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Withania somnifera (Ashwagandha) supplementation: a review of its mechanisms, health benefits, and role in sports performance

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Abstract
In recent years *Withania somnifera* (Ashwagandha) gained a lot of interest as an adaptogen, aiding sleep, stress management and presenting health and sports-related benefits. Although clinical effects have been previously reviewed, the specific mechanism of Ashwagandha's action and its impact on different aspects of physical performance, body composition, as well as medical effects need more thorough analysis. Therefore, this narrative review delves into the available research examining the effects of Ashwagandha supplementation on such qualities as: strength, endurance, power, recovery, muscle mass, body fat, fertility, anxiety, metabolic health and aging, with additional focus on potential mechanisms underlying these effects. Moreover, we propose future perspectives based on the gaps observed in Ashwagandha research up to date.

Keywords Anxiety, Endurance, Fertility, Sleep, Strength, Stress

Introduction

In recent years, characterised by a fast pace of life, intensive mental work and prevailing stressors, the decrease in sleep duration [1], and increase in stress levels [2] are observed. Due to those factors, there's a strong interest in strategies aimed at improving cognitive function and psychological well-being [3, 4]. Supplementation with adaptogens, i.e. herbs that normalize physiological processes and help the body adapt to changes in times of increased stress, seems to be a promising health-oriented strategy [5]. Among those, *Withania somnifera* (also known as Ashwagandha) has the potential to improve quality of life [6].

Recent systematic reviews showed that supplementing stressed adults with Ashwagandha can decrease morning cortisol levels, indicating stress-relieving properties [7]. Several studies presented benefits of Ashwagandha e.g. in fertility problems [8], anxiety [9], metabolic disorders such as dyslipidaemia, insulin resistance and diabetes [10], cognitive function [11], and obsessive-compulsive disorders [12].

Although some effects of Ashwagandha supplementation are well researched, there is a paucity of data on benefits related to physical performance and mechanisms underlying its action. A review by Bonilla et al. showed improvements in strength, power, vertical jump, maximum oxygen uptake (VO_{2max}) and reduced muscle

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fatigue. However, the number of studies examined was relatively small, especially in reference to trained subjects and athletes [13]. Since sport-related strategies for improving sleep, stress adaptation, physical performance and body composition are extensively researched, with Australian Institute of Sport classifying supplements such as polyphenols and antioxidants, multifaceted properties of Ashwagandha are emerging. Hence, the aim of this review is to gather current data on effects of Ashwagandha supplementation, especially related to sports performance, medical effects and mechanisms of its action, and provide a comprehensive set of perspectives for future health science research.

Potential mechanisms of action

Sleep and GABAergic activity

Insomnia and other sleep disorders can have a profound impact on health and quality of life [14]. Common drugs for insomnia can cause side effects such as: nausea, dizziness, daytime fatigue, headache, nightmares and drug dependence [15], thus alternatives such as herbal supplements are being proposed [16]. Rodent study suggested that Ashwagandha can improve sleep duration compared to placebo and decrease sleep latency in caffeine-induced insomnia model. It also impacts sleep architecture, with increased non-rapid eye movement and δ-wave sleep time (known as 'deep sleep phase') [17]. Those effects seem to be associated with the increase in expression of sleep-related gamma-aminobutyric acid (GABA) and its receptors - $GABA_A$, $GABA_B$, 5-hydroxytryptamine receptor also known as serotonin receptor ($5HT_{1A}$) and increase in brain GABA content. Ashwagandha's active compounds are directly binding to $GABA_A$ receptor, because $GABA_A$ receptor antagonists attenuated Ashwagandha's sleep-promoting effects [17].

Above mentioned mechanisms find reliable support in latest scientific data. A recent meta-analysis included 5 randomized controlled trials, combining data of 400 participants, examining effects of Ashwagandha on sleep quantity and quality. Ashwagandha effectively improved overall sleep, compared to placebo, and specific measurements of sleep such as Sleep Quality Scale, sleep onset latency, total sleep time, wake time after sleep onset and sleep efficiency. There was no significant difference in Pittsburgh Sleep Quality Index and total time in bed [18]. Analysed by participant background, those with insomnia demonstrated larger improvements than those without [16, 19–22]. Positive effect was also more profound with larger doses (≥ 600 mg/d compared to < 600 mg/d) and longer duration (≥ 8 weeks compared to < 8 weeks) [18]. Three studies that examined mental alertness on rising also showed a positive impact of Ashwagandha [16, 19, 21]. Sleep quality is also shown to be related to stress [23], another target of Ashwagandha supplementation.

