



Pharma's Next Big Opportunity:

Exploring the Potential of Herbal Medicines in Modern Healthcare



In Partnership with





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The nutraceuticals market and consumer trends: Ashwagandha and more

Interest in nutraceuticals and natural extracts have increased significantly since the onset of the COVID-19 pandemic and consumer health trends prioritising personalised and integrative medicine. Technological innovations and increased studies in extracts such as Ashwagandha are propelling the nutraceuticals market from traditional medicine to mainstream healthcare for the treatment of stress, anxiety, sexual dysfunction, endurance and performance, and much more.



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Navigating key challenges in the natural products industry

The natural products industry is not without its specific challenges. The supply chain remains fragile in response to increased consumer demands and logistics associated with sourcing and transporting the natural products that produce these extracts. Quality control and regulatory concerns remain a top priority in an industry that is susceptible to undisclosed adulteration and inconsistent regulatory guidelines.



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A sustainable Ashwagandha supply chain for all

Sustainability for natural product extracts like Ashwagandha root encompass not only environmental concerns, but also considerations for those that work in the farms, factories, and supply chains. KSM-66 Ashwagandha is a prime example of building a sustainable network to support everything from the Earth to the people in the Ashwagandha supply chain.



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Future opportunities for Ashwagandha

While consumer health trends have veered towards their roots in herbal medicines, Ashwagandha's route towards regulatory approval is mired by inconsistent guidelines and a lack of investment. Despite these challenges, healthcare and natural extract experts remain positive that, with continued focus on scientifically backed evidence for the root's benefits and the supply chain's ESG considerations and advantages, Ashwagandha root will lead the way towards establishing regulatory compliance and investor interest in high-quality herbal and natural extracts.

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Key Findings

1 From traditional use to evidence-based research

Ashwagandha (scientific name *Withania somnifera*) originates from a small shrub belonging to the Solanaceae family [i]. It has long been a highly regarded herbal ingredient in Indian Ayurveda, a 5000-year old traditional medicine system focused on maintaining balance in the body, mind, and spirit. Interest in Ashwagandha has led to the study of its efficacy in comparison to other herbal ingredients, with extensive rodent studies leading to further studies in a clinical setting [ii]. Recent interest in science-backed evidence for the effects of Ashwagandha has paved the way for research organisations to promote investment into the study and manufacture of Ashwagandha products – despite the financial implications of the herb as a non-patentable ingredient.

2 Therapeutic indications

Historically, Ashwagandha has been used to remedy stress, fatigue, inflammation, arthritis, and epilepsy, among other indications [iii]. Further clinical studies of the Ashwagandha root have investigated the active constituents of Ashwagandha, which comprise of alkaloids, steroidal lactones, saponins, and withanolides [iv]. These studies have demonstrated Ashwagandha's neuroprotective and anti-inflammatory properties. Within the Ayurvedic system, Ashwagandha is utilised most notably as a nervine tonic, where it is purported to be the most prominent Ayurvedic 'Rasayana' known for its adaptogenic abilities [i]. In this report, we will focus on the Ashwagandha root's adaptogenic effects for stress and anxiety, sleep problems, memory and cognition, sexual function, and endurance or sports recovery.



Key Findings

3 Regulatory considerations

Several challenges exist for proponents of herbal medicines, including Ashwagandha, which lacks the establishment of a proper regulatory framework. However, efforts are being made to address concerns surrounding undisclosed adulteration, the classification of herbal ingredients under food or drug laws, and the tracking of national developments. The principal of 'Mutual Recognition' and increased calls for satisfactory scientific backing are pushing pharmaceutical and nutraceutical companies to join in providing a comprehensive understanding of natural products and ingredients, and their place within a regulatory landscape that demands certainty [v].

4 Sustainability and culture

The impact of sourcing Ashwagandha and similar natural products on local communities and ESG principles cannot be understated. With rising consumer demand for environmentally responsible practices from companies and ethically sound farming, the Ashwagandha supply chain is well-positioned to demonstrate how a sustainable supply chain can be achieved.



The nutraceuticals market and
consumer trends:

KSM-66

**Ashwagandha
and more**



The nutraceuticals market and consumer trends:

KSM-66 Ashwagandha and more

Defined as a food or part of a food product that provides medical or specific health or nutritional benefits, nutraceuticals have been an increasing trend among consumers interested in taking charge of their healthcare outcomes, without the need for pharmaceuticals [vi]. The global nutraceuticals market grew to USD \$291.33 billion in 2022, and it is expected to grow at a CAGR of 9.4% between 2023–2030 [vi]. The global Ashwagandha extract market itself generated USD \$864.3 million in 2021 and is expected

to rise to \$2.5 billion by 2031 [vii]. The increasing awareness of health and wellbeing, combined with a growing interest in self-managed healthcare, along with advancements in food products and natural ingredients, could potentially lead the pharmaceutical supply chain to discover the next breakthrough product in the realm of nutraceuticals. This is particularly true given the surging demand for personalised medicines.

Interest in Ashwagandha is nothing new – as one of the most revered adaptogens for 5000 years, Ashwagandha has been a mainstay in Ayurvedic medicinal traditions [iii]. This natural ingredient extract has ranked amongst the top 40 herbs in marketplaces and trends on Google indicate double the amount of searches for Ashwagandha from 2020–2021 [iii]. In particular, KSM-66 Ashwagandha has elevated the Ashwagandha market to new proportions compared with 10 years ago [iii].

Produced by Ixoreal Biomed, KSM-66 was developed over the course of 14 years but is now the dominant leader in Ashwagandha root extract products, boasting a market



share of over 55% of all Ashwagandha sold globally. Moreover, it is now used as an ingredient in more than 2400 finished products in over 50 countries. [iii].

Understanding how consumer health trends are driving such massive interest and growth in Ashwagandha root extract is important to developing robust supply chains and rigorous quality control processes, and moving towards a regulated natural products sector in an industry of synthetic molecules [iii].



