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Controversial supplements and emerging doping alternatives in sports: A critical review of evidence, safety, and detection challenges

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Abstract
Background: The global rise in sports supplement use has led to the widespread availability of novel compounds marketed as performance enhancers. These include SARMs, NAD^+ precursors, synthetic peptides, and herbal adaptogens. However, most lack strong scientific validation and carry potential health risks.
Objectives: To critically evaluate the efficacy, safety, regulatory status, and detection challenges of controversial and emerging supplements in sports.
Methods: A narrative review was conducted using literature published between 2010 and 2025, identified via PubMed, Scopus, Web of Science, and regulatory agency sources (e.g., FDA, WADA). Inclusion criteria focused on studies related to ergogenic effects, health outcomes, and legal classification.
Results: SARMs and synthetic peptides are associated with significant health risks, including liver toxicity and hormonal disruption, despite limited clinical evidence supporting their use. NAD^+ precursors show minor metabolic benefits but remain under regulatory scrutiny. Herbal adaptogens offer mild performance effects yet lack standardization and long-term safety data. Detection of these substances poses major challenges due to chemical variability and limited reference standards.
Conclusion: The growing use of under-researched supplements raises ethical and regulatory concerns in sport. Clearer global standards, stronger clinical trials, and athlete education are essential to ensure safe and fair supplementation practices. Until such measures are implemented, caution is advised regarding the use of these compounds.

Keywords: SARMs, NMN, doping, ergogenic aids, regulation

1. Introduction
The current environment for competitive and recreational athletes revolves around improving performance metrics, recovery times, and optimizing body composition which has triggered a surge in the use of dietary supplements and performance enhancing substances (PES). The use of traditional dietary supplements such as whey protein, creatine, caffeine, and branched-chain amino acids (BCAAs) is commonplace and supported by literature (Kerksick *et al.* 2018) [15] promoting their use, however, more recently there has been an emerging category of controversial supplements that has garnered attention. This includes substances like Selective androgen receptor modulators (SARMs), some peptide hormones, and precursors to NAD+ regulators such as Nicotinamide Riboside (NR) and NMN, and herbal adaptogens like ashwagandha and *tribulus terrestris*. A majority of these are marketed as "natural" supplements that are safer than anabolic steroids and other banned stimulants.
Estimated at above USD 40 billion in 2022, the global sports nutrition market is expected to grow significantly due to increased consumer demand, vigorous online advertising, and the influence of unregulated digital promoters (Grand View Research, 2023). Within this industry, numerous products are developed and marketed without scientific scrutiny, clinical evaluation, or verifiable transparency concerning the rigor of ingredient screening. Additionally, the regulatory landscape concerning such products is heterogeneous within regions; some new substances circumvent established regulations by being termed "research chemicals" or "not for human consumption" (Cohen *et al.*, 2022) [3]. Such ambiguity allows unchecked marketing and chronic misuse by athletes looking to blend in with the competition.

Particularly concerning development is the rise of these substances among amateur athletes, adolescents, and even fitness enthusiasts, who often perceive them as low-risk options due to misleading marketing or anecdotal endorsements on social media platforms (Garthe & Maughan, 2018) [10]. Unlike traditional doping agents, these substances often reside in a regulatory grey area, neither explicitly banned nor medically approved, posing ethical, legal, and health-related dilemmas. Additionally, several case reports and toxicological analyses have raised red flags regarding the safety of these substances, including risks of hepatotoxicity, cardiovascular dysfunction, endocrine disruption, and psychiatric side effects (Thevis *et al*., 2021) [40].

From a regulatory standpoint, institutions like the World Anti-Doping Agency (WADA) face increasing challenges in identifying and controlling these rapidly evolving compounds. Detection methods often lag behind, and many emerging substances are either absent from the WADA Prohibited List or not yet fully validated by anti-doping laboratories. For instance, SARMs and peptide hormones, although prohibited, continue to escape detection in routine drug screenings due to their short half-lives, chemical variability, and limited reference standards (Mazzarino *et al*., 2017) [36].

This evolving landscape creates a critical need for a comprehensive, evidence-based evaluation of controversial supplements and novel doping alternatives. This review paper aims to systematically synthesize the current body of literature on these substances, with a particular focus on:

This review focuses on critically examining the proposed mechanisms of action and claimed performance benefits of emerging substances, evaluating the strength and limitations of existing scientific evidence, assessing documented health risks and safety concerns, analyzing the regulatory status and detection challenges, and considering the ethical implications associated with their use across elite, recreational, and amateur sports contexts.

By addressing these dimensions, the present review seeks to inform the sports science community, health professionals, regulatory authorities, and athletes themselves about the risks and realities of these under-researched substances. In doing so, it contributes to a more informed, responsible, and ethically grounded approach to supplement use in athletic contexts

2. Methodology of the Review

This narrative review was conducted to critically evaluate the current body of literature regarding controversial and emerging supplements used in sports. The review focused on assessing the evidence for efficacy, safety, detection challenges, and regulatory status of such compounds, including SARMs, NAD^+ precursors, synthetic peptides, and herbal adaptogens.

2.1 Databases and Search Strategy

A structured search was performed across the following scientific databases: PubMed, Scopus, Web of Science, and Google Scholar which are commonly used in health-related reviews due to their comprehensive indexing of biomedical and regulatory research (Methley *et al*., 2014) [32]. Additional sources included regulatory websites such as the World Anti-Doping Agency (WADA) and the U.S. Food and Drug Administration (FDA).

