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DECODING THE ROBUSTA PARADOX: PHARMACOGENETIC ANALYSIS AND STRATEGIES FOR PERSONALIZED CAFFEINE INTERVENTION IN VIETNAM'S ELITE SPORTS

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Abstract:

Problem Statement: In the increasingly rigorous landscape of elite sports, the pursuit of safe and legal ergogenic aids remains a paramount priority. Caffeine (1,3,7-trimethylxanthine) has established itself as the "gold standard" within this category. However, significant inter-individual variability in response, coupled with the unique coffee consumption culture in Vietnam, where the caffeine-dense Robusta variety is predominant, has created critical knowledge gaps regarding optimal dosage and practical efficacy (Guest *et al.*, 2021; Southward *et al.*, 2018). **Approach:** This study conducts a systematic and narrative review, synthesizing literature evidence from PubMed and Scopus databases, alongside consensus statements from the International Society of Sports Nutrition (ISSN) (Guest *et al.*, 2021). The methodology focuses on analyzing molecular mechanisms, the impact of pharmacogenetics (specifically the *CYP1A2* and *ADORA2A* genes), and empirical comparisons between Vietnamese consumption habits and international standards (Barreto *et al.*, 2023; Pickering & Kiely, 2024). **Purpose:** This report aims to elucidate the multidimensional mechanisms of caffeine on athletic performance, evaluate the impact of ethno-genetic factors, and develop an Optimized Intervention Framework (OIF) tailored to the specific profiles of Vietnamese athletes. By addressing the "Robusta Paradox," the study seeks to maximize athletic achievements while mitigating potential health risks. **Results:** Caffeine enhances endurance performance by 2–4% and muscular strength by 2–6% (Southward *et al.*, 2018; Szerej *et al.*, 2024). However, Vietnamese athletes face a higher risk of toxicity due to the caffeine content in domestic Robusta (2.2–2.7%), which is nearly double that of international Arabica (1.2–1.5%) (Cafely, 2024; Solaí Coffee, 2024). Regarding the *CYP1A2* gene, the AA genotype displays significant performance improvements, whereas the CC genotype may lead to ergolytic effects and adverse cardiovascular side effects (Barreto *et al.*, 2023; Pickering & Kiely, 2024). Recent studies from 2024–2025 confirm that a 3 mg/kg dose in capsule form is optimal for the vast majority of endurance athletes (Wang *et al.*,

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2025a). **Conclusions:** Caffeine intervention must be individualized based on genetic profiles and habitual consumption patterns. Vietnamese athletes should receive specific guidance on regulating dosages from natural coffee sources, while prioritizing alternative delivery formats such as caffeinated gum or mouth rinsing to achieve peak performance without compromising sleep quality or the recovery process (Silva *et al.*, 2025).

Keywords: caffeine; athletic performance; robusta; pharmacogenetics; Vietnam

1. Introduction

The modern era of sports science has witnessed a paradigm shift from traditional training methodologies to the comprehensive integration of ergogenic nutritional solutions. Among these compounds, caffeine (1,3,7-trimethylxanthine) occupies a unique position, attributed not only to its global ubiquity but also to its volatile regulatory history. Prior to 2004, the World Anti-Doping Agency (WADA) classified caffeine as a restricted substance, with a prohibited urinary threshold of 12 mg/mL (Navarro *et al.*, 2019; WADA, 2004). However, the recognition of caffeine as an integral part of global dietary culture led to its removal from the Prohibited List on January 1, 2004, subsequently transitioning it into the Monitoring Program to track potential abuse trends (Gonna Fuel, 2024; Navarro *et al.*, 2019).

Currently, it is estimated that 75–80% of athletes participating in World Championships and the Olympic Games utilize caffeine as part of their competitive strategy, particularly in endurance disciplines such as cycling, marathons, and triathlons (Guest *et al.*, 2021; Southward *et al.*, 2018). Although the efficacy of caffeine in enhancing endurance, strength, and cognitive function has been validated through thousands of studies, a major challenge persists: the immense inter-individual variability in response (Pickering & Kiely, 2024). A fixed dosage of caffeine may provide a winning advantage for one athlete while inducing tremors, anxiety, and performance impairment in another (Silva *et al.*, 2025). Modern nutritional science has begun to decode these discrepancies through the field of pharmacogenetics, focusing on single-nucleotide polymorphisms (SNPs) in genes such as *CYP1A2* (the metabolic enzyme) and *ADORA2A* (the target receptor) (Barreto *et al.*, 2023; Rahimi *et al.*, 2023).