Consumer trends driving demand for natural products

Integrative medicine, though not a standardised definition or practice in the healthcare industry, generally encompasses a patient-centred approach combining conventional Western medicine involving pharmaceuticals with so-called ‘alternative medicines’, drawing from ancient systems such as Ayurveda [viii].

In the last 5 years, the herbal supplements market grew by an estimated 17% increase in sales in 2020, with an additional 9% increase in sales in 2021, states **Mark Blumenthal, Editor-in-Chief and Publisher of HerbalGram**. “A lot of the [sales] were COVID-19 pandemic related buying by consumers looking to stock up on things like elderberry and other herbs that were reputed to provide some degree of relief, whether from an immunity point of view or symptomatic relief for upper respiratory tract infections,” he comments. With healthcare systems and available treatment options under scrutiny in recent years, there has been an increased demand for



alternative and integrative medicine and practices.

David Ridley, Senior Editor, HBW Insight at Citeline, states:

“Consumers are thinking more carefully about how they spend their disposable income, if they have any at all. Before the current phase of very high inflation, especially during the pandemic, consumers were keen to invest in a wide range of products that would maintain their general wellness, without worrying too much about the specific effects of individual ingredients, plants, minerals, bacteria, etc. With disposable income increasingly squeezed, consumers want to know what they are buying works. They are increasingly attracted to natural products for specific health issues that, on the one hand, may have been addressed by pharmaceutical products in the past – cough/cold, allergy, pain, sleep, sex/fertility, etc – or are not currently addressed by OTC medicines, such as mental health. Some ingredients that were particularly popular during the pandemic but have not proved their ‘value for money’ in the eyes of consumers, are seeing slower growth, for example CBD and general purpose pre or probiotics.”

By 2022 and into 2023, some herbal and natural products markets experienced a drop-off in sales, while others continued to see growth. “Sales in Bayer Consumer Health’s Nutritionals’ business fell back by 10.5% to €375m in Q1, which group CEO Werner Baumann noted was the first drop in turnover recorded by the category in three years,” states Ridley. “Weaker interest in supplements post-COVID contributed to a 7% drop in volumes at supplier Royal DSM’s Health, Nutrition & Care (HNC) group in Q1. In Europe specifically, VMS consumer demand continues, but at a slowing rate of growth. In Germany, for example, sales of vitamins, minerals, botanicals and other wellness-benefiting food supplements (VMHS) through German pharmacy (bricks-and-mortar and online) grew by 1.3% to €3bn (\$3.3bn) in 2022. This is down from a growth rate of 3.5% in 2021 and represents a three-year deceleration despite an overall expansion of the category during the coronavirus pandemic.”

Blumenthal offers an explanation for such an increase and levelling off of consumer activity, and how it will affect the



overall healthcare industry: “Worldwide (not just in the US), there’s a consumer preference associated with a natural disaffection towards the high cost of pharmaceuticals, and the perception that herbs can be utilised in place of pharmaceutical, OTC drug types not only for minor, self-limiting, self-diagnosable, self-treatable conditions but also for more serious conditions that require licensed healthcare professionals.” Ridley likewise cites a survey conducted by Food Supplements Europe, which found that around half of consumers expressed a preference for supplements labelled as organic, natural, or that had recyclable packaging.

Lisa-Maria Müllner, Research & Development, Team Lead:

Development Food Supplements at Ringana, expands:

“The market is witnessing a dual trend. On one hand, local ingredients and traditional practices like Ayurveda and Traditional Chinese Medicine (TCM) remain popular. Simultaneously, there’s a strong interest in cutting-edge innovations and technologies such as personalised nutrition or novel ingredients (e.g. plant cell cultures) cultivated in modern bioreactors or vertical farming.”

From traditional therapy to modern science Ashwagandha

As the #1 natural extract product in the US, Ashwagandha has been a staple in Ayurvedic medicine for over 3000 years [viii]. Ayurveda refers to a system of medicine originating in India and has been in practice for nearly 5000 years, advocating overall wellness through the balance of body, mind, spirit, and environment [ix]. Ashwagandha in particular has gained significant traction in the mainstream healthcare market, with sales of herbal supplements containing the root reaching USD \$7 million in 2018 – a 165.9% increase from the previous year [x]. Consumers are embracing the various health claims (scientifically backed and otherwise) boasted by the herb. “We say if you feel stressed, fatigued, anxiety, have issues with sleep, or lacking sex drive, then Ashwagandha is something you should try,” says **Co-Founder of MedicineGarden Tom Johnsson.**



Stress and anxiety

Cortisol plays an important role in the body's regulation and response to stress. As an adaptogen, Ashwagandha root has been extensively studied in a clinical setting to investigate its stress-relieving effects and the pharmacology of the extract. Various studies have investigated its promotion of homeostasis and general wellbeing. In a single-centre, prospective, double-blind, randomised, placebo-controlled trial, investigators studied a total of 64 healthy adults [xi].

Over 8 weeks, the patients were given either 300mg of KSM-66 Ashwagandha twice daily or a placebo, and results were measured via serum cortisol levels and three different scales and questionnaires [xi]. Those taking KSM-66 Ashwagandha reported a Perceived Stress Scale reduction of 44% and reduced serum cortisol levels by 27.9% [xi]. Other questionnaires saw a marked reduction in severe depression of 79.3% and 77.0% respectively [xi].

One trial looked into the effects of Ashwagandha on anxiety and food cravings in 52 participants with chronic stress [xii]. The subjects were assessed via the Perceived Stress

Scale and Food Cravings Questionnaire primarily, as well as the Oxford Happiness Questionnaire, Three-Factor Eating Questionnaire, serum cortisol, body weight, and body mass index. After 8 weeks of treatment with either 300 mg of KSM-66 Ashwagandha or a placebo, those who received the Ashwagandha root extract demonstrated improvements in each of the measures, with significant reduction in serum cortisol (22.2%) and food cravings questionnaire scores. This resulted in significantly reduced body weight (3.03%) and body mass index (2.93%), indicating that Ashwagandha could be used in mitigating weight-gain effects of chronic stress [xii].