Stress and cortisol

According to a systematic review of human trials, amongst many different supplements, Ashwagandha has the most profound effect on hypothalamic-pituitary-adrenal (HPA) axis. This effect on HPA axis, a main regulator of stress response, is evident through lowered morning cortisol levels (a biomarker of stress) following Ashwagandha supplementation [3].

Recent systematic review demonstrated that supplementation with 250–500 mg of Ashwagandha extract, daily for 4 to 13 weeks, significantly decreased morning cortisol levels in adults experiencing higher stress levels [7]. Secondly, improvement in this biomarker finds a reflexion in perceived stress. Multiple studies showed that supplementation with Ashwagandha improves subjective stress measured via Perceived Stress Scale as well as depression and anxiety [6, 11, 22, 24, 25]. However, some studies didn't find any difference between Ashwagandha and placebo with both decreasing stress with similar magnitude [26, 27]. It's worth noting that participants supplemented with Ashwagandha had higher scores of qualities of life [11, 25, 28]. It is hypothesised that some compounds in Ashwagandha (mainly Withaferin A) can directly interact with glucocorticoid receptors in the brain, thus affecting cortisol and stress levels. Other possible mechanisms are associated with GABAergic activity of Ashwagandha and positive impact on sleep quality, which reduce stress [7].

Testosterone

HPA axis hormones are not the only ones engaged in Ashwagandha's action, although their mediation in changes of testosterone levels is possible. Recent systematic review also concluded that Ashwagandha supplementation can increase testosterone levels in adults with no chronic disorders [29]. Significant increases in testosterone levels following Ashwagandha supplementation were also evident in adults subjected to strength training [30].

It cannot be excluded that sleep quality is another factor known to influence cortisol and testosterone levels [31], possibly mediating Ashwagandha's impact on those hormones. Changes in above-mentioned hormones might also be a consequence of other actions of Ashwagandha such as HPA axis regulation [32] or downregulation in inflammation and oxidative stress.

Oxidative stress and inflammation

Oxidative stress, which is an accumulation of highly reactive oxygen species is pointed as one of the underlying causes of neurodegenerative disorders [33]. It also contributes to other health problems such as cardiovascular diseases, insulin resistance, diabetes or cancers risk [34, 35]. Research conducted on glioblastoma and

neuroblastoma cells shows that Ashwagandha extract protects those cells from damage induced by oxidative stress. Withanone, one of withanolides which are considered the main active constituents of Ashwagandha extract, emerged as a compound profoundly responsible for this effect [36]. Similarly, systematic review and meta-analysis that included 28 rodent studies concluded that Ashwagandha prevents the decrease or augments the restoration of the key cellular antioxidants such as superoxide dismutase, catalase and glutathione peroxidase in brains of rats subjected to oxidative stress-induced interventions [37].

Human research on Ashwagandha and oxidative stress is not extensive. Recent systematic review identified 3 studies on this topic. Ashwagandha supplementation in healthy adults improved antioxidant status with two studies, in which reduced malondialdehyde levels were observed. Additionally, one study reported an increased superoxide dismutase levels and one study showed an increase in total antioxidant capacity [29].

There is some evidence showing benefits from Ashwagandha supplementation in inflammatory-driven chronic diseases [38]. Indeed, human studies showed decreases in some inflammation markers like Nuclear Factor Kappa B after Ashwagandha supplementation, suggesting anti-inflammatory properties [29]. The exact metabolic pathway(s) underlying this anti-inflammatory effect are not yet well understood, however, inflammatory/oxidative stress factors ↔ hormones crosstalk cannot be excluded. The clear hierarchy of mechanisms responsible for Ashwagandha's effects is unclear and demands further exploration. Potential mechanisms and their linkage are presented on Fig. 1.

Sports performance and body composition effects

Sports performance

Ashwagandha is suggested to have beneficial effects on athletic performance, through both indirect ways (improvement in sleep, regulation of stress and hormone levels) and direct actions such as anti-oxidative, anti-inflammatory properties [13], and possibly promotion of muscle cell differentiation [39]. First meta-analysis that examined effects of Ashwagandha on physical performance included 4 randomized trials with a total number of 142 participants and focused on VO_{2max} [40]. Participants were given Ashwagandha (total dose of 330 to 1000 mg/d) or placebo, for 2 to 12 weeks. Results showed that Ashwagandha was significantly better than placebo in improving aerobic capacity and aerobic performance in healthy adults [41, 42], hockey players [43], and elite cyclists [44]. Despite a multiplicity of valuable information and excellent direction of research, a limitation of this meta-analysis is a small number of studies and their high heterogeneity [40].