The search covered the period from January 2010 to March 2025, using combinations of Boolean operators and domain-specific keywords, as recommended by PRISMA and other evidence synthesis frameworks (Page *et al*., 2021):

- "SARMs" or "selective androgen receptor modulators" and "sports" or "doping"
- "nicotinamide riboside" or "NMN" and "athletic performance"
- "peptide hormones" or "BPC-157" or "TB-500" and "detection" or "anti-doping"
- "herbal adaptogens" or "testosterone boosters" AND "WADA" or "supplements"

2.2 Inclusion Criteria

Inclusion criteria were informed by previous sports nutrition reviews (Kerksick *et al*., 2018) [15] and included:

- Peer-reviewed original articles, systematic reviews, clinical trials, and case studies
- Studies examining ergogenic effects, safety profiles, or legal status
- Research involving human participants, particularly in athletic or recreational contexts.

2.3 Exclusion Criteria

- Non-English publications
- Animal-only studies without translational relevance
- Non-peer-reviewed sources
- Articles unrelated to athletic performance

Screening and Selection Process

A total of 270 records were screened by title and abstract after duplicate removal. Of these, 90 full-text articles were reviewed, and 54 studies were included in the final synthesis. The selection process followed general best practices for narrative reviews, including thematic filtering and targeted analysis (Ferrari, 2015) [31].

2.4 Data Extraction and Synthesis

Key data were extracted related to:-

- Mechanisms of action and compound classification
- Claimed vs. measured performance outcomes
- Adverse events and safety findings
- Regulatory and detection-related information

The extracted data were then organized thematically by substance category and critically reviewed to synthesize areas of convergence and research gaps.

3. Controversial and Emerging Supplements in Sports

3.1 Controversial and Emerging Supplements in Sports: Between Performance Enhancement and Regulatory Ambiguity

The expanding market for sports supplements has given rise to a category of substances that exist at the intersection of nutritional enhancement, pharmacological activity, and regulatory uncertainty. Unlike conventional ergogenic aids, such as creatine or caffeine, which are well-characterized and generally accepted for their performance-enhancing effects (Grgic *et al*., 2021) [12], these emerging supplements often lack standardized formulations, robust clinical validation, or long-term safety data. This section provides a detailed examination of four major categories of controversial substances gaining popularity in the athletic

community: Selective androgen receptor modulators (SARMs), NAD+ precursors, peptide hormones, and herbal adaptogens.

3.1.1 Selective Androgen Receptor Modulators (SARMs)

SARMs are a class of non-steroidal compounds that selectively bind to androgen receptors in muscle and bone tissues, mimicking the anabolic effects of testosterone without the full range of androgenic side effects typically associated with anabolic-androgenic steroids (Dalton *et al*., 2013) [5]. The most commonly encountered SARMs include Ostarine (MK-2866), Ligandrol (LGD-4033), and Testolone (RAD-140).

Originally developed for the treatment of conditions such as muscle wasting and osteoporosis, SARMs have become widely available through online vendors and are often marketed as "legal steroids" or "research chemicals." Despite their intended therapeutic potential, no SARMs are currently approved by the U.S. Food and Drug Administration (FDA) for human use outside of clinical trials (FDA, 2022) [7]. Several independent analyses have detected unapproved or misbranded substances within commercial SARM-labeled supplements, sometimes combined with other anabolic agents, posing serious health risks (Cohen *et al*., 2022) [3].

From a performance standpoint, limited clinical data suggest that SARMs may increase lean body mass and improve strength in hypogonadal or elderly populations, but evidence in trained athletes is sparse and methodologically weak (Basaria *et al*., 2013) [1]. Moreover, SARMs are explicitly banned by the World Anti-Doping Agency (WADA) and are listed under the "Anabolic Agents" category of its Prohibited List (WADA, 2024) [30].

Key concern: SARMs are detectable using sophisticated anti-doping tests, but due to their short half-lives and the constant emergence of novel analogues, they often evade routine screenings (Mazzarino *et al*., 2017) [36].

3.1.2 NAD+ Precursors: Nicotinamide Riboside (NR) and Nicotinamide Mononucleotide (NMN)

NAD+ (nicotinamide adenine dinucleotide) is a crucial coenzyme involved in cellular metabolism, mitochondrial function, and DNA repair. As NAD+ levels decline with age and physiological stress, the use of precursors such as NMN and NR has gained traction as potential anti-aging and performance-enhancing agents, particularly in endurance sports (Imai & Guarente, 2014) [14].

These compounds are often marketed for their role in boosting cellular energy, reducing fatigue, and enhancing recovery. While animal studies have demonstrated that NMN supplementation can improve mitochondrial function and physical endurance (Uddin *et al*., 2021) [28], human data remain inconclusive. Recent randomized trials report minimal to modest benefits in metabolic markers and no consistent improvements in athletic performance (Martens *et al*., 2018; Remie *et al*., 2022) [18, 38].

In 2022, the U.S. FDA ruled that NMN may no longer be legally marketed as a dietary supplement because it had been investigated as a new drug prior to being sold as a supplement (FDA, 2022) [7]. However, it remains available in some countries and through online retailers, leading to regulatory confusion and inconsistent enforcement.

Ethical dilemma: NMN and NR are not currently banned by WADA, but their classification may change as more data on performance enhancement become available.

3.1.3 Peptide Hormones and Growth Factors

Synthetic peptides such as BPC-157, TB-500, and IGF-1 LR3 are being increasingly promoted within sports and bodybuilding circles for their supposed regenerative properties. These compounds are often touted as agents that accelerate recovery from injury, enhance tissue repair, and improve joint health (Schroeder *et al*., 2020) [25].

However, many of these peptides are experimental, not approved for human use, and lack any substantial clinical evidence supporting their efficacy or safety. Their proliferation is largely driven by anecdotal reports and underground marketing. Compounding the issue, these peptides are often mislabeled, contaminated, or dosed inappropriately, increasing the potential for harm (Thevis *et al*., 2021) [40].

Peptides such as IGF-1, GH, and others are strictly banned by WADA due to their potent anabolic and recovery-enhancing effects. Moreover, their detection remains technically challenging, requiring advanced analytical methods like liquid chromatography-tandem mass spectrometry (LC-MS/MS) and isotope ratio mass spectrometry (IRMS), (Schanzer *et al*., 2017) [23].

