

# Ashwagandha: A Review of Clinical Use and Efficacy

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## Abstract

Ashwagandha has a long tradition of use in Ayurvedic medicine, and is best known as an adaptogen, a compound that can help increase our resistance to stress. Preclinical research has also shown ashwagandha to have anti-inflammatory, antimicrobial, antioxidant, antidiabetic, anti-tumour, anti-ageing and neuroprotective properties. Steroidal alkaloids and lactones, including withaferin A and withanolides, are thought to be some of the most active compounds of the herb. Clinical research in humans has shown ashwagandha to be safe and of benefit in a range of conditions, including stress/anxiety, athletic performance, cognition, diabetes, insomnia and male infertility. Ashwagandha is generally considered to be safe, with a few minor possible side-effects, although care should be taken alongside certain drugs.

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## Introduction

Ashwagandha (*Withania somnifera*), also known as Indian ginseng or winter berry, has been used in Ayurvedic medicine for more than 3000 years. It belongs to the Solanaceae (nightshade) family of plants, and grows wild in Africa, the Mediterranean and India. Ashwagandha is also cultivated for medicinal purposes.<sup>1</sup>

Although the berries and leaves appear to have some medicinal effects, it is mostly the roots that have been used traditionally and have been subject to modern medical research. The active constituents include steroidal alkaloids and lactones, including withaferin A and withanolides.<sup>2</sup>

In Ayurveda, ashwagandha has been used for a wide range of indications, including as a liver tonic, an anti-inflammatory, an astringent, an aphrodisiac and an adaptogen, for conditions such as insomnia, bronchitis, asthma, ulcers, emaciation and dementia. Modern preclinical research has confirmed anti-inflammatory, antimicrobial, antioxidant, anti-stress, antidiabetic, anti-tumour, anti-ageing and neuroprotective properties.<sup>1,3</sup>

## Clinical uses

### Anxiety/stress

Ashwagandha is considered to be an adaptogen, that is a compound that can modify our stress response in order to increase our resistance to stress.<sup>4</sup>

Ashwagandha is probably most revered for these adaptogenic properties, and its benefits in terms of reducing stress and anxiety have been extensively studied in both preclinical and clinical studies.

A number of double-blind, placebo-controlled trials have shown that ashwagandha can reduce anxiety scores by up to 70% or more in patients with anxiety disorders<sup>5,6,7</sup> or high stress levels.<sup>8,9,10,11</sup> Dosages in these studies ranged from 125 to 2000 mg per day of ashwagandha extract. Significant improvements in anxiety and depression

have also been seen with ashwagandha extracts, 1000 mg per day, in patients with schizophrenia, where positive outcomes were also observed in other disease parameters.<sup>12,13</sup>

A small double-blind, placebo-controlled trial also showed significant improvements in patients with obsessive compulsive disorder (OCD) who took ashwagandha extract, 120 mg per day, in addition to selective serotonin reuptake inhibitors (SSRIs), with a decrease in OCD severity from 26 to 18 (on a scale of 0–40), independent of whether patients suffered from concomitant anxiety disorders.<sup>14</sup>

Dosages as well as strengths of the extracts have varied in the above studies. A number of studies in people with high stress levels have shown a dose-dependent increase in efficacy, and levels of 300 mg twice a day have given the most benefits while also being safe.<sup>8,10,11</sup> Most studies had a duration of 2 months, with beneficial effects being observed as early as within 2 weeks of intervention.<sup>5</sup> Benefits usually increased over 6–10 weeks. Most studies used extracts of the root only, although some used extracts of both root and leaves.<sup>11</sup>

A number of mechanisms appear to contribute to the adaptogenic and anxiolytic properties of ashwagandha. Preclinical research has shown that ashwagandha extracts have  $\gamma$ -aminobutyric acid (GABA) ergic action, although neither withaferin A nor withanolide A appear to be responsible for this action.<sup>15</sup>

Clinical trials have shown that ashwagandha works by exerting a balancing effect on the hypothalamus–pituitary–adrenal (HPA) axis, lowering cortisol levels in stressed adults by 23–33%.<sup>9,10,11,16</sup>

It has also been suggested that withanolides are hormone precursors and that ashwagandha acts as an amphoteric, that is it can bind to hormone receptors and exert a mild effect where hormone levels are low, while blocking the receptor when hormone levels are too high.<sup>1</sup>

## Athletic performance

As an adaptogen, ashwagandha has been popular for increasing stamina and athletic performance, a use that is backed up by several clinical studies.

