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Review Article

Chemical Composition, Biological Activity, and Health-Promoting Effects of *Withania somnifera* for Pharma-Food Industry Applications

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The *Withania* genus comes from the Solanaceae family and includes around 23 species, spread over some areas of the Mediterranean, Asia, and East Africa. Widely used in traditional medicine for thousands of years, these plants are rich in secondary metabolites, with special emphasis on steroidal lactones, named withanolides which are used as ingredients in numerous formulations for a plethora of diseases, such as asthma, diabetes, arthritis, impotence, amnesia, hypertension, anxiety, stress, cancer, neurodegenerative, and cardiovascular diseases, and many others. Among them, *Withania somnifera* (L.) Dunal is the most widely addressed species from a pharmacological and agroindustrial point of view. In this sense, this review provides an overview of the folk uses, phytochemical composition, and biological activity, such as antioxidant, antimicrobial, anti-inflammatory, and cytotoxic activity of *W. somnifera*, although more recently other species have also been increasingly investigated. In addition, their health-promoting effects, i.e., antistress, anxiolytic, adaptogenic, antirheumatoid arthritis, chemoprotective, and cardiorespiratory-enhancing abilities, along with safety and adverse effects are also discussed.

1. Introduction

The genus *Withania* (Solanaceae) includes 23 species [1], mostly occurring in North Africa, Canary Islands, Southern Europe, and Asia (Figure 1) [2–7]. Of the known species, there are two of huge economic importance that are also mostly grown due to their wide applicability in natural medicine [8], namely, *Withania somnifera* (L.) Dunal and *Withania coagulans* (Stocks) Dunal. Both species are grown mainly in subtropical regions of India. However, *W. somnifera* even presents a greater economic significance [9, 10]. In Morocco and Algeria, *Withania adpressa* Cors. is also found as an endemic species [11], although both the morphological form and phytochemical composition of such plants undergo polymorphisms, conditioned by its occurrence in a given geographical area [5].

Although various *Withania* spp. have been used in traditional medicine for the management of different pathologies [12], *W. somnifera* and *W. coagulans* are the most widely recognized species not only for their economic value but also for their therapeutic potential, and they are largely commercialized and cultivated in Afghanistan, Iran, India, and Pakistan [13–20]. In this sense, this review aims to provide an overview of the botanical features, traditional uses, phytochemical composition, biological activities, and health-promoting effects observed in preclinical and clinical studies of *W. somnifera*, along with updated data on its safety and adverse effects.

2. Botanical Features

Plants under the *Withania* genus are evergreen with heights ranging from 0.5 to 2.0 m, present grasses, bush suburbs, branched or unbranched [21, 22]. The flowers are green or yellow, little pedicelled or pentameric umbels, sessile to subsessile, and hermaphrodites. They have simple leaves, petiolate, ovate, alternate, or in unequal pairs with a sharp apex. Fruits are berry of 6 mm in diameter, with orange-red color when mature, globous, and enclosed in the green calyx. Seeds are compressed, small, flat, yellow, reniform, reticulate to smooth, and very light [2, 23–28].

3. Traditional Uses

From a folk medicinal point of view, *W. somnifera,* known as "winter cherry," is the most important species belonging to the *Withania* genus, and that evidences the most renowned therapeutic abilities. This plant has been used in Indian medicine for a long time, and its roots are used in more than 200 formulations [2, 29, 30].

W. somnifera (called Ashwagandha, Indian ginseng) is the best-known species, widely used in natural medicine as it helps in many different ailments, namely, in boosting the immune and hematopoietic system, has an anti-inflammatory activity that helps in skin diseases and osteoarthritis, and also has antiaging effects. In addition, it is also used in hypothyroidism, cardiovascular diseases, diabetes, depression, and chronic stress [31, 32]. More recently, several clinical trials have also confirmed their therapeutic uses, namely, in the treatment of anxiety, insomnia, and Parkinson's disease [33]. In Ayurveda, *W. somnifera* is used for over 3000 years [9] and is considered to have excellent rejuvenating abilities, while it prolongs life and has strong aphrodisiac effects. Indeed, this plant is traditionally used in India to promote youthful vigor, strength, endurance, and health [20, 33], so that such restorative properties have led to *W. somnifera* roots being called Indian ginseng. *W. somnifera* may also be useful to treat various central nervous system (CNS) disorders, such as epilepsy, stress, and neurodegenerative conditions, like Parkinson's disease (PD), Alzheimer's disease (AD), and even cerebral ischemia. Ethnobotanically, it can be used as a hallucinogenic agent [34].

