Original Research Article

# A study of Phytochemical analysis and Pharmacological activities of *Withania somnifera*

## Abstract:

*Ashwagandha* roots (*Withania somnifera* L. Dunal) have a history of utilization in Ayurveda to address conditions such as fever, asthma, arthritis, rheumatism, inflammation, tuberculosis, mental disorders, and male sexual issues. Through phytochemical analyses, it has been determined that the plant predominantly contains alkaloids (such as withanine, sominiferine, tropine, isopelletierine, and anaferine) and steroidal lactones (including withanolides A-Y, withaferine A, withasominiferols A-C, withanone, and sitoindosides) as the active compounds. These constituents and extracts exhibit various pharmacological effects, encompassing antioxidant, antitumor, antimicrobial, antivenom, and anti-parkinsonian properties. This review provides an up-to-date overview of *ashwagandha*, focusing on its phytochemistry and pharmacology. The plant, along with numerous secondary metabolites, has displayed efficacy in ameliorating diverse human ailments. Nonetheless, additional research is imperative to ascertain the precise mechanisms underlying their actions.

*Withania somnifera*, *Ashwagandha*, Phytochemical analysis, Pharmacological activities, Medicinal plants, Traditional medicine, Ecological significance.

## Introduction

*Ashwagandha* (*Withania somnifera* L. Dunal), also referred to as Indian ginseng or winter cherry, is indigenous to the northwestern regions of India [1]. The term "*ashwagandha*" in Sanskrit translates to "horse’s smell" (ashwa - horse, gandha - smell), likely due to the fragrance of the plant's roots. Its distribution spans across countries including India, Pakistan, Sri Lanka, Afghanistan, Egypt, South Africa, Morocco, and Jordan. In India, it is predominantly cultivated in Uttar Pradesh, Madhya Pradesh, Punjab, Gujarat, and Rajasthan [2]. The Latin species name "*somnifera*" signifies "sleep-inducing" [3]. This plant's roots have been employed in traditional Asian medicine for over 3000 years to address a range of health issues [5]. Throughout India, *ashwagandha* goes by various vernacular names such as Amukkira (Tamil), Amukkiram (Malayalam), Punir or Asgandh (Hindi), Akshan (Punjabi), and Tilli (Marathi) [4]. The powdered root is traditionally consumed daily, believed to potentially delay aging, rejuvenate muscles and reproductive organs, and enhance fertility [6]. *Ashwagandha* leaves find use in the Ayurvedic and Unani systems for treating tumors [5]. *Ashwagandha* roots are integral to around

200 formulations in Indian folk medicine, used as an aphrodisiac and for ailments like asthma, inflammation, insomnia, anxiety, psoriasis, constipation, fatigue, weakness, impotence, premature aging, ulcers, and mental stress. The plant's root extracts and active compounds known as withanolides exhibit potent therapeutic properties, including antioxidant, immunomodulatory, anti-aging, adaptogenic, neuroprotective, and antitumor activities [7-13]. In traditional Indian medicine, *ashwagandha* root powder boiled with milk was believed to address female sterility [14]. Traditionally, the plant's roots are used to promote youthful vigor, strength, and enhance the production of vital fluids, blood, muscle fat, semen, and cells [15]. *Ashwagandha* fruits function as a bitter tonic for dyspepsia and infant growth promotion, also possessing sedative, blood-purifying, and diuretic qualities [16]. According to Patwardhan et al. [17], *ashwagandha* leaves are recommended for treating swelling, fever, and ophthalmitis. Moreover, this plant demonstrates antiserotonergic and anabolic properties and exhibits potential benefits in addressing geriatric issues, stress, and arthritis [18, 19]. In modern medicine, extracts from *W. somnifera* roots have shown promise in enhancing brain health, counteracting brain aging, and addressing locomotive syndrome [20]. They are also employed for conditions like weakness, epilepsy, memory loss, and neurodegenerative diseases including spinal cord injuries, Alzheimer's, and Parkinson's [2, 21, 22]. Furthermore, *ashwagandha* root extracts are utilized as dietary supplements in both developing and developed countries, including the United States [21]. Numerous animal and human studies have verified *ashwagandha* roots' aphrodisiac potential and their impact on testosterone activity [23-28]. Given these potential health benefits, *ashwagandha* has garnered significant attention in both traditional and modern medical practices. As such, this review underscores the prominent phytochemical and therapeutic advantages offered by *ashwagandha* extracts, encompassing their potential against various diseases.

