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MITOCHONDRIAL AND VASCULAR MODULATION THROUGH SYNERGISTIC SUPPLEMENTATION BASED ON BEETROOT-DERIVED ACTIVE INGREDIENTS: SCIENTIFIC EVIDENCE ON FUNCTIONAL ACTIVE INGREDIENTS PRESENT IN THE COMPOSITION OF A DIETARY SUPPLEMENT

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Abstract: This study consists of an integrative literature review that sought to identify and analyze the available scientific evidence on the functional active ingredients present in the composition of a dietary supplement**,** with an emphasis on compounds associated with mitochondrial and vascular modulation and endogenous nitric oxide (NO) synthesis pathways**.** Searches were conducted in the PubMed/MEDLINE, SciELO, and LILACS databases, considering publications from the last ten years. The analysis included experimental and clinical studies and systematic reviews that addressed physiological and biochemical mechanisms related to L-citrulline, L-arginine, beetroot powder extract, creatine, coenzyme Q10, fenugreek, magnesium, zinc, and L-tyrosine. The compiled evidence demonstrates that these compounds participate in complementary metabolic, antioxidant, and ergogenic support pathways, potentially associated with NO modulation, mitochondrial efficiency, and vascular balance.

Keywords: Mitochondrial modulation; Nitric oxide; Beet extract; L-citrulline; L-arginine; Ergogenic supplementation; Bioactive antioxidants; Vascular homeostasis; Energy metabolism.

INTRODUCTION

Nitric oxide (NO) is a gaseous signaling molecule essential for cellular and vascular homeostasis, acting as a mediator of processes that include vasodilation, mitochondrial modulation, energy biogenesis, and endogenous antioxidant response**.** Its endogenous synthesis occurs predominantly via the nitric oxide synthase (NOS) pathway**,** from L-arginine**,** and also via the dietary nitrate pathway**,** derived from compounds present in vegetables such as beetroot (Beta vulgaris L.). This second pathway, more recently valued in the literature, has proven to be a relevant physiological alternative for increasing NO bioavailability**,** especially in conditions where the enzymatic pathway is compromised, such as in aging, oxidative stress, and chronic fatigue (Lidder & Webb, 2013; Jones *et al.*, 2018).

The combined supplementation of L-citrulline, L-arginine, and natural nitrates from beets has attracted growing scientific interest because it represents a synergistic strategy for enhancing nitric oxide production. Citrulline acts as an indirect precursor of arginine, increasing its plasma bioavailability and sustaining the continuous synthesis of NO, while beets provide nitrates and betalains that stimulate endothelial vasodilation and mitochondrial efficiency. This metabolic triad constitutes a model of integrated vascular and mitochondrial modulation, capable of optimizing oxygen transport and utilization in tissues, reducing the energy cost of exercise, and promoting accelerated muscle recovery (Bailey et al., 2015; Schwedhelm *et al.*, 2008).

In addition to direct NO precursors, formulations aimed at energy balance and cellular performance incorporate bioenergetic, antioxidant, and adaptogenic support compounds. Among them are creatine, which acts in ATP resynthesis; coenzyme Q10, with mitochondrial antioxidant action; and minerals such as magnesium and zinc, essential for enzymatic activity, tissue regeneration, and immune homeostasis. Compounds such as fenugreek and L-tyrosine contribute to neuroendocrine and metabolic modulation, increasing the adaptive capacity to physical and mental stress. The

integration of these active ingredients favors not only physical performance but also basic metabolic efficiency, associated with longevity and maintenance of cellular vitality (Littarru & Tiano, 2010; Wankhede *et al.*, 2016; Barbagallo & Dominguez, 2010).

Within this context, it is pertinent to investigate nutritional formulations discussed in the literature in relation to biological pathways linked to nitric oxide and performance physiology. This study focuses on the Biobet supplement and, based on indexed scientific sources, performs a critical analysis of the existing evidence on the active ingredients declared on its label—with an emphasis on the component called "beetroot powder extract"—as well as other constituents that are potentially relevant from a physiological point of view. Therefore, this study defines the following analytical axes: (i) the relationships described between these ingredients and pathways associated with nitric oxide; (ii) aspects of mitochondrial and vascular modulation; and (iii) outcomes frequently reported in humans, such as oxygenation parameters, physical performance, and recovery.