With the rising number of literature available, it has also been indicated that such species may also exert cytotoxic effects, opening the possibility of its use in oncological therapies. According to Verma and Kumar [33], the chemopreventive properties of *W. somnifera* make it a potentially useful adjunct for patients undergoing radiation and chemotherapy. *W. somnifera* stimulates the immune system by stimulating the production of T lymphocytes and macrophages [35, 36], while Ziauddin et al. [37] stated a general increase in the number of white blood cells after administration of a root extract. *W. somnifera* application has also

Figure 1: Red spots indicate the geographical distribution of *Withania* spp.

been shown to be able to reduce the number of skin lesions relative to the control group and showed inhibition of cancer cell growth in breast, lung, and colon cancer, which, apart from its cytotoxic abilities, is linked to their excellent antioxidant effects [38, 39]. Other authors, namely, Panda and Kar [40] and Andallu and Radhika [41], also stated an increase in T4 thyroid hormone concentration following *W. somnifera* root powder application, so that its use may be helpful in controlling the levels of hormones in diseases linked to hypothyroidism. Some authors have also indicated that *W. somnifera* root may be used for preventing cardiovascular disease, such as atherosclerosis [40–42]. For instance, in a human trial, a significant decrease in blood glucose and cholesterol levels to the extent of 10% and 12%, respectively, was observed when compared to the group that received the conventional oral drug for type 2 diabetes (Daonil). These therapeutic effects could be due to one or more active principles in the roots of the plant. The hypoglycemic effect of *W. somnifera* root could be specifically attributed to its ability to enhance serum insulin levels and/or the antioxidant activities of catalase, superoxide dismutase, and glutathione peroxidase [40–42].

4. Phytoconstituents

Chemical analysis of different plant parts of *W. somnifera* has afforded numerous compounds belonging to various chemical classes. The biologically active chemical constituents of *W. somnifera* are alkaloids (isopelletierine, anaferine), steroidal lactones (withanolides, withaferins), saponins containing an additional acyl group (sitoindoside VII and VIII), and withanolides with glucose at carbon 27 (sitoindoside XI and X). Among them, withanolides (steroidal lactones) have been used in an increasing number of drug formulations, given their promissory therapeutic abilities [43].

Despite being widely reported by a plethora of studies, Table 1 and Figure 2 present some of the most important withanolides isolated from *Withania* spp., considering its abundance and bioactive effects and representative structures, respectively. Misra et al. [44] reported withanolide A, withanolide B, 27-hydroxy withanolide B, withanolide D, withaferin A, 16β-acetoxy-6α, 7α-epoxy-5α–hydroxy-1-oxowitha-2, 17 (20), 24-trienolide, 5, 7α-epoxy-6α, 20α–dihydroxy-1-oxowitha-2, 24- dienolide along with common steroids, β-sitosterol and sitosterol, and their glucosides in *W. somnifera*. Matsuda et al. [45] isolated 7 new withanolide glycosides from *W. somnifera* roots, named withanoside I to VII, among which class VI is more abundant. Similarly, Bessalle and Lavie [46] isolated two chlorinated withanolides, namely, withanolide C and 4-deoxyphysalolactone from dried leaves of *W. somnifera* (Table 1).

There have been also reports on other constituents from plants of the *Withania* genus, namely, fatty acids and volatile compounds. Misra et al. [57] have reported new ergosterol and 1, 4-dioxane derivatives along with various fatty acids

Table 1: List of selected withanolides and other compounds identified from *Withania somnifera* (L.) Dunal.

Plant parts	Compounds	References
Roots	Withanolide A, withanolide B, 27-hydroxy withanolide B, withanolide D, withaferin A, 16β-acetoxy-6α, 7α-epoxy-5α–hydroxy-1-oxowitha-2, 17 (20), 24-trienolide, 5, 7α-epoxy-6α, 20α–dihydroxy-1-oxowitha-2, 24-dienolide	[44]
	Withanoside I, withanoside II, withanoside III, withanoside IV, withanoside V, withanoside VI, withanoside VII, withaferin A, physagulin D, coagulin Q	[45]
	Withasilolide A, withasilolide B, withasilolide C, withasilolide D, withasilolide E, withasilolide F	[47]
	Withanolide E, withanolide F, withanolide G, withanolide H, withanolide I, withanolide J, withanolide K, withanolide L, withanolide M	[48]
	Withanolide Q, withanolide R	[49]
	Withanolide E, withanolide F, withanolide S, withanolide P	[48]
	Withanolide T, withanolide U	[50]
	Glucosomniferanolide	[51]
Stem bark	Withasomnilide, withasomniferanolide, somniferanolide, somniferawithanolide, somniwithanolide	[52]
Leaves	Withanolide C, 4-deoxyphysalolactone	[46]
	(20R, 22R)-14α, 2OαF-dihydroxy-1-oxowitha-2, 5, 16, 24-tetraenolide	[53]
	Withaferin A	[54]
	24,25-Dihydrowithanolide A, withanolide A, withanone, withaferin A, 27-hydroxy withanone, and 17-hydroxy withaferin A, 27-deoxy-16-en-withaferin A, 2, 3-dihydro-3β-hydroxywithanone, 2,3-dihydro withanone-3β-O-sulfate	[55]
Fruits	24,25-Dihydrowithanolide VI, withanoside IV, withanoside V, withanoside VI, withanamide A, withanamide B, withanamide C, withanamide D, withanamide E, withanamide F, withanamide G, withanamide H, withanamide I	[56]

