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INNOVATIVE DELIVERY TECHNOLOGIES AND PHARMACOKINETIC ADVANCEMENTS IN CAFFEINE SUPPLEMENTATION FOR HUMAN PERFORMANCE: A NARRATIVE REVIEW

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ABSTRACT

Background and aim: For decades, caffeine has been considered a widespread and universally beneficial ergogenic aid. This perspective is reflected in guidelines and standardized dosage recommendations. However, contemporary evidence indicates that the traditional approach is not entirely effective in practice, and the effectiveness of caffeine supplementation may be influenced by factors such as age, gender, carrying specific allegles of genes responsible for caffeine metabolism, type of undertaken physical activity, or even the time of the day and the route of supplementation. This review aims to synthesize recent high-level evidence regarding these modifying factors.
Description of the state of knowledge: Current data most often indicate that a safe dosage of caffeine falls within the range of 3–6 mg/kg of body weight. In the analyzed studies, this dosing regimen minimized the occurrence of bothersome side effects while consistently improving outcomes across mixed performance metrics. Specifically, caffeine enhances endurance, muscle strength - especially in the upper body when using free-weight loading - and the overall ability to undertake intermittent exercise, which is characteristic of team sports.
Conclusion: While caffeine has an ergogenic effect in the majority of athletic scenarios, the modern approach, combining sports medicine and personalized medicine, does not focus on proving caffeine's baseline efficacy but on determining in which contexts its effects are most beneficial. Therefore, further exploration of this topic is required, taking into account the emerging individual variables.

KEYWORDS

Caffeine; Exercise Performance; Ergogenic Aids; Nutrigenomics; Delivery Technologies; Personalized Medicine

CITATION

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1. Introduction

Caffeine (1,3,7-trimethylxanthine) remains one of the most widely consumed psychoactive substances and a well-established ergogenic aid in sports nutrition [1–3]. Although previously included on the World Anti-Doping Agency (WADA) Prohibited List, it was removed in 2004 due to difficulties in distinguishing performance-enhancing use from usual dietary intake, as well as a considerable individual variability in response to that kind of stimulation [1,4]. Despite its removal, caffeine remains under WADA's current Monitoring Program, but it does not interfere with ongoing scientific and practical interest in its use in sports, both professional and recreational [1,5].

In nature, caffeine is found in a variety of dietary sources, including coffee beans, tea leaves, guarana seeds, and cocoa beans [6]. Nowadays, caffeine is also widely available in commercial products, including energy drinks, caffeinated soft drinks, dietary supplements, and pharmacological preparations (e.g., pre-workout formulations, anhydrous caffeine capsules, and caffeine-containing analgesics) [1,7]. While the scientific literature evaluates caffeine across this entire spectrum of delivery vehicles, isolated anhydrous forms are frequently used as the experimental gold standard to allow for strict dosage standardization and to minimize confounding variables introduced by whole-food matrices [1,8].

The primary impact of caffeine is attributed to its antagonism of adenosine A1 and A2A receptors in the central nervous system; however, its active metabolites can also act through the peripheral nervous system, skeletal muscle, cardiovascular system, respiratory system, and kidneys [1,9]. Collectively, these mechanisms translate into a reduced rating of perceived exertion, enhanced central motor drive, increased vigilance, shorter reaction times, and faster decision-making [2,10].

Nevertheless, caffeine's ergogenic effects are thought to be dose-dependent, easily influenced by habitual caffeine intake, timing of ingestion, sex, training status, and genetic polymorphisms, particularly in the CYP1A2 and ADORA2A genes. Furthermore, its practical utility is frequently limited by side effects [1,8,11].

This narrative review aims to summarize the current evidence regarding the effects of caffeine supplementation on exercise performance, with a specific focus on standardized and isolated forms, integrate biochemical insights with practical applications, and highlight individual susceptibility to the positive effects of caffeine, safety considerations, and emerging perspectives in conducting new studies on caffeine [1,8].

2. Methodology

2.1. Search strategy and data sources

The relevant literature used in this narrative review was identified through a comprehensive structured electronic search of the PubMed database with the use of Medical Subject Headings (MeSH) and free-text keywords. The specific search string utilized was: *("Caffeine"[Mesh] OR "Caffeine"[Title/Abstract]) AND ("Exercise"[Mesh] OR "Athletic Performance"[Mesh] OR "exercise performance"[Title/Abstract])*. Our search focused on articles published in English between 2016 and 2026. The final database query was executed in June 2026.