Health risk: The unregulated nature and misuse of peptides raise significant concerns, including immune reactions, tumorigenic potential, and endocrine disruption.

3.1.4 Herbal Adaptogens and Natural Testosterone Boosters

Herbal supplements such as ashwagandha (*Withania somnifera*), *tribulus terrestris*, maca root, and fenugreek are often labeled as adaptogens or natural testosterone boosters. Their appeal lies in the perception of being "natural," "safe," and "legal," despite limited clinical evidence supporting their ergogenic claims.

Ashwagandha, for example, has been studied in a few randomized trials showing mild improvements in strength, VO_2 max, and testosterone levels in men (Lopresti *et al*., 2019) [16]. However, the heterogeneity of extracts, dosing, and study populations make generalization difficult. Similar concerns apply to *tribulus terrestris*, which has shown conflicting results regarding its impact on hormonal levels or performance enhancement (Sellandi *et al*., 2012; Rogerson *et al*., 2007) [26, 22].

While these botanicals are generally permitted for use and are not on WADA's Prohibited List, their unstandardized nature, potential for contamination, and pharmacodynamic unpredictability make them controversial-especially when used in high-performance settings.

Key insight: Even legal adaptogens may interfere with hormone levels, and their long-term safety profiles remain understudied. This conceptual framework provides a comparative overview of four major categories of controversial and emerging supplements commonly used in sports: Selective Androgen Receptor.

Table 1: Status of Emerging Supplements

Compound/Class	Legal Status	WADA Ban	Scientific Support	Major Concerns
SARMs	Not FDA-approved	Yes	Limited	Liver toxicity, detection issues
NMN/NR	Not FDA-approved (USA)	No (yet)	Inconclusive	Legal ambiguity, metabolic impact
Peptides	Experimental use	Yes	Weak	Contamination, tumor risk
Adaptogens	WADA Status as supplements	No	Mild to moderate	Variability, hormone interference

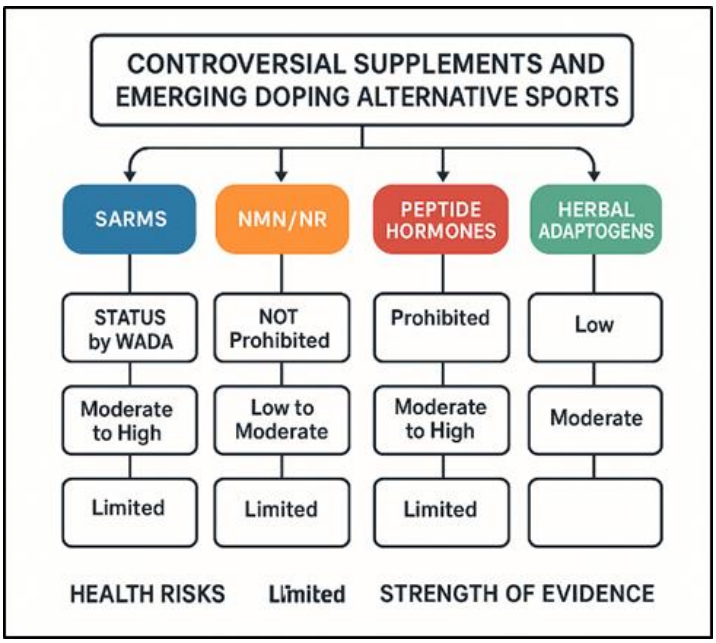

Fig 1: Classification of Emerging Supplements Based on WADA Status, Health Risk, and Scientific Support

Modulators (SARMs), NAD^+ precursors (NMN/NR), Synthetic Peptide Hormones, and Herbal Adaptogens. These substances were evaluated across three critical dimensions: regulatory status according to the World Anti-Doping Agency (WADA), the level of associated health risks, and the strength of scientific evidence supporting their use.

- SARMs and peptide hormones are classified as *WADA-prohibited substances*, with moderate to high health risks, including hepatotoxicity, hormonal suppression, and potential tumorigenic effects. Despite their widespread use in performance enhancement, the scientific evidence supporting their efficacy remains limited and inconclusive.
- NMN and NR are *not currently banned by WADA*, though they remain under scrutiny due to recent FDA reclassification and concerns over long-term mitochondrial stress. Their health risks are considered low to moderate, and their scientific support is primarily based on animal and metabolic studies, not performance-based trials.
- Herbal adaptogens, such as ashwagandha and *tribulus terrestris*, are *legally permitted* but raise concerns due to their hormonal effects, inconsistent formulations, and potential contamination. While generally perceived as low-risk, their efficacy as ergogenic aids is only modest and supported by variable human data.

This classification highlights the complex intersection of legality, safety, and evidence in supplement use. It underscores the need for athletes, coaches, and healthcare professionals to adopt a critical and informed approach when considering these substances, especially in competitive environments governed by strict anti-doping regulations.

4. Scientific evidence on the efficacy of controversial supplements

4.1 Evaluating the Scientific Evidence on the Efficacy of Emerging Supplements in Sports

Despite the increasing use of controversial and novel supplements among athletes and fitness enthusiasts, the scientific foundation supporting their efficacy remains variable, inconsistent, and, in many cases, underdeveloped. Unlike well-researched ergogenic aids with robust meta-analyses and consensus guidelines (e.g., caffeine, creatine), the majority of emerging compounds suffer from limited human trials, small sample sizes, and heterogeneity in study design. This section critically evaluates the available scientific literature for the most prominent substances identified in Section 2, with an emphasis on methodological rigor, clinical relevance, and applicability to athletic populations.