In another study, aqueous Ashwagandha significantly reduced the serum cortisol levels in 58 patients compared to placebo group participants, as well as improved sleep quality [xiii]. This is in line with Johnsson's description of how Ashwagandha has been traditionally used: "It is not a quick-acting herb – you need to have patience to notice effects, which I think one reason we've been so successful with KSM is that we have been very honest that Ashwagandha is not



a quick fix but acts in 2–4 weeks. Ashwagandha helps you to increase your resistance to stress – all the effects one feels from Ashwagandha is the result of a more moderate stress response, giving a feeling of relief from anxiety and more vitality and strength.” The corroboration of anecdotal evidence with that of scientifically rigorous clinical research marks a promising step towards establishing a scientific background on the adaptogenic effects of Ashwagandha.

Sexual function

Additionally, Ashwagandha’s stress relief effects have been investigated for potential use in treating sexual dysfunction for both males and females [xiv]. While studies have investigated Ashwagandha’s ability to increase testosterone levels and its effects as an aphrodisiac (one study looked at 50 participants perceived sexual wellbeing after 8 weeks of taking 300 mg of KSM-Ashwagandha twice daily. The study found a 16.65% increase in serum testosterone levels along with a significant increase in the Derogatis Interview for Sexual Functioning (DISF) domain scores) [xv].

A 90-day pilot study was conducted to provide research into the root’s ability to improve low sperm concentrations and the safety of supplementation. KSM-66 Ashwagandha from Ixoreal Biomed and placebo capsules were randomly given to 46 male patients experiencing oligospermia, with results measured by semen parameters and serum hormone levels [xiv]. Patients who received KSM-66 Ashwagandha treatments demonstrated a 167% increase in sperm count, 53% increase in semen volume, and 57% increase in sperm motility [xiv]. As one of the most prevalent causes of reduced fertility, individuals experiencing oligospermia may turn towards alternative therapies, necessitating the conduction of safety and efficacy studies for such treatments [xiv].

Concurrently, sexual dysfunction for women typically results in orgasm disorders and sexual difficulties. Stress increases the levels of cortisol in the blood, which has been reported to co-occur with depression, anxiety, and sexual dysfunction [xvi]. A randomised pilot study investigated the use of KSM-66 Ashwagandha in 50 women, measuring sexual function through two psychometric scales (Femal Sexual Function



Index FSFI and the Female Sexual Distress Scale FSDS) [xvi]. After 8 weeks, patients taking Ashwagandha reported an increase in mean total FSFI score, with arousal and lubrication the improving the most. While no difference in sexual activity was observed, higher sexual satisfaction and orgasm instances were achieved [xvi]. Though more safety studies should be conducted, the decrease in cortisol levels demonstrated through the consumption of Ashwagandha root of a high concentration may ease sexual arousal difficulties in women and vaginal pain caused by stress [xvi].

A second study looking into sexual satisfaction, sleep, and quality of life in 80 healthy women showed statistically significant increases in Female Sexual Function Index (FSFI) score (59.2%) and with significant increase in orgasm

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(75.7%) and desire (71.6%) domains after 8 weeks of a twice-daily dose of 300 mg of Ashwagandha root extract compared to the placebo [xvii].

Cognition and memory

The neuroprotective, anti-stress, and rejuvenating effects of Ashwagandha root extract has also been clinically studies for supporting brain and cognitive function [xviii]. 50 healthy adults were given either a full-spectrum root extract of KSM-66 Ashwagandha twice daily or a placebo. Efficacy parameters utilised scores on the Wechsler Memory Scale III for memory and cognition [xviii]. After 8 weeks, individuals taking the Ashwagandha extract demonstrated sustained attention improvements, reduction in information processing speed, improvement of immediate and general memory subsets, and no adverse events/excellent levels of tolerability [xiv].

With nations across the globe facing an aging population crisis, decline in cognitive function threatens the overall health and wellbeing of a significant proportion of the population. Safe and efficacious use of Ashwagandha root



extract in preliminary clinical trials can lead to larger studies to support its use for cognitive support [xviii].

Endurance and sports recovery

As a known adaptogen, Ashwagandha's effect on serum cortisol levels and energy promotion suggests benefits for enhancing physical performance [xix]. A randomised and placebo-controlled study investigated the effect of a high concentration of Ashwagandha root extract for cardiorespiratory endurance in 50 healthy adults, measured utilising a 20-minute Shuttle Rune Test for parameters including VO2 max and QOL measurement through the WHO QOL questionnaire [xix]. After 12 weeks, VO2 max for those taking KSM-66 Ashwagandha increased by 4.91% at 8 weeks and 5.67% at 12 weeks [xix]. QOL measures were increased by 9.46% from baseline at the conclusion of the study, with no changes in vital parameters [xix].

Another study looked at 50 athletic adults and the effects on maximum aerobic capacity and stress management using VO2 max and Total Quality Recovery Scores (TQR),

Recovery-Stress Questionnaire for Athletes (RESTQ), and Daily Analysis of Life Demands for Athletes (DALDA) questionnaires [xx]. After 8 weeks of receiving 300 mg dosage of KSM-Ashwagandha twice daily, or a placebo, the Ashwagandha cohort demonstrated a significant improvement in cardiovascular fitness according to the VO2 max (16.4% increase) compared to the placebo group.

Markedly improved outcomes were also seen in fatigue recovery, energy levels, daily life demands, and overall fitness in the Ashwagandha group [xx]. Also demonstrated were 37.36%, 60.71%, and 59.27% increases in the recovery-stress questionnaire for general stress, fatigue and general wellbeing domains respectively. A 6.67% increase was observed in Total Quality Recovery. It was noted by the researchers that this was a single-centre study, and it would be beneficial to see further analyses conducted in larger, multicentre studies, focusing on the potential effects of a more diverse patient population [xx].