## Phytochemical Analysis

*Ashwagandha* roots contain a diverse array of phytochemical constituents, encompassing amino acids, alkaloids, ergostane steroids, terpenes, and flavonoids, that possess the ability to directly or indirectly mitigate various diseases [19, 26]. Within the group of withanolides, essential bioactive compounds found in the roots include withaferin A, withanone, and withanolide, each with therapeutic benefits such as antioxidant, antidiabetic, antimicrobial, anticancer, antimalarial, immunomodulatory, antidepressant, anti-aging, anti-stress, and cardio-protective activities [29-41]. Withaferin A, specifically, displays potential in inhibiting angiogenesis, thereby offering protection against diverse forms of cancer [42]. Additionally, two glycowithanoloids sitoindoside-IX and sitoindoside-X have been identified for their stress-reduction and memory-enhancement capabilities in rats [43]. The nutritional composition of *ashwagandha* roots, leaves, and fruits is detailed in Table 1. *Ashwagandha* root comprises carbohydrates (63.4%), protein (1.6%), fat (1.1%), and ash (3.7%) [44]. In a 100 g serving of root, the presence of calcium (23 mg), copper (0.8–3.3 mg), manganese (1.2–5.9 mg), zinc (1.6–4.4 mg), iron (94.5 mg), total carotenoids (7.6 mg), and vitamin C (3.7 mg) has been noted

[45, 46]. These nutrients play integral roles in sustaining human physiological activities. Notably, *ashwagandha* leaves and fruits also contain significant levels of copper, manganese, and zinc (see Table 1). The composition of phytochemicals in *ashwagandha* exhibits substantial variability based on geographic distribution, as highlighted by Krishnamurthy and Sarala [44]. Among the medicinally relevant metabolites found in *ashwagandha* roots are flavonoids (rutin, myricetin, quercetin, quercitrin, kaempferol, and rhamnetin), as tabulated [47]. When cultivated in Indian soils, *ashwagandha* roots contain alkaloids ranging from 0.13% to 0.31% [48]. The plant's roots predominantly house alkaloids and steroidal lactones as their principal chemical constituents. Notable alkaloids in the root include withanine, pseudowithanine, somiferine, sominiferinine, somnine, tropine, pseudo-tropine, isopelletierine, cuscohygrine, anahydrine, and anaferine. As for ergostane steroidal lactones, they encompass withanolides A-Y, withaferin A, withasominiferin-A, withasominferols A-C, withanone, and sitoindoside VII, VIII, IX, and X [49-52]. The molecular structures of crucial bioactive alkaloids and steroidal lactones from *ashwagandha* root extract are depicted in Table 2 using ChemDraw software.

| **Compositions** | **Proximate[%]** | | | **Reference** |
|---|---|---|---|---|
| | **Fruite** | **Roots** | **Leaves** | |
| Protien | 11.0 | 1.6 | 5.3 | [44] |
| Ash | 9.1 | 3.7 | 8.6 | |
| Carbohydrates | 55.9 | 64.4 | 51.5 | |
| Crude Fiber | 4.0 | 5.0 | 2.3 | |
| Fat | 2.9 | 2.4 | 1.1 | |
| ***Minerals(mg/100g)*** | | | | |
| Copper | 4.2 | 0.8-3.3 | 3.5 | [45,46] |
| Calcium | - | 23 | - | |
| Iron | 60.2 | 74.0 | 94.5 | |
| Carotenoids | - | 7.6 | - | |
| Vitamin C | - | 3.7 | - | |
| Manganese | 3.7 | 1.2-5.9 | 3.4 | |
| Zinc | 4.0 | 1.6-4.4 | 3.6 | |
| ***Metabolites(mg/100g)*** | | | | |
| Alkaloids | | | | |