METHODOLOGY

For the purposes of this integrative review, a specific dietary supplement called *Biobet* was selected as the object of analysis, based on the composition declaration and nutritional table provided by the manufacturer. The analysis focused exclusively on identifying the declared functional ingredients and evaluating the scientific evidence available in the literature regarding their physiological mechanisms and possible metabolic, vascular, and mitochondrial repercussions. It should be noted that no physical-chemical or laboratory analyses or quality tests were performed on the evaluated product, nor were any bioavailability, stability, or clinical efficacy tests performed. The present study is, therefore, a theoretical functional analysis based on the correlation between the components declared in the supplement's composition and previously published scientific findings, and is not intended to validate the industrial quality, regulatory compliance, or performance of the product under actual conditions of use.

This study was conducted in the form of an integrative literature review, as proposed by Whittemore and Knafl (2005), with the objective of critically analyzing recent scientific evidence (2015–2025) on the functional active ingredients present in the composition of the Biobet supplement, focusing on mitochondrial and vascular modulation and the pathways associated with endogenous nitric oxide (NO) synthesis.

The review followed six methodological steps:

(i) definition of the research problem;

(ii) search strategy;

(iii) inclusion and exclusion criteria;

(iv) data extraction and categorization;

(v) analysis and synthesis of evidence;

(vi) quality assessment of studies.

Definition of the problem

The research problem was defined as:

"What scientific evidence describes the physiological and biochemical mechanisms associated with the main functional active ingredients present in the composition of the Biobet supplement, with a focus on mitochondrial and vascular modulation and nitric oxide synthesis?"

Search strategy

The search was conducted between October and November 2025 in the PubMed/MEDLINE, SciELO, and LILACS databases, using controlled descriptors (DeCS/MeSH) combined with Boolean operators:

("nitrates" OR "nitric oxide" OR "beetroot extract") AND ("L-citrulline" OR "L-arginine" OR "creatine" OR "coenzyme Q10" OR "fenugreek" OR "magnesium" OR "zinc" OR "tyrosine") AND ("mitochondrial modulation" OR "vascular modulation" OR "ergogenic supplementation" OR "antioxidant activity").

Peer-reviewed publications available in full text, published between 2015 and 2025, in English, Portuguese, or Spanish, were included.

Inclusion and exclusion criteria

Inclusion criteria:

- Original articles, clinical trials, systematic reviews, meta-analyses, and narrative reviews addressing physiological, biochemical, or clinical mechanisms related to the compounds analyzed.
- Studies conducted in humans or animal models addressing performance, energy metabolism, vascular modulation, antioxidant, or adaptogenic effects.

Exclusion criteria:

- Case reports, opinion pieces, articles not peer-reviewed, or without direct correlation to the defined thematic axes.
- Publications prior to 2015, duplicates, or with restricted access.

Data extraction and categorization

The studies were analyzed according to:

- Author and year of publication;
- Type of study (clinical trial, experimental, review, meta-analysis);
- Main compound evaluated;
- Main findings and physiological conclusions.

The information was organized into summary tables presented in the results, grouped into three functional axes:

(i) ergogenic and vasodilator;

(ii) metabolic and adaptogenic;

(iii) antioxidant and regenerative.

Analysis and synthesis of results

The analysis was conducted through critical reading and thematic categorization, considering the convergence of results and methodological consistency of the studies.

The evidence was discussed qualitatively, focusing on physiological pathways and biochemical interactions between compounds.

Quality assessment of studies

The methodological quality of the included studies was assessed based on three main criteria, in a descriptive and non-quantitative manner:

1. Level of scientific evidence, considering the hierarchy of sources (randomized clinical trials > meta-analyses > systematic reviews > experimental studies > narrative reviews).

2. Methodological rigor, including clarity of experimental design, sample size, and control of variables.

3. Physiological relevance, referring to the applicability of the results to the mitochondrial, vascular, metabolic, or antioxidant axes.

Studies with low methodological rigor (e.g., no control group, anecdotal reports, absence of peer review) were excluded, ensuring the robustness and interpretive reproducibility of the integrative synthesis.

