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ADVANCES IN THE PHARMACOLOGICAL AND CLINICAL RESEARCH OF *WITHANIA SOMNIFERA* (ASHWAGANDHA): A COMPREHENSIVE REVIEW

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Abstract

Withania somnifera (L.) Dunal, popularly referred to as Ashwagandha, is a key medicinal herb in the Ayurvedic Rasayana therapy and has been used for more than 3,000 years. In this article, the current knowledge concerning the chemical composition, pharmacological properties, clinical effects, and safety of W. somnifera is systematically reviewed. It contains several potent phytochemicals, notably withanolides like withaferin A and withanolide A, alkaloids, and flavonoids.Preclinical investigations confirm the adaptogen, neuroprotective, anti-inflammatory, immunomodulator, antitumor, and metabolic functions of W. somnifera through various pathways such as oxidative stress control, NF-κB inhibition, GABAergic action, and HPA axis regulation. Several clinical trials have confirmed its efficacy in relieving stress and anxiety, promoting quality sleep, increasing physical performance, and enhancing male reproduction. Its preclinical application in neurodegenerative conditions and cancer has been demonstrated, but further evidence from human subjects is warranted, safety assessments show that root extract preparations are well-tolerated under appropriate dosages, with most side effects being minor and self-resolving. Only rare cases of liver toxicity have been documented, mostly related to overdose, polyherb combinations, and contamination.

1. Introduction

W. somnifera, commonly known as Ashwagandha or Indian ginseng, is one of the most revered herbs in the traditional Indian medicinal system of Ayurveda. For nearly 3,000 years, it has held a comparable to that of ginseng in Chinese medicine, earning the botanical nickname "Indian ginseng" due to its rejuvenating and vitality-promoting properties [1, 2]. The plant's Sanskrit name, Ashwagandha, is etymologically significant: "ashwa" translates to horse, and "gandha" means smell or fragrance. This nomenclature serves a dual purpose. Firstly, it refers to the distinct, horse-like odor emitted by the fresh root, which is a key characteristic for identification. Secondly, it embodies the traditional belief that consuming the root imparts the strength, vigor, and sexual vitality of a stallion [3]. In Ayurveda, Ashwagandha is classified as a "Rasayana"a category of herbs and formulations that promote longevity, delay aging, and strengthen the body's resistance to disease and adverse environmental factors. It is specifically considered an "adaptogen," a term coined in modern pharmacology to describe substances that help the body non-specifically resist a wide range of stressors, whether physical, chemical, or

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biological [4]. Its traditional applications have been extensive, used as a tonic, aphrodisiac, narcotic, diuretic, anthelmintic, and anti-inflammatory agent.

In recent decades, the global scientific community has turned its attention to Ashwagandha, seeking to validate its traditional uses through modern pharmacological methods. This has resulted in a surge of research, with numerous *in vitro*, *in vivo*, and human clinical trials exploring its therapeutic potential. The focus of contemporary research has largely been on its neuroprotective, anti-stress, and anti-inflammatory properties, with emerging evidence supporting its use in managing a wide array of conditions, from anxiety and insomnia to metabolic disorders and even cancer [5].

1.1. Taxonomy and Classification

Understanding the taxonomic placement of *W. somnifera* is essential for accurate identification and for understanding its relationship to other medicinally important plants [6].

Kingdom: Plantae
Clade: Angiosperms
Clade: Eudicots
Clade: Asterids
Order: Solanales
Family: Solanaceae
Genus: *Withania*
Species: *W. somnifera*
Scientific Name: *W. somnifera* (L.) Dunal

Family Characteristics: The Solanaceae, or nightshade family, is a large and economically significant family that includes other important plants such as tomato (*Solanum lycopersicum*), potato (*Solanum tuberosum*), eggplant (*Solanum melongena*), chili pepper (*Capsicum* spp.), and the highly toxic belladonna (*Atropa belladonna*). Members of this family are known for producing a diverse range of alkaloids, many of which have potent pharmacological effects [7].

Common Names: The plant is known by various names across different cultures and regions [1]:
Ashwagandha (Sanskrit/Hindi): The most widely recognized name.
Indian Ginseng (English): A reference to its adaptogenic properties, like Panax ginseng.
Indian Winter Cherry (English): Due to its small, orange-red fruit enclosed in a papery calyx.
Asgandh (Urdu)
Amukkuram (Malayalam)
Vajigandha (Tamil)
Withania (French/German)

1.2. Botanical Description

W. somnifera is a small, woody, perennial shrub with distinct morphological features.

1.2.1. Root System: The root is the primary part used in herbal medicine. It is long, tuberous, fleshy, and unbranched, ranging from 10–30 cm in length and 0.5–2 cm in thickness. The outer surface is brownish-grey, while the inner core is whitish. The fresh root has a characteristic, pungent odor reminiscent of a wet horse, which is the source of the plant's common name, Ashwagandha. The odor becomes less pronounced upon drying [8].

1.2.2. Stem and Branches: The plant is an erect, branching shrub that typically grows to a height of 30–150 cm. The entire plant, especially the young stems and leaves, is covered with a dense covering of short, star-shaped hairs (stellate tomentose), giving it a velvety appearance [8].

1.2.3. Leaves: Leaves are simple, glabrous (smooth) on the upper surface and tomentose on the lower surface. They are typically ovate or elliptic, measuring 5–10 cm in length. Their arrangement on the stem is alternate, but near the inflorescence, they often appear opposite [8].

1.2.4. Flowers: The flowers are small, inconspicuous, and hermaphroditic (containing both male and female organs). They are borne in axillary, umbellate cymes (clusters). The calyx is green, bell-shaped (campanulate), and five-toothed. The corolla is small, consisting of five greenish-yellow or yellow lobes. The flowers are primarily self-pollinating [8].

1.2.5. Fruit and Seeds: The fruit is a small, globose, smooth berry, about 5–8 mm in diameter. When unripe, it is green and covered by the

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persistent, enlarged calyx. As it ripens, the berry turns a bright orange-red, while the surrounding calyx becomes papery and inflated, enclosing the fruit like a small lantern. This structure aids in seed dispersal. The berry contains numerous small, reniform (kidney-shaped), yellowish seeds [8].

1.3. Distribution and Habitat

W. somnifera is native to the drier regions of the Indian subcontinent, specifically the states of Madhya Pradesh, Rajasthan, Punjab, and Gujarat. However, its distribution is not limited to India. Due to its hardiness and medicinal value, it has naturalized or is cultivated across a wide geographic belt, including:

Africa: Throughout the continent, from the Mediterranean coast to South Africa.

Middle East and Mediterranean: Yemen, Oman, Saudi Arabia, Egypt, Morocco, Spain, Italy, Greece, and Turkey.
Asia: Pakistan, Sri Lanka, Bangladesh, Afghanistan, and China.

Islands: The Canary Islands and the Cape of Good Hope.

Australia: Cultivated in some regions [9].

Natural Habitat and Climate Conditions: Ashwagandha is a hardy, xerophytic plant, well-adapted to survive in arid and semi-arid conditions [10]. Its preferred habitat includes:

I. **Climate:** It thrives in warm, dry, subtropical climates with temperatures ranging from 20°C to 35°C. It is drought-tolerant and requires minimal rainfall, making it susceptible to damage in waterlogged or overly humid conditions. It prefers a sunny, exposed position [2].
II. **Soil:** It is not particularly demanding regarding soil type but shows a strong preference for well-drained, sandy loam or light, gravelly soil with a slightly alkaline to neutral pH (7.5–8.0). It is often found growing as a common weed in wastelands, open fields, along roadsides, and on dry, stony slopes at altitudes up to 1,500 meters above sea level [11].

2. Biochemical Characterization of *W. somnifera*

W. somnifera is rich in natural compounds that help fight harmful microbes. However, the levels of these active ingredients can vary depending on the plant part, growing conditions, and variety. This inconsistency makes it difficult to standardize herbal products or produce them on a commercial scale. Since the compounds interact with the body in complex ways, ensuring consistent health benefits across assorted products remains a major challenge [12]. Researchers have found that the leaves of *W. somnifera* contain 62 different primary and secondary metabolites, while the roots hold 48. Interestingly, 29 of these compounds are shared between both parts of the plant. Research has also identified several key bioactive components responsible for its health benefits, including steroidal flavanol glycosides, glycowithanolides, steroidal lactones, and phenolic compounds—some of which are illustrated in Figure 1. Below [13] .

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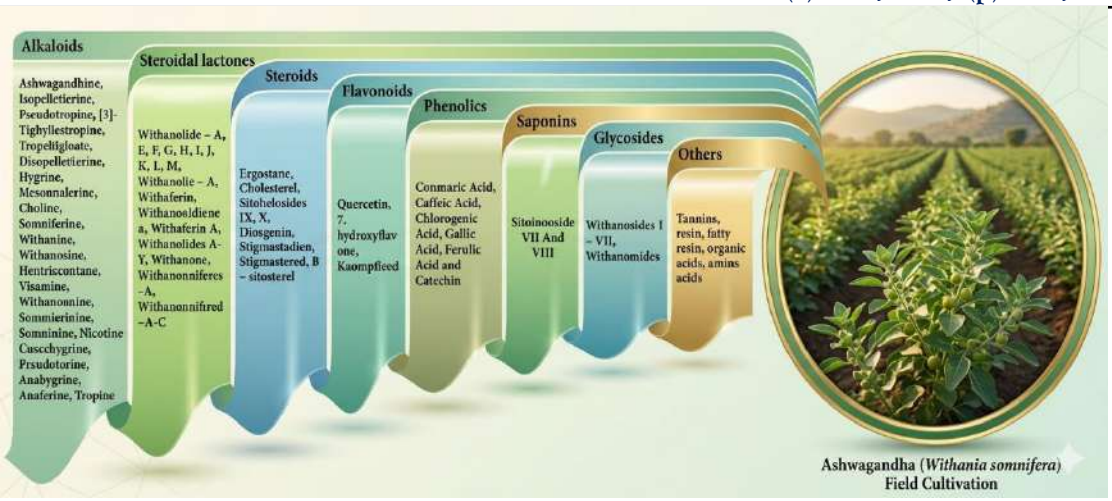


Figure 1. Diverse Classes of Bioactive Constituents Identified in *W. somnifera*.