4.1.1 SARMs: Evidence from clinical and preclinical studies

Selective Androgen Receptor Modulators (SARMs) have attracted significant interest due to their ability to promote lean mass and strength gains with fewer androgenic effects. However, despite their biological plausibility and promising preclinical findings, human trials remain scarce, and those that do exist often involve non-athletic populations or use surrogate markers rather than performance outcomes.

A landmark phase I clinical trial by Basaria *et al.* (2013) [1] investigated the safety and efficacy of LGD-4033 in 76 healthy men over a 21-day period. The study demonstrated dose-dependent increases in lean body mass but found no significant improvements in strength or physical performance measures. Importantly, the trial also reported

mild suppression of endogenous testosterone production, raising concerns about hormonal balance even at low doses.

Limitation: These findings may not translate to trained athletes or reflect long-term use scenarios, which are more relevant to real-world sport settings.

Other SARMs, such as Ostarine (MK-2866) and Testolone (RAD-140), have shown anabolic effects in animal models (Narayanan *et al*., 2018) [37], but peer-reviewed clinical data in humans are virtually nonexistent. Additionally, none of the SARMs are FDA-approved for any therapeutic indication, making the available evidence insufficient for supporting their use in sports.

4.1.2 NMN and NR: Metabolic Benefits vs. Performance Outcomes

The enthusiasm surrounding NAD+ precursors like NMN (nicotinamide mononucleotide) and NR (nicotinamide riboside) stems from their proposed role in enhancing mitochondrial function and cellular energy metabolism processes inherently relevant to endurance performance. However, the current body of human research is inconclusive and inconsistent when it comes to actual physical performance improvements.

A double-blind, placebo-controlled study by Martens *et al*. (2018) [18] on NR supplementation in healthy middle-aged and older adults revealed modest increases in NAD+ levels but no changes in physical activity or muscle function. Similarly, Remie *et al*. (2022) [38] found that NMN supplementation improved muscle insulin sensitivity but did not affect cardiorespiratory fitness or exercise capacity in their cohort.

Animal studies have provided more encouraging results for instance, Uddin *et al*. (2021) [28] demonstrated that NMN extended exercise endurance in aging mice but translating such results to human sport performance remains speculative at best.

Conclusion: While NAD+ precursors may offer cellular or metabolic advantages, there is insufficient evidence to support their classification as ergogenic aids.

4.1.3 Peptide Hormones: Anecdotes Outpace Data

Synthetic peptides such as BPC-157, TB-500, and IGF-1 derivatives are widely used in underground bodybuilding and athletic circles based on claims of accelerated recovery, tissue regeneration, and injury prevention. However, the scientific literature is dominated by preclinical studies, and no large-scale human trials have validated their efficacy for sports performance.

For example, most evidence supporting BPC-157 comes from rodent models of tendon and ligament healing (Chang *et al*., 2020) [2]. While such findings may be promising, the absence of dose-standardization, pharmacokinetic studies, and human safety data precludes any conclusions about their real-world applicability.

Similarly, TB-500 (a synthetic version of thymosin beta-4) lacks peer-reviewed human trials and is associated with significant concerns related to immune modulation and oncogenic potential (Schanzer *et al*., 2017) [23]. Despite this, these peptides continue to be sold online and used illicitly, particularly among athletes seeking faster recovery from injuries.

Critical gap: The gap between anecdotal reports and rigorous scientific validation is particularly wide in the case of peptides.

4.1.4 Herbal Adaptogens: Inconsistent Outcomes and Methodological Issues

Botanical supplements marketed as adaptogens or testosterone boosters such as ashwagandha, *tribulus terrestris*, maca root, and fenugreek have attracted considerable interest due to their "natural" profile. However, the scientific support for their ergogenic claims remains mixed.

A meta-analysis by Lopresti *et al*. (2020) [34] examined ashwagandha's effects on physical performance and found small-to-moderate improvements in strength and VO_2 max, especially in untrained or moderately trained individuals. However, significant heterogeneity across trials, along with the variation in extract standardization, limits the generalizability of results.

In contrast, the effects of *tribulus terrestris* have been largely discredited in the context of performance enhancement. A controlled trial by Rogerson *et al*. (2007) [22] found no significant changes in strength, body composition, or testosterone levels after supplementing with tribulus for 5 weeks in resistance-trained males.

Summary: Herbal adaptogens may offer mild physiological benefits, but claims of substantial performance enhancement remain unsupported by strong evidence. To better contextualize the quality and quantity of evidence, the table below provides a simplified scientific appraisal Table 2.

Table 2: Summary and scientific quality appraisal

Substance	Type of Evidence	Human RCTs?	Athletic Population?	Strength of Evidence
SARMs	Preclinical + Phase I trials	Limited	No	Low–Moderate
NMN/NR	Animal + Human metabolic trials	Yes	Rare	Low
Peptides	Preclinical (rodents)	No	No	Very Low
Ashwagandha	RCTs with variability	Yes	Partial	Moderate
Tribulus	RCTs (negative findings)	Yes	Yes	Very Low

In recent years, the global supplement market has witnessed a surge in novel compounds, many of which claim performance-enhancing benefits without sufficient clinical validation. Athletes often rely on social media trends, influencer endorsements, or unverified "biohacking" protocols, leading to increased consumption of substances with unclear regulatory status.

With the increasing availability of such products, distinguishing between legal, monitored, and banned supplements has become increasingly difficult for athletes and support personnel. Some supplements, while not explicitly banned, may fall into regulatory gray zones or be under active review by WADA and national anti-doping agencies.