Later systematic review took a wider look at sports performance, including clinical trials examining changes in muscle strength, VO_{2max}, muscle fatigue, tiredness and physical recovery [13]. 12 studies with participation of 615 young adults (17–45 years of age) with mixed sexes and various fitness levels inclusion, dosage range from 120 mg to 1250 mg daily, lasting from 2 to 12 weeks demonstrated diverse conclusions. Supplementation with Ashwagandha improved strength and power, measured via one repetition maximum in bench press, squat and leg extension [30, 45], maximum velocity and relative power in vertical jump [46], and testosterone levels [30]. Positive impact of Ashwagandha on cardiorespiratory fitness was also demonstrated with increases in VO_{2max} [40]. Compared to placebo, Ashwagandha was also significantly better at decreasing muscle fatigue measured via Perceived Recovery Scores [45]. Authors also performed a Bayesian meta-analysis and concluded that future studies will also bring positive effects [13]. Current literature on Ashwagandha and sports performance has some shortcomings. Total number of studies is very low, with even fewer performed on trained subjects.

Body composition

Body composition i.e. the percentage of fat tissue and muscle mass is an important element for both health and sports performance. Ashwagandha supplementation augments desirable body composition changes resulting from strength training [30]. It is known that sleep quality and quantity affect the proportion of fat mass reduction during weight loss and muscle mass gain with strength training [48]. Positive impact on body composition can also be potentially explained by the changes in cortisol and testosterone levels. Direct impact on body composition could involve both sides of energy balance – energy intake and expenditure. In rodents fed a high-fat diet, addition of Ashwagandha increased energy expenditure via enhanced mitochondrial activity, thus suppressing obesity [49]. However, this data cannot be extrapolated on humans, pointing out a need for further exploration. Interestingly, randomized controlled trials demonstrated a positive impact of supplementation with Ashwagandha on food cravings under chronic stress in adults [24], and college students [50], shedding light on other possible mechanisms of action.

Clinical and medical effects

Fertility

The largest number of research examining clinical benefits of Ashwagandha supplementation was conducted on fertility and reproductive system. It's not surprising, having considered Ashwagandha's impact on sleep, testosterone, cortisol and stress levels (see previous chapters). Evidence for beneficial influence of Ashwagandha