In a new randomised, double-blind, placebo-controlled study, researchers evaluated the ability of 8 weeks of KSM-



66 Ashwagandha root extract supplementation on muscle strength and recovery in 80 participants (40 men and 40 women).

The study found that participants who supplemented with KSM-66 Ashwagandha root extract (300 mg/twice a day) demonstrated an 8.11% and 10.07% increase in free testosterone and total testosterone in males ($p < 0.001$ and $p < 0.0001$). A 23.5% and 22.8% increase in bench press for both males and females respectively was demonstrated, with an overall 5.2% increase in muscle size for arm ($p < 0.0001$), thigh, and chest respectively; an overall 1.7% reduction in average body fat; a 9.51% and 7.15 % increase in maximal oxygen consumption ($VO_2 \text{ max}$) in both males and females respectively ($p < 0.0001$) and an overall 7.19% reduction in the serum creatinine phosphokinase indicating faster recovery ($p < 0.0001$) [xix]

Additionally, an 8-week, randomised, prospective, double-blind, placebo-controlled clinical trial published in the Journal of the International Society of Sports Nutrition included 57 men with little experience in resistance training.





Researchers assessed the subjects' muscle strength measured by a maximal single repetition load, muscle size, body fat percentage, and serum testosterone levels. The study found that participants who supplemented with KSM-66 Ashwagandha root extract (300mg/twice a day) demonstrated a 15.3% increase in serum testosterone ($p < 0.05$); more than 75% and 50% increases in muscle strength for bench press and leg extension exercise respectively ($p < 0.05$); a 8.1%, 17.1%, and 3.3% increases

in muscle size for thigh, arm, and chest respectively ($p < 0.05$); a 3.5% reduction in average body fat ($p < 0.05$) and a significant reduction in serum creatine kinase level indicating faster recovery [xxii].

Implications for Ashwagandha root extract in improving general vitality and stamina are not limited to athletes – Rasayanas such as Ashwagandha may have clinical significance for all in improving general weakness and endurance [xix].

While Ashwagandha's traditional use is well-documented in both alternative and clinical literature, the science to propel this shrub into mainstream pharmaceuticals/nutraceuticals remains tentative in its claims. The majority of clinical studies looking at the effects of Ashwagandha study the root extract, with the effects of other parts of the plant left unclear, especially when it comes to safety. As we will discuss in subsequent sections, the nascent clinical landscape of Ashwagandha with scientific evidence to back its traditional usages may contribute to challenges in its regulation and investment by the established industry.





Navigating key challenges in the natural products industry





Navigating key challenges in the natural products industry



Consumer demands and the chain of supply

The impact of such consumer demands can be felt throughout the supplement and ingredients supply chain, including healthcare manufacturers, suppliers, and national/international regulatory bodies. Manufacturers are navigating a relatively blurry supply chain where a lack of transparency stems from local markets with many traders and sellers and can lead to unsustainable sourcing of ingredients and unclear chains of responsibility [xxii]. An untransparent supply chain cannot boast resilience against disruptions such as the COVID-19 pandemic [xxii].

Ashwagandha is no exception to the industry – the supply chain remains difficult to monitor and understand where the Ashwagandha is sourced from. A traceable and transparent supply chain is a critical aspect for suppliers and manufacturers in the natural products and nutraceuticals industry to meet the strict demands and high importance placed on the supply chain by regulatory bodies [xxiii].



Aside from appeasing regulatory agencies, knowing where ingredients are being sourced from and how they are being processed is important for determining the precise bioactivity and efficacy of the product being made [xxiii]. For Ashwagandha, different geographies can give rise to varying ratios of bioactive compounds present in the root. The withanolide content in Ashwagandha, for example, can depend on such factors as soil conditions, affecting the quality of the Ashwagandha extract product [xxiii].

Additionally, the drive to meet consumer demands can be hampered by regulatory issues because of the lack of consensus on how to classify natural extracts affects how pharmaceutical and nutraceutical manufacturers can claim the benefits of their product, and ultimately how their products will be received by consumers.

Ridley explains: “Some trends that have been around since before the pandemic have continued but are changing. CBD is an excellent example. Mired in regulatory issues in both the EU¹ and UK², consumers are now completely confused as to the safety and efficacy of CBD food supplements. They

are still buying them, but growth is slowing, and due to the more difficult economic conditions, manufacturers that have gambled on the market maturing quick enough for debts to be paid are now going bust.” Looking at CBD as an example, Ridley states that products that do not hold up to the expectations of their consumers due to dosage issues and regulatory complications can determine a company’s route to success or failure.

“Brands that make unproven claims lose consumer trust and impact the whole industry negatively. Asking EU consumers why they haven’t used CBD, Prohibition Partners found that more than two in five said that the reason was a lack of faith in its claimed wellness effects, such as pain and anxiety relief and help with sleep,” Ridley comments. “Part of this scepticism comes from a lack of understanding about CBD dosage, Prohibition Partners suggests, for example where consumers try very small quantities or take CBD for an insufficient length of time to see its beneficial effects. ‘Manufacturers could potentially do more to educate consumers on appropriate dosing and the management



of expectations around which effects can be expected and when,' it suggests." A delicate balance must be maintained between the claims made by pharmaceutical and nutraceutical companies, and the supply chains that provide them with the extracts and manufacturing services to create their product.

"As consumer's wishes and values change, markets and ingredient's supply chains need to change too," Müllner states. "The biggest challenge: there is an imbalance in demand and supply of high-quality, clean, organic extracts that are both readily available and come at stable prices. Consumers want it all, at the same time, at an affordable price."

Quality control for Ashwagandha: getting to the root of undisclosed adulteration

A prevailing issue for natural extract products, including Ashwagandha, is the undisclosed adulteration of products. In this instance, it is important to distinguish the term 'undisclosed adulteration' as the intentional non-disclosure of added or changed ingredients in Ashwagandha products, Blumenthal highlights. "The primary way that Ashwagandha



has been adulterated is the admixture of leaf material with root material, where the admixture of the leaf is not disclosed,” he states.

“Traditionally in Ayurvedic medicine, it’s the root that has always been the preferable material from Ashwagandha. The leaf has some history of ethnobotanical use topically, either fresh, dried, or reconstituted into a poultice for certain topical skin issues. There’s very little, if any, evidence of historical use [of the leaf] in ethnobotany of traditional medicine – it’s always been the root that is used internally. So we have situations in which Ashwagandha leaf is added to the root to increase the amount of product with a lower cost ingredient.”

