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Central Stimulation and Peripheral Optimization: The Impact of Caffeine and Beetroot Juice Supplementation and Co-supplementation on Physical Performance - Review.

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Abstract

Background: Supplementation with inorganic nitrates (NO_3^-) and caffeine (CAF) is a common practice in competitive sports. Despite the documented ergogenic effects of both substances, their potential synergy across different exercise models remains a subject of scientific debate.

Objective: The aim of this systematic review was to evaluate and compare the impact of isolated and combined CAF and NO_3^- supplementation on mechanical and physiological parameters in resistance and endurance tests.

Methods: The review was conducted according to PRISMA guidelines by searching PubMed and Scopus databases. Experimental studies on healthy adults, published primarily between 2021 and 2026, regarding the effects of supplementation on power, strength, muscular endurance, and aerobic capacity were analyzed.

Results: Nitrates improved muscular endurance 65% one repetition maximum (65% 1RM) and fatigue resistance in sprints without affecting power at maximum loads (1RM). Caffeine increased power at 75–100% 1RM (primarily in the lower body) and the number of repetitions at 65% 1RM. Co-supplementation (CAF + NO_3^-) showed a significant additive effect only in muscular endurance tasks. No synergy was found in time trials (TT) or cardiorespiratory parameters (VO_2, heart rate).

Conclusion: The combination of caffeine and nitrates is a highly effective strategy for high-volume anaerobic efforts but offers no additional benefits in traditional endurance tests. Optimizing results requires individualizing CAF dosage based on genotype and maintaining proper timing for nitrate intake.

Keywords: caffeine, nitrates, beetroot juice, co-supplementation, physical performance, synergy.

1. Introduction

Modern competitive sports are characterized by an extremely balanced level of athlete preparation, necessitating the search for safe and legal methods to optimize physical performance. In this context, inorganic nitrates (NO_3^-), primarily sourced from beetroot juice (Beta vulgaris), are gaining importance as one of the most effective ergogenic supplements (Antonio et al. 2024). Their mechanism of action is based on the nitrate-nitrite-nitric oxide pathway ($NO_3^- \rightarrow NO_2^- \rightarrow NO$). Unlike the classic oxygen- and L-arginine-dependent synthesis (NOS pathway), nitrate reduction is independent of oxygen availability and is enhanced under conditions of hypoxia and low pH. These properties make it crucial for supporting the body during intense physical exertion (Zoughaib et al. 2024).

The physiological process begins after ingestion, when nitrates are reduced to nitrites by facultative bacteria residing in the oral cavity and subsequently converted to nitric oxide (NO) in the stomach and target tissues (Salem et al. 2025). As a key signaling molecule, NO regulates blood flow, muscle contraction kinetics, and mitochondrial efficiency (Rojas-Valverde et al. 2021). The primary benefits of supplementation include improved exercise economy through reduced oxygen cost and increased time to exhaustion (TTE) (Tian et al. 2025). Although nitrates were traditionally used in endurance sports, current evidence suggests their potential for improving anaerobic power generation and increasing resistance training volume (Rodríguez-Fernández et al. 2021).

However, it is worth noting that effects in elite athletes (VO_2 max > 60-65 ml/kg/min) are often less pronounced than in recreationally active individuals (Tian et al. 2025). These discrepancies may result from high levels of physiological adaptation and diverse protocols, ranging from acute doses taken 2–3 hours before exercise to chronic supplementation lasting several days (Ferrada-Contreras et al. 2023).

Parallel to nitrates, caffeine (CAF) remains one of the most widespread psychoactive compounds in sports. It is found in coffee, tea, energy drinks, and specialized pre-workout supplements. Its absorption rate is determined by the form of administration - forms such as chewing gums are absorbed faster through the oral mucosa compared to capsules or drinks (Heckman et al. 2010). Caffeine metabolism occurs 95% through the CYP1A2 enzyme, the activity of which is strictly genetically determined. Individuals who are "slow metabolizers" may achieve desired effects at lower doses, while in "fast metabolizers," the substance's half-life is shortened, which is further exacerbated by factors such as tobacco smoking. Genetic polymorphisms (e.g., rs5751876 T/T) are also significant, as they may predispose individuals to anxiety following acute caffeine ingestion (Ju-Ji Low et al. 2024)

Peak plasma concentrations of caffeine (T_{max}) usually occur between 30 and 120 minutes after administration (White Jr et al. 2016). Its ergogenic effect is particularly visible during high-intensity exercise. The CAF mechanism is based on blocking adenosine receptors (A1, A2a, A2b) in the central nervous system, resulting in increased concentrations of dopamine and norepinephrine, reduction in rating of perceived exertion (RPE), and analgesic effects. At the peripheral level, caffeine stimulates the release of calcium ions (Ca^{2+}) from the sarcoplasmic reticulum through ryanodine receptors (RyR) and increases the sensitivity of the contractile apparatus to these ions, potentiating muscle contraction force. Additionally, CAF affects sodium-potassium pump activity, which helps maintain membrane potential during intense work (Graham and Spriet, 1995).