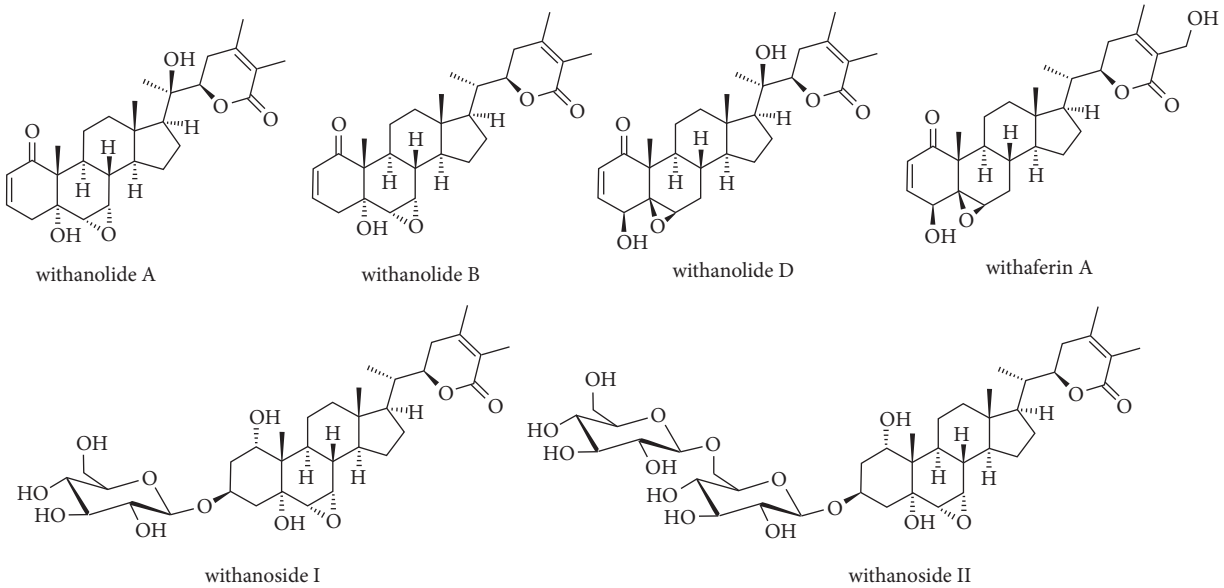

Figure 2: Chemical structures of some withanolide derivatives isolated from *Withania somnifera*.

(octacosane, oleic and stearic fatty acids), steroids, and oleanolic acid from *W. somnifera* roots. For example, Rautela et al. [58] studied the constituents of both ethanol and methanol extracts of *W. somnifera* leaves and roots and analyzed components by gas chromatography-mass spectrometry (GC-MS). Various compounds, including withanolide B, rosifoliol, and phytol, were reported [58]. Gulati et al. [59] studied the chemical composition of various extracts from *W. somnifera* roots of different genotypes and stated several metals in its composition, along with different concentrations of total sugars, alkaloids, and tannins. Bhatia et al. [60], studying the effect of chemotype variations in the chemical composition of *W. somnifera* fruits using GC-MS and nuclear magnetic resonance (NMR) spectroscopy, stated clear variations in metabolites contents in different chemotypes.

5. Biological Activities

Given the wide range of *Withania* species applications in Ayurvedic medicine for multiple aims, an increasing number of studies have progressively addressed their biological effects (Figure 3). Furthermore, with the popularization, the use of this plant as a food supplement in the market is also increasing. Indeed, both extracts and compounds isolated from the *Withania* species exhibit excellent