Industry competition in an ambiguous regulatory landscape for Ashwagandha extract products also contributes to difficulties around quality control. “Companies want to make their own proprietary blend and then they are tempted to use parts other than the root, because the root is the most expensive part,” Johnsson explains. “The leaves and stem are much cheaper and contain some of the same actives, but not in the same ratio. When you add leaves to the root, you

change the property of the extract, including the safety since the above-ground parts contain substances that are not suitable for long-term use, such as *withaferin A*.

As a result, several Food Authorities in Europe have expressed safety concerns since several animal studies where leaf extracts were used showed questionable results regarding, among other things, sex and thyroid hormones. The same questionable results have not been found for Ashwagandha root but since regulators consider everything as one, they put out a warning for Ashwagandha as a whole.”

Whether an ingredient or extract is approved or banned by regulators can simply depend on how it is categorised. Ridley further discusses the nuances of regulations concerning herbal extract products and botanicals: “It’s important to distinguish between herbal medicines and ‘botanicals’ – herbal ingredients in food supplements. These two forms of natural products come with different, national-cultural habits and are regulated differently at the European Union level. Germany, for example has its own tradition of herbalism with widespread use, distinct from Chinese and Indian traditions



that are currently very popular, with ingredients unfamiliar to many European herbal medicine consumers.”

Government of India Advisory

In response to the new use of aerial parts of Ashwagandha for internal purposes, India’s Ministry of Ayush has issued an Advisory against the use of Ashwagandha leaves, specifically stating: “No substantial evidence and literature is available to endorse the efficacy of crude drug/extract of *Withania somnifera* leaves. Considering this, it would not be appropriate to consider the *Withania somnifera* leaves as ASU (Ayurveda, Siddha, Unani) medicine at this stage. Extensive studies are required to establish the safety and efficacy of leaves of *Withania somnifera* for different indications. Till then, the usage of leaves may not be considered for therapeutic purpose in ASU systems” [xxiv].

The regulatory framework for herbal medicines is reasonably clear in the EU (and by extension, the UK) – ‘full/standalone, well-established use, or traditional use’ pathways depending on the kind of safety and efficacy

evidence available and how long the medicine in question has been used safely. There are a number of long-standing and successful medicines manufacturers in Europe that are as comfortable being associated with ‘health foods’ and health food shops [xxii].

Botanicals, by contrast, face far greater regulatory hurdles, and are marketed by a wide range of manufacturers that have differing views on how much such products should be regulated at all. More than 2000 health claims for botanicals are ‘on hold’ by the Commission, meaning that they can continue to be used despite being deemed to have unsatisfactory scientific backing. The unclear regulations surrounding natural products may lead to increased intentional adulterations by companies who do not meet any scientifically backed therapeutic or safety claims.

Recent proposals have attempted to define regulations for natural extracts and ingredients, with varying success. “Designed to protect consumers from unsubstantiated and unauthorised health-related claims for foods and



food supplements, the 2006 European Union Health Claims Regulation (EC 1924/2006) should have been fully implemented by 31 January 2010 at the latest," states Ridley. "However, due to concerns raised by several EU member states and industry stakeholders with regards to the different regulatory regimes for health claims in food and food supplements on the one hand, and traditional herbal medicines on the other, the EC initiated a period of reflection on the issue of botanicals. Pending the outcome of its reflection, the Commission asked EFSA, which had by this point rejected a number of botanical claims, to discontinue its scientific assessment of the health claims. Meanwhile, the European Commission continues to reject botanical health claims on the basis that scientific evidence does not live up to medicine-like cause-and-effect standards."

Despite the wide range of existing natural extracts, the path to regulated approval remains a challenge. Products under different labels such as botanicals, natural extracts, and novel foods are subject to different standards. "There's something called the Botanical Drug Approach that the FDA





set up about 20 years ago, which reduced the amount of preclinical toxicology testing required on animals for herbs like garlic and ginger,” Blumenthal explains. “Why do we have to prove on an animal test that it’s safe? We’re already taking it. So there’s a reduction in the amount of investment required in the testing. However, only two or three botanical drugs have gotten through approval in the 20 some years of this process.”

Ridley cites a ‘Novel Foods’ route to regulatory approval in the EU for ingredients that ‘do not have a significant history of consumption’ in the EU before 15 May 1997. “While the novel foods route offers manufacturers the opportunity to bring truly innovative products to the supplements market, the process can be long-winded and involves sizeable investment to collect the data required by EFSA.”

As of yet, Ashwagandha is not labelled a novel food in the EU, and can be used in food supplements. In US markets, Ashwagandha has been used prior to the Dietary Supplement Health and Education Act of 1994, and can

be included in dietary supplements as it is not considered a new dietary ingredient. In states such as Canada, Australia, Southeast Asia, and the African sub-continent, Ashwagandha is allowed.

These inconsistent regulations have hampered efforts to bring Ashwagandha into an established market, or have outright stopped the progress of Ashwagandha products. In 2011, Denmark banned Ashwagandha in dietary supplements, citing data that was not able to establish a safe lower limit for intake [xxv]. Despite this, Johnsson remains optimistic that the ban will not remain in place for long as more safety and toxicology studies are conducted for the increasingly popular Ashwagandha root. “Right now, the authorities in Denmark are stopping a boom in Ashwagandha, mainly caused by a misunderstanding that leaves, stem, and root are the same, and therefore have the same safety issues. There is one road forward and that is well-designed safety and efficacy studies. And they are coming – KSM-66 alone have published more than 10 studies only in the last year,” Johnsson says. “I am positive that [regulators] will change their minds. When



there is enough well-performed, conclusive studies – and we are getting there – the authorities in Denmark will re-evaluate and come to the conclusion that a well-defined Ashwagandha root extract is absolutely safe.”