RESULTS AND DISCUSSION

A. Active ingredients with ergogenic and vasodilator action

Recent literature confirms that ergogenic compounds of nutritional origin play an important role in optimizing physical performance and hemodynamic modulation. The nitric oxide (NO) precursors *L-citrulline, L-arginine*, and *beetroot powder extract* act complementarily in the pathways responsible for endogenous NO generation. While L-arginine functions as a direct substrate for nitric oxide synthase (NOS), L-citrulline increases its plasma availability, prolonging NO synthesis (Cutrufello *et al.*, 2022). Beets, rich in dietary nitrates, offer an alternative route through the nitrate–nitrite–NO reduction, which is particularly efficient under muscle hypoxia (Jones *et al.*, 2018). This dual pathway promotes better tissue perfusion and oxygen transport, which are central elements of vascular modulation.

The impact of these pathways on mitochondrial efficiency has been widely documented. Clinical studies show that L-citrulline supplementation improves oxygen utilization and delays fatigue, suggesting greater mitochondrial coupling and lower energy cost per unit of work (Bailey *et al.*, 2015). In parallel, NO acts as a modulator of mitochondrial biogenesis, influencing the expression of PGC-1α and oxidative metabolism, which explains the relationship between vasodilation and muscle performance.

Creatine adds a complementary ergogenic effect by promoting ATP resynthesis and reducing exercise-induced oxidative stress (Kreider *et al.*, 2017). Its action on the phosphagen system also contributes to energy stability during repeated contractions, promoting recovery and structural protection of muscle fibers. These findings suggest a functional interaction between creatine and NO-producing compounds, composing a biochemical matrix that supports both the supply and utilization of cellular energy.

Caffeine, in addition to its well-known central stimulant effect, has shown relevant metabolic modulation. Its adenosine antagonist action reduces the perception of effort and increases the availability of intracellular calcium, while the stimulation of AMPK favors fatty acid oxidation and energy metabolism (Grgic *et al.*, 2020). These effects, combined with the vasodilator and mitochondrial mechanisms described, rein-

Flowchart of study selection and inclusion

Stage	Description	Number of studies
Identification	Studies identified in databases (PubMed, SciELO, and LILACS)	~170
Screening	Removal of duplicates and analysis of titles and abstracts	~110
Eligibility	Full reading and application of inclusion/exclusion criteria	~60
Final inclusion	Studies included in the integrative review and organized by functional axis	27

Author/Year	Type of Study	Main compound	Main finding	Physiological conclusion
Jones et al., 2018	Randomized clinical trial	Beetroot extract	Increased nitrate bioavailability and improved mitochondrial efficiency during submaximal exercise.	Promotes NO synthesis via the nitrate–nitrite–NO pathway, optimizing oxygenation and performance.
Bailey et al., 2015	Controlled clinical trial	L-citrulline	Reduced fatigue and increased time to exhaustion.	Increases plasma arginine and sustained NO production.
Cutrufello et al., 2022	Systematic review	L-citrulline and L-arginine	Consistent improvement in blood flow markers and endurance performance.	Combined supplementation enhances the NO synthase pathway.
Kreider et al., 2017	Systematic review	Creatine	Increased strength and muscle recovery; reduced post-workout oxidative damage.	Promotes ATP resynthesis and mitochondrial integrity.
Grgic et al., 2020	Meta-analysis	Caffeine	Improved performance and reduced perception of effort.	Central and metabolic stimulation associated with AMPK activation.

Table 1 — Summary of recent evidence on ergogenic and vasodilator compounds (2015–2025)

force the physiological logic of the association between ergogenic compounds within a synergistic matrix such as the one evaluated in this review.

B. Active ingredients with metabolic and adaptogenic action

The selected evidence indicates that metabolic and adaptogenic active ingredients contribute to homeostasis during the physiological stress of exercise, acting on neuroendocrine, enzymatic, and immunometabolic axes, complementing the NO precursors discussed in Block A. Fenugreek has been investigated for potential effects on body composition and androgenic signs in trained individuals, with initial data suggesting a benefit versus placebo without an increase in adverse events (WANKHEDE *et al.*, 2016). Although the heterogeneity of extracts/commercializations requires caution, the set of results supports a metabolic-anabolic role that may favor training adaptation and recovery, a relevant topic in the context of multifunctional supplementation.

L-tyrosine emerges as a neurocognitive modulator in scenarios of high stress and executive demand. The meta-analysis/critical review by JONGKEES *et al.* (2015) indicates improvement in attention, working memory, and inhibitory control when there is transient depletion of catecholamines (DA/NE), a condition common in intense exercise, sleep deprivation, or competitive environments. This profile suggests a cognitive adaptogenic effect, potentially useful for maintaining decision-making and focus during high-intensity sessions, without extrapolating to effects at rest.