In Vietnam, this issue becomes more complex than ever due to specific geographical characteristics and agricultural culture. Vietnam is the world's largest producer of Robusta coffee (Interfresh, 2024). Unlike the Arabica variety prevalent in Western countries, Vietnamese Robusta contains nearly double the caffeine content (Cafely, 2024). This creates a "dosage paradox": Vietnamese athletes may inadvertently ingest massive quantities of caffeine through daily lifestyle habits (such as drinking traditional "phin" filter coffee), potentially leading to receptor saturation or chronic overdosage prior to professional interventions (Cafely, 2024). This report is developed to comprehensively analyze the mechanisms of caffeine's action, comparing the latest

international empirical data (2024–2025) with the current situation in Vietnam to propose a scientifically-grounded intervention roadmap.

2. Materials and Methods

This report was conducted based on a systematic review and meta-analysis of literature evidence spanning from 2018 to early 2025. The implementation process strictly adhered to the PRISMA 2020 (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines to ensure objectivity and transparency. Given the specific nature of the sports field, we also integrated methodological adjustments tailored to kinesiology to accurately reflect variables concerning exercise intensity and athletic proficiency levels.

3. Results

Our synthesis of contemporary literature reveals that caffeine does not function as a direct substrate for energy production; rather, it operates as a potent, multidimensional biochemical modulator that simultaneously optimizes neural and neuromuscular pathways. The empirical findings regarding its physiological mechanisms are classified into four primary dimensions.

3.1. Central Nervous System and Adenosine Receptor Antagonism

Physiological Mechanisms of Action: Decoding Multidimensional Effects Caffeine does not function as a direct energy source; instead, it acts as a potent biochemical modulator, simultaneously affecting multiple organ systems (Szerej *et al.*, 2024).

Adenosine Receptor Antagonism and the Central Nervous System: The most dominant mechanism, accounting for over 60% of caffeine's ergogenic effects, is the non-selective antagonism of adenosine receptors, particularly the A_1 và A_{2A} subtypes (Guest *et al.*, 2021; Szerej *et al.*, 2024). Adenosine is an inhibitory neurotransmitter that induces drowsiness and increases the Rating of Perceived Exertion (RPE). By blocking adenosine signaling, caffeine not only prevents the sensation of fatigue but also indirectly enhances the release of excitatory neurotransmitters such as dopamine, norepinephrine, and glutamate (Rahimi *et al.*, 2023).

3.2. Neuromuscular Excitation Contraction Coupling

Regulation of Calcium Ion Flux and Motor Units: Caffeine stimulates ryanodine receptors (RyR) on the sarcoplasmic reticulum (SR) membrane, promoting the release of Ca^{2+} ions into the sarcoplasm. This enhancement facilitates the formation of cross-bridges between actin and myosin filaments, thereby increasing muscular contractile force (Silva *et al.*, 2025; Szerej *et al.*, 2024).

Ion Homeostasis and the (Na+/K+-ATPase) Pump: Caffeine has been demonstrated to stimulate the activity of the Na+/K+-ATPase pump, facilitating the more

rapid reuptake of $K+$ into the intracellular space, thereby delaying the onset of localized muscular fatigue (Silva *et al.*, 2025; Szerej *et al.*, 2024).

3.3. Substrate Metabolism and High-Intensity Dynamics

Metabolic Effects: The classical hypothesis suggests that caffeine promotes "glycogen sparing" by enhancing lipolysis (Guest *et al.*, 2021). However, contemporary evidence indicates that at high intensities ($> 80\% VO2max$), this benefit serves as a positive secondary effect rather than the primary decisive mechanism (Szerej *et al.*, 2024).

4. Discussion

The synthesis of contemporary data underscores that caffeine's ergogenic utility cannot be evaluated through a monolithic lens. The subsequent sections contextualize the multi-systemic mechanisms of caffeine, its pharmacogenetic variations, discipline-specific efficacy, unique cultural implications within Vietnam, and targeted delivery strategies.

4.1. Comparative Analysis of Multi-Systemic Mechanisms

To provide a holistic overview of how caffeine interacts with various physiological domains, the primary molecular and metabolic pathways are systematically structured and compared below. The following table delineates the exact anatomical sites of action alongside their corresponding athletic performance outcomes:

Table 1: Comparison of Physiological Mechanisms of Caffeine Action (Guest *et al.*, 2021; Silva *et al.*, 2025; Szerej *et al.*, 2024)

Mechanism of Action (MoA)	**Site of Action**	**Performance Benefits**
Adenosine Antagonism	Central Nervous System (CNS)	Reduced RPE, enhanced focus, and delayed mental fatigue.
Ca^{2+} Release	Sarcoplasmic Reticulum (SR)	Increases contractile force and improves explosive power.
$Na+/K+$-ATPase pump	Sarcolemma	Maintains membrane potential and delays localized fatigue.
Lipolysis	Adipose tissue	Provides additional fuel substrates and supports weight management.
Glycogen Resynthesis	Post-workout musculature	Accelerates the recovery rate when co-ingested with carbohydrates.