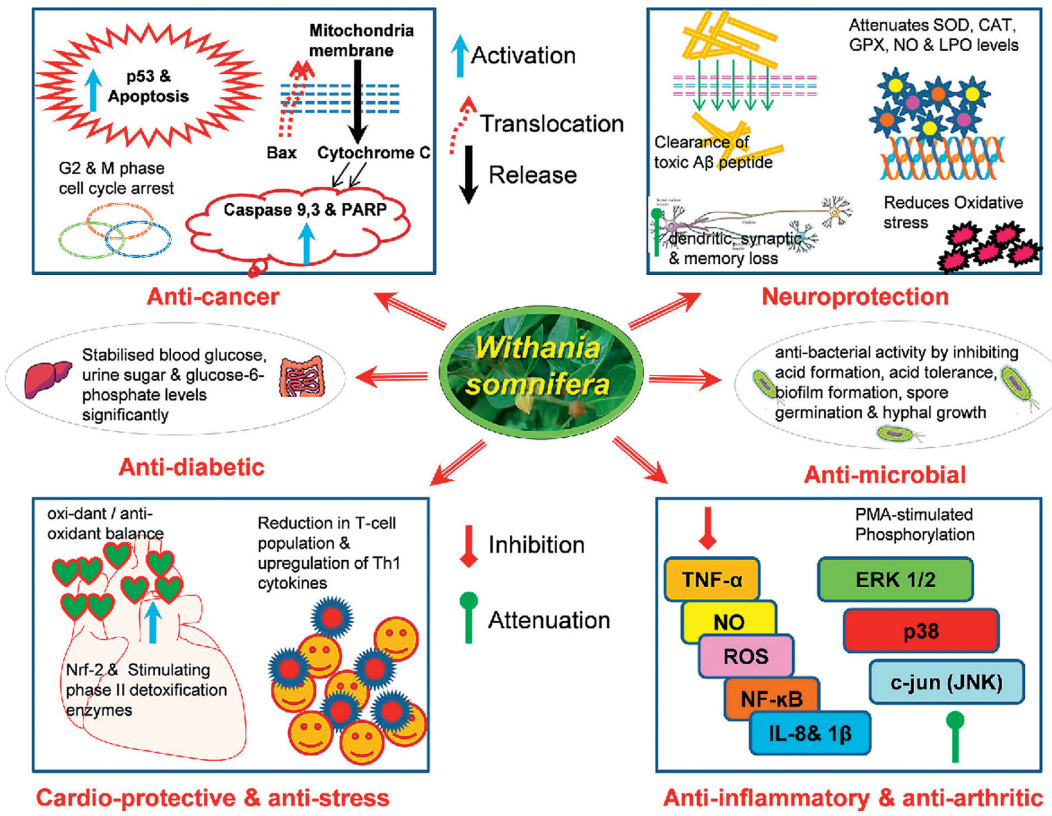

Figure 3: Major biological activities of *Withania somnifera*. Anticancer effects: *W. somnifera* exerts anticancer effects via multiple pathways, including nuclear factor (NFK-beta) and signal transducer and activator of transcription 3 (STAT3) signaling, PI3K (phosphoinositide 3-kinase)/AKT (a serine-threonine protein kinase) and mitogen-activated protein kinase (MAPK) signaling, angiogenesis inhibition, oxidative stress induction, and p53 signaling. Melanoma cells were destroyed by withaferin A via ROS-mediated apoptosis. This process activated the mitochondrial pathway, resulting in the downregulation of Bcl-2, translocation of Bax to the mitochondrial membrane, release of cytochrome c into the cytosol, abolition of transmembrane potential, and concomitant activation of caspases 9 and 3, resulting in the downregulation of proapoptotic protein, poly (ADP-Ribose) polymerase-1 (Parp-1) and DNA fragmentation. Neuroprotection: *Withania somnifera* reduced blood glucose, tissue lipid peroxidation (LPO), and glutathione (GSH) levels while increasing the activities of antioxidant enzymes such as glutathione peroxidase (GPx), glutathione reductase (GR), glutathione-S-transferase (GST), superoxide dismutase (SOD), and catalase (CAT). This demonstrates *W. somnifera's* significant free radical scavenging activity, as well as its ability to improve non-enzymatic and enzymatic antioxidants. *W. somnifera* root extract and withanolide A protected isolated hippocampus cells against hypobaric hypoxia-induced memory loss and neurodegeneration in vitro by stimulating the glutathione production pathway and decreasing glutathione (GSH) concentration. Furthermore, in cortical neurons treated with amyloid beta peptide, Withanolide A promoted both axonal and dendritic change as well as synaptic repair. Antidiabetic effects: *W. somnifera* leaf and root extracts showed antidiabetic activity by normalizing glucose uptake in skeletal myotubes and adipocytes in a dose-dependent manner. Furthermore, it considerably attenuated levels of urine and blood glucose, glucose 6-phosphatase, and tissue glycogen levels through nonenzymatic and enzymatic antioxidant mechanisms. Antimicrobial effects: the antimicrobial effect of *Withania somnifera* is attributed by inhibiting acid formation, acid tolerance, biofilm formation, spore germination, and hyphae growth, which in turn is mediated through gene silencing, immunopotentiation and cytotoxicity. Cardioprotective and antistress effects: the cardioprotective and cardiotropic properties of *W. somnifera* are demonstrated via nuclear factor erythroid 2-related transcription factor (Nrf)-2 and by activating phase II detoxification enzymes and abrogating apoptosis. Moreover, it is capable of alleviating chronic stress induced reduction of T-cell population and upregulated Th1 cytokines, thereby ensuring better stress endurance in animals as well as humans. Anti-inflammatory and antiarthritic effects: *Withania somnifera* alleviated inflammation by suppressing cytokines such as interleukin- (IL-) 8 and 1, tumor necrosis factor- (TNF-) α, nitric oxide (NO), and reactive oxygen species (ROS). Furthermore, withaferin A, one of the active ingredients of *W. somnifera,* inhibited the expression of cell adhesion molecules, leukocyte adhesion and migration, IL-6 and TNF-a production, and NF-k activation (nuclear factor kappa-light-chain-enhancer of activated B cells). Furthermore, it inhibited the phosphorylation of p38, extracellular regulated kinases (ERK 12), and c-Jun N-terminal kinase by phorbol-12-myristate-13-acetate (PMA) (JNK).

biological activities, including antioxidant, antimicrobial, anti-inflammatory, and chemopreventive abilities, as assessed by both in vitro and in vivo studies. Concerning its in vitro biological effects, studies performed so far generally focused on their antioxidant activity and total phenolic content (spectrophotometric and/or chromatographic analyses) [61–68] and antimicrobial effects (disc diffusion assay and/or minimum inhibitory concentration (MIC)) [65, 69–81]. In addition to in vitro studies, there has been a significant number of *in vivo* studies addressing the anti-proliferative, cytotoxic, and anti-inflammatory effects of *W. somnifera* extracts in animal models [62].