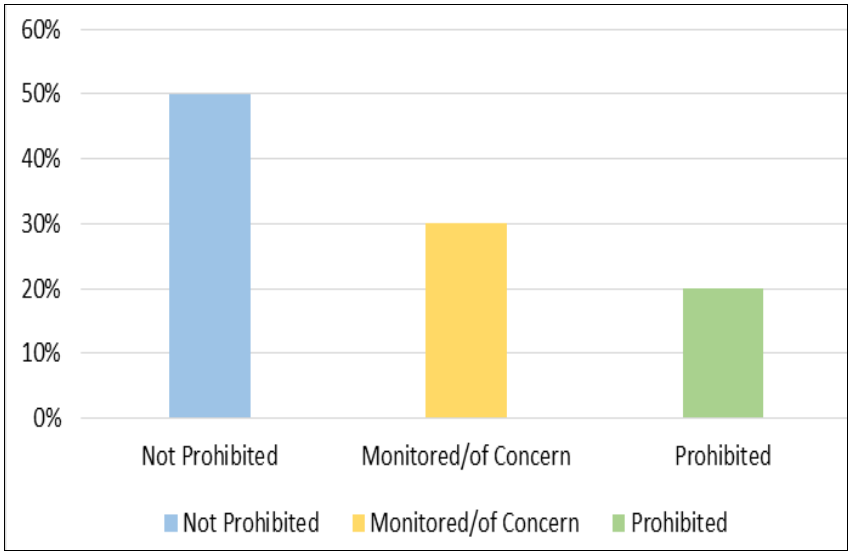

Fig 2: Categorization of performance supplements according to WADA Status (2024)

This figure presents the classification of performance-enhancing supplements based on their current WADA status. Notably, approximately 50% of commonly used supplements, such as creatine and beta-alanine, are not prohibited. Meanwhile, 30% fall into the "monitored" or "substances of concern" category this includes compounds like caffeine (at high doses), NMN, and herbal adaptogens like Ashwagandha. The remaining 20% are classified as prohibited substances, including SARMs, peptides, and metabolic modulators like GW501516.

This distribution underscores the complexity of the regulatory landscape and highlights the need for athletes to seek expert guidance before supplement use.

5. Health Risks and Safety concerns

5.1 Health Risks and Safety concerns associated with emerging and controversial supplements

While the appeal of novel supplements and quasi-pharmacological agents lies in their promises of performance enhancement, rapid recovery, and natural alternatives to banned substances, growing scientific and clinical evidence raises significant concerns regarding their safety profiles. Unlike approved pharmaceuticals that undergo rigorous testing for efficacy and safety, many of these compounds enter the sports market without sufficient toxicological evaluation or regulatory oversight. This section reviews the documented and potential adverse effects associated with selective androgen receptor modulators (SARMs), NAD+ precursors, synthetic peptides, and herbal adaptogens, highlighting both short-term risks and long-term health consequences.

5.1.1 SARMs: Hepatotoxicity, Endocrine Disruption, and Cardiovascular Risk

The most consistently reported health risk associated with SARMs is liver toxicity. Several case reports and observational studies have documented hepatocellular injury in users of commercial SARM products, often compounded by undeclared anabolic agents present in these formulations. A 2021 review of SARM-associated liver injuries revealed elevated ALT and AST levels, cholestasis, and jaundice in multiple users, some requiring hospitalization (Ganjhu *et al*., 2021) [9].

In addition to hepatotoxicity, SARMs may induce endocrine suppression, particularly through suppression of luteinizing hormone (LH) and follicle-stimulating hormone (FSH), resulting in reduced endogenous testosterone levels and impaired fertility in men (Basaria *et al*., 2013) [1]. These effects have been observed even at relatively low doses over short durations, raising concerns about prolonged use or off-label stacking of compounds, Figure 2.

Moreover, emerging data suggest a possible link between SARMs and cardiovascular risks, including altered lipid profiles, increased LDL cholesterol, and potential prothrombotic states although definitive causal relationships require further study (Narayanan *et al*., 2018) [37].

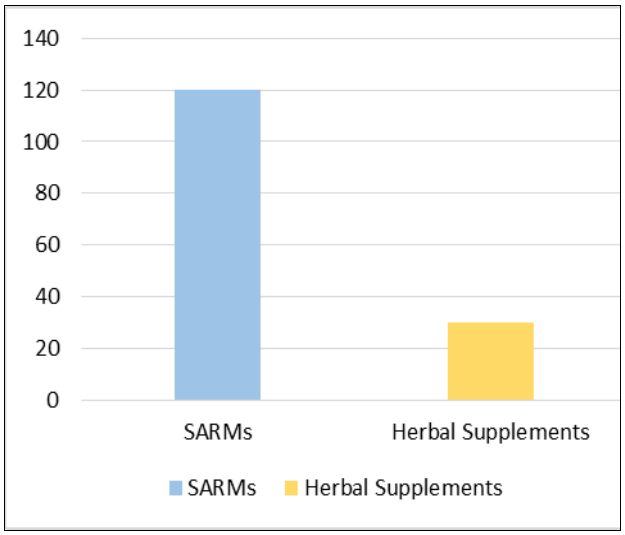

Fig 3: Comparison between SARMs and herbal supplements in reported liver injuries

The bar chart in Figure 3 highlights the pronounced disparity in liver toxicity profiles between synthetic selective androgen receptor modulators (SARMs) and herbal supplements. According to recent pharmacovigilance data and clinical case reports, SARMs have been implicated in a significantly higher number of liver injury cases estimated to be approximately four times greater than those associated with botanical products.

This disproportionate risk profile underscores the growing concern over the widespread, often unsupervised use of SARMs among young recreational athletes and bodybuilders, many of whom are unaware of the potential for hepatotoxicity, endocrine suppression, and cardiovascular complications. In contrast, herbal supplements such as ashwagandha and *tribulus terrestris* have been associated with mild or rare cases of liver dysfunction, typically under conditions of excessive or prolonged use.

While herbal adaptogens are generally regarded as safe when used within recommended dosages, the data clearly support the regulatory stance of the FDA and WADA in restricting SARMs due to their unfavorable risk-benefit profile. This figure further illustrates the need for evidence-based education, proper label transparency, and clinical monitoring when evaluating performance-enhancing substances.