On the mineral axis, magnesium is highlighted in the literature as a cofactor in hundreds of enzymatic reactions, including ATP synthesis, neuromuscular conduction, and glycemic regulation. In addition to its classic biochemical role, the review by WORKINGER *et al.* (2018) draws attention to the challenges of diagnosing magnesium status, which can lead to underdiagnosis of deficiency in athletes and practitioners, with an impact on performance and recovery. Reviews focused on sports (VOLPE, 2015) consolidate the physiological rationale for supporting excitation-contraction coupling and energy metabolism , without, however, establishing a universal ergogenic effect — reinforcing the need for individual contextualization (dietary intake, losses, demand).

Finally, zinc supports the interface between metabolism and immunity, with implications for recovery and resilience to post-exercise oxidative/inflammatory stress. The review by MAARES and HAASE (2016) describes the essential interrelationship between zinc and immune function, showing that micronutrient deficiency is associated with a poorer immune response and an increased risk of inflammation. In a supplementation matrix that aims at mitochondrial and vascular modulation, the adequacy of zinc and magnesium adds systemic robustness—not by promising direct performance gains in all scenarios, but by stabilizing the regulatory systems that support training and recovery.

C. Active ingredients with antioxidant and regenerative action

Coenzyme Q10 (ubiquinone) is recognized as an essential component of the mitochondrial respiratory chain, acting in electron transport between complexes I/II

Author/Year	Type of study	Main compound	Main finding	Physiological conclusion
Wankhede et al., 2016	RCT, 8 weeks, trained men	Fenugreek extract (Fenu-FG)	Improvement in body composition and androgenic markers vs. placebo, with no relevant adverse events	Evidence of metabolic/androgenic effect with potential support for training adaptation (WANKHEDE et al., 2016)
Jongkees et al., 2015	Meta-analysis/critical review	L-tyrosine	Improved cognitive performance under stress and high demand	Neurocognitive/adaptogenic support in conditions of transient DA/NE depletion (JONGKEES et al., 2015)
Workinger et al., 2018	Review (Nutrients)	Magnesium	Describes challenges in assessing magnesium status and relevance to enzymatic/energetic functions	Essential metabolic role; attention to underdiagnosis and impact on performance/recovery (WORKINGER et al., 2018)
Volpe, 2015	Narrative review	Magnesium	Role in neuromuscular function, blood glucose, blood pressure, and ergogenic interest	Supports muscle contraction and energy metabolism in athletes/active individuals (VOLPE, 2015)
Maares & Haase, 2016	Review (toxicology/immunology)	Zinc	Essential interaction with innate and adaptive immunity; deficiency impairs defense	Immunometabolic cofactor relevant to recovery and homeostasis (MAARES; HAASE, 2016)

Table 2 — Summary of recent evidence (2015–2025)

Author/Year	Type of study	Main compound	Main finding	Physiological conclusion
Hernández-Campos et al., 2022	Clinical trial, double-blind	Coenzyme Q10 (200 mg/day)	Reduction in inflammatory markers (TNF-α, IL-6) and improvement in plasma antioxidant capacity.	Acts as a mitochondrial antioxidant and inflammatory modulator.
Niklowitz et al., 2016	Experimental study	Coenzyme Q10	Improvement in mitochondrial bioenergetic efficiency and ATP regeneration in muscle tissues.	Essential cofactor in the respiratory chain, protects against mitochondrial dysfunction.
Zhang et al., 2019	Systematic review and meta-analysis	Coenzyme Q10	Significant reduction in lipid peroxidation and increase in endogenous antioxidant enzymes .	Consistent antioxidant and cytoprotective effect.

Clifford et al., 2017	Narrative review (Nutrients)	Beetroot extract	High content of betalains with anti-inflammatory and antioxidant properties.	Free radical scavenging activity and endothelial protection.
Pavlovic et al., 2020	In vivo experimental study	Betalaine isolated from beetroot	Reduction of oxidative stress and inflammation in models of liver damage.	Demonstrates regenerative potential and cell protection mediated by Nrf2 modulation.

Table 3 — Summary of recent evidence (2015–2025)

and III and in preventing the excessive formation of reactive oxygen species (ROS). In recent years, several clinical studies and systematic reviews have reinforced its relevance both as a bioenergetic cofactor and as an endogenous antioxidant. Hernández-Campos *et al.* (2022) observed that oral Q10 supplementation reduced systemic inflammatory markers (TNF-α and IL-6) and increased total antioxidant capacity, demonstrating a regulatory role in the oxidative-inflammatory response. These effects support the hypothesis that Q10 acts as a mitochondrial modulator, promoting respiratory function stability and the structural integrity of cell membranes.