5.1. Antioxidant Activity. The biological effects, and particularly the antioxidant potential and phytochemical constituents of *W. somnifera*, along with the other plants of the *Withania* genus, vary depending on the extraction method [61]. Methanol-chloroform-water (1 : 1 : 1) extract of *W. somnifera* roots, with the highest content of all phytochemical constituents except tannins, had higher antioxidant and reducing activities when compared to water, acetone, and aqueous methanol (1 : 1) extracts (i,e. total antioxidant capacity of methanol-chloroform-water (1 : 1 : 1) was 83.354 ± 1.828, aqueous methanol (1 : 1) was 76.978 ± 2.210, and water was 68.439 ± 1.000) [62]. Alkaloid content was found to be a leading contributor to the overall antioxidant and reducing activities of the extracts, closely followed by flavonoids and withanolides. Moreover, different parts of the plant may have different levels of antioxidant capacity [62]. For instance, Sumathi and Padma [82] reported that the leaves and fresh and dry tubers of *W. somnifera* had high contents in antioxidant compounds, while those present in tender roots and stems were not so high. Similar findings were also stated in other studies [63–65], with Alam et al. [66] also reporting that *W. somnifera* presents a good antioxidant activity, with catechin being the major polyphenol present in the highest concentration (13.01 ± 8.93 to 30.61 ± 11.41 mg/g). High concentrations of polyphenols (gallic, syringic, benzoic, p-coumaric, and vanillic acids as well as catechin, kaempferol, and naringenin), flavonoids, and DPPH (1, 1-diphenyl-2-picrylhydrazyl) radical scavenging activities were detected in 80% methanolic extracts of *W. somnifera* fruits, roots, and leaves, ranging from 17.80 ± 5.80 to 32.58 ± 3.16 mg/g (dry weight), 15.49 ± 1.02 to 31.58 ± 5.07 mg/g, and 59.16 ± 1.20 to 91.84 ± 0.38 mg/g, respectively [66]. Other authors also reported that *W. somnifera* root extract (0.7 and 1.4 mg/kg daily by gastric intubation method for 20 days) improves oxidative damage due to lead intoxication in mice by significantly decreasing lipid peroxidation and significantly increasing superoxide dismutase and catalase enzyme activities [67]. Free radical scavenging activity (FRSA) and metabolic profile of in vitro cultivated and field-grown *Withania somnifera* roots were examined by Samir et al. [68]. In vitro produced roots had significantly higher levels of FRSA, total phenolic content (TPC), and total flavonoid content (TFC) than field-grown samples. Furthermore, as compared to 45-day-cultured samples, 30 day-cultured in vitro root samples had considerably greater FRSA, TPC, and TFC. Gas chromatography-mass spectrometry study detected a total of 29 compounds in in vitro cultivated and field-grown roots. Alcohols, organic acids, purine, pyrimidine, sugars, and putrescine were among the metabolites identified. Vanillic acid was found only in in vitro cultured root samples, and it was found in higher concentrations in 30 day-cultured in vitro root samples than in 45 day-cultured samples. As a result, 30 day-cultured in vitro root samples are recommended as a substitute for field-grown roots in the development of medicinal and functional food products.

5.2. Anticancer, Anti-Inflammatory, and Cytotoxic Activity. Regarding the anticancer and cytotoxic effects of *Withania* species, Samir et al. [68] reported that ethanol extracts of aerial parts of *W. somnifera* demonstrated cytotoxic activity against human liver (HEPG-2) and breast (MCF-7) cell lines with half-maximal inhibitory concentration (IC_{50}) of 8.5 μg/mL and 9.4 μg/mL for HEPG-2 and MCF-7, respectively. Cytotoxic activity of *W. somnifera* extracts was found to be at the stage of the G2/M phase and sub-G0 by arresting the cell cycle. Similarly, Naidoo et al. [83] reported that *W. somnifera* root extract effectively regulates the levels of the inflammatory cytokines while inhibiting the cancer cells' growth. Closely linked to the antioxidant activity, the cytotoxic activity of *W. somnifera* leaf extract against hepatocellular carcinoma cell line was also reported by Ahmed et al. [84]. In another study, it was observed that hydroalcoholic extract of *W. somnifera* root exhibited chemopreventive activity in mice with skin cancer [39] and fibrosarcoma [85]. Similarly, Padmavathi et al. [86] reported that *W. somnifera* root exerts chemopreventive effects against forestomach and skin carcinogenesis in mice.