Müllner adds: “Challenges arise from legal inconsistencies within the EU legislative framework and the ongoing debate about how to classify actives, whether as pharmaceuticals or food supplements.”

“The most important factor to ensure the highest quality is a profound cooperation and transparency from the roots to the consumer,” she emphasises. “Quality control is a shared responsibility across the supply chain involving producer, distributors, and end-product manufacturers.

Collaborative efforts ensure comprehensive analysis and checks are conducted at every stage. Regular assessments are imperative from field to end-product. Relying solely on documentation is not an option. Thorough testing is our practice – assurance comes from validation, not assumption.”

Cyclic cause-and-effect: increasing investment, regulations, and quality control for Ashwagandha

The competition within an industry that profits from patents and proprietary ingredients and procedures can also drive investment away from products containing ingredients that are non-patentable. “In most cases, these herbs are not patentable because they’re part of an inherited culture of humanity,” Blumenthal states. “They are medicines that have been handed down for generations, so you simply can’t patent these things unless you find a new use or a process patent for a certain type of extraction to make a certain type of patented formulation.

That means there’s little to no financial incentive for pharmaceutical companies to invest millions of dollars to submit an herbal extract to government regulatory agencies.”



The lack of studies conducted on Ashwagandha in Western markets in turn provides regulators with less scientific backing to provide these products with approval. With inconsistent regulations based on the few trials conducted, Ashwagandha's quality control remains precarious.

But Blumenthal offers a way out of this cycle for Ashwagandha:

"We said these foods and dietary supplements should be classified under the food law, not the drug law. And that's how we got around it. Otherwise, what was going to happen was many of these items would not be available to consumers because they were classified as unapproved drugs." Reclassifying ingredients and extracts as foods/dietary supplements enable consumer access to natural products such as Ashwagandha. "Just because you take a food and put it into a dosage form that limits bad or objectional taste, smell, colour etc. doesn't necessarily turn it into a drug." With this potential route to approval, more pharmaceutical companies may be incentivised to produce scientifically-backed studies and invest in

procurers and suppliers of high-quality Ashwagandha root. This will offer regulators the safety and toxicological data they need to establish more concrete requirements to implement the kind of quality control currently lacking from the Ashwagandha market.



Ad



A sustainable Ashwagandha supply chain for all





A sustainable Ashwagandha supply chain for all

As with any product, especially those taken from nature, concerns surrounding Ashwagandha's sustainability are increasing in tandem with its usage. Key considerations for those involved in bringing Ashwagandha products to consumers include how the procurement of Ashwagandha affects both the natural environment in which it is found, and the people involved in its harvesting, manufacturing, and distribution.

A 1992 UN Conference on the Environment established

a pact known as The Convention on Biological Diversity, focusing on the conservation of biological resources and sustainable uses for those resources [xxv]. Implementing sustainable principles into the harvesting and cultivation of Ashwagandha plants remains an essential part of ESG strategies for many Ashwagandha manufacturers. These principles can include the cultivation of Ashwagandha with no toxic agri-poisons, protecting the soil, water, and air free of toxins [xxv]. Additionally, toxin-free soil is more fertile and produces a product that does not harbour chemicals that may bioaccumulate [xxvi].

A surprising aspect scientists and manufacturers have investigated is the farming of Ashwagandha as opposed to the wild harvesting of the plant [xxvi]. There are marked differences between foraged Ashwagandha and farmed species demonstrated by high-performance liquid chromatography, which gives wild Ashwagandha a superior active compared to farmed Ashwagandha [xxvii]. To maintain the balance between quality and sustainability, manufacturers use organic cultivation of Ashwagandha as



the optimal choice to maintain sustainable, commercial production [xxvii].

“I would say many consumers don’t yet realise the special benefits of eating a sustainable supplement, a result of not seeing all the work that lies behind organic production,” Johnsson claims. “Since day one, [MedicineGarden] have worked very hard on sustainability with KSM-66. I’m absolutely certain that in the long run, Ashwagandha will be more important. It is a high value, effective, and safe extract for the price the consumer pays. That is a concept of a long-term winner. For example, Ixoreal’s (producers of KSM-66 Ashwagandha) setup is an organic, vertical integration that has 100% control from seed to finished extract. Another important part of Ixoreal’s sustainability thinking is to ensure that all their employees have access to free schools and healthcare.”

Sustainability goals for Ashwagandha manufacturers extend beyond the natural resources. A truly sustainable system ensures that everything involved in the process does not get left behind, including the people. The toxin-



free environment ensures that farm workers are not exposed to potentially harmful chemicals [xxvi]. As Ashwagandha is native to developing areas, manufacturers and scientists are implementing methods of creating a sustainable supply chain for the plant [xxvii]. Outreach strategies to build relationships with the local communities not only offers resources back to the people but also builds trust within a business community to ensure a high-quality product [xxvii].

Ashwagandha's inherent growth cycle also contributes to the sustainability of those who work on the farms and in the factories. Crops such as ginseng take many years to mature, while Ashwagandha can be harvested in approximately 6 months from planting [xxvii]. Ashwagandha has now been adapted and perfected to life on the farm, making it a valuable cash crop to contribute to the economy of the area [xx]. Funding can be provided to schools in the community, and bring necessary jobs and healthcare to the area should the company be invested in true sustainability [xxviii].

A vertically integrated supply chain is not just for pharmaceutical vendors – a vertically integrated

Ashwagandha supply chain can ensure quality control and supply chain security for the products [xxvii]. Oversight across farms, extraction facilities, and distribution operations enables companies to deliver high-quality Ashwagandha products consistently. It also allows for the securitisation of their supply chain to ensure the sustainability of their workforce and operations [xxvii].

“Ashwagandha stands out as a resilient root, requiring minimal specific conditions for growth, rendering it crisis-resistant,” Müllner states. “Logistics is a crucial factor when it comes to the global distribution of products like Ashwagandha, which is predominantly cultivated in regions like India. Ensuring a reliable and efficient transportation network is essential to maintain the quality as it travels from its origin to destinations like Europe.” Johnsson adds: “The only thing that might not be sustainable is the transportation from India to the West, but everything else is.”