| | | | | |
|---|---|---|---|---|
| Berberine | - | 0.41 | - | [47] |
| Harmine | - | 0.26 | - | |
| Caffeine | - | 1.22 | - | |
| Papaverine | - | 0.16 | - | |
| Noscapine | - | 0.32 | - | |
| Theobromine | - | 0.26 | - | |
| ***Flavonoids*** | | | | |
| Kaempferol | - | 0.78 | - | [47] |
| Myricetin | - | 0.22 | - | |
| Rutin | - | 4.21 | - | |
| Quercetin | - | 7.21 | - | |
| Quercitrin | - | 5.22 | - | |
| Rhamnetin | - | 1.15 | - | |
| ***Phenolic acids*** | | | | |
| Coumaric acid | - | 0.67 | - | [47] |
| Caeic acid | - | 1.99 | - | |
| Chlorogenic acid | - | 1.03 | - | |
| Ferulic acid | - | 0.55 | - | |
| Gallic acid | - | 4.02 | - | |

Table 1
Proximate, mineral and metabolites concentration of *Withania somnifera*

## Pharmacological Activities

The pharmacological effects of *W. somnifera* have been comprehensively evaluated in preceding articles [2, 5, 11, 50, 53-57], encompassing research conducted up until 2015. In recent times, two additional reports [58, 59] have also addressed specific facets of *ashwagandha's* pharmacological activities, spanning up to 2020. To provide an updated perspective on this pivotal Ayurvedic herb, we have undertaken a review of pharmacological studies conducted between 2015 and 2020, which were not encompassed in earlier reviews. This review aims to analyze the advancements made during these years in comparison to the preceding ones. The extracts and bioactive components derived from *ashwagandha* exhibit a

diverse array of pharmacological effects, including antioxidative, anticancer, and immunomodulatory activities. A compilation of the significant pharmacological activities attributed to *ashwagandha* is presented in Table 3.

**Neuroprotective activity**

Elhadidy et al. [74] conducted a study exploring the neuroprotective effects of *ashwagandha* against aluminium chloride-induced neurotoxicity in rats. The research revealed that administering *ashwagandha* extract at a dose of 200 mg/kg p.o. per day for 30 days exhibited significant antioxidant and anti-inflammatory properties against aluminium-induced neurotoxicity. In a separate investigation, Dutta et al. [75] assessed the impact of *ashwagandha* extract on motor performance, lifespan, and the count of motor neurons in the lumbar spinal cord of SOD1(G93A) mice with amyotrophic lateral sclerosis (ALS). This study also observed that *ashwagandha* extract administration inhibited glial activation and suppressed NF-κB phosphorylation.

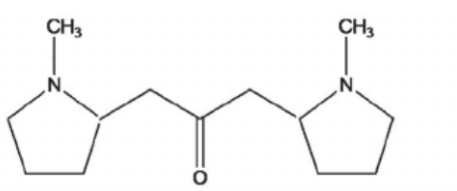
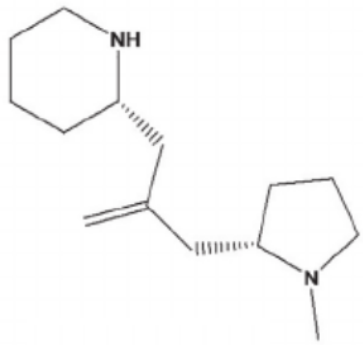
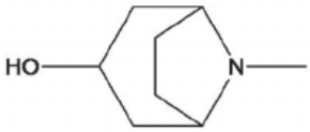
However, preceding research uncovered that co-treatment of ethanolic *ashwagandha* root extract with toxins Maneb (MB) and paraquat (PQ) effectively mitigated classical markers of Parkinson's disease in mice, including reduced dopamine levels in the substantia nigra and oxidative damage [12, 13].