4.2. Pharmacogenetics: Why "One Size Does Not Fit All"

Pharmacogenetics: Why "One Size Does Not Fit All"? The discrepancy in caffeine efficacy among athletes largely resides in their genetic blueprint (Pickering & Kiely, 2024).

The CYP1A2 Gene: The Key to Metabolic Rate: Over 95% of caffeine is metabolized in the liver by the CYP1A2 enzyme (Barreto *et al.*, 2023). Individuals possessing the AA genotype ("fast metabolizers") derive the most significant performance enhancements, ranging from 2% to 5% (Barreto *et al.*, 2023; Pickering & Kiely, 2024). Conversely, those

carrying the AC or CC genotypes ("slow metabolizers") may experience a decline in performance when consuming high doses (Barreto *et al.*, 2023; Pickering & Kiely, 2024).

The ADORA2A Gene: Receptor Sensitivity The rs5751876 polymorphism is closely associated with the sensitivity of adenosine receptors. Individuals carrying the TT genotype typically exhibit high sensitivity; while they are more prone to anxiety, they may also experience more potent neural stimulation (Rahimi *et al.*, 2023).

Table 2: Strategic Stratification based on CYP1A2 Genotype (Barreto *et al.*, 2023; Pickering & Kiely, 2024)

Genotype	Phenotype	Caffeine Response	Practical Guidelines for Athletes
AA	Fast Metabolizer	Substantial performance improvement	Standard dose: 3–6 mg/kg, 60 minutes pre-competition.
AC	Intermediate Metabolizer	Variable response	Trial low dose (1–3 mg/kg).
CC	Slow Metabolizer	Risk of ergolytic effects	Limit high doses; prioritize caffeine mouth rinsing.

Empirical Efficacy across Sports Disciplines (2024–2025 Data).

4.3. Optimization Intervention Framework (OIF) for Vietnamese Athletes

To assist coaches and sports scientists in cross-referencing these outcomes, the empirical effects of caffeine have been categorized by athletic discipline. The following dataset presents the estimated extent of performance variation:

Table 3: Summary of Caffeine Efficacy by Sports Discipline (Southward *et al.*, 2018; Szerej *et al.*, 2024; Wang *et al.*, 2025b)

Sports Category	Improved Metrics	Extent (Estimated)
Endurance	Completion Time	2.0% - 4.5%
Strength	1RM & Volume load	2.0% - 6.0%
Team Sports	RSA & Accuracy	3.0% - 5.0%
Skill-based Sports	Alertness & Smash Performance	5.0% - 8.0%
Precision Sports	Precision Stability	Ergolytic

4.4. Vietnam's Context: Robusta and the "Robusta Paradox"

Vietnam's Robusta beans contain significantly higher caffeine content (2.2% – 2.7%) compared to Arabica (1.2% – 1.5%) (Cafely, 2024; Solaí Coffee, 2024). A single cup of traditional morning "Phin" coffee can deliver between 150 and 300 mg of caffeine (Cafely, 2024; Hello5Coffee, 2024). This high exposure leads to caffeine tolerance, which reduces the sensitivity of adenosine receptors (Guest *et al.*, 2021; Silva *et al.*, 2025).

The consequences of this include:

- **Caffeine Tolerance:** Continuous high-dose consumption reduces both the density and sensitivity of adenosine receptors. Consequently, caffeine loses its ergogenic effect, providing only a "baseline maintenance" effect.
- **Adrenal Fatigue Syndrome:** Constant stimulation of norepinephrine can lead to chronic fatigue and impaired natural recovery capacity.

- **Acute Caffeine Toxicity:** Symptoms such as tremors, nausea, dizziness, and heart palpitations factors that directly compromise athletic performance.

Table 4: Caffeine Content: A Comparison between Vietnam and International Standards (Cafely, 2024; Hello5Coffee, 2024; Solaí Coffee, 2024)

Drink Type	Bean Origin	Serving Size	Caffeine (mg)
Traditional Vietnamese Drip Filter Coffee	100% Robusta	100 ml	100 - 250
Espresso Standard	100% Arabica	30 ml	60 - 80
Energy Drinks	Composite	250 ml	~100

4.5. Delivery Forms and Ingestion Timing Strategies

Caffeine absorption rates are highly dependent on the delivery form. In elite sports, selecting the correct "delivery vehicle" can be a decisive factor between success and failure.