Advocating for sustainability, while an inherently moral standard to practice, has the added benefit of meeting consumer health trends [xxviii]. 65% of consumers are now



interested in buying purpose-driven brands that advocate sustainability, with 62% of millennials stating they are willing to pay more for environmentally responsible practices [xxviii]. Such consumer trends can leave companies uninterested in investing sustainable practices behind, while those that implement ESG principles into their operations can find demand for their products increase [xxviii].

Ashwagandha has demonstrated enormous potential amongst consumers, especially in the US – it is ranked seventh out of the top 40 bestselling herbal ingredients in the natural channel, and is among the top 40 bestselling herbal ingredients in the mainstream channel in 2018 [xxviii]. Companies that work to incorporate Ashwagandha into their portfolios can benefit from including a manufacturer that upholds ESG practices. Sustainability operates well beyond simply 'protecting the environment'. The rise in interest for Ashwagandha products along with an increasing demand for sustainable industry operations has positioned the Ashwagandha market as an innovator for a sustainable supply chain, setting an example for all other product supply chains.





Future opportunities for Ashwagandha





Future opportunities for Ashwagandha

“Embracing heritage has become stylish, giving a boost to the adoption of Ayurvedic nutraceuticals and Ashwagandha,” Müllner states. “These natural products have been utilised and proven their effects for centuries.” Advocacy for Ashwagandha is high for a number of indications by those who use it, manufacturers, and scientists dedicated to the establishment of scientifically-backed evidence for natural extracts.

As a trending herb in the US market for herbal ingredients and extracts, Ashwagandha remains one of the most Googled superfoods [xxix], with celebrity endorsements from the likes of Gwyneth Paltrow, Jennifer Lopez, and the

Kardashians recommending Ashwagandha extract to their audiences. Despite some challenges, Ashwagandha is well on its way to becoming a mainstream ingredient in North American markets, with European markets following suit [xxx].

The pharmaceutical industry is also taking notice of nutraceutical and herbal ingredients. Major players such as GSK, Bayer, P&G, Nestle, Sanofi, and others have successfully launched various products containing Ashwagandha [xxx]. One such notable commercial product containing comprehensive KSM-66 Ashwagandha root extract is Panadol in Australia [xxxi].

“There are many good herbs that are approved like ginseng, but I don’t think anything can beat Ashwagandha,” Johnsson states. “Ashwagandha fulfils the needs of a modern-day, stressed-out person. It balances your stress response, it can be taken in the long-term, and it has a long tradition of satisfactory results. If you took five different herbs and did the same marketing on all of them, I would say Ashwagandha would be the winner out of all them because of these reasons.”



Though expert and traditional advocacy for Ashwagandha extract products are resolute in the root's health benefits and sustainability of their supply chains, Ashwagandha still faces regulatory hurdles in some parts of the world like LATAM. Companies such as Ixoreal dedicated to the manufacturing of high quality Ashwagandha extracts and investment in scientifically-sound studies are helping to lead the way for establishing regulatory compliance for high-quality herbal and natural extracts.

“Natural products are revolutionising healthcare and are driving choices in the nutritional and pharmaceutical sphere. With easy access, they offer simple opportunities to healthier living through nourishing foods and supplements.”

Lisa-Maria Müllner, Research & Development,
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References





References

- [i] Singh N, Bhalla M, de Jager P et al. An Overview on Ashwagandha: A Rasayana (Rejuvenator) of Ayurveda, *Afr. J. Tradit. Complement. Altern. Med.* 8(5), 208–213 (2011) <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3252722/>
- [ii] Chandrasekha K, Kapoor J, and Anishetty S. A Prospective Randomized Double-Blind, Placebo-Controlled Study of Safety and Efficacy of a High-Concentration Full-Spectrum Extract of Ashwagandha Root in Reducing Stress and Anxiety in Adults, *Indian J. Psychol. Med.* 34(3), 255–262 (2012) <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3573577/>
- [iii] Ashwagandha Market Continues to Gain Critical Mass [Accessed 8 September 2023] [https://www.nutraingredients-usa.com/News/Promotional-Features/Ashwagandha-Market-Continues-to-Gain-Critical-Mass#:~:text=Currently%2C%20Ashwagandha%20is%20ranked%20in,127%3A54%2D69\).](https://www.nutraingredients-usa.com/News/Promotional-Features/Ashwagandha-Market-Continues-to-Gain-Critical-Mass#:~:text=Currently%2C%20Ashwagandha%20is%20ranked%20in,127%3A54%2D69).)
- [iv] Ashwagandha [Accessed 14 August 2023] <https://www.mskcc.org/cancer-care/integrative-medicine/herbs/ashwagandha>
- [v] EU regulatory update on ashwagandha [Accessed 19 September 2023] <https://www.vitafoodsinsights.com/regulation/eu-regulatory-update-ashwagandha>
- [vi] Global Nutraceuticals Market Size & Trends [2023 Report] [Accessed 14 August 2023] <https://www.grandviewresearch.com/industry-analysis/nutraceuticals-market>
- [vii] Sourcing ashwagandha sustainably: Supply chain challenges and opportunities [Accessed 15 August 2023] <https://www.vitafoodsinsights.com/sustainability-and-transparency/sourcing-ashwagandha-sustainably-supply-chain-challenges-and>
- [viii] Song E, Ang L, and Lee MS. Increasing trends and impact of integrative medicine research: From 2012 to 2021, *Integr. Med. Res.* 11(4), 1–3 (2022) <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9424573/>
- [ix] Review of the Therapeutic Effects of Ashwagandha (*Withania somnifera*) [Accessed 15 August 2023] https://www.herbalgram.org/resources/herbclip/issues/2004/bin_269/review44003/
- [x] India lockdown affecting ashwagandha supply, but US inventories remain strong [Accessed 16 August 2023] <https://www.nutraingredients-usa.com/Article/2020/04/02/India-lockdown-affecting-ashwagandha-supply-but-US-inventories-remain-strong>
- [xi] Chandrasekhar K, Kapoor J, and Anishetty S. A Prospective, Randomized Double-Blind, Placebo-Controlled Study of Safety and Efficacy of a High-Concentration Full-Spectrum Extract of Ashwagandha Root in Reducing Stress and Anxiety in Adults. *Indian J. Psychol. Med.* 3(34), 255–262 (2012) <https://journals.sagepub.com/doi/10.4103/0253-7176.106022>