2.2. Inclusion and exclusion criteria

We selected literature for this review by limiting the initial search results through a set of methodological boundaries. Our inclusion criteria focused on peer-reviewed papers: randomized controlled trials (RCTs), clinical trials, comparative or multicenter studies, systematic reviews, and meta-analyses. In our research, we put emphasis on studies focusing on both elite athletes and recreationally active individuals, regardless of sex. We considered protocols using either clean, isolated caffeine or commercial sports formulations, provided the dosage occurred shortly before or during physical exertion. Studies had to have direct, measured, and objective performance variables, such as muscular strength, power output, aerobic endurance, and time to exhaustion. While building this review, we purposefully prioritized high-level data from meta-analyses and official position statements published by international sports science societies.

On the other hand, we established exclusion criteria to eliminate lower-quality or confounding data. Non-peer-reviewed materials: brief conference abstracts, editorials, and popular media columns were rejected. We also omitted animal models, *in vitro* cell-culture designs, and studies involving children or adolescents. Finally, we excluded trials where caffeine was combined with other potentially ergogenic aids like creatine or beta-alanine, but only in the case where the study design failed to isolate and prove caffeine's independent contribution to the changes in performance.

3. Results and description of the state of knowledge

3.1. Pharmacokinetics and mechanisms of action

Isolated caffeine is an amphipathic compound characterized by rapid and effective absorption within the area of highly vascularized mucosa of the gastrointestinal tract [1–3]. Anhydrous caffeine has good bioavailability and presents nearly identical plasma concentration curves when administered orally or intravenously [1,2]. That confirms the absence of hepatic first-pass elimination effect [1,4]. Following ingestion, the concentration of caffeine in plasma reaches a peak level within 30 to 120 minutes [1,2,8]. This timeline depends on the delivery route and type of co-ingesting food [1,4]. Consuming caffeine supplements alongside a full meal delays gastric emptying, whereas chewing caffeinated gums enables bypassing the gut entirely through direct absorption in the oral cavity via the buccal tissue [1,4,12]. Faster onset of action and avoidance of the digestive tract's restrictions are essential in this case because of the diminished splanchnic blood flow that can occur during intense physical activity [1,2,13].

Caffeine circulating in the bloodstream undergoes hepatic metabolism, roughly 95% of which is mediated by the cytochrome P450 1A2 (*CYP1A2*) enzyme [1,4,14]. This enzyme demethylates caffeine into three active metabolites [1,14]. Paraxanthine (~84%) acts as a competitive adenosine antagonist and accelerator of peripheral lipolysis; theobromine (~12%) causes vasodilation and smooth muscle relaxation; and theophylline (~4%) leads to cardiac stimulation and bronchodilation [1,2,9,14]. *CYP1A2* activity is highly variable and can be accelerated by chronic smoking and excessive habitual caffeine intake, but is severely depressed during pregnancy, hepatic dysfunction, or the current use of oral contraceptives [1,14,15]. Once formed, active metabolites are able to penetrate fluid compartments and biological barriers and to reach their target tissues, with ultimate clearance conducted mainly through the kidneys [1,2,14]. In order to maintain narrative clarity of this review, the physiological and ergogenic outcomes will refer to "caffeine administration" encompassing the collective action of both the main chemical compound and its downstream metabolites [1,2].

The most important effect of caffeine is attributed to its stimulation of the central nervous system by acting as a non-selective antagonist of adenosine A_1 and A_{2A} receptors [1,2,10]. Crucially, caffeine not only

diminishes the fatigue-promoting role of adenosine but also increases the synaptic availability of excitatory neurotransmitters, especially dopamine, noradrenaline, serotonin, acetylcholine, and glutamate, which leads to a rise in alertness and the promotion of motivational processes [2,10,16]. Another significant dopamine-related route suppresses ascending nociceptive pathways, which is thought to reduce the subjective Rating of Perceived Exertion (RPE) [1,2,5].