5.1.2 NAD+ Precursors: Mitochondrial Stress and Unknown Long-Term Effects

Though marketed as cellular enhancers and "anti-aging" molecules, NAD+ boosters such as NMN and NR may exert complex metabolic effects that are not yet fully understood. Current clinical studies report high tolerability and few adverse events (Remie *et al*., 2022) [38], but the long-term implications of chronic NAD+ elevation remain unknown. Some animal studies have suggested that sustained NAD+ upregulation could lead to mitochondrial overactivation, potential oxidative stress, or unanticipated interference with circadian regulation and sirtuin pathways (Schondorf *et al*., 2018) [24].

There is also concern that increased NAD+ availability could promote the survival of pre-malignant cells, particularly in tissues under chronic inflammatory stress or aging-related DNA damage though this remains speculative and unconfirmed in humans (Verdin, 2015) [29].

Regulatory note: Given the lack of long-term safety data, the FDA removed NMN from the list of permitted dietary supplements in 2022 (FDA, 2022) [7].

5.1.3 Synthetic Peptides: Tumorigenic Potential and Immune Reactions

Among the riskiest substances in the emerging supplement category are synthetic peptides, such as BPC-157, TB-500, and GH-releasing peptides (GHRPs). These compounds interact with complex signaling pathways, including angiogenesis, growth factor modulation, and immune system activity all of which pose significant risks when deregulated. Preclinical studies have linked TB-500 and similar peptides with uncontrolled cellular proliferation, leading to concerns over their tumorigenic potential (Mazzarino *et al*., 2017) [36]. Additionally, the use of peptide analogs in non-clinical settings often involves unregulated dosing, lack of sterility, and contamination creating risk for severe immune reactions, such as anaphylaxis or cytokine storms (Thevis *et al*., 2021) [40].

Furthermore, peptide use may impair natural hormonal balance, especially when used in cycles with other anabolic agents, which can amplify the risk of endocrine disruption and cardiovascular dysfunction.

5.1.4 Herbal Adaptogens: Hormonal Imbalances and Interactions

Although perceived as safe and natural, botanical supplements particularly those used for testosterone boosting are not without risk. For example, *tribulus terrestris* has been associated with gynecomastia, mood swings, and altered libido in anecdotal reports, likely due to its mild androgenic activity (Sellandi *et al*., 2012) [26].

Ashwagandha, while generally well-tolerated, has been reported to cause hyperthyroidism-like symptoms, including palpitations, anxiety, and insomnia, especially when taken in high doses or combined with other stimulants (Lopresti *et al*., 2020) [34]. Moreover, ashwagandha may interact with sedatives, thyroid medication, and immunosuppressants making it unsuitable for certain clinical populations.

Importantly, herbal supplements often lack standardization of active constituents, meaning that dose and potency can vary drastically between brands and batches, increasing the risk of under or over-exposure (Cohen *et al*., 2022) [3].

5.1.5 Contamination, adulteration and labeling mismatch

Perhaps the most overlooked risk across all supplement categories is contamination or intentional adulteration with undeclared pharmaceutical agents. Multiple studies have identified the presence of anabolic steroids, stimulants, or banned drugs in supplements marketed as "natural" or "legal alternatives" (Geyer *et al*., 2008) [11]. In a 2020 analysis of over-the-counter performance-enhancing supplements, nearly 40% were found to contain unlisted synthetic compounds, some of which were previously removed from the market due to adverse events (Cohen *et al*., 2022) [3].

Athletic consequence: This poses a grave risk for athletes, as inadvertent doping can occur when consuming contaminated products not listed on anti-doping registries, leading to sanctions or disqualification despite no intentional misconduct.

Table 3: Summary of health risks by substance

Substance	Major Health Risks	Clinical Evidence Level
SARMs	Liver injury, hormonal suppression, cardiovascular risk	Moderate (case reports + trials)
NMN/NR	Mitochondrial overactivation, unknown cancer risk	Low (speculative)
Peptides	Immune reactions, tumorigenesis, endocrine disruption	Very Low (preclinical)
Adaptogens	Thyroid imbalance, interactions, hormonal shifts	Low–Moderate
All (general)	Contamination, adulteration, mislabeled doses	High (documented in market studies)

The pie chart in Figure 4 illustrates the estimated distribution of dietary and performance supplements based on their safety profile. According to recent literature and regulatory findings, approximately 45% of marketed supplements are considered safe for consumption under recommended dosages and guidance. However, 35% fall under the potentially risky category due to factors such as undeclared ingredients, unverified claims, or lack of sufficient clinical trials. Notably, about 20% of supplements, including SARMs, certain peptides, and

contaminated herbal products are classified as prohibited by regulatory bodies like the FDA and WADA due to their adverse health effects or performance-enhancing properties.

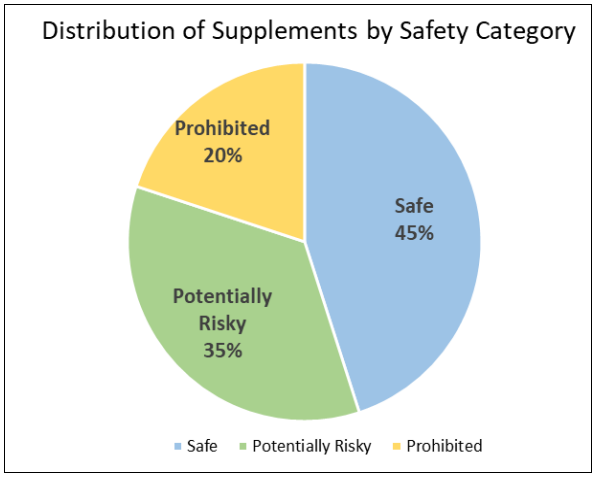

Fig 4: Distribution of supplements by safety category

This distribution emphasizes the need for cautious evaluation of supplement safety, particularly among athletes who may be subject to anti-doping regulations and vulnerable to marketing misinformation.