References

[xii] Choudhary D, Bhattacharyya S, and Joshi K. Body Weight Management in Adults Under Chronic Stress Through Treatment With Ashwagandha Root Extract. *J. Evid. Based Complementary Altern. Med.* 22(1), 96–106 (2017) <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5871210/>

[xiii] KSM-66 Ashwagandha for Stress, Sleep, and Anxiety [Accessed 8 September 2023] <https://ksm66ashwagandhaa.com/clinical-studies/>

[xiv] Ambiyé VR, Langade D, Dongre S et al. Clinical Evaluation of the Spermatogenic Activity of the Root Extract of Ashwagandha (*Withania somnifera*) in Oligospermic Males: A Pilot Study. *Evid. Based Complement. Altern. Med.* (2013)

[xv] Chauhan S, Srivastava MK, Pathak AK. Effect of standardized root extract of ashwagandha (*Withania somnifera*) on well-being and sexual performance in adult males: A randomized controlled trial. *Health Sci. Rep.* 5(4): e741 (2022) <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9297375/>

[xvi] Dongre S, Langade D, and Bhattacharyya S. Efficacy and Safety of Ashwagandha (*Withania somnifera*) Root Extract in Improving Sexual Function in Women: A Pilot Study. *Biomed. Res. Int.* (2015)

[xvii] Ajgaonkar A, Jain M and Debnath K. Efficacy and Safety of Ashwagandha (*Withania somnifera*) Root Extract for Improvement of Sexual Health in Healthy Women: A Prospective, Randomized, Placebo-Controlled Study. *Cureus.* 14(10): e30787 (2022). <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9701317/>

[xviii] Choudhary D, Bhattacharyya S, and Bose S. Efficacy and Safety of Ashwagandha (*withania somnifera*) Root Extract in Improving Memory and Cognitive Functions. *J. Diet. Suppl.* 14(5), 599–612 (2017) <https://doi.org/10.1080/19390211.2017.1284970>

[xix] Choudhary B, Shetty A, and Langade DG. Efficacy of Ashwagandha (*Withania somnifera*) in improving cardiorespiratory endurance in healthy athletic adults. *Ayu.* 36(1), 63–68 (2015)

[xx] Tiwari S, Gupta SK and Pathak AK. A double-blind, randomized, placebo-controlled trial on the effect of Ashwagandha (*Withania somnifera* dunal.) root extract in improving cardiorespiratory endurance and recovery in healthy athletic adults. *J. Ethnopharmacol.* 272:113929 (2021) <https://pubmed.ncbi.nlm.nih.gov/33600918/>

[xxi] Verma N, Gupta SK, Patil S et al. Effects of Ashwagandha (*Withania somnifera*) standardized root extract on physical endurance and VO₂max in healthy adults performing resistance training: An eight-week, prospective, randomized, double-blind, placebo-controlled study. *F1000 Research*, 12(335) (2023) <https://doi.org/10.12688/f1000research.130932.1>

[xxii] Wankhede S, Langade D, Joshi K et al. Examining the effect of *Withania somnifera* supplementation on muscle strength and recovery: a randomized controlled trial. *J. Internat. Soc. Sports Nut.* 12 (2015) <https://doi.org/10.1186/s12970-015-0104-9>



References

[xxiii] KSM-66 Ashwagandha: defining sustainability [Interview] [Accessed 31 August 2023] <https://www.vitafoodsinsights.com/ksm-66/ksm-66-ashwagandha-defining-sustainability-interview>

[xxiv] Selecting the Right Ashwagandha Supplier [Accessed 31 August 2023] <https://ksm66ashwagandhaa.com/wp-content/uploads/2018/04/Report-Selecting-the-Right-Ashwagandha-Supplier.pdf?%3E>

[xxv] Ayush Advisory on Ashwagandha [Accessed 19 September 2023] <https://ayushnext.ayush.gov.in/detail/writeUps/ayush-advisory-on-ashwagandha>

[xxvi] Sustainability is in Our Roots [Accessed 1 September 2023] <https://www.nutraingredients-usa.com/News/Promotional-Features/Sustainability-is-in-Our-Roots>

[xxvii] Ashwagandha meets sustainability [Accessed 1 September 2023] <https://www.naturalproductsinsider.com/sustainability/ashwagandha-meets-sustainability-case-study>

[xxviii] Ashwagandha Sustainability and Traceability [Accessed 31 August 2023] <https://sustainableherbsprogram.org/explore/plants-in-commerce/ashwagandha/>

[xxix] KSM-66 Ashwagandha: Rooted in sustainability – infographic [Accessed 1 September 2023] <https://www.naturalproductsinsider.com/sustainability/ksm-66-ashwagandha-rooted-in-sustainability-infographic>

[xxx] These States are Most Interested in Vitamins and Superfoods [Accessed 19 September 2023] <https://www.modernsalon.com/1087463/fl-named-state-most-interested-in-vitamins-and-superfoods>

[xxxi] PanaNatra Sleep & Pain Relief [Accessed 19 September 2023] <https://www.panadol.com/en-au/naturally-derived-pain-relief/pana-natra-sleep/>

Contributor references

1. EU CBD Novel Food Applications on Hold as EFSA Considers Health Risks [Accessed 19 September 2023] <https://hbw.citeline.com/RS152630/EU-CBD-Novel-Food-Applications-On-Hold-As-EFSA-Considers-Health-Risks>
2. First UK CBD Novel Food Authorizations Not Expected Until 2024 at the Earliest [Accessed 19 September 2023] <https://hbw.citeline.com/RS153541/First-UK-CBD-Novel-Food-Authorizations-Not-Expected-Until-2024-At-The-Earliest>