In the peripheral nervous system, caffeine has two main roles: 1) lowering the recruitment threshold of motor units; 2) improving nerve conduction velocity, thereby optimizing efferent signals sent to the muscles [1,2,17]. In the skeletal muscles, caffeine is thought to directly target the ryanodine receptors (RyR1) inside the sarcoplasmic reticulum [1,2,9]. That kind of stimulation provokes fast release of calcium ions into the sarcoplasm, counteracting fatigue-induced calcium loss, preserving myofilament sensitivity, and maximizing actin-myosin cross-bridge cycling [2,9,17]. Concurrently, the compound upregulates peripheral Na^+/K^+-ATPase activity, helping to stabilize the sarcolemmal membrane potential required for repetitive muscle depolarization and maximal force production [2,9].

Within the myocardium, caffeine elicits positive chronotropic and inotropic responses driven by two primary mechanisms: the antagonism of peripheral adenosine receptors and the subsequent enhancement of catecholamine release [1,2,9,14]. Another important influence is the relaxation of smooth muscle in the respiratory system that contributes to bronchodilation and enhanced ventilation [1,2,14]. Concurrently, caffeine triggers cerebral vasoconstriction while strategically maintaining robust blood flow to active skeletal muscles, thereby securing efficient oxygen delivery during exercise [2,9]. At elevated concentrations, it further inhibits phosphodiesterase enzymes, preventing cAMP degradation; this results in intracellular cyclic AMP accumulation and the prolonged activation of signaling pathways central to lipolysis and metabolic substrate mobilization [1,2,9]. Ultimately, these multifaceted physiological pathways operate in synergy to comprehensively augment overall exercise capacity [1,2,18,19].

3.2. Endurance performance

In elite sports, outcomes often depend on small differences in performance. For instance, in short Olympic track cycling events that last under 8 minutes, an improvement of velocity of less than 1% can determine the results of the competition [1,2,8]. These tight margins find their expression in the vivid interest in caffeine among competitive athletes [1,4]. Analysis of over 20,000 anti-doping urine samples showed that 74% of elite athletes have ingested caffeine before or during events, with endurance sports displaying the highest usage rates [1,4,7].

Meta-analyses confirm that regular caffeine supplementation improves global endurance performance by 2% to 4% [1–3]. A large review of 46 randomized controlled trials analyzed different time trials [1,18]. The data showed that caffeine shortened completion times by an average of 2.3 ± 2.6% (effect size: 0.28) [1,18]. Concurrently, mean power output rose by 2.9 ± 2.2% (effect size: 0.22) [1,18]. Caffeine also provides physiological benefits during prolonged tasks or ultra-endurance events lasting over 2 hours, such as marathons or long-distance cycling [1,2,9,13]. In testing models where subjects performed submaximal exercise combined with high-intensity intervals, introducing a small "topping-up" dose during the later stages of activity (such as the 80th minute) significantly enhanced final time-trial performance in a dose-dependent manner [1,8,12]. Additionally, adding caffeine during continuous endurance sessions improves late-stage cycling time trials by 3% to 7% [1,12,19]. This proves that the compound works well as a dynamic, mid-race choice rather than just a pre-workout option [1,12].

While global meta-analyses show clear benefits across mixed types of physical activity, a major review focusing strictly on 14 randomized controlled trials (which included 22 different comparisons between caffeine and a placebo) provides important, specific insights into running performance [18]. When looking at all the running data together, caffeine significantly improved performance, reducing the time needed to complete a running time trial by an average of 0.71% ± 0.83% [18]. However, a closer look at these running metrics revealed an interesting nuance [18]. When the researchers divided the runners into separate groups based on their training level, the clear statistical advantage of caffeine disappeared [18]. The supplement did not show a definitive standalone benefit when evaluating only highly trained runners or only recreational runners in isolation [18]. A similar lack of a clear standalone effect was noted when looking specifically at middle-distance or long-distance races on their own [18]. From a practical perspective, this running data indicates that in real-world time trials—where athletes must pace themselves over a fixed distance—the actual performance gains from caffeine are very small (under 1%) [18]. This narrow margin is mathematically difficult to prove in small samples of elite or recreational runners [18]. Still, even a 0.71% performance change can dictate victory

or defeat [1,18]. This makes caffeine a valuable tool, despite its seemingly minor impact in certain sub-categories [1,18].

Despite some of the running-specific nuances, the collective findings establish caffeine as one of the most credible ergogenic aids for extending time to exhaustion and improving pacing strategies [1–4]. Those findings have the potential to be utilized in numerous traditional sports disciplines, including cycling [1,19], running [1,18], and rowing [1,24].