6. Regulatory status and detection challenges of emerging supplements in sports

6.1 Regulatory status and detection challenges of emerging supplements in sports

As the line between nutrition and pharmacology continues to blur, governing bodies and anti-doping organizations face escalating difficulties in regulating and monitoring emerging supplements. Unlike established pharmaceuticals, many of these substances are marketed as dietary aids or research chemicals, enabling them to bypass strict drug regulations. This section examines the regulatory classification and detection hurdles of SARMs, NAD^+ boosters, synthetic peptides, and herbal adaptogens, particularly in the context of elite sports governed by the World Anti-Doping Agency (WADA) and national health authorities.

6.1.1 Regulatory Gaps: Between therapeutics and supplements

SARMs

- SARMs are classified as investigational drugs by the U.S. FDA, with no currently approved medical uses.
- Despite this, they are widely sold online as supplements or "research-use only" compounds.
- The FDA has issued multiple warning letters and enforcement actions against companies mislabeling SARMs (FDA, 2022).

WADA status: SARMs are explicitly banned under the "S1. Anabolic Agents" category of the WADA Prohibited List.

NMN & NR (NAD^+ Boosters)

- Initially marketed as dietary supplements, NMN was reclassified by the FDA in 2022 as a non-dietary ingredient due to its prior use in drug trials (FDA, 2022) [7].
- This means NMN can no longer be legally sold as a supplement in the U.S., although enforcement remains inconsistent, especially for international e-commerce platforms.
- NR remains available in many markets, although its status is under scrutiny.

WADA status: Not currently banned but may fall under "Substances with Similar Biological Effect" if shown to enhance performance.

Peptides (BPC-157, TB-500, IGF-1 analogs)

- Classified as experimental drugs or unapproved substances, often sold illegally or labeled as "for laboratory use only".
- Peptides like IGF-1, GHRPs, and growth hormone analogs are explicitly prohibited by WADA under "S2. Peptide Hormones, Growth Factors, and Related Substances".
- Regulatory action is limited due to the grey market nature of peptide distribution and difficulty in enforcement.

Key challenge: These peptides often evade customs and doping control systems due to their novel structures and lack of detection benchmarks.

Herbal Adaptogens (Ashwagandha, Tribulus, etc.)

- Considered dietary supplements and regulated accordingly in most jurisdictions (e.g., U.S. under DSHEA 1994).
- However, they are not subjected to pre-market approval, and testing for contaminants or hormonal activity is rare.
- Some countries impose limits on dosage or restrict certain plant derivatives due to pharmacological effects.

WADA status: Not currently prohibited, but some adaptogens may influence hormone profiles and could pose risks for athletes unaware of indirect performance enhancement.

6.1.2 Detection Limitations and Analytical Challenges

SARMs Detection

- WADA-accredited laboratories use liquid chromatography tandem mass spectrometry (LC-MS/MS) to detect SARMs in urine and blood.
- However, the short half-life and constant emergence of new analogs make detection challenging.
- Research by Mazzarino *et al*. (2017) [36] showed that many modified SARMs evade standard anti-doping tests unless specifically targeted.

Peptides Detection

- Peptides are particularly difficult to detect due to their rapid metabolism, low plasma concentration, and similarity to endogenous hormones.
- Advanced techniques like isotope ratio mass spectrometry (IRMS) and protein mass fingerprinting are sometimes required (Thevis *et al*., 2021) [40].
- Laboratories may also use biological passport markers to infer doping indirectly, but this is more feasible for long-term monitoring than for single-event detection.

Adaptogens and Botanicals

- Most herbal adaptogens do not have direct doping markers.
- However, contamination with banned substances (e.g., prohormones, stimulants) is common in some brands.
- A 2008 study by Geyer *et al*. found that nearly 15% of over-the-counter supplements contained undeclared anabolic steroids.

Inadvertent doping remains a critical concern when products are contaminated or mislabeled.

6.1.3 Global inconsistencies in regulation and enforcement

- There is no global consensus on how to regulate many of these compounds.
- A substance may be legal in one country, banned in another, and sold online globally, creating legal grey zones.
- Even WADA relies on national anti-doping organizations (NADOs) for enforcement, which may differ in resources and capabilities.

Table 4: Regulatory and Detection Landscape

Substance	FDA Status	WADA Status	Detection Challenge
SARMs	Not approved	Banned (S1)	Medium–High (short half-life, analogs)
NMN / NR	NMN not allowed as supplement (USA)	Not banned (yet)	Low (no specific markers)
Peptides	Unapproved / experimental	Banned (S2)	High (poor bioavailability, rapid clearance)
Adaptogens	Approved dietary supplements	Not banned	Low–Moderate (due to contamination risk)

7. Ethical Implications and Future Directions

7.1 Ethical implications and the future of supplementation in sport

The rapid emergence of novel supplements particularly those that blur the line between nutritional aids and pharmacological agents raises profound ethical questions. Athletes, coaches, medical teams, and regulatory bodies now face unprecedented dilemmas regarding fairness, informed consent, and the long-term health consequences of using poorly studied compounds.

7.1.1 Fair Play and the Spirit of Sport

The fundamental ethos of competitive sport is rooted in fairness, integrity, and respect. The use of substances that confer a biochemical advantage without adequate safety validation or regulatory approval can undermine the level playing field, especially when access is unequal. For example, elite athletes with access to private medical teams or international vendors may gain early, exclusive access to experimental agents like SARMs or peptides. In contrast, others may either abstain due to ethical reservations or unknowingly consume contaminated supplements and risk unintentional doping violations (Geyer *et al*., 2008) [11].

This disparity raises the question: is it ethical to allow performance gains from compounds that are not yet fully understood, variably accessible, or selectively regulated?