Ashwagandha extracts have been shown to increase athletic performance in both the general healthy adult population<sup>17,18,19</sup> and professional/elite athletes.<sup>20,21</sup>  $VO_2$  max, a measure of cardiovascular fitness, has been shown to increase by 6–14% over study periods of 4–12 weeks.<sup>17,18,19,20,21</sup> Ashwagandha extracts have also been found to increase muscle mass and strength, and improve muscle recovery.<sup>22,23</sup>

Quality of life scores (including physical health, psychological health, social relationships and environmental factors) have also been reported to improve significantly more with ashwagandha than with placebo in athletic adults,<sup>18</sup> although another trial found no difference in exercise-related emotional/mental factors.<sup>22</sup>

Dosages used have been in the range of 330–1000 mg per day. Apart from one study that used an extract from roots and leaves,<sup>22</sup> all of the above trials used root extracts. Benefits have been seen after 4 weeks,<sup>17</sup> although most trials ran for 8 or 12 weeks.

Several mechanisms have been discussed to explain the results seen in athletic performance. The ability of ashwagandha to increase testosterone in men and reduce cortisol would be expected to promote muscle development, while its antioxidant and anti-inflammatory properties may support muscle recovery. Ashwagandha appears to support mitochondrial function and as such energy levels, while its adaptogenic effects on the nervous system may also have benefits in terms of athletic performance.<sup>18,23</sup> Increases in haemoglobin have been seen in clinical trials, which may contribute to increased athletic performance.<sup>20</sup>

## Cognitive function/memory

Ashwagandha has shown favourable results with regards to cognitive function and

neuroprotection in preclinical research. While animal research looks promising in a number of conditions, including Alzheimer's disease and Parkinson's disease, human trials in this area to date are limited to cognitive function.<sup>24</sup>

Significant benefits in terms of cognitive function and psychomotor performance have been observed in a number of different patient populations, including healthy men,<sup>25</sup> people with mild cognitive impairment<sup>26</sup> and bipolar disorder.<sup>27</sup>

Dosages have been in the range of 300–500 mg of ashwagandha extract (twice a day). While one study used an extract of the root only,<sup>26</sup> two other studies used extracts of root and leaves.<sup>25,27</sup> In healthy men, significant improvements were seen in as little as 2 weeks; in other studies, benefits increased over the 8-week study periods.

A number of possible mechanisms have been discussed in the literature. Neuroinflammation plays an important role in the development of neurodegenerative disorders, so the anti-inflammatory properties of ashwagandha are likely to contribute. Ashwagandha has also been found to increase brain-derived neurotrophic factor, thus protecting brain cells and promoting neuroplasticity.<sup>28</sup> Ashwagandha also modulates oxidative stress markers in the brain, including levels of superoxide dismutase, catalase, lipid peroxidation and glutathione.<sup>24</sup>

## Diabetes

Ashwagandha has shown beneficial effects on blood glucose, fasting glucose and HbA1c in animal models; however, there is limited evidence from randomised-controlled clinical trials for its use in diabetes.<sup>29</sup>

In a double-blind, placebo-controlled trial of ashwagandha extract, 1200 mg per day for 30 days, levels of fasting blood glucose and serum triglycerides significantly improved in patients with schizophrenia and metabolic syndrome, while no improvements were seen in the placebo group.<sup>30</sup>

Improvements in glycaemic control have also been seen in two other studies,<sup>31,32</sup> although these were small, open-label trials, and in one of them patients were also given dietary and lifestyle advice.<sup>31</sup>

Two further studies showed benefits in endothelial function, lipid profile and oxidative stress in patients with type 2 diabetes that was well controlled with metformin. One study<sup>33</sup> compared 250 mg twice a day and 500 mg twice a day of an ashwagandha root extract versus placebo for 12 weeks; the other<sup>34</sup> compared 500 mg twice a day of an ashwagandha root and leaves extract versus another herb, versus a combination of the two herbs for 12 weeks. Significant improvements over placebo were seen with 500 mg of ashwagandha extract per day, but were significantly greater with 1000 mg per day. Increases of 31% and 43% in glutathione, respectively, were observed in the two studies.