On the other hand, closely linked to both antioxidant and anti-inflammatory effects, Khadrawy et al. [87] reported that *W. somnifera* demonstrated excellent effects against aluminum chloride ($AlCl_3$)-induced neurotoxicity in rats. Aluminum increased lipid peroxidation and nitric oxide levels in the cortex, hippocampus, and striatum while lowering glutathione levels in the hippocampus and striatum. Lipid peroxidation, nitric oxide, and reduced glutathione levels were not significantly different in rats protected with *W. somnifera* extract. Furthermore, it inhibited the increased activity of acetylcholinesterase and Na^+, K^+, ATPase in the cortex, hippocampus, and striatum caused by $AlCl_3$, apart from preventing a significant increase in tumor necrosis factor-α induced by $AlCl_3$ in the cortex and hippocampus. These findings imply that *W. somnifera* extract can protect against aluminum neurotoxicity by acting as an antioxidant and anti-inflammatory agent. Furthermore, it helps to prevent the decline in cholinergic activity by maintaining normal acetylcholinesterase activity. The latter effect may support the use of *W. somnifera* as a memory booster. Also, Pingali et al. [88] reported that withaferin A of *W. somnifera* can cause type II collagen expression and increase reactive oxygen species and cyclooxygenase-2 expression in rabbit articular chondrocytes depending on dose and time.

5.3. Cardioprotective Activity. Udayakumar et al. [89] suggested that the flavonoids and phenolics present in both root and leaf extracts of *W. somnifera* can be effective in reducing the blood glucose levels in diabetic rats. It was also reported that *W. somnifera* was effective in decreasing hyperlipidemia and oxidative stress in type 2 diabetic rats. When *W. somnifera* was given orally to type 2 diabetic rats at dosages 200 mg/kg and 400 mg/kg, it led to significantly reduced serum levels of total cholesterol, triglyceride, low-density lipoprotein-cholesterol, and very-low-density lipoprotein-cholesterol while high-density lipoprotein-cholesterol levels increased significantly when compared to the diabetic control group [90]. Moreover, Udayakumar et al. [89] claimed that phenolic contents of the extracts of *W. somnifera* leaf and root were helpful in decreasing blood

glucose levels in diabetic rats. Elkady and Mohamed [91] also reported that *W. somnifera* can be effective in protecting the occurrence of cardiotoxic effects induced by γ-rays in rats. A similar finding was also reported by Hosny Mansour and Farouk Hafez [92] that *W. somnifera* reduced hepatotoxicity in rats exposed to γ-radiation by significantly lowering serum hepatic enzymes, hepatic nitrate/nitrite, and malondialdehyde levels, significantly increasing antioxidant activity, and significant heme oxygenase (HO-1) induction. HO-1 enzymes protect the cell from injury due to oxidative and pathological stress, having a central role in cardiovascular protection [93].

5.4. Antimicrobial Activity. The antimicrobial activity of the *Withania* species is also remarkable. For example, methanol extracts of *W. somnifera* roots, fruits, and leaves have been revealed to be highly effective against gram-negative bacteria, including *Klebsiella pneumoniae, Citrobacter freundii, Salmonella typhi, Pseudomonas aeruginosa, and Escherichia coli*, as shown by Alam et al. [65]. Modulation of physiological functions of gut microbiota is involved in the mode of action of Withania somnifera root extracts. Similarly, the dichloromethane and ethyl acetate extracts of aerial parts of *W. somnifera* also evidenced excellent effects against *Staphylococcus aureus* and methicillin-resistant *Staphylococcus aureus* by disc diffusion assay, as shown by Mwitari et al. [69] and Hussain et al. [94].

The antimicrobial activity depends on the extraction method where ethanolic and methanolic extracts of *W. somnifera* root did not exhibit antibacterial activity against *K. pneumoniae* and methicillin-resistant *S. aureus*, whereas these microorganisms were inhibited by chloroform extracts of stem and leaves [70]. Moreover, the antimicrobial activities of different extracts of *W. somnifera* against different bacteria were reported by AbdEislam et al. [71]. The antibacterial activity of aqueous extract of *W. somnifera* against *E. coli* was higher compared to that of the alcoholic extract [72]. The extracts of *W. somnifera* root were also effective against multidrug-resistant *S. aureus* [73], with methanol extract of *W. somnifera* being also effective in inhibiting oral bacteria, like *Streptococcus mutans* and *Streptococcus sobrinus* [74]. Halamova et al. [75] investigated the antimicrobial activity of *W. somnifera* against human pathogenic bacteria and observed that those pathogens were more susceptible to extracts compared to beneficial *Bifidobacteria*. Interestingly, Zahran et al. [95] also reported that the dietary supplementation with *W. somnifera* root powder exhibited immunotherapeutic activity against *Aeromonas hydrophila* in Nile tilapia.