7.1.2 Informed Consent and Athlete Vulnerability

A major ethical concern is the autonomy and informed decision-making capacity of athletes, particularly youth and amateur competitors. Many supplements are marketed using pseudo-scientific language, exaggerated testimonials, and influencer endorsements that obscure the limited or non-existent clinical evidence. Athletes may perceive these products as "natural" and harmless when in fact, some contain experimental chemicals or mislabelled pharmaceuticals.

Moreover, peer pressure, sponsorship demands, and the culture of "marginal gains" can coerce individuals into using untested substances without fully understanding the consequences. This violates the principle of informed consent and places responsibility not just on users, but also on coaches, sports organizations, and even manufacturers.

7.1.3 Health versus Performance: A False Tradeoff

Another ethical tension lies in the trade-off between short-term performance enhancement and long-term health risk. While some substances might offer modest ergogenic effects, the absence of long-term safety data particularly for NMN, SARMs, or synthetic peptides means athletes are effectively volunteering as test subjects without ethical oversight. This contradicts medical ethics principles like non-maleficence ("do no harm") and challenges the role of sports medicine in protecting athletes from harm (Verdin, 2015; Basaria *et al*., 2013) [29, 1].

7.1.4 The need for evidence-based regulation and global oversight

From an ethical standpoint, the current fragmented regulation of supplements is insufficient. National agencies, sports federations, and anti-doping bodies must work toward a unified global framework that:

- Distinguishes between food supplements and pharmacologically active agents
- Enforces accurate labelling and contamination controls
- Promotes public education regarding risks and evidence levels
- Invests in clinical trials and post-marketing surveillance

Develops rapid and reliable detection tools for doping control

Without such frameworks, we risk a landscape where scientific ambiguity is exploited for commercial gain, and athlete health is jeopardized in pursuit of performance.

7.1.5 Future Research Priorities

Given the current knowledge gaps, future research should focus on:-

- Long-term safety trials for NAD^+ precursors and synthetic peptides
- Dose standardization and purity analysis for herbal adaptogens
- Mechanistic studies on SARMs' effects on metabolism, recovery, and hormonal health
- Detection technologies for evolving analogs in doping control
- Behavioral and ethical studies assessing supplement decision-making in youth athletes

Moreover, interdisciplinary collaborations between sport scientists, endocrinologists, toxicologists, and ethicists are essential to create a comprehensive risk-benefit framework for supplement use.

8. Conclusion and Recommendations

The landscape of sports supplementation is evolving rapidly, driven by the introduction of controversial compounds with limited scientific validation. While some agents like NR or ashwagandha show moderate promise in specific contexts, the majority of emerging supplements such as SARMs and unregulated peptides raise significant concerns regarding safety, efficacy, legality, and fairness in sport.

Without robust regulatory frameworks and evidence-based guidance, athletes remain exposed to misinformation, unintentional doping, and long-term health risks. A proactive, multi-sector response is required to ensure ethical and informed use of supplementation in athletic contexts.

8.1 Research Gaps

Despite the growing use of novel supplements, major scientific gaps remain:-

- A lack of large-scale randomized controlled trials (RCTs) assessing performance outcomes in athletic populations.
- Insufficient long-term safety data, particularly for SARMs, NAD^+ precursors, and synthetic peptides.
- Limited research on dose-response relationships, contamination risks, and interaction effects with other supplements or medications.
- Underrepresentation of female athletes, adolescents, and non-elite populations in existing studies.

8.2 Policy Implications

Current supplement regulations are fragmented and poorly enforced:-

- Agencies should distinguish clearly between nutritional aids and pharmacologically active agents.
- Require pre-market safety testing, clear labeling, and mandatory reporting of adverse events.
- Establish penalties for manufacturers found guilty of mislabeling or adulteration.
- Integrate supplement surveillance into national anti-doping and public health strategies.

8.3 Call for Global Harmonization

To reduce legal loopholes and protect athletes across borders:-

- Develop a global classification framework for supplements and gray-zone substances.
- Promote international collaboration between WADA, national anti-doping organizations, regulatory bodies, and health authorities.
- Standardize detection methods and update the WADA Prohibited List more dynamically in response to emerging substances.

8.4 Athlete Education Strategies

Education remains the frontline defense against misuse:-

- Integrate evidence-based supplement education into sports academies, federations, and coaching curricula.
- Target youth and amateur athletes with awareness campaigns on supplement risks and safe alternatives.
- Equip athletes with access to verified supplement databases (e.g., Informed Sport, NSF Certified).
- Encourage shared decision-making with sports physicians and nutrition experts before initiating supplement use.

9. Moving Forward

To address these gaps, we recommend the following:-

- Stronger clinical research mandates, particularly long-term safety trials for widely used but poorly studied compounds.
- International regulatory alignment to close legal loopholes and standardize supplement classification.
- Enhanced detection infrastructure for novel doping agents using advanced proteomic and metabolomic tools.
- Educational initiatives targeting athletes, coaches, and support staff on evidence-based supplementation and associated risks.
- Ethical oversight in supplement development and marketing, including transparency in ingredient sourcing, manufacturing, and claims.

Ultimately, the integration of supplements into sport must not compromise the foundational principles of health, fairness, and informed choice. Scientific rigor not commercial momentum must guide decisions regarding what is permissible, beneficial, and ethical in athletic performance.

Until then, the use of unregulated or poorly understood supplements should be approached with caution, skepticism, and a commitment to athlete well-being over short-term gains.

10. Use of generative AI Tools

This manuscript was prepared with language support from ChatGPT (OpenAI, July 2025 version). The tool was used to improve linguistic clarity and assist with visual conceptualization (e.g., infographics). No part of the scientific content, data interpretation, or original analysis was generated by the AI. The author affirms full responsibility for the originality, accuracy, and integrity of all content presented in this work.

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