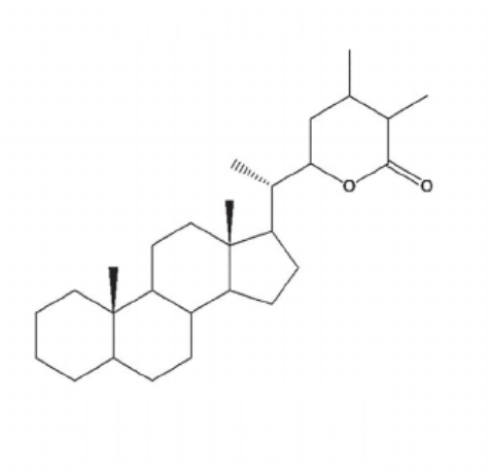
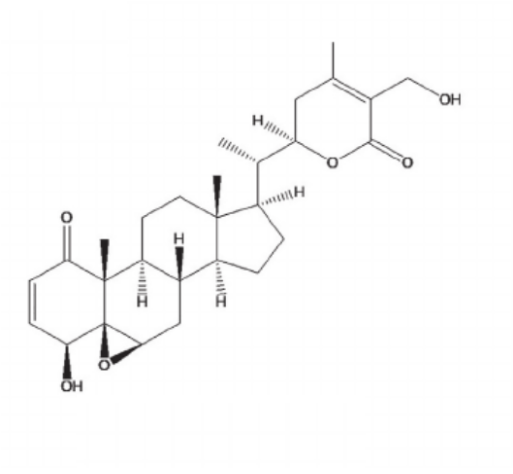
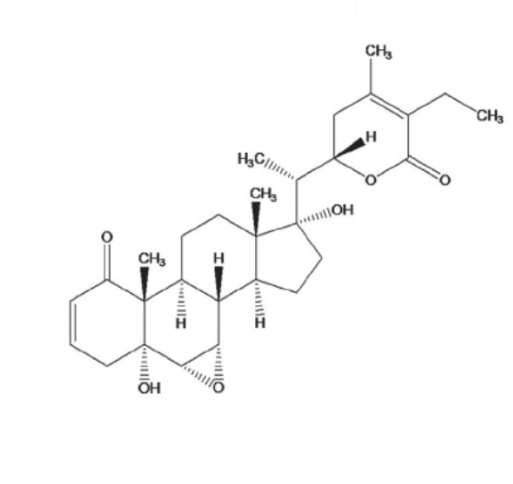
While there have been limited investigations into the nootropic potential of *ashwagandha* extracts, all of them have been conducted using animal models. Consequently, future studies should validate the bioactivity of *ashwagandha* root extract through clinical trials involving human participants.