3.3. Strength and power output

Weightlifting and powerlifting are characterized by short and intensive efforts. Those athletes aim to accelerate the barbell rapidly during explosive lifts like the snatch or clean and jerk, while maintaining high neuromuscular stability under heavy loads. Therefore, supplements are expected to maximize both the firing frequency of motor units and absolute strength [4,17,25].

Data from a recent meta-analysis reveal an unexpected disparity in maximal strength between upper and lower body musculature. Subgroup analyses consistently showed a statistically significant increase in acute maximal upper body strength following caffeine ingestion [17]. In contrast, lower body dynamic strength outcomes often appeared less definitive [17]. This pattern challenges earlier literature suggesting that larger muscle groups should exhibit a superior performance response compared to smaller structures [2,17].

This difference likely comes down to how researchers measure strength. When studies look at machine-based exercises like the leg press, it is hard to find clear improvements from caffeine [8,17]. However, tests using free-weight compound movements, especially the barbell back squat, regularly show major strength gains [4,17]. On top of that, isometric tests confirm that caffeine increases static force production in the lower body [17]. The mixed results in dynamic lower-body tests probably happen because many studies rely strictly on machines, while failing to report how reliable their testing protocols actually are [17].

Beyond the upper-versus-lower body debate, another factor is how much total muscle mass takes part in the movement. According to this view, engaging large muscle complexes creates a high physical demand that responds better to caffeine [1,2]. For example, moderate doses of 3 mg/kg improve cognitive reaction times, double-task response speeds, and submaximal force [1,2,10]. Yet, the same doses often fail to change isolated maximum voluntary contractions (MVC) when only a small muscle group is tested [1,17]. Ultimately, caffeine seems to work best when athletes perform multi-joint compound actions rather than isolated, single-joint movements [4,17].

3.4. High-intensity intermittent exercise

Assessment of anaerobic power output during short-term, high-intensity efforts mainly consists of the 30-second "all-out" Wingate cycling test. This test is typically performed at external resistances adapted to the body mass. Literature describing the direct impact of caffeine on single-bout, intensive Wingate performance presents highly mixed outcomes. Data from meta-analyses suggest that caffeine ingestion can modestly enhance mean power output by approximately 3% (effect size: 0.18) and peak power output by 4% (effect size: 0.27) [1,2,17]. These findings are supported by individual testing models, which show performance gains of greater than 3% in task completion times, mean power, and peak power during standalone anaerobic activities lasting between 1 and 2 minutes [1,2]. When transitioning from single-bout sprints to repeated-sprint protocols—common in running, swimming, and cycling disciplines—the efficacy of caffeine appears to be tightly regulated by the recovery structure between efforts [1,8].

Previous studies that focused on caffeine supplementation combined with elongated recovery frames (e.g., eighteen 4-second sprints interspersed with 2-minute active recovery periods) demonstrated solid improvements in mean power output by 7% and total sprint work by 8.5% [1,2]. Intermittent field tests with a 90-second recovery interval showed similar improvements in sprint performance; however, this benefit was diminished as the rest period shortened. For example, in protocols with 20-second intervals, caffeine failed to improve repeated-sprint metrics [1,8].

Another important consideration is the non-cyclical nature of team sports, which is hard to mimic in the continuous laboratory repeated-sprinting. Some of the comprehensive meta-analyses confirm that during consecutive sprints with rapid turnarounds, key markers like total work, best sprint time, and last sprint performance remain unaffected [1,8]. On the other hand, in intermittent team games (such as soccer, rugby, and basketball) in a natural environment, where sprint durations are typically shorter and separated by longer, variable recovery periods of lower intensity, the ergogenic effects of caffeine re-emerge [1,21]. Simulation models tracking these multi-directional team-sport activities show that caffeine can successfully enhance total work output and repeated sprint capacity by a margin of 1% to 8% [1,21], but to fully validate these simulation-based findings in practical field settings, researchers have to implement standardized intermittent recovery

protocols. For instance, in soccer-specific research utilizing the Yo-Yo Intermittent Recovery Test Level 1, caffeine supplementation led to a small but significant 2.0% increase in total distance covered (effect size: 0.33), alongside a 2.2% improvement in countermovement jump height (effect size: 0.3) [21]. In contrast, trials using the Yo-Yo Intermittent Recovery Test Level 2—which forces the body into extreme anaerobic metabolism—reported no significant differences in final velocity or total distance [21]. Interestingly, these neutral outcomes persisted even when differentiating between athletes who exhibited low versus high physiological absorption of the substance, suggesting that under extreme, intermittent fatigue, the standalone ergogenic advantage of caffeine is limited [1,21,22].