Three of the above studies used dosages higher than generally given for other indications: 1000–1200 mg of extracts and 3000 mg of root powder per day,<sup>30,33,34</sup> although beneficial effects were also seen with lower dosages: 500–600 mg of extract per day.<sup>31,33</sup> One study compared 500 mg with 1000 mg per day, and found benefits to be better with the higher dose.<sup>33</sup> Durations of treatments ranged from 1 to 3 months, with improvements noted after 1 month.<sup>30,32</sup>

*In vitro* studies suggest that the antidiabetic actions of ashwagandha are mediated through an increase in cellular glucose uptake in both skeletal and fat cells, and an increase in insulin secretion. While both leaf and root extract produce the former mechanism, the latter only occurs with leaf extracts. The main active compound responsible for these actions appears to be withaferin A.<sup>35</sup> The antioxidant potential of ashwagandha has been shown in healthy volunteers<sup>36</sup> and confirmed in some of the above studies, and may contribute to the positive effects seen in type 2 diabetics. Due to the fact that stress, and elevations in

cortisol levels, can have a negative effect on blood glucose control, the antidiabetic effects of ashwagandha may also be mediated in part through its balancing effect on the HPA axis.<sup>31</sup>

### Insomnia/sleep

The Latin name of ashwagandha, *Withania somnifera*, alludes to its sleep-promoting properties, ‘somni-fera’ meaning ‘sleep-inducing’. The herb is thought to ‘rejuvenate the nervous system’, easing stress and thus promoting sleep without being sedating.<sup>37</sup>

Over the past few years, five double-blind, placebo-controlled trials have confirmed the sleep-promoting effects of ashwagandha in healthy adults,<sup>38</sup> stressed healthy adults,<sup>10</sup> adults with anxiety and insomnia,<sup>6</sup> adults with insomnia,<sup>38</sup> healthy subjects scoring high on non-restorative sleep,<sup>39</sup> and healthy elderly people.<sup>40</sup>

Various outcome measures were used in these studies, including actigraphy (collection of sleep parameter measures using a watch-like device) and sleep questionnaires, with improvements observed using both. Improvements in sleep quality were in the range of 30–72%, with improvements generally higher in people with sleep problems.<sup>38</sup>

Most studies used an ashwagandha root extract, 600 mg per day, while one study used an extract of both roots and leaves, 120 mg per day.<sup>39</sup> The latter gave the biggest improvements in sleep quality as assessed by questionnaire – 72%. The duration of treatments ranged from 6 to 12 weeks, with gradual improvements over the study periods where outcomes were measured at different time points.<sup>6,40</sup>

The stress-relieving properties of ashwagandha are likely to play an important role in improving sleep. Studies in animal models suggest that ashwagandha has GABAergic properties, which would also contribute to its benefits.<sup>39</sup>

## Male fertility

The Sanskrit name ashwagandha means ‘smell of a horse’, and refers to the herb’s smell, as well as indicating that it transfers the virility and strength of a horse.<sup>8</sup> Although beneficial effects on male sexual function have not been confirmed in clinical trials (see below), five human studies have shown beneficial effects in male infertility.

Three of these were open-label studies that compared infertile men with normal sperm count and motility (normozoospermic), low sperm count (oligozoospermic) or low sperm motility (asthenozoospermic) with fertile controls. Infertile men were given an ashwagandha root powder, 5000 mg per day, for 3 months.<sup>41,42,43,44</sup> In one of these studies, sperm count increased by 363% in those with low sperm counts, while sperm motility increased by 149% in those with low sperm motility.<sup>42</sup> In another study, the partners of 14% of the initially infertile men got pregnant during the 3-month study period.<sup>41</sup>

These studies also looked into a number of parameters to establish possible mechanisms. They found that ashwagandha increased testosterone and luteinising hormone (LH), while decreasing follicle-stimulating hormone (FSH)<sup>41,42,44</sup> and also decreasing cortisol levels in stressed men.<sup>41</sup> The potential of ashwagandha to support a healthy HPA axis, normalising cortisol levels and raising testosterone levels in stressed men has been confirmed in other studies.<sup>9</sup>

The above studies also showed that, compared with healthy fertile men, sperm of the men in the infertile groups had higher levels of oxidative stress and apoptotic cells, and lower levels of antioxidants, which improved with ashwagandha supplementation.<sup>43</sup> This suggests that the antioxidant and possibly nutritional properties of ashwagandha may also contribute to the observed improvements in fertility.