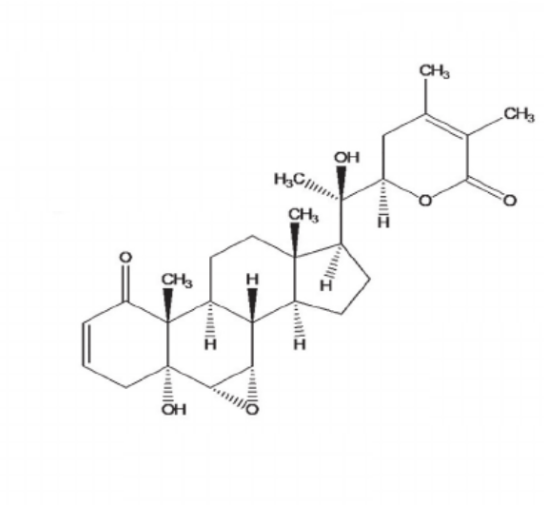
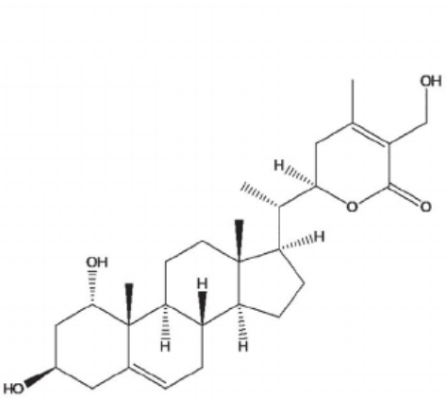
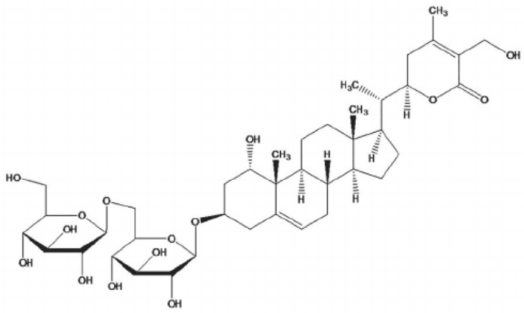
Regarding antitumor activity, numerous studies spanning the past three decades have demonstrated that *ashwagandha* extracts possess the capability to inhibit various human cancer cell types, encompassing lung, colon, prostate, pancreatic, and kidney cancer cells [76-81]. Lee et al. [82] examined the apoptotic effects of *ashwagandha* methanol extract on HNSCC cells, revealing a growth inhibition effect dependent on caspase-induced apoptosis. A recent investigation found that daily administration of *ashwagandha* extract at a dose of 200 mg/kg over 7 months led to tumor reduction in lung adenomas of urethane-induced adult male albino mice [83]. Additionally, withaferin A displayed significant impact on the A549 cell line of non-small cell lung cancer (NSCLC), associated with ROS-induced cellular damage [84]. Kim et al. [85] studied the inhibitory influence of withaferin A on Helicobacter pylori-induced IL-1 production in murine bone marrow-derived dendritic cells (BMDCs), noting a dose-dependent reduction in IL-1 output.

In the context of breast cancer cells, the protein fraction of *ashwagandha* exhibited apoptotic behavior through mitochondria-mediated ROS generation, caspase activation, and Bax/Bcl-2 regulation [63]. However, only a limited number of studies with proper controls and dosages have comprehensively explored the anticancer potential of *ashwagandha* extract and its active

constituents.As a result, future research should be dedicated to evaluating the anticancer efficacy of *ashwagandha* extracts and bioactive components through rigorous clinical trials with appropriate controls and scientifically validated dosages.

| **Bioactive constituents** | **Chemical structures** |
|---|---|
| Cuscohygrine |  |
| Anahygrine |  |
| Trophine |  |

| | |
|---|---|
| Steroidal Lactone |  |
| Withaferin A |  |
| Withanone |  |

| | |
|---|---|
| Withanolide A |  |
| Sominone |  |
| Withanoside IV |  |

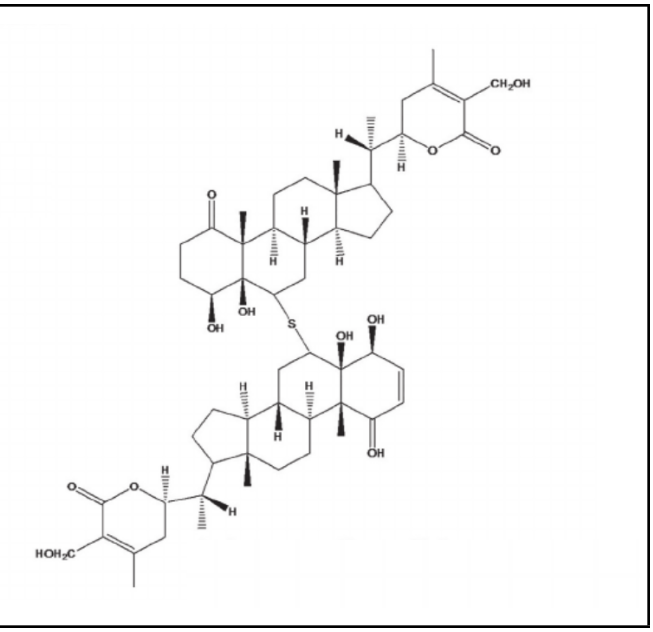
| | |
|---|---|
| Ashwagandhanolide |  |