The legal status of both substances should be emphasized. Caffeine is not currently on the WADA Prohibited List; however, it is in the 2026 Monitoring Program to detect potential patterns of misuse. Nitrates are included in neither the Prohibited List nor the Monitoring Program.

The hypothesis of synergy between CAF and NIT is based on the assumption that combining central stimulation (CAF) with metabolic and vascular optimization (NIT) will yield an additive effect exceeding the benefits of isolated use. Since caffeine does not directly affect NO concentration, these mechanisms appear complementary. Despite theoretical consistency, the results of human studies remain inconclusive, creating a significant Research Gap (Gilsanz et al. 2024). This paper provides a comprehensive synthesis of current knowledge regarding the effects of isolated and combined caffeine and nitrate supplementation on physical performance.

2. Materials and Methods

2.1. Search Strategy and Data Sources

This systematic review was conducted in accordance with PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines. The literature search was performed in two international databases: PubMed and Scopus. The search strategy was based on a combination of keywords using logical operators: "beetroot juice" OR "nitrate" AND "caffeine" AND "supplementation" AND "exercise performance."

The primary chronological scope included publications issued between 2021 and 2026 to ensure the timeliness of data regarding the direct impact of supplementation on performance. However, to provide a reliable presentation of biochemical foundations and physiological mechanisms of action for nitrates and caffeine, this range was extended to include key source works without time restrictions.

2.2. Inclusion and Exclusion Criteria

Articles meeting the following inclusion criteria were eligible for analysis:

Population: Studies conducted exclusively on healthy adult humans (both athletes and recreationally active individuals).

Intervention: Papers investigating the effects of acute supplementation of beetroot juice/nitrates and caffeine.

Study Type: Experimental studies with a control group (RCT - Randomized Controlled Trials), reviews, and meta-analyses.

Language: Publications in English.

The analysis excluded: animal studies, case studies, and studies where the dietary intervention was not precisely defined in terms of dosage.

2.3. Data Extraction and Quality Assessment

The literature selection process was carried out in stages: (1) screening of titles and abstracts, (2) analysis of full texts for compliance with inclusion criteria. This process was conducted independently by the authors without the use of automated tools such as Rayyan.

3. Results

3.1. Beetroot Juice (BJ) Supplementation

Analysis of the collected data shows that beetroot juice (BJ) supplementation induces specific adaptations in muscle contraction mechanics. It was demonstrated that BJ administration leads to a statistically significant increase in power production in both the concentric (CON) and eccentric (ECC) phases during a squat (Rodríguez-Fernández et al. 2021).

However, the effectiveness of nitrates is strictly correlated with the intensity of the generated load. In the case of maximal efforts (75–100% 1RM), acute BJ supplementation did not contribute to improved velocity or power production in resistance-trained males. Conversely, a clear ergogenic effect was noted in muscular endurance trials (at 65% 1RM), where BJ administration resulted in an increased number of repetitions and improved mean velocity and power (Montalvo-alonso et al. 2025).

In the area of intermittent efforts, nitrate supplementation with BJ proves to be an effective method for improving fatigue resistance during repeated sprints, manifesting as a better ability to maintain power and velocity in subsequent sets (Rojas-Valverde et al. 2021). Regarding physiological parameters, nitrates influence heart rate and oxygen uptake (VO_2) during submaximal efforts; however, their isolated use does not yield significant benefits in time trial (TT) results (Gilsanz et al. 2024).

3.2. Caffeine (CAF) Supplementation

3.2.1. Impact of Genotype on Ergogenic Efficacy

Analysis shows that caffeine supplementation efficacy is strongly determined by genetic factors, specifically the CYP1A2 gene polymorphism. The highest ergogenic effect is observed in individuals with the AA genotype (fast metabolizers), who derive the greatest benefits from this substance (Barreto et al. 2024). In individuals with the AC genotype (intermediate metabolizers), the impact on performance is very small, while in slow metabolizers (CC genotype), no statistically significant differences in results were found after excluding systematic bias, unless higher doses of 6 mg/kg body mass were used alongside an extended waiting period before exercise. Crucially, genetics does not affect baseline results (placebo trials), but only the body's reaction to the supplement (Barreto et al. 2024).