Two more recent double-blind studies have confirmed these results. One found that the

same ashwagandha regimen as in the above studies was as effective as the infertility drug pentoxifylline in improving sperm count, motility and morphology.<sup>45</sup> The other study used an ashwagandha root extract, 675 mg per day for 3 months, which led to significant increases in sperm concentration, semen volume and sperm motility by 168%, 53% and 57%, respectively, as well as a 17% increase in testosterone and a 34% increase in LH. All results were statistically significantly better than in the placebo group, which saw no improvements.<sup>46</sup>

## Ageing

Based on its traditional use, ashwagandha has been suggested as an anti-ageing herb. However, although positive effects on cognitive function and increases in testosterone in men have been observed, further evidence to support the use of ashwagandha in this area is scarce.

One double-blind, placebo-controlled trial found a 15% increase in quality of life in elderly, generally healthy people with an ashwagandha root extract, 600 mg per day for 12 weeks, as well as improvements in sleep and mental alertness (see the section: ‘Insomnia/sleep’).<sup>40</sup> However, another study found no improvement in fatigue, vigour, sexual and psychological wellbeing in overweight men with mild fatigue, aged 40–70 years, with an extract of ashwagandha root and leaves, 600 mg per day for 8 weeks.<sup>47</sup>

## Arthritis/joint pain

Considering the general popularity of ashwagandha and its known anti-inflammatory properties, there are surprisingly few studies published on its use in arthritis or other inflammatory conditions, other than neurological.

An open-label study of 77 patients with rheumatoid arthritis, published in 1999, found ashwagandha root powder, 3000 mg per day for 6 weeks, to be effective in relieving symptoms. Unfortunately, this study did not have a control group.<sup>48</sup>

Only one study, in 2016, investigated ashwagandha on its own in a double-blind, placebo-controlled design. Patients with knee pain received either 250 mg or 500 mg per day of an aqueous extract of ashwagandha root and leaves, or placebo, for 12 weeks. There was a gradual improvement in symptoms over the study period, with pain, stiffness and disability reduced by about a third at the end of the 12 weeks in the group receiving the higher dose, and by about 18–20% in the lower-dose group. These results were statistically significantly better than placebo.<sup>49</sup>

The authors of the above study attribute the analgesic activity of ashwagandha mostly to withaferin A, which has been shown to reduce the production of prostaglandins, mediating pain by inhibiting cyclo-oxygenase (COX). They also suggest that the soothing action of ashwagandha on the nervous system may contribute to the analgesic effects.<sup>49</sup>

Three further studies evaluated mixtures of various Ayurvedic herbs and minerals, which included ashwagandha, and found beneficial effects in osteoarthritis<sup>50,51</sup> and rheumatoid arthritis.<sup>52</sup>

### **Hypothyroidism**

Increases in thyroxine levels with ashwagandha have been observed in mice, and so thyroid parameters were studied as part of a safety evaluation in a trial of ashwagandha on cognitive function involving 60 patients with bipolar disorder, where thyroid disorders are a common co-morbidity.<sup>27</sup> Researchers saw ‘abnormal’ thyroid results in 10 patients.<sup>52,53</sup> Three patients receiving ashwagandha extract had abnormal thyroid function tests at baseline, one with elevated thyroid-stimulating hormone (TSH), one with elevated T3 (possibly due to lithium treatment) and one with low T4. At the end of the study all three patients’ thyroid function tests had normalised, and all three had increases in T4 ranging from 7 to 24%. Of the seven patients on placebo who had abnormal thyroid function tests at baseline, six showed a reduction in T4, and only one showed an increase.<sup>53</sup>