Table 2

Chemical structures of the major bioactive constituents of *Withania somnifer a*

| Activity | Extract Type | Methods Used | $IC_{50}$/dosage | References |
|---|---|---|---|---|
| Adaptogenic and anxiolytic activity | Root extract | Fiy-eight male and female participants with a baseline perceived stress scale (PSS) score >20 | 250 and 600 mg/twice/day, 8 weeks | [69] |
| | | | | |
| Anticancer | Methonol ectract | HepG2 hepatoma cell line | $IC_{50}$:1.89 µg/ml | [65] |
| Anticancer | withaferin A | Transgenic adenocarcinoma of mouse prostate(TRAMP) model | 5 mg/kg/day; 8 week | [64] |
| Anticancer | Methonol ectract | HCT 116 human colorectal cell line | $IC_{50}$:2.19 µg/ml | [65] |
| Anticancer | *W. somnifera* protein fraction | MDA-MB-231 human breast cancer cells | $IC_{50}$:92 µg/ml | [63] |
| Anti-neuro inflammatory | Leaf extract | *Ashwagandha* leaf water extract using β-amyloid and lipopolysaccharide (LPS)- stimulated primary microglial cells and BV-2 microglial cell line | $IC_{50}$:0.2%; 48h | [61] |
| Anti-neuro inflammatory | Chloroform fraction | Chloroform fraction IV (FIV) using β-amyloid and lipopolysaccharide (LPS)-stimulated primary microglial cells and BV-2 microglial cell line | $IC_{50}$:15 µg/ml; 48h | [61] |

| | | | | |
|---|---|---|---|---|
| Antioxidant activity | Extract type root extract | Lipid peroxides (LPO), superoxide dismutase (SOD) and glutathione (GSH) were tested in adult male Wistar rats | 500 mg/kg, p.o once a day from day 14 to day 21 | [60] |
| Antiarthritic activity | Root extract | Assessed the level of inflammatory cytokines such as Tumor Necrosis Factor (TNF)-α, IL-1β, IL-6 and IL-10 in collagen-induced arthritic (CIA) rats | 300 mg/kg/day; 20 days | [62] |
| Body strength | aqueous extract (Sensoril®) | 19 recreationally active men were randomized in a double-blind fashion to placebo or Sensoril® | 500 mg/day; 12 week | [67] |
| Cytotoxic activity | Root extract | The crude extract of Withania was tested for cytotoxicity against A375 cells by MTT assay | 350, 250 and 200 µg/ml for 24, 48 and 72 h, respectively | [68] |
| Insomnia and anxiety | Root extract | 60 patients were randomly divided into two groups: ashwagandha (n=40) and placebo (n=20) | 300 mg, 2 doses/ day; 10 weeks | [72] |
| Increased testosterone level | withanolide glycosides | 43 people completed the 16-week period of trial | 21 mg/day for 8 weeks. | [71] |
| Insomnia | Root extract | 150 subjects divided into two groups: ashwagandha (n=75) and placebo (n=75) | 600 mg/once/ day; 42 days | [73] |
| Nephroprotective | Root extract | Gentamycin-induced nephrotoxicity in adult male Wistar rats | 500 mg/kg, p.o once a day from day 14 to day 21 | [60] |

Table 3

Pharmacological activities of *W. somnifera* root extracts and alkaloids

LC50 – lethal concentration; IC50 – inhibitory concentration

**Antimicobial activity**

Numerous investigations into *ashwagandha* roots have highlighted their potent antimicrobial properties. Methanolic leaf extracts of *ashwagandha*, administered at a dosage of 2 mg/ml, demonstrated significant inhibition against pathogenic gram-positive bacteria like *Staphylococcus aureus* and *Enterococcus sp*., resulting in average zone of inhibition measurements of 20.6 mm and 19.4 mm at 2 mg/ml, respectively [86]. In a recent study, the methanolic extract of *ashwagandha* exhibited activity against S. aureus and *E. coli*, showing zones of inhibition ranging from 17 mm to 24 mm, respectively, at a 2 mg/disk concentration [87].

