygen diversion to non-respiratory substrates and ROS production with potentially destructive effects (158). These NO-elicited events operate as triggers by which mitochondria regulate signal transduction cascades engaged in the excitation of defense mechanisms and adaptive responses in cells (159).

One of the main components of BR is flavonoids. Flavonoids can affect mitochondrial Ca^{2+} uniporter within the cell and increase mitochondrial Ca^{2+} concentrations. Ca^{2+} regulates various pathways, including the pathway that stimulates eNOS, helps increase NO production, stimulates the flow of K^{2+} and Ca^{2+} , and increases the polarization of cell membranes in endothelial cells (160). These cause the muscles in the blood vessels to relax, thereby lowering blood pressure and enhancement blood flow (17, 161). Also, an increase in mitochondrial Ca^{2+} may by upregulation pyruvate dehydrogenase and increasing the potential of the mitochondrial membrane, stimulate oxidative metabolism; increasing the concentration of ATP produced reduces oxidative stress and muscle damage, and ultimately increases productivity power (162).

Results of Santana et al. (52) and Wylie et al. (163) showed that the NO_3^- can transfer energy source from anaerobic to oxidative sources. They stated that the benefits of NO_3^- consumption on the concentration of blood lactate in endurance running or strenuous exercise depended on the period of supplementation, and the level of physical fitness of the subjects. In addition, the results of Papadopoulos et al. (35) and Whitfield et al. (49) showed that the mechanical basis for reducing VO_2 of the whole body after receiving NO_3^- in the diet does not seem to be an increase in the oxidative efficiency of the muscle or mitochondria, but improving some other mechanisms is inherent; for example, improved contractile performance (59), which is associated with the reduced ATP contraction costs (20). In contrast, the results of Pawlak-Chaouch et al. stated that 3 day the BR supplementation had no effect on the VO_2 and local muscle O_2 delivery and extraction in elite endurance athletes (53). Moreover, Wickham et al. showed that acute (2.5 h) and chronic (8 day) BR consumption has no ergogenically effect among the active women and does not improve aerobic function (54). Furthermore, Arnold et al. concluded that the acute (2.5 h) NO_3^- ingestion did not increase the performance of endurance runners in normobaric hypoxia. They stated that the dose used in this study was not sufficient to produce positive effects. The effects of NO_3^- consumption on the athletic performance in hypoxia depend on the duration, and intensity of exercise (47). According to research (Table 2), acute (2.5–3 h)

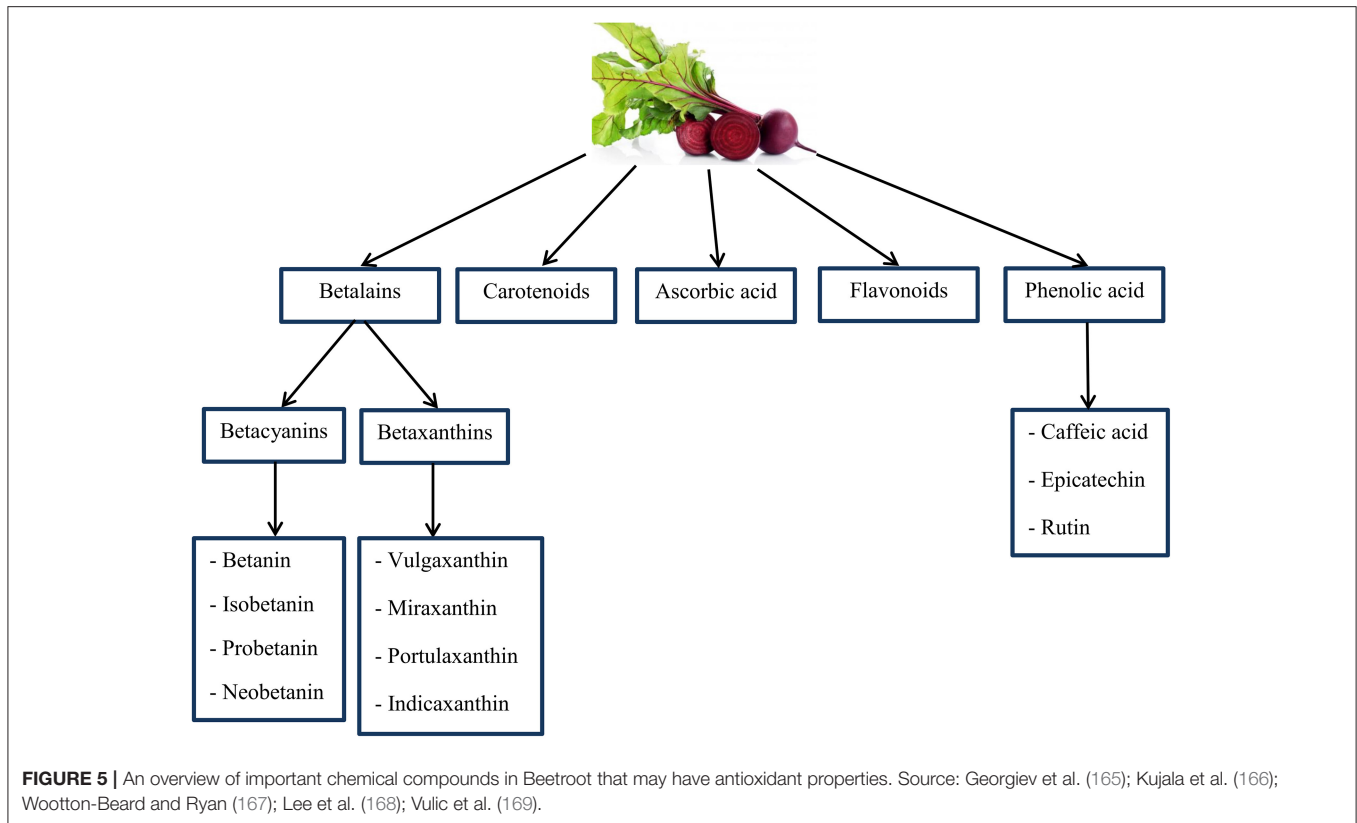
BR supplementation (18, 48–50, 55, 56) does not seem to have much effect on the O_2 Cost and mitochondria, and seems short-term (<15 day) (45, 46, 51, 54, 55) and long-term (≥ 15 day) (51, 52) BR supplementation to have a greater effect. The level of exercise/fitness of the subjects are a very important factor in the effect of the BR supplementation (21, 164). In endurance-trained subjects, especially elite endurance athletes, fewer adaptations occur as a result of the BR supplementation (21). The BR supplementation is less effective in people who are higher fitness level (164). Considering the fitness level of the subjects, it can be said that acute supplementation (2.5–3 h) in trained people probably has no effect (47, 48, 50) and requires longer supplementation courses.