In 2018, a double-blind, placebo-controlled trial of 50 patients with mild hypothyroidism (TSH 4.5–10 IU/l) confirmed a positive effect of an ashwagandha extract, 600 mg per day for 8 weeks, on thyroid function. Levels of TSH, T4 and T3 improved significantly after 4 weeks, and continued to improve further over the next 4 weeks, with final improvements of 17.4%, 19.6% and 41.5%, respectively. All results were significantly better than in the placebo group, which saw no significant improvements.<sup>54</sup>

The beneficial effect of ashwagandha on thyroid function may be mediated by its effect on the HPA axis, which in turn is inversely related to the hypothalamus–pituitary–thyroid (HPT) axis, in that chronically elevated cortisol can inhibit the HPT axis and lead to reductions in T4 and T3. The dopaminergic and anti-inflammatory properties of ashwagandha may also affect both the HPA and HPT axes.<sup>54</sup> Animal studies also suggest that ashwagandha may have a direct effect on thyroid activity and thyroid hormone metabolism.<sup>55</sup>

No further clinical trials have been published to date but, in view of such positive results and the clinical observation that thyroid dysfunction is often correlated with stress, ashwagandha appears to have potential therapeutic value for patients with subclinical hypothyroidism.

### **Sexual dysfunction, male and female**

Ashwagandha is also often touted as an aphrodisiac, but scientific evidence is scarce in women and does not support this use in men. One double-blind, placebo-controlled pilot study found that an ashwagandha extract, 600 mg per day for 2 months, improved sexual function in otherwise healthy women with sexual dysfunction,<sup>56</sup> while a study in men with erectile dysfunction found no benefit of ashwagandha powder, 6000 mg per day for 2 months, over placebo on a number of measures and parameters.<sup>57,58</sup> A study in 40–70-year-old men with mild fatigue also found no improvement in sexual health despite increases in testosterone with an ashwagandha extract, 240 mg per day for 2 months.<sup>47</sup>

## Safety

A review of 39 preclinical and 30 human trials,<sup>2</sup> including two in children, concluded that ashwagandha root extracts are safe and efficacious in a number of clinical applications. Preclinical safety and toxicity studies showed root extracts to be safe, with the only noted side-effects being mild depression of the central nervous system and an increase in thyroxine. No mutagenicity or genotoxicity was reported in preclinical experiments.

Human trials did not observe any serious side-effects or changes in vital signs, haematological and biochemical markers. A number of mild to moderate transient adverse events have been reported in clinical trials, including somnolence, giddiness, drowsiness, hallucinations, vertigo, nasal congestion (rhinitis), cough, cold, decreased appetite, nausea, epigastric pain/discomfort, gastritis, flatulence, loose stools, constipation, dry mouth, hyperactivity, nocturnal cramps, blurring of vision, hyperacidity, skin rash and weight gain.<sup>2</sup> However, where these were placebo-controlled studies there was no statistically significant difference in the number of adverse events between the ashwagandha and placebo groups,<sup>8,13,45,54,59</sup> except for somnolence, which was noted to be more common in the ashwagandha group (21%) than in the placebo group (9%) in a trial in patients with schizophrenia.<sup>13</sup>

A safety study in 18 healthy volunteers in 2012 evaluated increasing dosages of an ashwagandha extract (750 mg, 1000 mg and 1250 mg) for 10 days each. All but one volunteer tolerated the herb well at all dosages, and vital signs, blood glucose, uric acid, haematological and liver function tests remained in the normal range. Serum creatinine increased and blood urea nitrogen decreased on the highest dose, suggesting some negative effect on the kidneys. One volunteer experienced increased appetite and libido, and hallucinations with vertigo after 3 days on the lowest dose and had to withdraw from the study; the effects resolved on discontinuation of the herb.<sup>60</sup>

A case series from Iceland and the USA described five cases of liver toxicity attributed to ashwagandha supplements. Patients developed jaundice, and symptoms including nausea, lethargy, pruritis (itching) and abdominal discomfort within 2–12 weeks of starting the herb. None of them developed liver failure, and liver tests normalised within 1–5 months after stopping ashwagandha in four of the patients; the fifth was lost to follow-up. None of them took any hepatotoxic medication, although four of them also took other supplements.<sup>61</sup> The possible mechanism is unclear, and in clinical trials no elevations of liver enzymes or other hepatotoxicity have been observed. Contamination of herbs can occur, although this was ruled out in these cases.<sup>62</sup>

An investigation in 2011 looked into contamination of herbs with heavy metals and pesticides.<sup>63</sup> The authors found that samples of ashwagandha had levels of mercury and lead that were below maximum levels set by the World Health Organization, while arsenic and cadmium were below the detection threshold. The 28 pesticides that were tested for were also not detectable.