When looking at the effect of *W. somnifera* isolated constituents, flavonoids have shown excellent antimicrobial effects against *C. albicans, S. aureus, Proteus mirabilis, E. coli*, and *P. aeruginosa*, although no effects were noted against *Aspergillus flavus* or *Aspergillus niger* [76]. Interestingly, the minimum inhibitory concentration (MIC) of *W. somnifera* methanol extract against *C. albicans* and *Neisseria gonorrhoeae*was reported as 20 mg/mL and 0.5 mg/mL, while that of water extract against *N. gonorrhoeae*was 10 mg/mL [77]. In addition, *W. somnifera* glycoprotein revealed antibacterial effects against *Clavibacter michiganensis* subsp. *michiganensis* and antifungal activity against *A. flavus, Fusarium oxysporum,* and *Fusarium verticillioides* [78]. Also, it was reported that *W. somnifera* can be utilized in the synthesis of silver nanoparticles with excellent antioxidant, antimicrobial, and anticancer potential [79–81].

6. Health-Promoting Effects

As previously mentioned, *Withania* has been used since a long time ago for different clinical purposes. In the traditional system of medicine, *Withania somnifera* has been used for anti-inflammatory, anticancer, antioxidant, adaptogenic, and antistress purposes, along with as an immunomodulator. Moreover, it also exerts a positive influence on endocrine, cardiorespiratory, and central nervous system (CNS) levels. For instance, it was stated that *W. somnifera* is a powerful help in cancer management, with good tolerance [96]. Recently, upon evaluating the clinical evidence base and investigating the potential role of *W. somnifera* in managing cognitive dysfunction, Ng et al. [97] found that *W. somnifera* extract improved performance on cognitive tasks, executive function, attention, and reaction time. It also appears to be well tolerated, with good adherence and minimal side effects. Using standardized *W. somnifera* extracts or its bioactive ingredients, new and more effective medications to treat cognitive impairment could be produced [97]. Notwithstanding, despite the broad spectrum of preclinical data available, the number of clinical trials performed using *W. somnifera* is markedly scarcer (Table 2).

7. Food-Pharma Industry: Safety and Adverse Effects

W. somnifera has traditionally been available in the form of capsules and powder, being most often sold as a supplement. However, it can now be found in a variety of food products, including ghee, honey, and kombucha. More recently, *W. somnifera* has also been incorporated in baked goods, juices, and beverages, respectively, sweets (candies/snacks), and dairy products marketed as "Functional Foods" or "Nutraceuticals." The worth of note is that the amount of *W. somnifera* in food can vary widely, where the addition of powder can range from 1 to 10% depending on the product (baked good vs. beverage). Also, levels of *W. somnifera* up to 5% have also been found to have acceptable sensorial features [114].

Herbal cookies designed as functional foods have also been developed with *W. somnifera* leaf powder, with the final product presenting with an acceptable color, taste, and texture while maintaining an acceptable shelf-life [115]. Incorporating *W. somnifera* into foods can serve several functions; for example, it can provide excellent antioxidant and human health benefits. Moreover, the addition of *W. somnifera* to ghee (clarified butter fat) was found to be an effective natural antioxidant to prevent oxidative degradation (less than synthetic antioxidant BHA, butylated hydroxyanisole) apart from providing health-promoting benefits. The antioxidant activities evaluated were

Table 2: Health-promoting effect of *Withania somnifera*.