ANTIOXIDANT EFFECTS OF THE BR SUPPLEMENTATION

BR is the main source of chemical compounds including: ascorbic acid, carotenoids, phenolic acid, flavonoids (165–167), and betalains (a group of bioactive pigments) (168, 169). Many animal models have displayed that betalains contain vast anti-inflammatory and antioxidant features properties (169–173). In addition, highly active phenolics include caffeic acid, epicatechin, and rutin are known as the organic antioxidants (165, 174) (as shown in Figure 5). Also, the BR is a dense origin of inorganic NO_3^- , as a substrate for the NO synthesis (175). Some studies have reported that NO_2^- and NO to inhibit radical stablishment and repel ROS and RNS; this is indicating the antioxidant effects of NO_3^- (176, 177).

Betalains and betacyanins (betanin and isobetanin) are complementary components of the BR juice that protect against DNA, protein and lipid damage (178, 179). Physical exercise releases oxidative stress and BR phytochemicals prevent the formation of radicals (2,2-diphenyl-1-picrylhydrazyl and 3-ethylbenzothiazoline-6-sulfonic acid) (180). According to research, administration of the NO_3^- at a rate of 8 ml per kg of body weight per day reduces protein oxidation, DNA damage and lipid peroxidation in rats (178). Wootton-Beard and Ryan recognized the increment in simulated digestion, by the consumption of BR juice as a function of antioxidant and also affirm the juice components are phytochemicals which show similar functions and their structure are changed (167). BR supplement provides a significant source of dietary polyphenols and due to the many health benefits of polyphenols, supplements containing large amounts of it can be beneficial to individuals (167). However, the BR shows possible antioxidant properties via scavenging mechanism regarding radical species. Phytochemicals of BR through signaling pathways inhibit inflammatory diseases (181).

Among the betalains, betanin (betanidin 5-O-b-D-glucoside) is a major phytochemical representative, a water-soluble nitrogen heterocyclic compound that gives the BR a red-violet color (182). In addition, the betanin could inhibit low-density lipoprotein (LDL) and lipid membranes peroxidation because of its bioactive composition, modulating ROS production and gene expression to reduce the inflammatory release of cytokines



and increase antioxidant enzyme activities (183). Some biological effects shown by betanin are reduced in two redox-sensitive pathways, nuclear factor kappa B (NFκB) and nuclear factor erythroid-2-related factor (Nrf2)—antioxidant response element (ARE) are the major transcription genes for inflammatory responses, and are detoxifying/antioxidant (184, 185). The betanin resists gastrointestinal digestion, is absorbed by intestinal mucosal epithelial cells, and actively reaches plasma. With the help of hydrogen or electrons, betanin preserves lipid structures and LDL particles, while inducing the transcription of antioxidant genes through the Nrf2 and also simultaneously suppressing pre-inflammatory NFκB pathways, has the ability to scavenge free radicals (186). Also, flavonoids are able to scavenge free radicals directly by donating hydrogen atoms, a capacity that depends on the total number of hydroxyl groups, the pattern of substitution, and the order of the functional groups in terms of nuclear structure (187). The presence of a catechol group in the B-ring, due to its ability to donate hydrogen, increases the formation of a relatively stable flavonoid-derived radical, which is the most important determinant of reactive oxygen and nitrogen species (RONS) inhibition (188). Flavonoids are not only able to activate enzymatic defense, also can regulate the oxidative status of cells by inhibiting oxidative enzymes responsible for the generation of superoxide (include: xanthine oxidase and protein K) (189). Has been shown that flavonoids inhibit nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, cyclooxygenase, lipoxygenase, and microsomal succinoxidase (190).