However, older research revealed that leaf extracts of *ashwagandha*, at doses of 6.25 mg/ml and 12.5 mg/ml, significantly impeded the growth of various gram-negative bacterial species, including *E. coli*, S. *typhi*, K. *pneumonia*, P. *aeruginosa*, and C. *freundii*, in a dose-dependent manner [88]. Furthermore, leaf extract at a concentration of 100 mg/ml effectively suppressed the proliferation of pathogenic bacteria such as *Staphylococcus aureus*, *Streptococcus sobrinus*, *Streptococcus mutans*, and *Salmonella paratyphi* B [89, 90].

The majority of studies investigating the antimicrobial potential of *ashwagandha* extracts and bioactive metabolites have employed the disc diffusion method. However, this method carries inherent limitations, emphasizing the necessity for further relevant Minimum Inhibitory Concentration (MIC) assays to complement the findings [91].

**Anti depressant activity**

In a six-week trial, the administration of *ashwagandha* root extract at a dosage of 120 mg/day exhibited a significant enhancement in sleep quality among 150 healthy participants in the treatment group, in comparison to the placebo group ($p<0.001$) [92]. This recent study further noted that, following six weeks, the treatment group displayed noteworthy improvements in sleep efficiency, total sleep time, sleep latency, and wake after sleep onset compared to the placebo group.

Salve et al. [69] conducted a study where root extract was given at dosages of 250 mg/day and 600 mg/day for a span of eight weeks. This intervention led to a notable reduction in perceived stress scale (PSS) scores and serum cortisol levels in a cohort of 58 healthy participants, distinct from the placebo control group. In a different study, the administration of 240 mg of *ashwagandha* extract per day over a period of 60 days resulted in significant stress reduction when compared to a control placebo group [28].

However, in earlier investigations, oral administration of *ashwagandha* (at doses of 20, 40, and 50 mg/kg/once daily for five days) effectively diminished anxiety levels in animal models [34, 93].

**Anti-inflammatory activity**

Inhibition of inflammation is noteworthy as demonstrated by the 47% methanolic extract, which effectively curbed lipopolysaccharide (LPS)-induced nitric oxide production (IC50=33.3 μM) and TNF-α production within RAW 264.7 cells (IC50=40.9 μM). This anti-inflammatory effect was supported by Western blotting, revealing reduced iNOS protein expression and transcriptional activity [94]. Additionally, a human study involving an aqueous *ashwagandha* root extract at a dose of 300 mg/kg/wt. exhibited enhanced IL-10 secretion and suppressed NF-κB activity [62]. Gupta and Singh [95] found that *ashwagandha* doses of 600 and 800 mg/kg/body weight significantly attenuated arthritis severity by effectively inhibiting inflammatory mediators in experimental rats. In contrast, previous research highlighted that lower doses (100 mg/kg/orally for 15 days) of root extracts significantly alleviated arthritis in

Freund's adjuvant-induced rats, surpassing the anti-inflammatory effect of the standard drug hydrocortisone [96]. Al-Hindawi et al. [97] reported that *ashwagandha* effectively inhibited granuloma formation in a cotton tablet implantation rat model.

**Spermatogenic Activity**

In the realm of male fertility, *ashwagandha* has shown promise. Several studies have indicated that *ashwagandha* can enhance semen quality by reducing oxidative stress and elevating male reproductive hormone levels [23, 26, 71, 98]. Sahin et al. [99] demonstrated that *ashwagandha* supplementation at a dosage of 300 mg/kg for 8 weeks improved sperm count and motility in rats. Another investigation focused on the effects of *ashwagandha* root extract on arsenic-induced testicular impairment in rats, revealing a notable increase in sperm count and motility at a dosage of 100 mg/kg for 30 days [100]. Additionally, a dose of 200 mg/kg led to a reduction in sperm morphological abnormalities in alcohol-treated rats [101].