Different chromatographic techniques had allowed the researchers to extract, identify, and use different chemical constituents from different plant parts of *W. somnifera* i.e., in table 1.1. The bioactive chemical constituents of *W. somnifera* include withanolides, which have been quantified within a range of 0.001% to 1.5% of the plant's dry weight. Alkaloids constitute approximately 0.13% to 0.31%, while flavonoids are present at a concentration of 43.51 mg RE/g. These phytochemicals are collectively recognized as the primary contributors to the species' established therapeutic properties [14].

TABLE 1. DISTINCT WITHANOLIDES AND THEIR STRUCTURAL DERIVATIVES EXTRACTED FROM DIFFERENT ORGANS OF W. SOMNIFERA

Plant Parts	Bioactive Compounds	Functions
Shoots	Withanolide A (2.88 mg/g DW), Withanolide B (1.48 mg/g DW), Withanolide D (0.30 mg/g DW), Withaferin A (3.79 mg/g), Withasomnillide, Withasomniferanolide, Somniferwithanolide, Somniwithanolide, Withanone (0.022 mg/g)	Supports endocrine function by helping regulate thyroid hormones; Promotes reproductive health; Enhances energy metabolism and reduces fatigue; Improves overall vitality; Exhibits nootropic properties, supporting memory and cognitive function. [15-17]
Roots	Withanolide A (5.4 mg/g DW), Withanolide B (2.59 mg/g DW), Withanolide C, Withanolide D, Withanolide E, Withaferin A (2.36 mg/g DW), Withanone (4.32 mg/g DW), Withanosides I–VII, Withasomniferol A–C, Coagulin H, Coagulin S, Physagulin D, β-sitosterol, tropine, cuscohygrine, anaferine, anahygrine, choline, withanine, visamine and many other withanolide derivatives	Reduces aging-related debility, manages rheumatism, relieves constipation, treats goiter, helps cold/cough, ulcers, carbuncles, relieves colic, treats insomnia, manages leucoderma, strengthens nervous system, increases white

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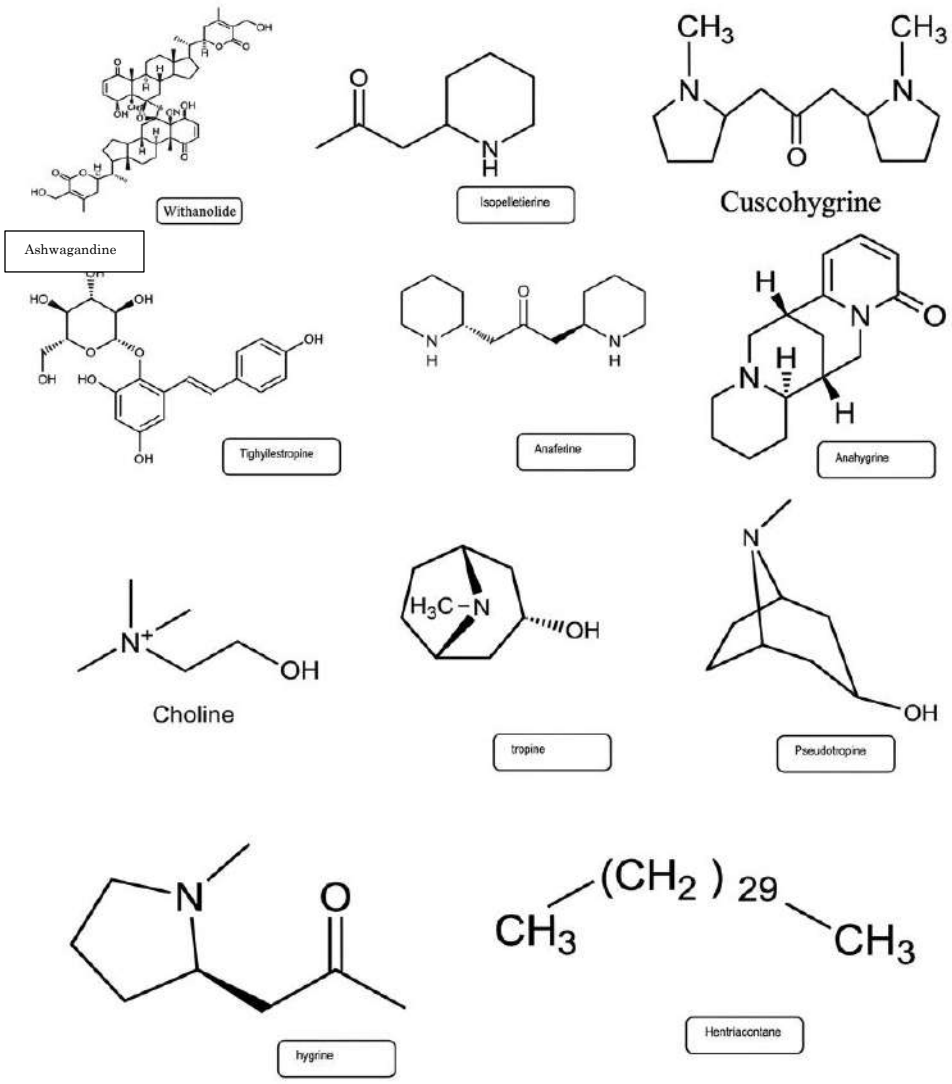
		blood cells, regulates blood sugar, aids weight loss [15, 18]
Fruits (Seeds and Berries)	Linoleic acid (0.23%), Elaidic acid (0.01%), Withanolide D (0.22%), L-asparaginase, fatty acids, sterols, Withanamide A–I, tocopherols, squalene, tetracosanoic acid (0.880%), oleic acid (0.14%)	Anthelmintic (removes intestinal worms), diuretic, helps treat chest ailments [15, 18, 19]
Leaves	Withaferin A (1.35 mg/g), 17α-Hydroxy Withaferin A, Witharistatin, Withanolide A–Z (multiple forms), Withanoside IV–XI, Coagulin Q, Viscosalactone B, Sitoindoside IX, Physagulin D, Withanone (1.312%) and other derivatives	Anthelmintic, used for fever, wounds, painful swelling; kills lice; useful in conjunctivitis [14]
Bark	Somnifera withanolide, Withanolide, Somniwithanolide, Withasomniferanolide, Somniferanolide, Withasomnilide	Used in treatment of asthma and bed sores [20, 21]

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2.1. Chemical structures

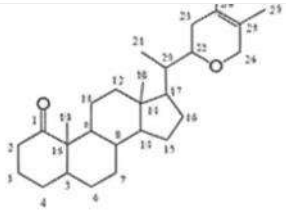
Alkaloids



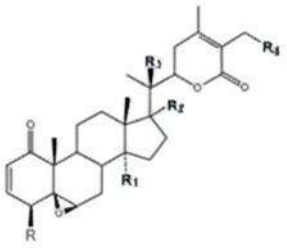
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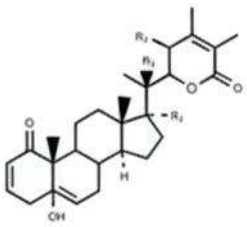
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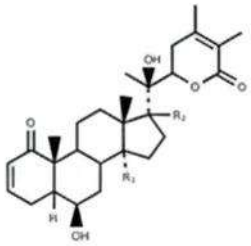
Withanolide skeleton



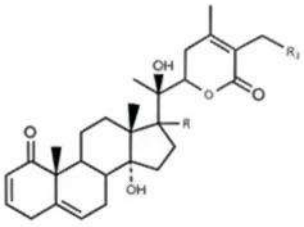
Withaferin A
Withaferin E = β-OH, R1-αH,β-R-OH, R4-OH, A4-OH
Pubescenscenone F = βOH, R1-OH, 44-OH



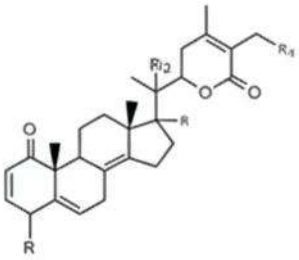
Withanolide A
Withanolide B, R3-OH, R3-OH
R = βOH, R= H R1, R1-βOH, R3-OH, R3-βOH



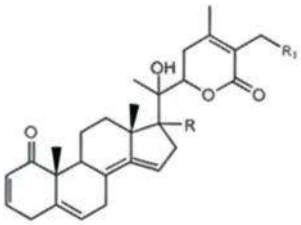
Withanolide A
Withanolide S R-βOH, R3-OH, R3-OH
Withanone F = R βOH, R1, R2-OH, R2-βOH



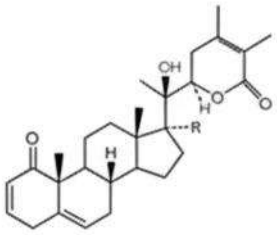
Withanolide J
Withanolide H R-βOH, R11, R3-OH
Withanolide F R=βOH, R1-βOH, R2-βOH



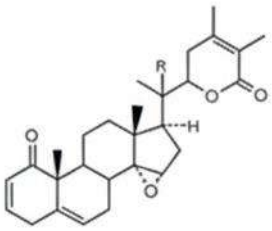
Withanolide A R-αOH
Withanolide E R- R1-OH, R2-OH
Withanolide G R-βOH, R1-αOH, R1-OH



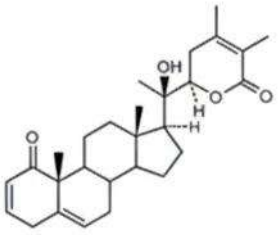
Withanolide G R-H, R1-H
Withanolide I R- H, R1-H
Withanolide R R-OH, R1-H