Kozłowska et al. stated that the chronic BR consumption enhances lipid peroxidation, and improvement of VO_{2max} after the BR supplement consumption seems to be dependent on baseline lactic acid dehydrogenase (LDH) activity, and also, on the serum concentrations of malondialdehyde (MDA) and β -carotene. It is suggested that alterations in the ergogenic effect of BR are negatively dependent to alter in serum concentration of MDA, β -carotene, and the activity of LDH (57). Singh et al. stated that the BR ingestion significantly declined the stress markers of plasma hydroperoxides and improves the antioxidant status (40). Furthermore, Vidal et al. showed a 32% decrease in the function of inflammatory enzymes lipoxygenase and cyclooxygenase by the phenethylamine—betaxanthin and detalan (173) (Table 2). The BR compounds can (antioxidant phytochemicals, iron, vitamin A and vitamin B6) protect the liver against the oxidative stress and inflammation and increase regular detoxification activity (173). It not only prevents oxidative stress, but also reduces anemia. The BR is rich in iron and effectively improves tissue oxygenation and reduces the symptoms of anemia (191). Moreover, with its antioxidant and low fructose properties and high sucrose content, it plays an important role in the diet of athletes (191).

Studies showed that dietary NO_3^- exerts protective effects on the kidneys, heart and arteries by increasing the bioavailability of NO and reducing the oxidative stress (192, 193). NO_3^- significantly reduces the production of NADPH-dependent O_2 in the kidney. It seems that the protective effects of NO_3^- and

its antioxidant properties may be due in part to a decrease in NADPH oxidase activity and O_2^- production (194). Additional NO signaling mechanisms include the production of other bioactive nitrogen mediators through nitrosation and nitration of proteins and lipids, leading to changes in the protein function and fat signaling (195, 196). Although extra generation of NO and superoxide anions has toxic influences via the formation of peroxynitrite, NO itself can operate as an antioxidant by repressing other reactive radicals (195, 196).

CONCLUSION

Overall, evidence suggests that the NO_3^- supplementation [acute (2–3 h), short-term (<15 day) and long-term (≥ 15 day)] can modulate contractile function by modulating Ca^{2+} handling and contractile proteins, improve skeletal muscle metabolic control by reducing the cost of high-energy phosphates in the contraction and accumulation of fatigue-related metabolites, and improve skeletal muscle perfusion and may increase the performance of resistance training. It may also improve and maintain muscle productivity strength by improving blood flow to the type 2 fibers, and ultimately improve the performance of resistance training. BR due to its ability to increase NO_2^- and NO in plasma can increase adaptation to endurance training. By increasing mitochondrial function, decreasing the cost of muscle contraction oxygen, and increasing the contractile force in the fast-twitch muscles, it can increase the intensity of exercise (short-term (<15 day) and long-term (≥ 15 day) BR supplementation to be more effective). The amount of BR used and the time of its consumption is one of the important and

influential factors on its effects on the athletic performance. BR also affects anabolic hormones through NO. It seems that different concentrations of NO can alter the hormonal response of cortisol and testosterone. NO is an intracellular and extracellular messenger for regulating certain cellular functions, including changes in the hormone secretion for the anabolic and catabolic purposes. Few researches have been done in this field (Table 2) and more research are needed for more accurate results.

In addition, the BR is the main source of compounds including: ascorbic acid, carotenoids, phenolic acid and flavonoids, and betalains. The betalains have high antioxidant and anti-inflammatory properties. In addition, highly active phenolics such as caffeic acid, epicatechin, and rutin are known as the organic antioxidants and protect against DNA, protein, and lipid damage. In addition, in terms of RPE, the BR can play a role in reducing muscle RPE and improving function by increasing cerebral blood flow, but the results of research in this regard have been contradictory. Regarding the BR neuronal function, the role of NO can be mentioned, which has numerous molecular purposes among other servo-regulatory control functions, including neurotransmission. In all brain structures, NO appears to regulate the release of several neurotransmitters; NO donors increase the release of noradrenaline from the hippocampus. Further studies are needed to draw more accurate conclusions in this regard.

AUTHOR CONTRIBUTIONS

HA designed the review. HA and EE wrote the review. Both authors read and approved the final manuscript.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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