## Cultivation of *Withania somnifera*

Field cultivation of *ashwagandha* plants has been observed to yield more fruits and seeds compared to greenhouse cultivation. Early preparation of seedlings is crucial to allow ample time for fruit production during the vegetation season. Withaferin A and withanolide D were detected in *W. somnifera* grown under both conditions [102]. Salinity of the soil has a direct impact on plant growth, with soil salinity reducing the height, flower count, branches, and head diameter of *W. somnifera* [103]. Additionally, increased concentrations of Withaferin A and glutathione were noted when plant shoots were cultivated with enhanced ZnSO4 concentrations [104].

## Limitations and Future Directions:

This review acknowledges certain limitations that should be taken into account while interpreting the findings. One notable limitation is that some of the conducted pharmacological studies lacked proper control groups and detailed dosage information. This shortfall in experimental design could potentially lead to misleading positive outcomes. Therefore, future research endeavors should prioritize conducting studies with meticulous attention to control groups and well-defined dosages.

Another aspect to consider is the historical focus on organic extracts of *ashwagandha* roots in pharmacological examinations, which has somewhat overshadowed the potential of aqueous extracts. It is important to fill this gap by comprehensively exploring both organic and aqueous forms of *ashwagandha* to provide a more holistic understanding of its traditional uses.

While *ashwagandha* roots have demonstrated a range of therapeutic effects, such as antioxidative, antimicrobial, anti-depressant, and antitumor activities, the majority of these studies have been limited to animal and cellular models. The translation of these findings to human clinical trials has been limited. Thus, it is crucial for future research to shift focus towards comprehensive human clinical trials involving *ashwagandha* extracts, active alkaloids, and steroidal lactones. This expansion in research will provide a clearer understanding of the bioactivity of *ashwagandha* and its potential pharmaceutical applications.

An additional consideration is the need for further investigation into the identified bioactive constituents, such as withanosides and steroidal lactones, within *ashwagandha*. By unraveling the bioavailability and pharmacokinetics of these compounds, researchers can gain insights into the metabolites responsible for the plant's therapeutic effects.

In a broader context, the presence of biologically active alkaloids (e.g., withanine, sominiferine, tropine, isopelletierine, and anaferine) and steroidal lactones (including withanolides A-Y, withaferine A, withasominiferols A-C, withanone, and sitoindosides) within *ashwagandha* highlights its potential for pharmaceutical applications. Exploring the ethnobotanical and modern medicinal uses of *W. somnifera* will provide a more comprehensive understanding of its potential benefits for human health and well-being. This holistic approach will pave the way for maximizing the benefits of *ashwagandha* in various contexts.

## Conclusion:

In summary, this review underscores the ethnopharmacological applications, phytochemical composition, and biological implications of ashwagandha, a widely utilized remedy for various human conditions. Through a comprehensive analysis of the available literature, it becomes evident that ashwagandha holds significant potential as a therapeutic agent against a range of ailments. The collective findings from diverse studies highlight its efficacy in addressing conditions such as ulcers, insomnia, memory impairment, anxiety, bronchitis, and mental as well as neurological disorders. The presence of bioactive elements like withaniferins and sitoindosides has demonstrated their ability to mitigate cellular damage, reduce lipid peroxidation, and counteract both acute and chronic illnesses. Moreover, the deliberate examination of ashwagandha extracts and their active constituents has yielded insights into their favorable impacts. However, it is important to recognize the existing gaps within the scientific exploration of ashwagandha, as these warrant attention for the purpose of validation and further investigation.

## Declarations

### Ethical Approval

The conducted research does not pertain to the involvement of either human or animal subjects.

**Availability of data and materials**

not applicable

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