## Cautions

Due to some of the therapeutic effects of ashwagandha, caution should be exercised in patients with certain conditions or on certain drugs, as there may be additive effects.<sup>64</sup> It should be noted that there are no reports of serious adverse interactions in the literature.

## Diabetes

As ashwagandha may have antidiabetic effects, in theory ashwagandha may cause blood glucose levels to drop too low in diabetics on antidiabetic medication. Extra monitoring and adjustment of medication is recommended. A number of clinical trials used ashwagandha alongside oral antidiabetic medication and no untoward effects were noted.<sup>31,33,34</sup>

## Hypothyroidism/hyperthyroidism

As ashwagandha can increase thyroid hormones, it should be used with caution/extra monitoring in people with hyperthyroidism or hypothyroidism and on hormone replacement (thyroxine) therapy to ensure thyroid hormones do not go too high.

## Sedative medications, including benzodiazepines

Although ashwagandha is not considered to be sedative as such, sedation and depression of the central nervous system have been observed in humans and in animal models.<sup>65</sup> Concomitant use with sedative medications should therefore be avoided, to prevent excessive sedation. This effect should also be taken into account when anaesthesia is planned, and the herb should be stopped 2 weeks before surgeries.<sup>64</sup> In a clinical trial in patients with schizophrenia, ashwagandha was taken alongside antipsychotic and other medications. Although overall there was no difference in the occurrence of side-effects between the ashwagandha and placebo groups, somnolence was noted to be more common in the ashwagandha group (21%) than in the placebo group (9%).<sup>13</sup>

## Blood pressure

Ashwagandha may lower blood pressure,<sup>66</sup> so patients on blood-pressure-lowering drugs or with low blood pressure should monitor their blood pressure more closely, and the dosage of any medication may need to be adjusted.

## Autoimmunity

Ashwagandha may increase the function of the immune system, and as such interfere with immunosuppressant drugs; it should be used with care in patients with autoimmune conditions.<sup>64</sup>

## Pregnancy and breastfeeding

The seeds of ashwagandha have traditionally been used in parts of India to enhance lactation; however, there is no information from clinical trials regarding the safety of ashwagandha during breastfeeding, and it should therefore be avoided.<sup>67</sup>

Ashwagandha may lead to miscarriage, and so should be avoided during pregnancy or when pregnancy is planned.<sup>64</sup>

## Age limits/minimum age

Ashwagandha has traditionally been used as a tonic and growth promotor for malnourished children.

Two studies<sup>2</sup> have investigated the use of ashwagandha in children: one uncontrolled open-label study in 8–12 year olds with mild nutritional deficiencies; and one double-blind, placebo-controlled trial in healthy 8–12 year olds. In both studies, children took 2 g per day of an ashwagandha root powder for 60 days. Increases in body weight, haemoglobin and handgrip strength were seen in those children receiving the active herb, and no adverse effects were observed.

When root powders were used in studies in adults, dosages generally ranged from 3 to 5 g, so halving an adult dose for children aged 8–12 years appears to be an appropriate dose.

Another study compared two different traditional ashwagandha formulations, Ghrita (made with ghee) versus granules versus placebo in 111 children aged 3–12 years.<sup>68</sup> Aerobic capacity, body composition and muscular strength improved the most in the Ghrita formulation group, and the least in the placebo group. Children aged 3–7 years old received 2.5–4 g, and 8–12 year olds received 6–8 g daily for 6 weeks. The formulations and their strengths were not further described, and it is therefore difficult to extrapolate to pure root powders or extracts.

## Conclusion

Human trials have confirmed the adaptogenic potential and clinical benefits of ashwagandha in a number of diverse conditions. The herb is generally safe in both adults and children, with only mild to moderate adverse effects reported during clinical trials. Care should be taken when ashwagandha is used alongside certain medications.



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## Review

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