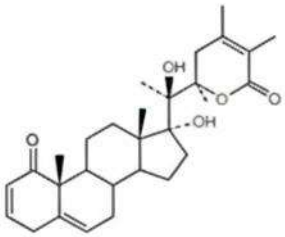
Withanolide K



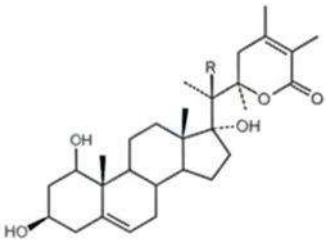
Withanolide M



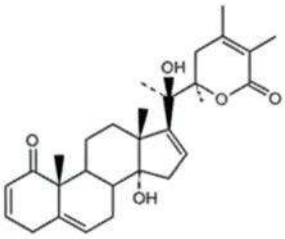
Withanolide N



Withanolide P



Withanolide U



D16-α-withanolide

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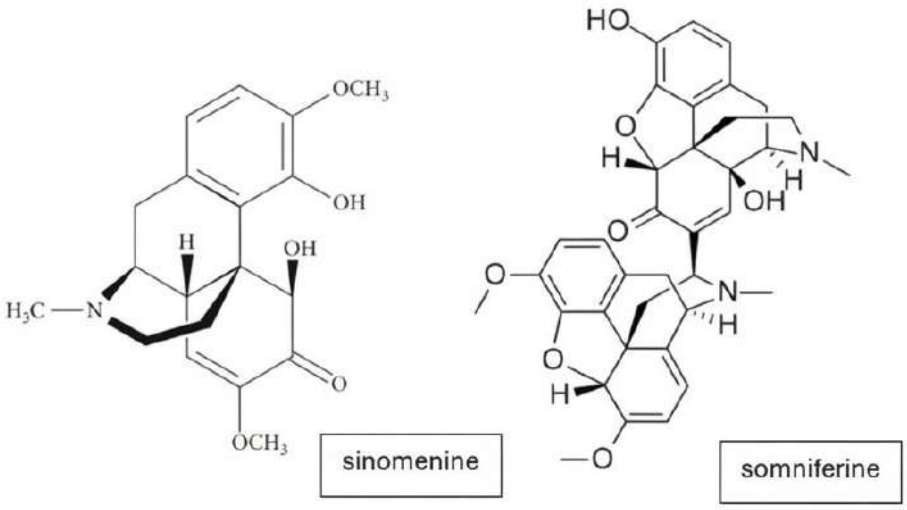


FIGURE 2. MAJOR PHYTOCHEMICALS PRESENT IN W. SOMNIFERA

3. Pharmacological Concern

3.1. Pharmacokinetics of *W. somnifera*

Research was conducted by Lokmanya Medical Research Centre, Chinchwad, Pune, Maharashtra, India, to understand how the body processes key compounds from Ashwagandha root, in accordance with Declaration of Helsinki and approved by the Institutional Ethical Committee of Lokmanya Medical Research Centre, Chinchwad, Pune, Maharashtra, India. In this open-label study, 12 healthy adults (six men and six women) took a single 400 mg dose of standardized *W. somnifera* root extract capsules. Each capsule contained approximately 2.5% total withanolides, meaning each person received about 10 mg of active compounds. Over the next 24 hours, blood samples were collected at 13 different times to track four specific bioactive components: Withanoside IV, Withanolide A, Withaferin A, and 12-Deoxy Withastramonolide [22].

3.1.1. Examinations

Using a highly sensitive UHPLC-MS/MS technique, the research team could detect even minute amounts of these compounds in human plasma. The method proved reliable enough to measure concentrations well below the levels typically seen in participants, ensuring accurate tracking throughout the study period [22].

3.1.1.1. Peak Levels in Blood

In men: 12-Deoxy Withastramonolide reached the highest concentration (about 4.47 ng/mL), followed by Withaferin A (3.56 ng/mL), Withanolide A (2.98 ng/mL), and Withanoside IV (0.47 ng/mL) [22].

In women: The pattern was similar, with 12-Deoxy Withastramonolide peaking highest (3.21 ng/mL), then Withaferin A (1.93 ng/mL), Withanolide A (1.41 ng/mL), and Withanoside IV (0.67 ng/mL) [22].

3.1.1.2. Peak Levels

For most compounds, blood levels peaked between 1 and 1.5 hours after taking the capsules. Withaferin A reached its highest level fastest—at about 1 hour in men and just under 1 hour in women [22].

3.1.1.3. Bioavailability

The total exposure, measured as area under the curve, varied considerably among the different compounds.

In men: 12-Deoxy Withastramonolide showed the greatest overall presence in blood (13.32

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ng/mL·h), followed by Withanolide A (10.96 ng/mL·h), Withaferin A (8.09 ng/mL·h), and Withanoside IV (2.05 ng/mL·h) [22].

In women: Again, 12-Deoxy Withastramonolide led (7.62 ng/mL·h), followed by Withaferin A (3.57 ng/mL·h), Withanolide A (2.76 ng/mL·h), and Withanoside IV (2.54 ng/mL·h) [22].

3.1.1.4. Half-life

In men: Withanoside IV lasted longest (about 5 hours), followed by Withanolide A (4.6 hours), Withaferin A (4.1 hours), and 12-Deoxy Withastramonolide (2.5 hours) [22].

In women: Withanoside IV again persisted longest (4.4 hours), then Withanolide A (3.8 hours), 12-Deoxy Withastramonolide (2.1 hours), and Withaferin A (1.7 hours) [22].

3.1.1.5. Average time compounds remained in the body:

This ranged from about 3.7 to 7.5 hours in men, and 2.8 to 7.1 hours in women, with Withanoside IV showing the longest presence in both groups [22].

3.1.1.6. Clearance

The rate at which the body eliminated these compounds also differed.

In men: Withanoside IV was cleared most rapidly, while 12-Deoxy Withastramonolide was cleared most slowly [22].

In women: Withaferin A showed the fastest clearance, while 12-Deoxy Withastramonolide again cleared most slowly [22].

3.1.1.7. **Notable Differences Between Men and Women**

The study revealed some interesting gender-based differences in how the body handles these compounds:

- Women generally showed lower peak concentrations and overall exposure compared to men for most compounds
- Compounds tended to leave women's bodies faster, with shorter half-lives and residence times
- Clearance rates were typically higher in women
- These differences suggest that male and female bodies may metabolize these compounds differently, possibly due to variations in liver enzyme activity
-

3.1.1.8. **Compounds Detected**

In men: Withanolide A remained detectable for up to 15 hours, while the other three compounds could be measured for about 12 hours [22].

In women: Detection windows were shorter—Withanoside IV and 12-Deoxy Withastramonolide for about 9 hours, Withaferin A and Withanolide A for about 6 hours [22].

This longer detection time in men suggests slower elimination, possibly because of differences in how these compounds are broken down in the digestive tract and liver, or how they bind to tissues.

3.1.2. Findings

This study shows that the active compounds in Ashwagandha root are absorbed quickly, reach peak levels within about an hour, and remain in the body for several hours afterward. The four compounds behave quite differently from one another, some reach higher levels but leave faster, while others linger longer at lower concentrations. The noticeable differences between men and women highlight that gender may influence how these compounds are processed, pointing to the need for personalized approaches in future research. These findings provide a solid foundation for understanding how Ashwagandha works in the body and will help guide future studies on its effects and optimal use [22].

3.2. Pharmacodynamics

3.2.1. In cancer treatment

Recent research over the past two decades has validated the plant's traditional use in treating cancer, demonstrating its anticancer properties against various types, including prostate, colon, lung, breast, leukemia, pancreatic, kidney, and head and neck cancers [23-26]. Its anticancer effects have been confirmed in animal models against forestomach and skin cancers in mice [27]. Ashwagandha's therapeutic effects, particularly its anticancer properties, are attributed to its withanolides—highly oxygenated natural steroids

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[24, 28]. Withanolides employ a multi-pronged anticancer strategy, including direct cytotoxicity, inducing differentiation, chemoprevention, and inhibiting enzymes like COX-2 and quinine reductase. Withaferin-A is the most potent anticancer withanolide in *W. somnifera*[29]. Its power lies in its ability to disrupt the very machinery that allows cancer cells to thrive and survive, primarily by steering them toward a programmed cell death known as apoptosis (see Figure 3).

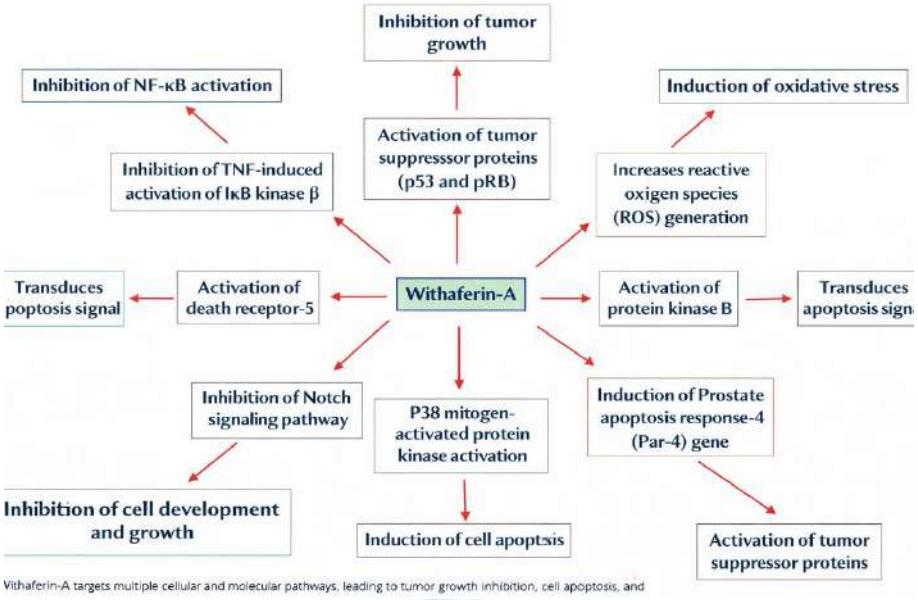


Figure 3. A schematic representation of the key molecular pathways through which Withaferin-A induces apoptosis in cancer cells.

Withaferin-A induces apoptosis by blocking the NF-κB pathway via a redox-sensitive thio-alkylation mechanism and activating tumor suppressors p53 and pRB [30].

Withaferin-A further induces apoptosis by increasing reactive oxygen species (ROS), leading to oxidative stress that activates p38 MAP kinase and tumor suppressor Par-4 [24]. Withaferin-A also dismantles pro-survival networks by inhibiting Notch and Akt pathways and alters cell surface proteins to favor death signaling—up-regulating death receptor 5 while down-regulating the inhibitor c-FLIP [24, 31, 32].

In human cancer cells, Withaferin-A inhibits proteasome activity (chymotrypsin-like) and disrupts the cytoskeleton by covalently binding to vimentin and annexin-II, leading to their aggregation and degradation [33, 34].

Cancer-Specific Actions of Withaferin-A

Withaferin-A selectively targets the distinct vulnerabilities of different cancer types.