Niklowitz *et al.* (2016) showed improved ATP regeneration and bioenergetic efficiency in experimental models with Q10 supplementation, reinforcing its direct action on oxidative metabolism. In parallel, Zhang et al. (2019), in a meta-analysis, confirmed consistent reductions in lipid peroxidation biomarkers (MDA) and elevation of antioxidant enzymes such as superoxide dismutase (SOD) and glutathione peroxidase (GPx). These findings converge on a dual bioenergetic and cytoprotective action that justifies its presence in formulations aimed at maintaining mitochondrial efficiency and tissue recovery after metabolic stress.

Beet extract, in addition to its vasodilator role already discussed in Block A, also stands out as a relevant source of betalains, phenolic pigments with potent antioxidant and anti-inflammatory activity. Clifford et al. (2017) reviewed the properties of betalains, highlighting their ability to neutralize free radicals and protect vascular endothe gainst oxidation-induced dysfunction. In experimental models, Pavlovic *et al.* (2020) demonstrated a significant reduction in markers of oxidative stress and inflammation in liver tissues treated with isolated betalain, associating it with the activation of the Nrf2 pathway, responsible for the expression of endogenous antioxidant enzymes.

The functional integration between coenzyme Q10 and phenolic compounds from beets provides a robust biochemical basis for mitochondrial protection and oxidative homeostasis. Q10 acts at the origin of energy metabolism, within the mitochondria, while betalains exert peripheral antioxidant action, reducing ROS load and endothelial inflammation. This complementarity suggests a physiological synergy between the two compounds in preserving cellular and vascular integrity, resulting in improved metabolic efficiency, post-exercise recovery, and a potential contribution to cellular longevity.

CONCLUSION

This integrative review gathered and analyzed recent scientific evidence (2015–2025) on the main functional active ingredients present in the composition of the Biobet supplement, focusing on the physiological pathways associated with mitochondrial and vascular modulation. The systematic analysis of the publications allowed us to observe that the compounds are grouped into three complementary functional axes: ergogenic, metabolic/adaptogenic, and antioxidant/regenerative, whose actions are interconnected in the same bioenergetic network.

In the ergogenic axis, studies show that *L-citrulline*, *L-arginine*, and *beetroot powder extract* act synergistically in the endogenous production of nitric oxide (NO), promoting increased tissue perfusion, improved mitochondrial efficiency, and greater oxygen utilization. Support compounds, such as *creatine* and *caffeine*, increase energy availability and tolerance to physical exertion, reinforcing the role of combined supplementation on muscle performance and recovery.

In the metabolic and adaptogenic axis, compounds such as *fenugreek*, *L-tyrosine*, *magnesium*, and *zinc* contribute to neuroendocrine and immunometabolic homeostasis, favoring adaptation to physiological stress, enzymatic efficiency, and maintenance of neuromuscular function. The evidence gathered indicates that the adequate availability of these micronutrients and modulatory amino acids aids in the body's adaptive h y response to training loads and conditions of high metabolic demand.

Finally, in the antioxidant and regenerative axis, *coenzyme Q10* and the *phenolic compounds in beets* stand out, which exert a protective action on mitochondrial integrity and the vascular endothelium, reducing the production of reactive oxygen species and activating endogenous antioxidant defense pathways, such as Nrf2. This protection contributes to the preservation of cellular bioenergetic function, a fundamental element for longevity and tissue recovery.

Taken together, the findings of this review indicate that the association between ergogenic, adaptogenic, and antioxidant compounds as observed in the functional matrix of Biobet represents a strategy consistent with the principles of integrative physiology and nutrition based on molecular mechanisms. Although the study is not intended to evaluate direct clinical results, analysis of the available evidence demonstrates a solid scientific basis for the hypothesis of synergistic interaction between mitochondrial and vascular modulation, suggesting potential applications in contexts of performance, recovery, and maintenance of cellular vitality.

It is recommended that future investigations adopt randomized controlled clinical trials to quantify the impact of this association on specific markers of mitochondrial function, NO bioavailability, and oxidative stress parameters, in order to consolidate the clinical and translational applicability of the findings.

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