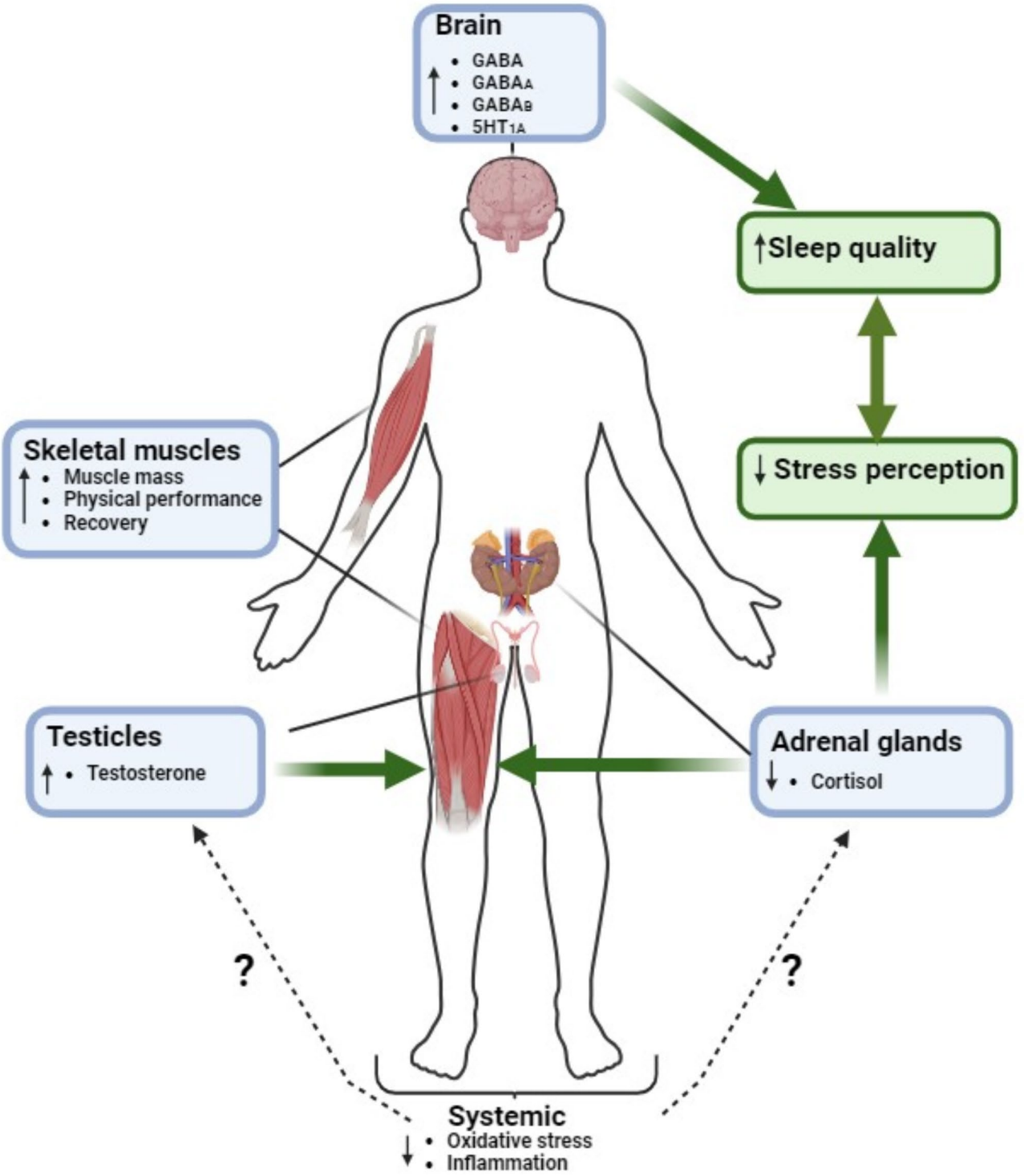

Fig. 1 Potential mechanisms of action and their linkage following Ashwagandha supplementation; GABA - gamma-aminobutyric acid; $GABA_{A/B}$ - gamma-aminobutyric acid receptors $_{A/B}$; $5HT_{1A}$- 5-hydroxytryptamine receptor $_{1A}$

supplementation on male fertility is rather promising with significant increase in sperm concentration, semen volume, sperm motility, testosterone and luteinizing hormone levels [8]. Ashwagandha decreased infertility in males through enhanced spermatogenesis and sperm-related indices [51]. Research on fertility in females is scarcer, but there seems to be a potential for Ashwagandha to increase sexual function, decrease sexual distress [52, 53], and enhance sexual behaviours [51] in females.

Anxiety

Another psychological area potentially affected by Ashwagandha is anxiety. It's the most common mental disorder, causing a disruption in health and quality of life [54]. Early systematic review identified 4 randomized controlled trials comparing the impact of Ashwagandha supplementation on Hamilton Anxiety Scale or Beck Anxiety Inventory. Compared to placebo Ashwagandha significantly decreased anxiety scores in 3 out of 4 experiments, although all studies had uncleared or high risk of bias [9]. Effective doses ranged from 125 mg/d to 1000 mg/d [55–57]. In a more recent systematic review, all 3 studies examining the impact of Ashwagandha on anxiety levels (Hamilton Anxiety Scale) showed significantly positive results [18]. Further randomized trials confirmed the anxiolytic effect of Ashwagandha in both healthy participants [25], and in adults with Generalized Anxiety Disorder [58].

Metabolic health

Due to its anti-oxidative and anti-inflammatory qualities, Ashwagandha has a potential to benefit metabolic health. Systematic review and meta-analysis showed that a supplementation with Ashwagandha can improve weight loss, blood glucose and glycosylated haemoglobin, presenting a utility in managing insulin resistance or diabetes. Similarly beneficial results were reported for lipid profile i.e. decrease in total cholesterol and LDL-cholesterol [10]. Positive impact of Ashwagandha on total cholesterol and triglycerides was also confirmed [59]. Number of studies is still relatively low, with most of the data coming from mechanistic and pre-clinical research, thus this area needs further exploration.

