

# Ashwagandha

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**Ashwagandha** (*Withania somnifera* (L.) Dunal; Solanaceae), is native to Southern Europe, the Middle East, Africa, and parts of Asia, including central China, India and Myanmar. Ashwagandha grows in stony and semi-arid regions. It is a perennial woody shrub with bright greenish-yellow flowers that can develop into orange-red berries. The plant can grow up to 150 cm tall.

Ashwagandha root has a long history of use in Ayurvedic medicine for over 3000 years. Ashwagandha is an ingredient in many Ayurveda product formulations. It is used traditionally in Ayurveda for various indications, including fever, pain, gout, infections, asthma, cough, neurological disorders, and as an antidote to poisons. In Ayurvedic medicine, ashwagandha is considered to be an adaptogen and is claimed to promote longevity, improve memory, enhance fertility for both males and females, to balance aggravated 'vata' (as a nervine tonic and sedative), as a sleep aid, and to relieve general debility, especially during convalescence or old age.<sup>1</sup>

## Common names

Asgandh [*Hindi*], amukkara [*Sinhalese*], asan, asgand, gandhrapatri [*Unani*], eskandeh [*Persian*], babu [*Arabic*], winter cherry, Indian ginseng [*English*],<sup>2</sup> among many others. [NB: the common name 'winter cherry' is also used for several other (unrelated) plants].

## Preparations

Traditional preparations of ashwagandha use the dried root or whole plant, and are prepared in various dose forms, including *quatha* (decoction), *lepa* (paste), *taila* (medicated oils), *ghrita* (clarified-butter/ghee-based preparation) and others for internal or external use. Contemporary preparations in the global market are usually solid-dose forms (typically capsules, tablets, powders, gummies), formulated mainly as single- and, sometimes, multi-ingredient products (with other herbal and non-herbal ingredients).<sup>1</sup> Some marketed ashwagandha extracts are standardised for their withanolide content.

## Summary message

*Withania somnifera* (L.) Dunal, commonly known as ashwagandha, is promoted for its reputed effects in many conditions, including anxiety, stress, infertility and sleep disorders, and is said to be an 'adaptogen'. The main bioactive constituents in ashwagandha root, the part of the plant usually used medicinally, include withanolides. Evidence from preclinical studies supports ashwagandha's antioxidant, anti-cancer, anti-ageing, anti-diabetic, anti-stress, adaptogenic, immunomodulatory, cardioprotective, and neuroprotective effects. Clinical studies on ashwagandha root extracts have reported positive outcomes in several conditions, particularly in improving symptoms of anxiety and stress, sexual function, and physical performance. However, clinical research on ashwagandha extracts has methodological limitations and, currently, there is no high-certainty evidence to support ashwagandha's efficacy in treating any specific health condition. Large, robust, long-term studies using ashwagandha extracts that meet acceptable botanical quality standards required for therapeutic purposes are needed.

In September 2023, the Netherlands pharmacovigilance centre raised a safety signal concerning liver toxicity associated with products containing ashwagandha based on several spontaneous reports. Similar cases have been documented in the literature, but, to date, causality has not been definitively established. Concerns about product quality also remain. Comprehensive investigation of the clinical safety profile of ashwagandha, including long-term use, is required.

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## Manufacturers' claims

Ashwagandha-containing products are marketed as having 'adaptogenic' properties and, as such, are claimed to support skin health, strengthen immunity, and improve endurance and energy. Ashwagandha products are also promoted for their anti-stress and anti-anxiety effects, among other claims.

## Active constituents

The main constituents of ashwagandha are withanolides, withaferins and withanosides, which are steroidal lactones. Several alkaloids (eg ashwagandine, ashwagandinine and others) have also been isolated from ashwagandha. Evidence from preclinical studies suggests that most pharmacological activities are attributable to withanolides A and D, and withaferin A; several other constituents have also been reported to be bioactive.<sup>1</sup>

## Evidence for efficacy

Preclinical studies testing different ashwagandha root extracts (including ethanolic, methanolic, and/or standardised extracts) and root powder have described antioxidant, anti-cancer, anti-ageing, anti-diabetic, anti-stress, adaptogenic, immunomodulatory, cardioprotective, and neuroprotective effects.<sup>1</sup>