3.5. Dosage, timing, and individual responsiveness

3.5.1. Optimal and Threshold Dosages for Ergogenic Efficacy

To maximize the ergogenic efficacy of caffeine, several key variable factors must be considered. Firstly, it is important to ingest a concrete and precise amount of caffeine. Most studies and guidelines show that doses ranging from 3 to 6 mg per kilogram of body weight (BW) have the most favorable balance between performance improvement and potential side effects [1,2]. Some emerging evidence, however, indicates that the lower threshold may be as low as 2 mg/kg BW [22], but probably using doses below 3 mg/kg BW might demand dynamic distribution: both before and during a prolonged training session [1]. Small quantities as low as 40 mg in total (approximately 0.5 mg/kg BW) are thought to be effective at enhancing cognitive function, vigilance, and reaction time [1,2]. This might be valuable in athletic scenarios involving severe sleep deprivation, where low-dose caffeine successfully offsets both physical and mental performance degradation [2]. Conversely, administering large caffeine doses is limited by the ceiling effect; exceeding 9 mg/kg BW fails to provide any further statistical increase in outcomes [1] and is connected with a higher incidence of adverse side effects, which will be discussed in another section.

The dosage may be slightly modified to maintain safety and effectiveness while exercising in challenging environmental conditions, for example, for high ambient temperatures, a standard dose of 3 to 6 mg/kg BW remains sufficient [1,2]. In contrast, at high altitudes with compromised oxygen availability, a slightly higher dose of 4 to 6 mg/kg BW has been shown to preserve performance capacity effectively [2,22].

Table 1. Comparison of different caffeine sources, their concentrations, standard serving sizes, and applications in sports science

Caffeine Source	Mean Caffeine Concentration [mg/ 100 ml]	Standard Serving Size (Volume/Mass)	Approximate Caffeine Content per Serving [mg]	Sports Science Application & Specifics [1,7,12]
Brewed / Filtered Coffee	~40–90	1 cup (150 ml)	~60–135	High variability in caffeine concentration depending on bean type and brewing method; contains polyphenols.
Espresso Coffee	~130–200	1 single shot (30 ml)	~40–60	Highly concentrated volume; convenient for rapid pre-exercise ingestion without fluid overload.
Energy Drinks	~30–32	1 can (250 ml / 500 ml)	~80–160	Co-ingested with carbohydrates (usually), taurine, and B-vitamins; carbonation may cause gastric distress in some athletes.
Energy Shots	~130–330	1 mini bottle (60 ml)	~80–200	Concentrated anhydrous dose in low volume; minimizes gastrointestinal discomfort prior to high-intensity training.
Caffeinated Chewing Gum	*Solid matrix*	1 piece of gum	~50–100	Rapid rate of absorption via the buccal mucosa (within 5–15 min); bypasses first-pass hepatic metabolism; ideal for late-exercise fatigue.
Caffeinated Energy Gels	*Solid/ Gel matrix*	1 gel sachet (~40 g)	~25–50	Simultaneously delivers ergogenic doses of caffeine alongside exogenous carbohydrate fractions during endurance tasks.
Tablets / Capsules (Anhydrous)	*Solid matrix*	1 pill/ capsule	~100–200	Considered the gold standard for experimental rigor; provides precise dosing without confounding nutritional compounds.

Source: Adapted from [1], [7], and [12].

3.5.2. Individual variability in response

Even with regular, habitual coffee consumption for stimulation and increased alertness, individual responsiveness to its effects varies significantly. This difference is also significant when caffeine is consumed for athletic performance. One of the most important mechanisms that may underlie these observations is genetic variability, which primarily involves polymorphisms in two genes: *CYP1A2* and *ADORA2A* [1,2,8].