Aging and cognition

Aging is associated with decreased vitality and increased general fatigue [60]. Also, sarcopenia which is a continued loss of muscle mass and strength inherently connected with aging poses a health threat. Randomized crossover study on aged, overweight males showed that compared to placebo, Ashwagandha supplementation was associated with 18% and 14.7% increase in dehydroepiandrosterone sulfate and testosterone levels, respectively. However, subjective measures of fatigue, vigor and sexual well-being didn't differ significantly between groups [61].

Optimising cognitive function is important not only for athletes but also for people occupied with mentally tasking jobs or in aging [62]. Chronic supplementation with Ashwagandha significantly improved cognitive functions such as recall memory, total error rate in recalling patterns [11], cognitive flexibility, visual memory, reaction time, psychomotor speed, and executive functioning [26], sustained attention and information-processing speed [63]. Moreover, it seems that even acute Ashwagandha supplementation (400 mg) could present some benefits in improving executive function, short-term memory and sustaining attention [64], however, human studies exploring Ashwagandha supplementation on cognition during aging are still required.

Safety

One of the biggest concerns of Ashwagandha supplementation is its safety, especially with long-term and/or high dosing protocols. Several randomized controlled trials examined the safety of dosing 300–600 mg of Ashwagandha extract daily, for 8 to 12 weeks, in both males and females. No changes in haematological and thyroid function parameters were observed [65]. Similarly, no adverse events were reported [11, 53, 65]. Recent systematic review included 30 clinical trials documenting safety of a wide range of Ashwagandha supplementation protocols. None of those studies reported any serious adverse events or changes in vital signs, haematological and biochemical parameters. Most of them reported no adverse events at all in both adults and children, while others reported transient adverse events of mild to moderate severity with somnolence, giddiness, drowsiness, epigastric pain/discomfort and vertigo as the most common. What is worth noting, above mentioned side effects occurred frequently also in placebo groups [66].

Six cases of liver injury attributed to Ashwagandha supplementation have been documented. All cases had a similar pattern with jaundice and other symptoms which occurred 2 to 12 weeks into supplementing Ashwagandha or Ashwagandha-containing supplements, with daily doses ranging from 450 mg to 1350 mg. All cases were reversible, with liver tests normalizing after 1–9 months after cessation of supplementation [67]. Contrary, other clinical studies didn't notice any changes in hepatotoxicity markers after Ashwagandha supplementation [65, 66].

Although most research data indicates that Ashwagandha supplementation is safe and tolerable, more data is needed to evaluate safety of higher doses and longer periods of supplementation, especially regarding its impact on hepatotoxicity.

Future perspectives

A wide range of gaps in the current literature on Ashwagandha is emerging. The effectiveness of Ashwagandha supplementation is rather clear, but specific mechanisms of its action need further exploration. Potential mechanisms worth looking into are sleep-promoting GABAergic activity, augmenting antioxidant capacity, hormones such as cortisol and testosterone. Another interesting subject is potential crosstalk between those mechanisms and their hierarchy.

Positive impact of Ashwagandha on sleep quality and quantity is considered one of its primary mechanisms of action. However, further research should implement higher quality methods of measurement, such as lab-based polysomnography, as compared to actigraphy [18]. Also, specific mechanisms underlying these effects need better elucidation.

Although Ashwagandha seems to repetitively decrease stress and anxiety, it's important to further examine its impact on different populations e.g. professional athletes during competition season or demanding training camps. The most intriguing populations to research in this area would be athletes engaged in weight-dependent sports, which can cause disruption in both sleep and stress management. Examples of such sports are aesthetic disciplines (ballet, figure skating, gymnastics, bodybuilding), combat sports with weight categories, rowing, ski jumping or horse riding. It's also necessary to further examine optimal dosing protocols, other training modalities and outcomes, different populations and precise compounds and mechanisms underlying those effects.

Ashwagandha presents quite a few possible clinical applications. Besides its impact on psychological aspects such as insomnia, anxiety, depression or obsessive-compulsive disorder, it's worth exploring Ashwagandha's effects on fertility, sexual function, vitality and cognitive function, especially in aging and cardiometabolic-diseased people.

Author contributions

MS prepared the initial draft of the manuscript and participated in all discussions and revisions. RL made a funding acquisition as well as critical review. ZJ provided draft preparation, substantive critical review and comments. All authors approved the final version submitted for publication.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

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Competing interests

The authors declare no competing interests.

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