3.2.2. Muscular Strength and Power

Caffeine has a significant impact on mechanical parameters in resistance training, but its action is characterized by specificity regarding the involved muscle groups and the load magnitude. Improvements in velocity and power production were noted at high loads (75–100% 1RM) in lower-body exercises, such as the back squat, while no similar effect was observed in upper-body exercises, such as the bench press. In muscular endurance tasks (65% 1RM load), caffeine supplementation allows for an increased number of repetitions and improved mean velocity and power (Montalvo-Alonso et al. 2025).

3.2.3. Endurance Capacity and Team Sports

The impact of caffeine on aerobic capacity depends on the type of exercise test. In middle- and long-distance time trials (TT), the ergogenic effect is described as small, while significantly more favorable results are recorded in exercise tests conducted to exhaustion (Time to Exhaustion) (Wang et al. 2022). Furthermore, alternative administration routes such as caffeine mouth rinsing have been shown to provide a small but measurable improvement in endurance performance and information processing speed. Optimal results are achieved through short exposure (approx. 5 s) with a low dose (~32 mg), particularly in a fed state, although this method does not significantly impact cognitive accuracy or exhibit a linear dose-response relationship (Deng et al. 2026) In team disciplines, such as football, basketball, or handball, a dose of 3 mg/kg body mass results in increased distance covered during the match, sprint speed, and the number of dynamic accelerations and decelerations (Naulleau et al. 2022). In anaerobic tests (e.g., Wingate test), caffeine increases peak power regardless of the menstrual cycle phase in women (López-Torres et al. 2022).

3.2.4. Subjective Parameters and Dosage

Regardless of the type of effort, caffeine consistently lowers the rating of perceived exertion (RPE), allowing athletes to maintain higher training intensity. The most commonly used doses range from 3 - 6 mg/kg body mass, with studies showing that 3 mg/kg is often sufficient to achieve an ergogenic effect, and higher doses (6 mg/kg) do not always provide additional statistical benefits in muscular endurance (López-Torres et al. 2022). The standard time for taking the supplement is approximately 60 minutes before starting the activity (Barreto et al. 2023).

Caffeine demonstrates efficacy in lower-load tasks (65% 1RM), influencing an increase in the number of repetitions and mean movement velocity (Montalvo-Alonso et al. 2025). The mechanism of CAF action in endurance tests (TT) is significant, but comparative analysis indicates that its influence on physiological parameters, such as heart rate or oxygen uptake, is constant and does not undergo further optimization with changes in supplementation protocols (Gilsanz et al. 2024).

3.3. Synergistic Effect of Caffeine and Nitrates (CAF + NIT)

Studies on co-supplementation suggest that combining central stimulation with caffeine and peripheral metabolic optimization with nitrates yields an additive (summative) effect only under specific exercise conditions. It was observed that the combined intake of CAF and BJ leads to the greatest improvement in performance during fatiguing tasks at 65% 1RM, manifested by an increased number of repetitions and better stabilization of power and velocity compared to isolated supplementation (Montalvo-Alonso et al. 2025).

However, the phenomenon of synergy is not confirmed in classic endurance tests or in the body's physiological responses. Meta-analysis showed that the combination of CAF + NIT does not improve results in time trials (TT) compared to the administration of caffeine alone or nitrates alone. Similarly, combined supplementation did not induce significant changes in heart rate or oxygen uptake (VO_2) beyond values recorded in protocols using only one of these substances (Gilsanz et al. 2024). These results indicate that the synergistic potential of this combination is primarily reserved for high-volume anaerobic efforts (muscular endurance) rather than continuous efforts.

4. Discussion

The primary objective of this review was to evaluate the impact of isolated and combined caffeine (CAF) and nitrate (NO_3^-) supplementation on exercise parameters. Analysis showed that both substances have documented ergogenic effects, but their efficacy is strictly dependent on the type of effort, intensity, and in the case of caffeine genetic predispositions. The most significant finding of this work is the confirmation of a synergistic effect in muscular endurance tasks (65% 1RM) alongside the absence of such benefits in classic endurance trials (TT).

4.1. Mechanisms of Nitrate Action in Resistance Training

Results indicating improved power production in concentric and eccentric phases (Rodríguez-Fernández et al. 2021) and increased training volume at 65% 1RM can be explained by the influence of nitrates on calcium (Ca^{2+}) homeostasis. Nitric oxide (NO) increases calcium release from the sarcoplasmic reticulum and improves the sensitivity of the contractile apparatus, which is particularly important under conditions of increasing fatigue. The lack of BJ impact on maximal loads (75–100% 1RM) suggests that nitrates exhibit preferential action in glycolytic-type efforts where Type II fibers, which are more susceptible to NO-induced metabolic optimization, are recruited.