I. **Prostate Cancer:** In prostate cancer cells, Withaferin-A throws a wrench in the cell division cycle, causing an arrest at the G2/M phase. It achieves this by manipulating the activity of key cell cycle regulators. It increases the activity of proteins like phosphorylated Wee-1 and Aurora B targets while simultaneously decreasing the levels of cyclins (A2, B1, E2). This disruption forces the cells into a catastrophic and abnormal division, ultimately leading to their death [35].

II. **Colon Cancer:** Against colon cancer cells, Withaferin-A again targets the Notch-1 pathway and dismantles the Akt/NF-κB/Bcl-2 survival network. It also leverages the generation of damaging ROS to push the cells over the edge into apoptosis (Koduru et al., 2010). *In vivo* studies

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have reinforced these findings, showing that whole-plant extracts can significantly alter immune cell profiles (lymphocytes, neutrophils) and starve cancer cells by suppressing key metabolic enzymes in the mitochondria [36, 37].

III. **Breast Cancer:** The compound shows great promise against breast cancer by not only inducing cell death but also by preventing metastasis. It inhibits cell migration and invasion by turning off the STAT3 signaling pathway [24]. It also lowers the levels of proteins that help cancer cells resist death, such as survivin, XIAP, and cIAP-2 [38]. Once more, its ability to disrupt the vimentin cytoskeleton and increase ROS production by interfering with mitochondrial respiration proves critical in triggering apoptosis in breast cancer cell lines like MDA-MB-231 and MCF-7 [39, 40].

IV. **Other Cancers:** The versatility of Withaferin-A extends further. In malignant pleural mesothelioma (MPM), it inhibits the proteasome, leading to a buildup of pro-apoptotic proteins and activation of the death protease caspase-3 [41]. In renal cancer, it blocks the STAT3 signaling pathway by inhibiting upstream Janus-activated kinase 2, thereby silencing the genes that help the cancer cells survive [32]. For notoriously difficult-to-treat pancreatic cancers, Withaferin-A takes a different tack, inhibiting the Hsp90 chaperone protein, which many cancer cells rely on to keep their growth-driving proteins stable [34]. Finally, research on brain cancer (glioma) has shown that even high-concentration water extracts of Ashwagandha leaves can be potently cytotoxic to both human and rat glioma cell lines [42].

3.2.2. Neuroprotective and Anti-Neurodegenerative Effects:

As populations age worldwide, more people are facing dementia—a condition that slowly destroys higher brain functions like memory, thinking, and emotional control [43]. Neurodegenerative diseases cause irreversible damage to the central nervous system, leading to steady decline.

Research increasingly backs Ashwagandha for treating everything from anxiety and depression to major disorders like Alzheimer's and Parkinson's. Its neuroprotective power comes from antioxidant, anti-inflammatory, and nerve-regenerating properties driven by bioactive withanolides (Figure 4). Beyond the brain, Ashwagandha also boosts athletic performance by increasing hemoglobin and red blood cells, improving oxygen delivery to muscles [44, 45]. The root is packed with proteins, amino acids, starch, and phenolic compounds that add to its reputation as a rejuvenating tonic [46].+

Mechanisms of Neuroprotection

Early research found that glycowithanolides in Ashwagandha protect neurons by stopping lipid peroxidation. Withanolides and sitoindosides also boost antioxidant enzymes like catalase and glutathione peroxidase in key brain regions. The plant improves cognition by increasing muscarinic acetylcholine receptors in the cortex, pointing to effects on cholinergic signaling [47].

More recent work has uncovered multiple protective pathways (Figure 4):

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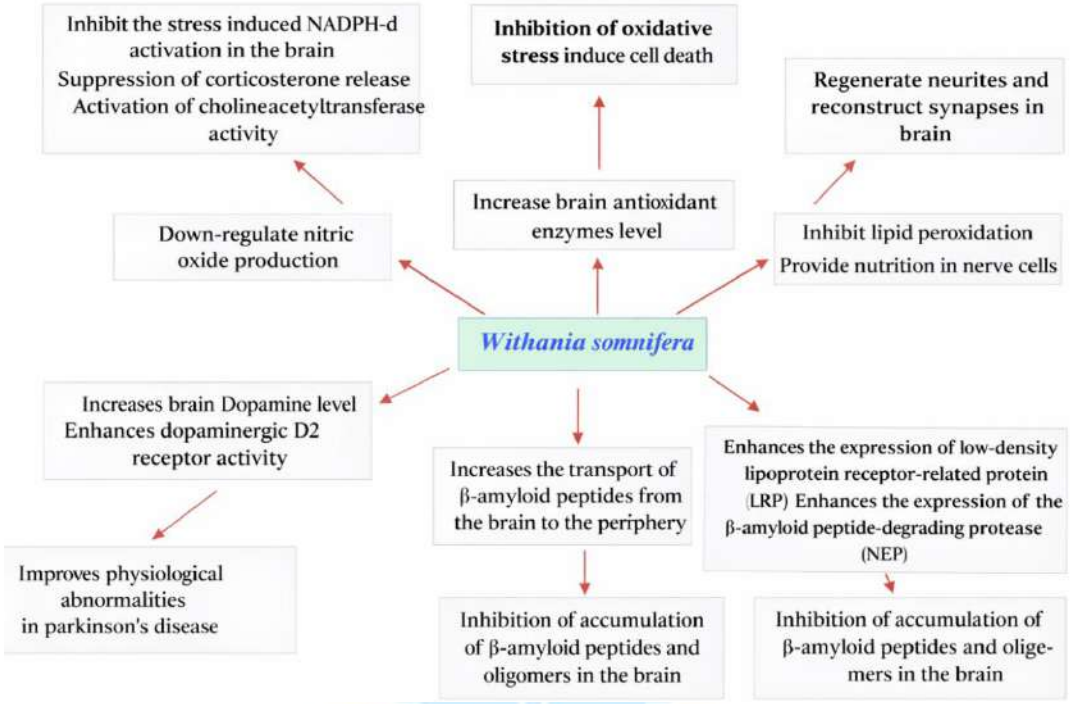


FIGURE 4. A SUMMARY OF THE KEY MECHANISMS THROUGH WHICH W. SOMNIFERA AND ITS BIOACTIVE WITHANOLIDES EXERT THEIR NEUROPROTECTIVE EFFECTS

Stress Response Modulation: Ashwagandha lowers nitric oxide production and stress-induced enzyme activation in the brain by suppressing corticosterone release and boosting choline acetyltransferase [46].

Antioxidant Enzyme Enhancement: Root extract increases brain levels of SOD, catalase, glutathione, and related enzymes to protect against toxin exposure [48].

Neural Regeneration: Withanolide A at 10 μmol/kg regenerates damaged neurons and rebuilds synapses, offering hope for conditions like diabetic neuropathy [49].

Blood-Brain Barrier Penetration: Intranasal withanolide A reaches the cortex and cerebellum, reducing stroke damage, improving barrier function, and normalizing neurotransmitter levels. The 10 mg/kg dose cut cell death and tissue damage significantly [50].

3.2.2.1. Ashwagandha in Alzheimer's Disease

In Alzheimer's, β-amyloid proteins build up into plaques, triggering free radical damage and killing neurons. Hyperphosphorylated tau proteins form tangles around these plaques, while microglia—meant to clean up—release toxins that worsen inflammation [43].

Neutralizing β-Amyloid Toxicity: Ashwagandha reverses β-amyloid damage in human nerve cells, including those affected by HIV infection [51].

Inhibiting Amyloidogenic Enzymes: The compound vitanon improves cognition by reducing β-amyloid 42, calming inflammatory cytokines, and lowering activity of β- and γ-secretase—the enzymes that create amyloid plaques [52].

Withaferin A Mechanisms: Withaferin A cuts amyloid aggregation, stops tau buildup, calms inflammation, and regulates heat shock proteins [53]. It also blocks NF-κB-driven inflammatory gene expression [54, 55]. Computer models show

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withanolide A inhibits acetylcholinesterase, offering another therapeutic angle [56].

LRP1-Mediated Amyloid Clearance: Transgenic mice given withanolide-enriched extract showed more LRP1 in the liver, which helps clear amyloid from the brain [57, 58]. LRP1 also influences amyloid production and tau spread [59, 60]. The extract boosted LRP1 in brain blood vessels and increased neprilysin, an enzyme that breaks down amyloid.

Direct Interaction with β-Amyloid: Withanolide A and related compounds directly bind to the hydrophobic core of amyloid oligomers, stopping them from clumping further [61, 62].

Bioconverted Derivatives: Fungus-treated Ashwagandha produced a glutathione derivative (CR-777) with strong neuroprotective effects [63].

Cholinergic Modulation and Canine Cognitive Dysfunction: Ashwagandha cut free radicals and inhibited acetylcholinesterase in nerve cells, suggesting benefits for both canine cognitive dysfunction and Alzheimer's [64].

3.2.2.2. Ashwagandha in Parkinson's Disease

Parkinson's involves loss of dopamine neurons in the nigrostriatal pathway, throwing off the balance between dopamine's inhibitory action and the excitatory effects of acetylcholine and glutamate. Causes include genetics, toxins, oxidative stress, and reduced growth factors [65].

Preclinical Evidence: Ashwagandha boosts brain dopamine and corrects Parkinson's-related abnormalities. It improves lipid peroxidation, antioxidant enzymes, catecholamines, D2 receptor binding, and tyrosine hydroxylase expression [66]. In 6-hydroxydopamine-treated rats, three weeks of Ashwagandha at 100-300 mg/kg cut oxidative damage, boosted antioxidants and catecholamines, improved dopamine receptor function, and raised tyrosine hydroxylase levels [66-68].

Studies in fruit flies and mice confirmed these benefits, with treated mice showing less motor impairment [69]. Ashwagandha raised dopamine and its metabolites while normalizing oxidative markers in the striatum [66]. Combined with L-Dopa, it also prevented drug-induced motor side effects [70].

3.2.2.3. Ashwagandha in Huntington's Disease:

Huntington's is an incurable genetic disorder where mutant huntingtin protein accumulates, triggering neuronal death and disrupting dopamine, GABA, and other neurotransmitters [71].

3-Nitropropionic Acid Model: 3-NP is a toxin that mimics Huntington's by blocking mitochondrial energy production. Chronic Ashwagandha treatment improved motor function and biochemical markers in this model—cutting oxidative damage, boosting antioxidants, and restoring mitochondrial function. Effects were dose-dependent at 100-200 mg/kg.