The *CYP1A2* gene encodes cytochrome P450 1A2 (*CYP1A2*), which is directly responsible for caffeine metabolism. A single nucleotide change, 163A>C (rs762551), results in distinct genotypes within the population, which translates into different rates of caffeine metabolism and divides people into fast (AA genotype) or slow (AC and CC genotypes) caffeine metabolizers [1,8,14]. However, the rate of caffeine metabolism does not solely influence the absence or presence of ergogenic effects and should be assessed within a broader spectrum. In one study, ingesting a moderate caffeine dose of 4 mg/kg caused an exceptional 6.8% improvement in cycling time trials for fast metabolizers; conversely, the exact same dose impaired performance in slow metabolizers by 13.7% [1,8]. Other data show that fast metabolizers demonstrated a higher total training volume during repeated resistance exercise and superior maintenance of vertical jump velocity under progressive fatigue during game simulations [1,21]. Interestingly, when considering a general population, habitual caffeine intake among slow metabolizers was associated with an elevated risk of myocardial infarction, hypertension, and pre-diabetes [8,14]. These results may indicate that genetic division impacts not only athletic outcome but also cardiovascular safety [1,14].

The second genetic factor is the polymorphism of the *ADORA2A* gene, which encodes adenosine A_{2A} receptors. The substitution in 1083 T>C (rs5751876) determines individual adenosine receptor sensitivity and clinically translates into the observed individual response after caffeine intake: beneficial stimulation with enhanced focus or an acute anxiogenic effect [1,2,8]. The preliminary cycling trials focusing on the described gene indicate that among people with the TT genotype, a higher percentage experience the ergogenic effect of caffeine than in the group of C allele carriers [1,8]. Interestingly, when considering performing under sleep deprivation and severe fatigue, individuals with the CC genotype show greater resilience and a higher level of cognitive processing in comparison to carriers of the T allele [2,10].

In addition to genetic factors, training status is another individual variable worth considering. Direct comparative studies indicated that trained and untrained individuals, in general, experience similar relative performance improvements after caffeine ingestion [1,8]. Meta-analytic data confirms that there is no statistically significant difference in muscle endurance enhancements between these two cohorts [1,17]. However, when examining the influence of the time of day on the effectiveness of supplementation, it was observed that while both groups benefit equally from morning supplementation, untrained individuals experience larger performance gains during evening testing compared to their highly trained counterparts [1,8].

3.6. Adverse Side Effects and Safety Considerations

Among the many common opinions on caffeine consumption, considerable attention is directed toward its potential negative impacts on the human body, in particular on heart function, blood pressure stability, sleep architecture disruption, dehydration, and, finally, a wide range of gastrointestinal ailments.

3.6.1. Dose-Dependent Toxicity and Multi-Stimulant Risks

Adverse effects are predominantly associated with excessive caffeine intake and comorbidities [1,4]. Detailed guidelines for safe dosing are discussed in Section 3.5.

The severity and frequency of adverse reactions are closely related to the dose administered per kilogram of body weight [1,3]. When the dose exceeds 7 mg/kg of BW, the physiological burden on the body becomes excessive, and the ergogenic effect diminishes [1]. At doses exceeding 8 mg/kg of BW, especially with concomitant prolonged sleep deprivation, the most frequently reported symptoms include nausea and uncontrollable tremors [2].

The general lethal dose of caffeine for an adult human is approximately 5 g [14]; however, cases documented in the literature indicate that rapid ingestion of as little as 3 g (equivalent to approximately 35–40 mg/kg BW) can induce fatal arrhythmias [4,14]. Often, the risk becomes challenging to assess due to the difficulty in accurately determining how much caffeine is in the form consumed—for example, espresso—which, depending on the type of coffee beans used, can contain 58–185 mg [1]. Although this narrative review focuses primarily on isolated forms of caffeine, it's worth mentioning that additional intake of other stimulants (e.g., ephedrine) can also act synergistically and cause spikes in blood pressure and heart rate [4,14].

3.6.2. Somatic and Psychological Symptomatology

Caffeine intake, regardless of training status [1,8], but especially in individuals taking it sporadically or who demonstrate increased sensitivity to it, can cause both somatic and psychological side effects [1,4]. The most frequently reported side effects within the nervous system and muscles include irritability, tremor, increased anxiety, and acute headaches [2,8]. Due to its positive chronotropic and inotropic effects on the myocardium, an increase in resting heart rate and arrhythmogenic potential may occur [4,14]. Furthermore, caffeine can induce transient increases in blood pressure—about 5–10 mmHg in systolic and diastolic blood pressure—mediated by sympathoadrenal activation [14].

The most common gastrointestinal complaints include nausea, cramping, bloating, diarrhea, and gastroesophageal reflux [1,14]. It should be mentioned that the stress associated with professional competition can lower the pain threshold and promote the perception of discomfort from visceral stimuli [11].