4.2. Specificity of Caffeine Action and the Role of Genotype

Caffeine showed efficacy in improving power at high loads, but with a clear advantage in lower-body exercises (Montalvo-Alonso et al. 2025). This may result from the larger muscle mass involved in the squat, translating into a stronger cumulative response to central nervous system stimulation and adenosine receptor blockade. A key factor moderating these effects is the CYP1A2 gene polymorphism. The fact that only "fast metabolizers" (AA genotype) achieve full ergogenic benefits highlights the need for individualizing supplementation in competitive sports (Barreto et al. 2024).

4.3. Analysis of the Absence of Synergy in Endurance Efforts

The greatest interpretive challenge is the lack of additional benefits from combining CAF and NO_3^- in endurance time trials (TT). Although both substances improve performance in isolation, their simultaneous administration does not result in an additive effect on physiological parameters such as heart rate or VO_2 (Gilsanz et al. 2024). This may be due to a "ceiling effect" in trained individuals, where physiological mechanisms are already optimized to such an extent that further improvements in exercise economy (by BJ) and central stimulation (by CAF) do not translate into results in continuous-type trials. Another explanation may be caffeine's masking (by raising heart rate and blood pressure) of the vascular benefits derived from nitrate supplementation.

5. Limitations

Despite rigorous literature selection, this review has limitations. The year range (2021–2026) limited the number of analyzed papers, making it difficult to draw unequivocal conclusions for all sports disciplines. Furthermore, differences in protocols (acute vs. chronic supplementation) may influence the final interpretation of nitrate efficacy.

6. Practical Applications

The results of this systematic review allow for the formulation of precise guidelines for athletes and coaches aiming to optimize performance through caffeine and nitrate supplementation:

6.1. Caffeine (CAF) Supplementation Strategy:

- **Dosage and Timing:** A dose of **3–6 mg/kg body mass** in capsule or drink form is recommended **30–60 minutes** before exercise. For caffeine chewing gums, this time is reduced to **5–15 minutes** due to direct absorption through the oral mucosa.

- **Genetic Individualization:** For athletes with the AA genotype (fast metabolizers), a dose of **3 mg/kg body mass** is usually sufficient. Slow metabolizers (CC genotype) should consider a dose of **6 mg/kg body mass** and extend the time between consumption and activity.
- **Movement Specificity:** Caffeine exhibits stronger effects in exercises involving large muscle mass (e.g., lower body).

6.2. Nitrate (BJ) Supplementation Strategy:

- **Dosage:** An effective ergogenic dose should provide **300 to 500 mg** of nitrates (**5–16.8 mmol**). In practice, this corresponds to approximately 140 ml of concentrated beetroot juice.
- **Timing:** Acute supplementation should be planned **2–3 hours** before exercise to allow for the conversion of nitrates to nitrites by oral bacteria.
- **Chronic Protocol:** To maximize adaptation (e.g., improved muscle oxygenation and recovery), supplementation lasting **3–6 days** at doses of approximately **450 mg nitrates per day** is recommended.

6.3. Optimization of Co-supplementation (CAF + BJ):

- Combining both substances is particularly recommended for fatiguing muscular endurance tasks (e.g. training sets at 65% 1RM). This allows for increased training volume (number of repetitions) while maintaining movement velocity and power.

6.4. Key Notes for Practitioners:

- **Oral Hygiene:** During nitrate supplementation, antibacterial mouthwashes and chewing gums (including caffeinated ones) should be avoided, as they can disrupt the oral microflora necessary for nitrate reduction, which may completely block the ergogenic action of beetroot juice.
- **Fatigue Management:** Both substances effectively lower the rating of perceived exertion (RPE), allowing athletes to maintain higher training intensity for longer.

7. Conclusions

1. Supplementation with beetroot juice-derived nitrates (BJ) significantly improves performance in muscular endurance tasks and fatigue resistance during repeated sprints, but does not exhibit ergogenic efficacy in maximal load trials (1RM).
2. Caffeine (CAF) is an effective agent for improving velocity and power production, especially at high loads (75–100% 1RM) and in exercises involving large muscle groups, with its efficacy strictly dependent on the CYP1A2 gene polymorphism.
3. Co-supplementation of CAF and BJ exhibits a synergistic (additive) effect only in fatiguing muscular endurance tasks (65% 1RM), allowing for the maintenance of higher mechanical parameters (repetitions, power) compared to isolated supplementation.
4. In continuous endurance efforts (TT trials) and in physiological responses (heart rate, oxygen uptake), the combination of caffeine and nitrates does not yield additional benefits compared to their separate use.

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