Withaferin A in HD: In another mouse study, withaferin A helped cells maintain protein balance by activating the heat shock response. Treated Huntington's mice lived longer, regained weight, and showed better behavior and motor function. Brain studies confirmed less mutant protein buildup, improved striatal function, and reduced inflammation [72, 73].

3.2.3. Antiepileptic Activity:

In both lab and animal studies, researchers found that Ashwagandha can calm overactive nerve cells and make it harder for seizures to take hold. The key seems to be how it balances brain chemicals and cuts down on oxidative stress, which often fuels seizure activity.

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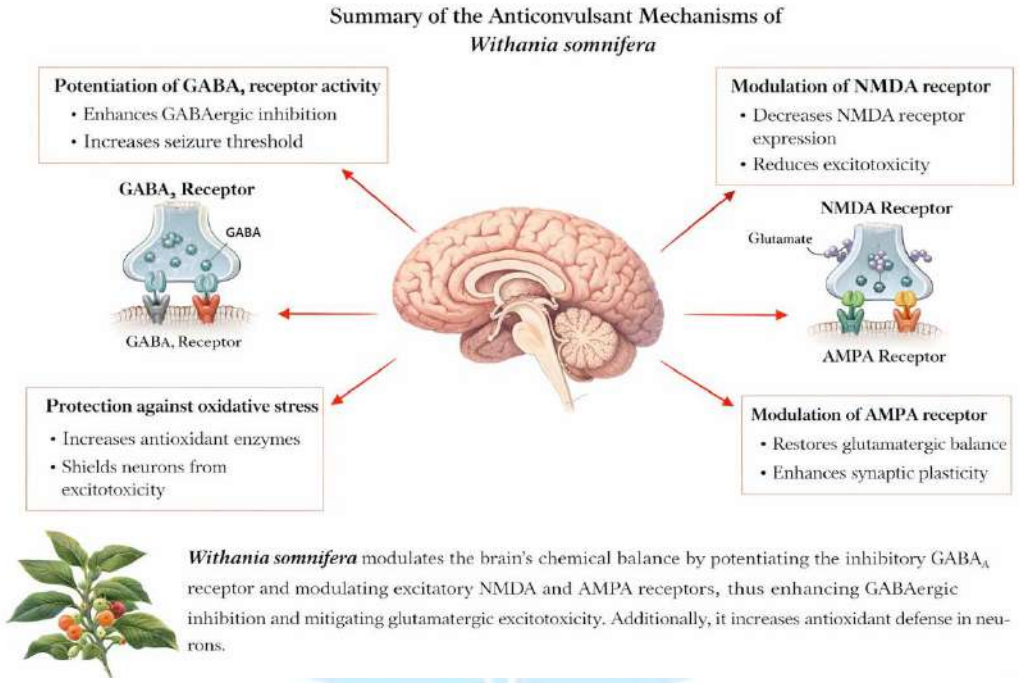


FIGURE 5. A SUMMARY OF THE ANTICONVULSANT MECHANISMS OF W. SOMNIFERA, ILLUSTRATING ITS MODULATION OF KEY NEUROTRANSMITTER RECEPTORS AND PATHWAYS IN THE BRAIN

3.2.3.1. Modulating the Brain's Chemical Balance

A big part of how Ashwagandha works against seizures comes down to its effect on GABA—the brain's main calming chemical. Think of GABA as the brain's brakes, keeping nerve cells from firing out of control. Research showed that a low dose of Ashwagandha root extract, when combined with a small amount of GABA or the anti-anxiety drug Diazepam, made it much harder for seizures to start. This teamwork effect means Ashwagandha helps boost the brain's natural ability to put the brakes on runaway electrical activity [74].

But that's not all—Ashwagandha also helps control the overactive excitatory system in the brain, which is a big part of what drives seizures. In epilepsy, glutamate receptors like NMDA get too revved up, causing nerve cells to fire nonstop and get damaged in the process. One study found that Ashwagandha root extract and its active compound withanolide A helped fix memory problems in rats with epilepsy. The reason? It calmed down oxidative stress and lowered the overexpression of NMDA receptors—which is exactly what leads to the memory troubles people with chronic epilepsy often face [75].

Further evidence for this protective mechanism comes from in vitro work using human neuroblastoma cells. Researchers found that leaf extracts of *W. somnifera* could shield these neurons from glutamate-induced excitotoxicity, a form of cell death caused by overstimulation. This protective action was linked to the inhibition of stress-induced proteins, specifically the 70 kilodalton heat shock proteins, which are often overexpressed in response to cellular injury [76].

3.2.3.2. Restoring Motor Function and Synaptic Plasticity:

The impact of Ashwagandha on glutamatergic signaling extends beyond simple neuroprotection to the restoration of normal brain function. In a follow-up study using a pilocarpine-induced model of temporal lobe epilepsy, the same research group investigated the plant's effects on motor learning. Temporal lobe epilepsy is often associated with disruptions in the dopaminergic system and impairments in motor skills. The results showed

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that treatment with *W. somnifera* root extract and withanolide A led to a significant improvement in motor learning. This behavioral recovery was correlated with a normalization of glutamate levels and a regulation of another key glutamate receptor subtype, the α-Amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor, within the dopaminergic system of the brain [77].

3.2.4. Anxiolytic and Antidepressant Activity

In Ayurveda, Ashwagandha has always been known as a rasayana (a rejuvenating tonic for the mind and body), as it is traditionally used to ease anxiety and lift mood. Now modern science is catching up, confirming those benefits and starting to map out exactly how it calms the brain and steadies' emotions.

Early pharmacological studies established the anxiolytic and antidepressant potential of *W. somnifera*, attributing these properties to its glycowithanolide constituents [78]. More recently, a study found that Ashwagandha root extract at 40 mg/kg worked as a powerful antidepressant in several different animal models [78]. This preclinical work has been complemented by clinical evidence. Human trials have shown that Ashwagandha extract can improve mental and motor skills in people dealing with anxiety and depression—offering real, noticeable benefits [79].

Interestingly, this gets into the *how* behind Ashwagandha's calming effects. Unlike standard anti-anxiety meds, it seems to work by lowering nitric oxide production in the brain. Since too much nitric oxide can stress out neurons and make them overactive, cutting back on it gives us a clue as to why Ashwagandha helps take the edge off [80].

3.2.5. Treatment of Sleep Disorders

Sleep makes up about a third of our lives, so when something disrupts it, the whole body feels the effects [81]. Insomnia—the most common sleep issue—is more than just not sleeping enough. It's a complex condition where someone sleeps too little for their body's needs, and it shows up as trouble falling asleep, staying asleep, or waking too early. The fallout spills into daytime too: poor concentration, mood swings, fuzzy thinking, and zero motivation. It messes with work, relationships, and quality of life. Women deal with insomnia more often than men, and age raises the risk. Despite more people turning to sleep meds, the problem is still underdiagnosed, and numbers vary widely depending on where you look [81]. Because conventional sleep aids come with heavy side effects, herbal options are getting more attention. Ashwagandha has stepped into that spotlight.

3.2.5.1.1. Clinical Evidence for Sleep Improvement

In one 10-week trial, people taking Ashwagandha root extract (300 mg twice daily) slept better and fell asleep faster. Researchers think it could help people wrestling with both insomnia and anxiety, though more studies are needed [82]. Older adults (65-80) also benefited. After taking Ashwagandha, they slept better, woke up sharper, and felt generally improved. The extract was safe, well-tolerated, and effective across the board [83].

But which part of the plant does the work? In mice, an alcohol extract packed with withanolides did nothing for sleep. An aqueous extract, though—with triethylene glycol as the star player—triggered NREM sleep. Pure triethylene glycol did the same thing, hinting that this compound drives Ashwagandha's sleep benefits [84].

3.2.5.1.2. Effects on Non-Restorative Sleep

Non-restorative sleep (NRS) is that groggy, unrefreshed feeling in the morning, even if you clocked enough hours. It's more common in women and people with depression, affecting about 10% of people worldwide [85]. A six-week study gave adults with NRS a standardized Ashwagandha extract (Shoden®, 120 mg daily). The results were striking: 72% of the treatment group improved their sleep, compared to just 29% on placebo. They slept more efficiently, stayed asleep longer, and woke up less often. Mood, energy, and overall well-being climbed too—with zero side effects [86].

3.2.5.2. Protection Against Sleep Deprivation

Skimping on sleep doesn't just fog up your brain—it hits the whole body hard, wrecking mood, focus,

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and health [87, 88].In one rat study, a week of sleep deprivation tanked to antioxidant levels. But rats given Ashwagandha extract fared much better: less oxidative damage, more antioxidant activity, and higher dopamine and serotonin. The message is clear—Ashwagandha might help cushion the blow of lost sleep [89].Pairing Ashwagandha with diazepam has also shown promise, pointing to possible synergy [90].

3.2.5.3. Evidence in Student Populations

College students are no strangers to stress and bad sleep. In one qualitative study, students on Ashwagandha reported better sleep, more energy, and clearer thinking than those on placebo [91].A follow-up double-blind trial backed that up with hard numbers: Ashwagandha significantly lowered stress and boosted sleep quality in students, though it didn't touch food cravings [92].

3.2.5.4. Anti-inflammatory and Antiarthritic Activity

Inflammation is at the core of many chronic illnesses, from arthritis to inflammatory bowel disease. Ashwagandha has a long history in traditional medicine for treating these issues, and modern research has backed that up. The plant's active compounds—especially Withaferin-A—are now known to be behind its powerful anti-inflammatory and antiarthritic effects. Ashwagandha's anti-inflammatory power comes from its ability to tackle inflammation on multiple fronts. Recent animal studies found that root extract at higher doses (600-800 mg/kg) helped ease arthritis by calming down inflammatory chemicals while also helping motor function bounce back [93]. The therapeutic reach of these effects extends beyond arthritis, with evidence supporting the use of *W. somnifera* and its withanolides in managing inflammatory conditions such as cystic fibrosis and irritable bowel syndrome [94].

At the molecular level, Withaferin-A works through a few key pathways. One of the main ways is by blocking NF-κB—think of it as a master switch that flips on inflammatory genes. By shutting that down, Withaferin-A stops inflammation right at the source [31]. This then brings down levels of specific inflammatory messengers—like prostaglandins, histamine, and various cytokines—that cause pain, swelling, and tissue damage. Plus, Withaferin-A also blocks COX-2 and acts as an antioxidant, giving it even more ways to shut down those harmful signals [94].