Clinical studies of ashwagandha root (and, sometimes, leaf) extracts have explored effects in various indications, including stress, anxiety, insomnia, schizophrenia, obsessive-compulsive disorder, diabetes, male infertility, and hypothyroidism.<sup>1,3</sup> A systematic review found that most clinical studies of ashwagandha administered as a single active herbal ingredient have examined its effects in stress, anxiety, sexual function and fertility, and on physical performance. Many of these studies reported benefits with ashwagandha across several different outcome measures. However, typically, these studies involved small numbers of participants and had other methodological limitations, hence, at present, there is no definitive evidence for efficacy in these conditions. In addition, different formulations, doses and dosages of ashwagandha were tested in the studies. KSM-66<sup>®</sup>, an ashwagandha root extract manufactured in India, was the most frequently investigated product. Across all studies, the risk of bias was considered low for those exploring the effects of ashwagandha on stress, anxiety, and physical performance, while studies in sexual function and fertility carried some risk of selection and reporting bias.<sup>3</sup>

A meta-analysis of randomised controlled trials of ashwagandha for stress and anxiety indicated that ashwagandha significantly reduced anxiety (SMD:  $-1.55$ , 95% CI:  $-2.37$ ,  $-0.74$ ;  $P = 0.005$ ,  $I^2 = 93.8\%$ , 8 studies, 540 participants) and stress (SMD:  $-1.75$ , 95% CI:  $-2.29$ ,  $-1.22$ ;  $P = 0.005$ ,  $I^2 = 83.1\%$ , 7 studies, 286 participants), compared with

placebo.<sup>4</sup> However, studies tested different doses of ashwagandha, and there was considerable heterogeneity across study designs, along with small sample sizes, and other methodological limitations, resulting in low certainty of evidence. Thus, further trials are required to confirm the findings. The meta-analysis did not further address formulation-specific variations in terms of quantification of bioactive phytoconstituents and other quality-related botanical specifications, which are critical when assessing trials of herbal products. This meta-analysis also did not analyse safety outcomes.

## Adverse effects

Limited data from small clinical trials indicate that ashwagandha is generally well-tolerated: non-serious, mild gastrointestinal symptoms are the most frequently reported adverse effects.<sup>3</sup> However, comprehensive investigation of the clinical safety profile of ashwagandha and its important constituents when used in a pharmaceutical/medicinal context, including long-term use, is required.

Spontaneous reports of adverse reactions associated with ashwagandha include diarrhoea, vomiting, nausea, abdominal pain, jaundice, pruritus and others; causality has not necessarily been established in these cases. In September 2023, the Netherlands pharmacovigilance centre (Lareb) published a safety signal relating to the potential risk of liver toxicity with products containing ashwagandha after receiving four reports of hepatitis, abnormal hepatic function and jaundice, cholestasis and transaminitis in patients who had used ashwagandha for 3–10 months. Causality has not been established definitively in these cases: three patients used other herbal, and/or non-herbal supplements, and/or other medication, concurrently. Also, the possibility that the adverse reactions are due to poor-quality products could not be ruled out.<sup>5</sup> VigiBase, the World Health Organization's (WHO) global database of individual case safety reports of suspected adverse drug reactions, maintained by the Uppsala Monitoring Centre on behalf of WHO, contains 15 reports of hepatobiliary disorders and investigations associated with ashwagandha.<sup>5</sup> Published case reports and case series have also described liver injuries associated with ashwagandha. To date, hepatotoxicity and abnormalities in liver enzyme concentrations have not been reported in clinical trials.

Given the limited availability of safety data, the use of ashwagandha by children, pregnant, and breastfeeding women should be avoided.

## Interactions

Due to limited evidence that ashwagandha may reduce blood glucose concentrations, caution should be exercised (eg consider recommending an increase in blood-glucose

concentration monitoring) if ashwagandha is used concurrently with conventional antidiabetic medicines. Ashwagandha may also affect thyroid hormone concentrations, and caution is advised if ashwagandha is used concurrently with thyroid hormones or antithyroid agents.<sup>6</sup> Similarly, given ashwagandha's potential immunomodulatory activity, concurrent use with immunosuppressant agents should be undertaken with caution. The clinical relevance of these interactions is unknown.

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