Sleep is one of the most essential elements allowing the body to recover, and unfortunately, the suboptimal timing of caffeine ingestion can also significantly disturb it [11,22]. For example, administering 400 mg of caffeine even six hours prior to bedtime significantly increases sleep latency, reduces total sleep duration, and compromises overall sleep efficiency [1,11]. In these contexts, stress and competitive anxiety may exacerbate the described irregularities [11,15].

Caffeine has a diuretic effect; however, it is so mild that the physiological mechanisms that adapt the body to exertion (decreased renal blood flow, sweating) attenuate this response, leading, on the contrary, to a reduction in the volume of excreted urine [1,4,12]. Moreover, there is no clear evidence that caffeine itself exacerbates sweat or urinary losses of key electrolytes such as sodium or potassium under typical sport dosing [1,18].

3.6.3. Dependence and the Withdrawal Confounder

Repeated, extended use of high doses of caffeine can lead to physical dependence [1,8]. Standard experimental designs often comprise a 24-hour period of caffeine abstinence before the actual testing [1,17]. Results show that for habitual users, this abstinence period is frequently associated with headaches, irritability, and excessive sleepiness [8]. Such withdrawal symptoms often impair participant performance during placebo trials [1]. Hence, questions have been raised regarding whether the documented "ergogenic benefit" is actually a mere reversal of withdrawal—returning the athlete to their baseline performance level via caffeine re-consumption—rather than an absolute enhancement of physical capacity [8]. However, this hypothesis cannot fully explain caffeine's universal efficacy; evidence demonstrates that doses as low as 1 to 2 mg/kg consistently enhance both cognitive and physical performance in non-consumers and regular users alike, independent of the pre-test abstinence window duration [1,8,22].

4. Discussion: Emerging perspectives in caffeine research

Although research on the ergogenic effects of caffeine is quite extensive, a critical evaluation of the available studies still reveals areas requiring more detailed analysis [1,8]. A number of biological factors are crucial for achieving specific performance outcomes. Among these, aspects related to nutrigenomics, discussed in more detail above, should be highlighted, because they allow for the segmentation of the population based on both metabolic rate and susceptibility to adverse effects of caffeine [1,8,14].

Demographic disparities are also noticeable: to date, studies have predominantly focused on young, male cohorts [1,8], while further research that also includes older adults could provide data on the effects of caffeine on maintaining cognitive function and physical mobility during the natural aging process [2,20]. Additionally, studies should include a broader representation of women [15,23]. Further exploration is needed into the effectiveness of caffeine during different phases of the menstrual cycle and during oral hormonal contraception [1,15,23].

Due to concerns about side effects, especially those affecting the gastrointestinal tract, traditional forms of caffeine supplementation are sharing the spotlight with modern solutions [4,12]. Caffeinated chewing gums, caffeine mouth rinses, nasal sprays, and inhalation powders containing caffeine are gaining popularity [1,12]. Their innovative nature lies in their primary anatomical site of absorption: they bypass the mucosa of the small intestine in favor of the buccal mucosa or nasal epithelium [12]. However, to reliably assess the usefulness and safety of each alternative form, thorough studies must be conducted on the rate of their absorption and excretion, the dynamics of the changes they cause in plasma caffeine concentration, and the athletic performance achieved under their influence [8,12].

5. Conclusions

Caffeine is one of the most widely utilized and extensively investigated ergogenic supplements [1–3]. It acts mainly as an adenosine receptor antagonist and modulates the central and peripheral nervous system, the circulatory system, the respiratory system, and the skeletal muscles [1,2,9,10]. Many studies confirm that, when used at an appropriate dose (3-6 mg/kg of body weight), it has a positive effect on areas such as endurance and strength [1,2,17,18]. It also has a beneficial effect on the functioning of the nervous system, generally improving focus and reducing the rate of perceived exertion (RPE) [2,10,16].

However, its effects on individuals remain diverse and underscore the need for further research to clarify the influence of genotype, age, and biological sex on the achieved effects [1,8,15,23]. Alternative forms of caffeine supplementation with different absorption routes and pharmacokinetics are also an important aspect determining future development directions [4,12]. Full optimization, enabling the achievement of the best possible athletic performance while maintaining a safe use profile and minimizing adverse effects, therefore requires a comprehensive approach to the topic, as well as further clinical research [8,11,22].

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