Beyond that, Withaferin-A also supports bone health. Studies show it helps stimulate osteoblasts—the cells that build bone—by switching on the genes responsible for bone formation. This could be especially helpful for things like menopausal osteoporosis or bone injuries [95]. Complementing its anti-inflammatory and bone-protective effects, *W. somnifera* has also demonstrated significant analgesic activity in several rodent models, making it a valuable candidate for comprehensive pain management strategies [96, 97].

3.2.6. Spermatogenic Activity

The World Health Organization defines infertility as the inability to achieve pregnancy within one year of regular, unprotected intercourse. This condition affects an estimated 1.5 million couples in Poland alone, with rising numbers seeking medical assistance in recent years. Beyond its physiological causes, infertility carries profound social, emotional, and demographic consequences [98]. In this context, *W. somnifera* has emerged as a promising natural therapeutic agent, with a growing body of clinical evidence supporting its traditional use for enhancing reproductive health in both men and women. The most compelling evidence for Ashwagandha's fertility-enhancing properties comes from clinical studies in men with various fertility challenges. In men diagnosed with oligospermia (low sperm count), treatment with *W. somnifera* for 90 days produced significant improvements across multiple semen parameters. Patients showed increased sperm count, greater semen volume, and enhanced sperm motility. These physical improvements were accompanied by favorable hormonal changes, including elevated testosterone and luteinizing hormone levels, alongside reductions in prolactin (PRL) and follicle-stimulating hormone (FSH) [99-101].

Remarkably, similar benefits have been observed in men with normozoospermia (normal baseline

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sperm parameters). Administration of powdered Ashwagandha root significantly improved semen quality across the board, with increases in sperm count, improvements in sperm morphology, greater semen volume, and enhanced sperm motility. These improvements translated into a tangible clinical outcome: an increased likelihood of pregnancy in their female partners [99-101].

The mechanisms underlying these effects extend beyond simple hormonal modulation. Treated men showed improved hormonal profiles alongside elevated levels of antioxidant enzymes and antioxidant vitamins (A, C, and E) in their seminal plasma. This antioxidant enrichment appears to protect sperm from oxidative damage, as evidenced by inhibited lipid peroxidation and reduced levels of protein carbonyl groups (CO)—a reliable and early biomarker of protein oxidation that is elevated in many disease states [102, 103]. Importantly, no adverse side effects were observed in any of these studies, highlighting the safety profile of Ashwagandha supplementation.

For men with idiopathic infertility (infertility of unknown cause), *W. somnifera* offers a particularly attractive option. It improves sperm parameters effectively while avoiding the side effects associated with conventional treatments, leading some researchers to suggest it as a potential alternative to pentoxifylline, a commonly prescribed medication for male fertility [100]. Despite these promising results, the authors note that further research is needed, as the exact molecular mechanisms of action for *W. somnifera* and its active constituents in the context of male infertility remain incompletely understood [4].

3.2.6.1. Effects on Female Sexual Function

While most of the research has focused on male fertility, emerging evidence suggests that Ashwagandha may also benefit female reproductive health. In one study, oral supplementation with a high-concentration Ashwagandha root extract (HCARE) was shown to improve sexual function in healthy women. Compared to the placebo group, women receiving the extract reported significant improvements in sexual arousal, lubrication, orgasm, and an increase in the number of successful sexual encounters [104].

3.2.7. Hepatoprotective Activity

Given how often Ashwagandha is used as a rejuvenating tonic, researchers have also started looking at how it might protect one of the body's most essential organs—the liver. And sure enough, studies now suggest it has real liver-protective powers, shielding against damage from chemicals and even radiation. In one study using paracetamol to trigger liver damage in rats, Ashwagandha root extract at 500 mg/kg showed real protective effects. It dropped levels of key liver enzymes and bilirubin in the blood—all signs that liver cells were under less stress. At the tissue level, it worked by fighting oxidative damage. The extract lowered lipid peroxidation (which basically means it prevented further cell damage) while revving up the liver's own antioxidant defenses—things like glutathione and protective enzymes that help clean up the mess [105, 106].

Ashwagandha also protects the liver from radiation damage. In one study, rodents exposed to gamma radiation (relevant to both accidental exposure and cancer radiotherapy) were given 100 mg/kg of the root extract. The results were clear: the extract lowered radiation-induced spikes in liver enzymes and cut back on oxidative stress markers like malondialdehyde and nitrates. It also tamped down heme oxygenase-1, a stress-related enzyme, while boosting protective antioxidants like superoxide dismutase and glutathione peroxidase [107].

3.2.8. Antibacterial Activity

A growing number of studies have shown that extracts from both the leaves and roots of Ashwagandha possess broad-spectrum antimicrobial activity, affecting a wide range of disease-causing bacteria and fungi. This property positions the plant as a potential source of new antimicrobial agents, particularly valuable in an era of rising antibiotic resistance. The antibacterial effects of *W. somnifera* are both potent and broad, extending to clinically significant Gram-negative and Gram-positive bacteria. Leaf extracts have been shown to inhibit the growth of five common Gram-negative pathogens—*Escherichia*

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coli, *Salmonella typhi*, *Citrobacter freundii*, *Pseudomonas aeruginosa*, and *Klebsiella pneumoniae*—at concentrations of 6.25 mg/ml and 12.5 mg/ml [108]. The bioactive constituents responsible for this activity have been further isolated and identified. Flavonoids and alkaloids derived from the plant demonstrated growth inhibitory effects against an even wider panel of bacteria, including *Enterobacter aerogenes*, *Proteus mirabilis*, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Bacillus subtilis*, *Klebsiella pneumoniae*, *Raoultella planticola*, and *Agrobacterium tumefaciens*, at a remarkably low concentration of 0.039 mg/ml [109].

The clinical relevance of these findings has been underscored by studies testing crude leaf extracts against pathogens commonly encountered in human infections. At a volume of 100 µl (from a 100 mg/ml stock), extracts effectively inhibited the growth of *Staphylococcus aureus*, *Proteus mirabilis*, *Streptococcus mutans*, *Streptococcus sobrinus*, and *Salmonella paratyphi* B [110, 111]. Collectively, this body of work confirms that *W. somnifera* exhibits antibacterial activity against both Gram-positive and Gram-negative organisms, making it a broad-spectrum agent [112].

The antimicrobial reach of Ashwagandha extends beyond bacteria. Studies have reported moderate to good activity against fungal pathogens, including *Microsporum gypseum*, *Candida albicans*, and *Cryptococcus neoformans* [113]. Of particular interest is the plant's potential activity against *Mycobacterium tuberculosis*, the causative agent of tuberculosis. Specific withanolides—namely withanolide D, E, and F—have shown potent activity against the PknG target in *M. tuberculosis*, a serine/threonine protein kinase essential for bacterial survival within host macrophages [114].

Several mechanisms have been proposed to explain the antimicrobial potency of *W. somnifera*. Its well-documented antioxidant properties, attributed to constituents such as ascorbic acid, anthocyanins, and polyphenols, are thought to play a role [108]. These compounds may inhibit microbial growth through iron deprivation—starving pathogens of an essential nutrient—or through hydrogen bonding with vital microbial proteins, such as enzymes, thereby disrupting their function [115]. Additionally, researchers have suggested that the plant's antimicrobial effects may be linked to cytotoxicity against microbial cells, gene silencing, and immune potentiation. For instance, aerial extracts at a concentration of 1.56 mg/ml demonstrated good antimicrobial potency, and the same extract was shown to enhance immune responses by increasing IL-7 mRNA expression twofold [113]. With a favorable safety profile (IC50 of 200 mg/ml), *W. somnifera* presents a compelling combination of efficacy and low toxicity.

3.2.9. Hypoglycemic and Hypolipidemic Activity

The traditional use of *W. somnifera* in Ayurvedic medicine extends to the management of metabolic disorders, particularly diabetes and obesity. In recent years, modern scientific investigations have begun to validate these traditional applications, revealing that Ashwagandha possesses genuine hypoglycemic (blood sugar-lowering) and hypolipidemic (lipid-lowering) properties. These findings position the plant as a promising adjunctive therapy for metabolic syndrome and its associated complications.

3.2.9.1. Blood Glucose Regulation

Several studies have confirmed the ability of *W. somnifera* to reduce elevated blood glucose levels in experimental animals. The flavonoids present in the roots have been identified as key contributors to this effect. At a dose of 100 mg/kg, the root extract significantly reduced both blood glucose and lipid levels in treated animals [66]. Similarly, another study demonstrated that Ashwagandha powder administered at 200 mg/kg produced a marked reduction in blood glucose concentrations [116].

The mechanism underlying this hypoglycaemic action appears to be multifaceted. Researchers have proposed that *W. somnifera* acts directly on the pancreatic β-cells, stimulating the release of insulin—a hormone essential for glucose uptake from the bloodstream [116, 117]. Beyond insulin secretion, the plant and its glycowithanolides have

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been shown to enhance glucose transport into cells by increasing the activity of GLUT transporters, the proteins responsible for shuttling glucose across cell membranes [118, 119]. This dual action—boosting insulin availability and improving cellular glucose uptake—provides a robust physiological basis for its antidiabetic effects.

3.2.9.2. Lipid Profile Improvement

In addition to its effects on glucose metabolism, *W. somnifera* has demonstrated significant benefits for lipid homeostasis. Studies have shown that incorporating Ashwagandha into the diet leads to favorable changes in the lipid profile, most notably a significant increase in plasma HDL-cholesterol—the so-called "good" cholesterol [119]. This positive shift was accompanied by an increase in HMG-CoA reductase activity and elevated bile acid content in the liver. Since HMG-CoA reductase is a key enzyme in cholesterol synthesis and bile acids are the primary route for cholesterol excretion, these findings suggest that Ashwagandha may promote the elimination of cholesterol from the body, thereby contributing to its overall lipid-lowering effects.

4. Adverse effects

Ayurvedic herbs are not risk-free, and liver toxicity has been documented across several botanicals [120]. Yet the claim that *W. somnifera* (ashwagandha) is hepatotoxic remains contested and poorly substantiated [120].

In controlled studies involving 191 volunteers taking KSM66 for up to 12 months, ashwagandha was no different from placebo in causing itching, stomach upset, drowsiness, or headache [121]. No liver or thyroid-related red flags—such as jaundice, abnormal liver enzymes, weight loss, or tachycardia—were observed [121]. This reassuring trend is echoed across multiple reviews and meta-analyses. Still, most trials lasted only 1–3 months, while rare adverse events have surfaced after 3 months, and in one case, after more than a year and a half of daily use.