Capsules reach peak concentration after 45–60 minutes, whereas caffeine gum is absorbed through the oral mucosa in just 15–20 minutes (Guest *et al.*, 2021; Wang *et al.*, 2025a). Caffeine mouth rinsing is a sophisticated option for sensitive athletes or those with a slow-metabolizer genotype (Wang *et al.*, 2025a).

Table 5: Comparison of Caffeine Delivery Forms in Sports (Guest *et al.*, 2021; Wang *et al.*, 2025a)

Delivery Form	Tmax (Minutes)	Advantages	Practical Application
Capsules	45 - 60	Standard dosage, cost-effective.	Pre-competition (Long-duration)
Caffeinated Gum	15 - 20	Rapid absorption	Extra time / Substitutes
Mouth Rinse	Immediate	No cardiovascular side effects	Slow metabolizers, late-game fatigue

4.6. Optimization Intervention Framework (OIF) for Vietnamese Athletes

We propose a 4-step model:

- **Screening:** Assess individual sensitivity and genotype (Pickering & Kiely, 2024; Rahimi *et al.*, 2023).
- **Source Management:** Control "Phin" coffee intake and transition to capsules during competition (Cafely, 2024).
- **Dosage:** Establish a baseline dose of 3 mg/kg body mass (Wang *et al.*, 2025a).
- **Sleep Protection:** Implement a "Caffeine Cut-off" rule after 2:00 PM (Silva *et al.*, 2025).

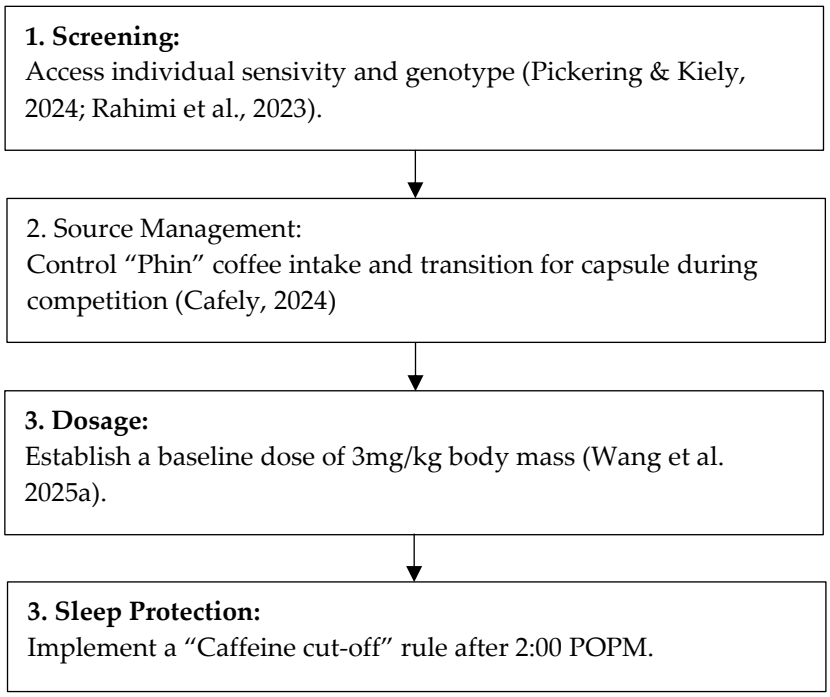

Figure 1: Overview of the Optimized Intervention Framework

4.7 Side Effects and Risk Management

In tropical environments, high caffeine doses (>6 mg/kg) can trigger cardiac arrhythmias and exacerbate gastrointestinal reflux (Silva *et al.*, 2025; Szerej *et al.*, 2024). Athletes must ensure adequate water intake to mitigate the potential diuretic effects (Wang *et al.*, 2025a).

5. Conclusion

Caffeine is a powerful tool, yet it demands a profound understanding of individual genetics (Pickering & Kiely, 2024). Vietnamese athletes must regulate their consumption of traditional Robusta coffee to prevent receptor saturation and prioritize personalized dosing strategies (Cafely, 2024; Barreto *et al.*, 2023). From this comprehensive review, the following key conclusions can be drawn:

First, the efficacy of caffeine in enhancing endurance and strength is indisputable; however, the "golden" dosage trend is gradually decreasing. Data from 2024–2025 indicate that a low dose (3 mg/kg) typically yields the highest net benefit when accounting for potential side effects.

Second, Vietnamese athletes operate in an environment with exceptionally high natural caffeine concentrations due to Robusta beans. The lack of regulation regarding daily coffee habits remains the most significant barrier to optimizing caffeine use in professional competition.

Third, ethnic genetic diversity must be respected. Identifying individual genotypes or assessing personal sensitivity is the foundation for preventing adverse reactions in slow metabolizers (CC genotype).

Conflict of Interest Statement
The author declares that there is no conflict of interest regarding the publication of this work.

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