When hepatologist Professor Nilsson reviewed the sparse case reports, he found no clear causal link between ashwagandha and liver disease [122]. He concluded that if injury occurs, it is likely a rare idiosyncratic drug-induced liver injury (DILD) with a mixed cholestatic–hepatocellular pattern. Given ashwagandha's massive global footprint, such reactions appear extraordinarily uncommon—probably rarer than the idiosyncratic liver injuries triggered by everyday over-the-counter drugs like ibuprofen, diclofenac, or paracetamol [122].

A closer look at the documented cases reveals important nuances. Many involved combination products or possible adulteration with leaf extracts, which carry higher levels of withaferin A and withanone—compounds implicated in toxicity [122-126]. Product contamination, mislabeling, and megadosing have all been floated as explanations [127]. In the rare instances where pure root extract was used alone, liver injury was typically self-limiting: patients presented with jaundice, itching, and elevated ALT, AST, or bilirubin, but values normalized within 1–8 months after stopping the herb [123-126]. The exact biochemical culprit remains unknown [123-126]. Simon Mills places these events in the broader context of idiosyncratic reactions seen with foods, herbs, and drugs[127]. Genetic enzyme deficiencies, hormonal variation, DNA adduct formation, and low glutathione stores may render a small minority of individuals vulnerable. Because the liver metabolizes most xenobiotics, any hepatotoxic phytochemical could tip the balance in someone already depleted. Notably, we still know very little about how ashwagandha interacts with prescription or over-the-counter medications, especially in people with compromised livers.

With roughly 2.5 billion doses of KSM66 sold annually—650,000 in Europe and nearly half of all U.S. ashwagandha sales—one would expect a far larger wave of liver injuries if the herb were genuinely dangerous [123, 125, 126, 128, 129]. Some affected patients already had severe underlying liver disease before taking ashwagandha. When stacked against the daily liver damage caused by alcohol, paracetamol [130], and NSAIDs [131, 132], the risk attributed to ashwagandha looks vanishingly small.

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In animal models, ashwagandha has never caused liver toxicity, even at doses 5- to 200-fold above human equivalents [133-135]. Instead, it appears hepatoprotective: it boosts hepatic antioxidants like superoxide dismutase and catalase [105, 136, 137], protects against paracetamol-induced damage[105] and non-alcoholic steatohepatitis [138, 139], and likely does so by supporting glutathione levels [140]—the same pathway that helps humans recover from alcohol-related liver injury [140].

Worldwide reports remain rare and geographically scattered:

India: Eight cases; three had pre-existing chronic liver disease, two were diagnosed with underlying liver failure during evaluation. Four deaths occurred from acute-on-chronic liver failure (ACLF), driven by pre-existing disease rather than ashwagandha itself [127].

USA: Six cases by 2021; five reversed, one required transplant in a patient with prior thyroid cancer on corticosteroids—an outlier where enzymes rose even after stopping ashwagandha [123, 125].

Iceland: Three cases in 2020; all normalized after withdrawal, though product details were unclear [126].

Ireland: One 39-year-old woman with recent alcohol abstinence developed cholestatic hepatitis after 45 days
of ashwagandha combined with basil and biotin; she recovered within a month [123].

Netherlands: Four cases (2018–2023) after 3–10 months of use, mostly in polyherbal regimens; three recovered within a month, one within three months [129]. Since 2023, Lareb reported eight additional cases, some in individuals with underlying liver abnormalities [141, 142].

Japan: A 20-year-old man taking more than double the recommended dose for one month developed cholestasis and recovered fully after 150 days [123].

Poland & Germany: Single cases in young and older adults, respectively, both on single-ingredient supplements, with complete resolution within 3–4 months [123, 128].

In nearly all instances, confounders abound: unknown dosages, alcohol use, concurrent medications, and polyherbal use muddy the causal waters.

The literature presents a blurred but broadly reassuring picture. Ashwagandha demonstrates hepatoprotective potential in animals and a clean short-term safety record in humans. The rare hepatotoxicity reports likely reflect a cocktail of adulteration, leaf contamination, excessive dosing, polyherbal interactions, and genuine idiosyncratic susceptibility—not an intrinsic danger of the root itself. Longer, well-controlled studies are still needed to map out herb–drug interactions and confirm the safety margins of chronic use. For now, millions of daily doses consumed worldwide with only sporadic, mostly reversible adverse events suggest that a high-quality, well-characterized root extract remains generally safe for the vast majority of users [141, 142].

5. Commercially Available Doses

Below table explains the popular use of this plant in Ayurvedic and herbal commercial formulations as shown in table 2 [19].

Table 2. Commercially Available Products

MANUFACTURER	PRODUCT	INGREDIENTS	USED AS/AGAINST
	Ashvagandha Capsule	Ashvagandha (*W. somnifera*)	Long-term stress

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Himalaya Drug Company	Mentat Syrup	Madhukaparni (Centella asiatica), Brahmi (Bacopa monnieri), Ashvagandha (*W. somnifera*)	Enhancing memory and learning capacity
	Tentex Forte Tablets	Cowhage (Mucuna pruriens), Shilajeet, Gokshura (Tribulus terrestris), Ashvagandha (*W. somnifera*)	Sexual dysfunction
	Quista PRO	Ashvagandha (*W. somnifera*), Hadjod (Cissus quadrangularis), Pomegranate (Punica granatum), Taurine, Vitamin B complex, Vitamin E, Vitamin C	Adult nutrition
	Stress Relief Massage Oil	Country Mallow (Sida cordifolia), Ashvagandha (*W. somnifera*), Indian Tinospora (Tinospora cordifolia), Indian Madder (Rubia cordifolia)	Stress relief
Charak Pharma	Manoll Nutra Syrup and capsule	Ashwagandha (*W. somnifera*), Amalaki (Emblica officinalis), Yastimadhu (Glycyrrhiza glabra), Guduchi (Tinospora cordifolia)	Stress relief, promote immunity
	Zoazest Nutra Tablets	Kapikachu (Mucuna pruriens), Ashwagandha (*W. somnifera*), Amalaki (Emblica officinalis), Carnitine, Lycopene, N-Acetyl Cysteine, C0-enzyme Q-10, Selenium, Zinc, Vitamin A, Folic acid, Vitamin B 12	Fertility, sperm health
	Addyzoa Capsule	Shilajit, Kapikachchhu (Mucuna pruriens) Guduchi (Tinospora cordifolia), Amalaki (Phyllanthus emblica), Shatavari (Asparagus racemosus), Ashwagandha (*W. somnifera*)	Fertility, sperm health
	Gynelth nutra Tablets	acid, Vitamin B 12 Twak (cinnamon), Ashwagandha (*W. somnifera*), Guggul (Commiphora wightii), Shunth (Zingiber officinale), Zinc, N- Acetylcysteine, Folic acid, B vitamins, Magnesium, Iron, Calcium, Folic acid.	Menstrual health
	Pallrywyn Forte Tablet	Jaiphal (Myristica fragrans), Akkalkara (Anacyclus pyrethrum), Ashwagandha (*W. somnifera*), Kapikachchhu (Mucuna pruriens), Lavang (Syzygium aromaticum), Amalaki (Phyllanthus emblica), Gokshur (Tribulus terrestris)	Fertility
	Vigomax Forte Tablet	Ashwagandha (*W. somnifera*), Kapikachchhu (Mucuna pruriens), Gokshur (Tribulus terrestris), Salep, Safed musli (Chlorophytum borivilianum), Erandmula (Ricinus communis)	Fertility
	Endotone Capsules	Musta (Cyperus rotundus), Haridra (Curcuma longa), Lodhra (Symplocos racemosa), Ashwagandha (*W. somnifera*), Twak (Cinnamomum cassia), Shunthi (Zingiber officinale)	Endometriosis related pain control
	M2 Tone Syrup and Tablet	Ashwagandha (*W. somnifera*), Shatavari (Asparagus racemosus), Jatamansi (Nardostachys jatamansi), Devadaru (Cedrus deodara), Lodhra	Menstrual cycle

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		(Symplocos racemose), Nagakeshar (Mesua ferrea), Ashoka (Saraca asoca), Suddha Kasis	
	Evanova Capsule	Soya (Glycine max), Ashwagandha (*W. somnifera*), Brahmi (Bacopa monnieri), Jyotishmati (Celastrus paniculatus), Jatamansi (Nardostachysjatamansi), Arjun (Terminalia arjuna), Abhrak Bhasma, Kukkutandatwak Bhasma	Insomnia, Osteophoresis
	Sumenta Tablet	Ashwagandha (*W. somnifera*), Brahmi (Bacopa monnieri), Jyotishmati (Celastrus paniculatus), Tagar (Tabernaemontana divaricate), Jatamansi (Nardostachys jatamansi)	Neuroprotective action
	Cognium Tablet and syrup	Ashwagandha (*W. somnifera*), Brahmi (Bacopa monnieri), Arjun (Terminalia arjuna), Shankhapushpi (Convolvulus pluricaulis), Jyotishmati (Celastrus paniculatus)	Cognitive functions
	ZZOWIN Tablets	Ashwagandha (*W. somnifera*), Tagar (Tabernaemontana divaricata), Yashtimadhu (Glycyrrhiza glabra), Jatamansi (Nardostachys jatamansi), Mandukparni (Centella asiatica), Pippali (Piper longum)	Anxiety, relaxation, sleep deprivation
	Chropaxe tablet	Ashwagandha (*W. somnifera*), Tagar (Tabernaemontana divaricata), Gokshura (Tribulus terrestris), Shunthi (Zingiber officinale), Shyonak (Oroxylum indicum)	Chronic pain
Patanjali	Ashwagandha Churna and CapsuleAshwagandha (*W. somnifera*)	Ashwagandha (*W. somnifera*)	Stress reliever
	Spirulina Capsule with Ashwagandha	Shaivaal (Spirulina sp.), Ashwagandha (*W. somnifera*)	Superfood
	Peedantak Kwath	Peeplamul (Piper longum), Nirgundi (Vitex negundo), Ashwagandha (*W. somnifera*), Rasna (Alpinia galanga), Nagarmotha (Cyperus rotundus), Arendmul (Ricinus communis), Aaunth, Nagkesar (Mesua ferrea), Gajpeepal (Scinadapsus officinalis), Jasmine (Jasminum sp.) Carom (Trachyspermum ammi)	Pain reliever
	Divya Vatari Churna	Ginger (Zingiber officinale), Kutki (Picrorrhiza kurroa), Fenugreek (Trigonella foenum- graecum), Ashwagandha (*W. somnifera*), Suranjana (Colchicum luteum)	Gastric problems
	Glucoshakti	Glucose, Ashwagandha (*W. somnifera*), Satavar (Asparagus racemosus), Aloe (Aloe verai)	Energy booster
	Ashvashila Capsule	Shilajit, Ashwagandha (*W. somnifera*)	Sexual wellness
Muniyal Ayurveda	Geriton Leha Tonic	Kantakari (Solanum virginianum), Hareetakee (Terminalia chebula), Ashwagandha (*W.*	Chronic respiratory problems,

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		somnifera), Pippali (Piper longum), Abhraka Bhasma	constipation, and loss of appetite
	Munipayn Tablets	Guggulu (Commiphora wightii), Ashwagandha (*W. somnifera*), Rasna (Alpinia galanga), Bala (Sida cordifolia), Guduchi (Tinospora cordifolia), Shatavari (Asparagus racemosus)	Rheumatism and arthritis
	Muniojus Tablets	Ashwagandha (*W. somnifera*), Nimba (Azadirachta indica), Shuddha Shilajatu, Dhataki (Woodfordia fruticosa)	Anti-viral (HIV)
	Muneks Tablets	Kanchanara (Bauhinia variegata), Shuddha Guggulu (Commiphora Mukul), Ashwagandh(*W. somnifera*)	Anti-cancer
	Heartogen Tablets	Shuddha Shilajith, Ashwagandha (*W. somnifera*), Bala (Sida cordifolia), Shuddha Guggulu (Commiphora Mukul), Arjuna (Terminalia arjuna), Pravala Bhasma	Cardioprotective
Herbsforever	Ashwagandha Capsules	Ashwagandha (*W. somnifera*)	Anti-stress and energy
	Ashwagandha Bala Shatavari Oil	Ashwagandha (*W. somnifera*), Bala (Sida cordifolia), Shatavari (Asparagus racemosus)	Nerves, skin, muscles and bones strengthening.
	Ashwagandha Powder	Ashwagandha (*W. somnifera*)	Anti-stress and energy
Veria Id	His 60 Tablets	Ashwagandha (*W. somnifera*), Fenugreek (Trigonella foenum- graecum), Gokhshura (Tribulus terrestris), Atmagupta (Mucuna pruriens), Bhunimba (Andrographis paniculata), Musli (Chlorophytum borivillianum)	Man health
Dr. Vaidya's	Herbobuild powder	Ashwagandha (*W. somnifera*), Safed musli (Chlorophytum borivilianum), Shatavari (Asparagus racemosus)	Bodybuilding
	Herbo 24 Turbo capsules	Kamal Gota (Nelumbo nucifera), Mastaki (Pistacia lentiscus), Kesar (Crocus sativus), Jayfal (Myristica fragrans), Ashwagandha (*W. somnifera*), Shudh Shilajit, Shatavari (Asparagus racemosus), Vidari Kand (Pueraria tuberosa), Sweet Museli (Chlorophytum borivilianum), Salam Panja (Dactylorhiza hatagirea), Amla ghan (Emblica officinalis), Gokhru (Tribulus terrestris), Akalkara (Anacyclus pyrethrum), Tej Patra (Cinnamomum tamala), Elaichi (Elettaria cardamomum), Lavang (Syzygium aromaticum), Sunth (Zingiber officinale), Kababchini (Piper cubeba), Pimplimool (Piper longum), Taj	Men stamina

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	Shardardaghna	Goudanti Bhasma, Praval Pish, Shringa Bhasma, Jatamansi ghan (Nardostachys jatamansi), Brahmi (Bacopa monnieri), Ashvagandha (*W. somnifera*), Nagarmotha ghan (Cyperus rotundus), Khurasni ghan (Hyoscyamus niger)	Migraine
Baidyanath	Leukonil Tablets	Ashwagandha (*W. somnifera*), Vidhara (Argyreia speciosa), Badi Elaichi (Amomum subulatum), Majuphal (Quercus infectorial)	Leucorrhoea
	Rhuma Gel, oil, spray, capsule	Blue gum (Eucalyptus globulus), Ashwagandha (*W. somnifera*), Satavar (Asparagus recemosus), Amada (Curcuma amada), Til (Sesame indicum).	Pain relief
	Rumartho Gold and Gold plus Capsules,	Guggul (Commiphora wightii), Ashwagandha (*W. somnifera*), Iron Powder, Bishop's Weed (Aegopodium podagraria), Gold	Rheumatoid arthritis and osteo arthritis
	Baidyanath Vita-Ex Gold and Gold plus capsules	Kaunch Beej (Mucuna pruriens), Shodhit Shilajit, Safed Musli (Chlorophytum borivilianum), Ashwagandha (*W. somnifera*), Purified Kuchla (Strychnos nux-vomica), Dalchini (Cinnamomum verum), Samudra Sokh, Salam Mishri, Vang Bhasm, Abhrak Bhasm, Jaiphal (Myristica fragrans), Javitri (Myristica fragrans), Akarkara (Anacyclus pyrethrum), Laung (Syzygium aromaticum), Kant Lauh Bhasm, Kesar (Crocus sativus), Swarna Bhasm	Men energy, vigor, and stamina
	Vita-Ex Massage Oil	Velvet Bean (Mucuna pruriens), Ashwagandha (*W. somnifera*), Nutmeg (Myristica fragrans), Swarna Bhasma	Aphrodisiac and sexual wellness
Dabur	Ashwagandha Churna	Ashwagandha (*W. somnifera*)	Stamina and energy
	Stresscom Capsule and Syrup	Ashwagandha (*W. somnifera*) root powder	Anxiety, stress and fatigue
	Dabur Shila-X Oil	Shuddha Shilajatu, Nutmeg oil (Myristica fragrans), Clove Oil (Syzygium aromaticum), Shatavari (Asparagus racemosus), Amalaki (Emblica officinalis), Ashwagandha (*W. somnifera*), Bala (Sida cordifolia), Shveta Chandana (Santalum album), Jivanti (Leptadenia reticulata), Yashti (Glycyrrhiza glabra), Kumkuma (Crocus sativus), Kamala (Nelumbo nucifera), Utpala (Nymphaea stellata), Sukshmaila (Elettaria cardamomum)	Weakness of local muscular and nervous tissues
	Ashwagandharishta	Ashwagandha (*W. somnifera*), Mushali (Chlorophytum borivilianum), Manjishtha (Rubia Cordifolia), Haritaki (Terminalia chebula), Nisha (Curcuma longa)	Depression, Anxiety and Stress

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	Dashmularishta	Dashmula, Ashwagandha (*W. somnifera*), Manjishta (Rubia Cordifolia) Draksha (Vitis vinifera)	Post-delivery weakness.
Cureveda	Debility Elixir	Dashmula, Ashwagandha (*W. somnifera*), Shatavari (Asparagus racemosus)	Paralysis
	Joyful Joints	Ashwagandha (*W. somnifera*), Salai guggul (Boswellia serrata), Rose Hip and Curcumin	Joint support and flexibility
	Male mate	Gokhru (Tribulus terrestris), Cowhage (Mucuna pruriens) and Safed musli (Chlorophytum borivilianum), Ashwagandha (*W. somnifera*)	Vitality and vigor
	Mood Elixir	Ashwagandha (*W. somnifera*), Anantmool (Hemidesmus indicus), Bramhi (Bacopa monnieri)	Mood management
	Stress Shield	Ashwagandha (*W. somnifera*), Brahmi (Bacopa monnieri), Jatamansi (Nardostachys jatamansi)	Anxiety and stress support
Man Matters	Perform Vitality Tablets	Ashwagandha (*W. somnifera*), Safed musli (Chlorophytum borivilianum), L- arginine	Energy and Vigour
Seniority	Performance Capsules	Ashwagandha (*W. somnifera*), Safed musli (Chlorophytum borivilianum), Kali Musli (Curculigo orchioides), Koch Beej (Mucuna pruriens)	Men Sexual Wellness
Maharishi Ayurveda	Ashwagandha Churna	Ashwagandha (*W. somnifera*)	Semen disorders, Oligospermia, Premature ejaculation, Prameha.
Amar Healthcare	Sahi Veerya Paushtik churan	Gokshura (Tribulus terrestris), Ashvagandha (*W. somnifera*), Tal Makhana (Euryale ferox), Koch Beej (Mucuna pruriens)	Erectile dysfunction
	Protex Powder	Ashwagandha (*W. somnifera*), Shatavari (Asparagus racemosus), Mukta Sukhti Pisti, Loh Bhasma, Soya, Milk	Anemia, weakness, fatigue
	Trankula Capsules and Tonorex Syrup	Brahmi (Bacopa monnieri), Ashvagandha (*W. somnifera*), Shankhapushpi (Convolvulus pluricaulis)	Hyper tension
Avestia Pharma	Ashwagandha Root Extract Capsule	Ashvagandha (*W. somnifera*)	Stress relief
Morpheme Remedies	Ashwagandha Capsule	Ashvagandha (*W. somnifera*)	Stress relief

6. Conclusion

The evidence reviewed in this paper confirms that *W. somnifera* is a well-documented medicinal plant

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whose wide therapeutic potential is based on scientific evidence. It owes its multi-target effects to the abundance of withanolides, which contribute to antioxidant, anti-inflammatory, neurochemical, and endocrine mechanisms.Its efficacy in stress management, sleep promotion, metabolism control, and male reproductive health is backed by numerous experimental and clinical studies. In addition, preclinical studies indicate its promise in neurodegenerative disorders and cancer. This broad range of biological activities is consistent with its adaptogenic properties and systems pharmacology trends. Notably, *W. somnifera* has demonstrated a relatively safe pharmacological profile with few side effects, especially at standard doses of root extracts. However, adverse effects have been reported in some cases, but most of them were caused by the poor quality of products, adulteration, or overdose. Nevertheless, there are several gaps in research concerning *W. somnifera*, including inadequate information about the long-term safety profile, interactions with other drugs, and commercial formulation variability. The future research needs to concentrate on clinical trials, proper standardization of extracts, and pharmacokinetic and interaction studies. These studies are important for the safe use of Ashwagandha in modern medicine.

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