Biological activity	Dose/duration	Study design/subjects	Effect	References
Antistress and antianxiety	500 mg dried aqueous extract of roots and leaves/twice a day for 14 days	Double-blind, placebo-controlled, randomized, crossover study ($n = 20$ healthy men)	Decrease aortic pressure	[88]
	300 mg roots extract/day, 45 days	Prospective double-blind, randomized, placebo-controlled trial ($n = 64$ subjects with a history of chronic stress)	Reduce cortisol levels and the scores of stress-assessment scales	[98]
	500 mg powder capsule/ twice a day, twice a day, 30 days	Single-trial group ($n = 30$ subjects with generalized weakness)	Reduce fatigue symptoms, improve workability and quality-of-life dimension scores	[99]
	120 mg root extract/day, six weeks	Double-blind placebo-controlled trial ($n = 30$ individuals with the obsessive-compulsive disorder)	Improve effect in Yale-Brown obsessive-compulsive scale (symptoms severity)	[100]
	300 mg root extract/day 12 weeks	Clinical control-placebo trial ($n = 55$ type II diabetics, under oral hypoglycemics)	Improvement in stress and complaints	[101]
	250 mg root ethanol extract/twice a day, 6 weeks	Double-blind, placebo-controlled study ($n = 39$ subjects with generalized anxiety disorder, mixed anxiety and depression, panic disorder, and adjustment disorder with anxiety)	Improvement in anxiety score across time	[102]
	1000 mg standardized root extract/day, 12 weeks	Randomized, placebo-controlled, double-blind ($n = 66$ patients with depression and anxiety symptoms)	Improvement in depression single-item and anxiety-depression cluster scores and anxiety symptoms	[103]
Cognitive	500 mg standardized root extract/day 8 weeks	Randomized placebo-controlled ($n = 53$ patients with bipolar disorder)	Improvement in auditory-verbal working memory (digit span backward)	[104]
	250 mg dried aqueous extract of roots and leaves/twice daily, 14 days	Prospective, double-blind, placebo-controlled, crossover ($n = 20$ healthy men)	Improvement in the cognitive and psychomotor performance	[105]
	300 mg root extract/twice daily, 8 weeks	Prospective, randomized, double-blind, placebo-controlled ($n = 50$ healthy man and female adults)	Improvement in general memory and executive function	[106]
Cardiorespiratory	300 mg roots extract/ twice daily, 12 weeks	Randomized, double-blind, and placebo-controlled ($n = 50$ healthy athletic male and/or female adult)	Enhances the cardiorespiratory endurance, improvement in the self-reported quality-of-life questionnaire	[107]
	250 mg standardized root extract/twice daily, 14 days	Prospective, double-blind, randomized, and placebo-controlled ($n = 50$ healthy men)	Increased velocity, power, and maximum oxygen consumption	[108]
	500 mg standardized root extract/day Sensoril®, 12 weeks	Randomized, double-blind, placebo-controlled ($n = 40$ healthy, recreationally active men)	Improves upper- and lower-body strength in active men	[109]
Analgesic/anti-inflammatory	1000 mg standardized root extract/day, 10–14 days	Randomized placebo-controlled ($n = 26$ healthy men)	Increased mean pain threshold time	[110]
	250–125 mg standardized root extract/twice daily, 12 weeks	Randomized, double-blind placebo-controlled ($n = 16$ patients with knee joint pain and discomfort)	Reduced pain and disability scores (both doses), and promoted a better response (at a higher dose)	[111]
	450 mg root extract/day, 15 days	Double-blind, placebo-controlled, crossover ($n = 42$ patients with osteoarthritis)	Reduced severity pain and a disability score	[112]
Chemoprotective	2000 mg root extract/day every 8 h during chemotherapy cycles	Open-label prospective nonrandomized comparative trial ($n = 100$ patients with breast cancer in all stages)	Reduce score Piper's fatigue score Reduced Schwartz's cancer fatigue score and improved quality-of-life questionnaire scores	[113]

β-carotene bleaching assay, DPPH assay, and Rancimat method, and the doses evaluated were 1.0% and 0.5% (w/w) for aqueous and ethanolic *W. somnifera* extract, respectively. Perhaps not surprisingly, much food product development research has focused on incorporating *W. somnifera* into foods commonly consumed in India. Nonetheless, as foods containing *W. somnifera* are becoming widely available, increasing attention and consideration must be given to the potential occurrence of adverse effect(s) as a result of overingestion [116].

7.1. From Therapeutic to Safety Profile. Animal and human studies have been conducted to determine the potential impact in the treatment of a wide range of diseases, including but not limited to cancer, immunosuppressive diseases, anxiety and depression, Parkinson's disease (PD), and fertility [117]. Studies performed so far suggest that the consumption of up to 100 mg per kg of body weight in a single dosage or approximately 21 g per day is safe. Typically, a therapeutic dose is ≤10 g/day, so that a total intake can be more closely controlled when consumed in a capsule form. In an animal model, *W. somnifera* extract was given for 28 days at oral doses of 0, 500, 1000, and 2000 mg/kg body weight, and data obtained suggest that the administration of *W. somnifera* extract up to 2000 mg/kg/day did not trigger adverse effect [118].

Several review articles broadly cover various human clinical trials suggesting that *W. somnifera* has no adverse health effects during long-term (≥one-year) administration [119]. For example, a group of 64 subjects aged from 18 to 54 received a 300 mg capsule of *W. somnifera* root extract for a period of 60 days [98]. Any incidences of adverse events were comparable in the placebo-control group and *W. somnifera* group, with the difference being not statistically significant. Another study investigated the use of *W. somnifera* in reproductive issues; for that, a group of 41 men received a dose of 4 tablets (500 mg each) 3 times/day (i.e., 6 g/day) containing *W. somnifera* root powder through oral route after intake of food for 60 days [120]. The placebo (wheat powder) received a tablet form, consisting of 4 tablets (500 mg each) 3 times/day (i.e., 6 g/day) ($n = 45$). No adverse health effects were stated using the *W. somnifera* root powder.

The impact of *W. somnifera* root extract supplementation in muscle strength and recovery of 57 male subjects (18 to 50 years old) was also evaluated [121]. Subjects in the treatment group received 300 mg of *W. somnifera* root extract twice daily for 8 weeks, and no adverse health events were reported. Taken together, data obtained so far appears to support that *W. somnifera* has no toxic effects; however, such studies were not specifically designed to address safety and adverse effects. Also, most studies were of short duration and, as such, may not be indicative of the long-term impact of *W. somnifera* intake in human health.

7.2. Pregnancy and Teratogenicity. To what concerns, the safe use of *W. somnifera* during pregnancy, whether as a supplement or in food, remains uncertain. Reports suggest that *W. somnifera* might have abortifacient properties during pregnancy, indicating classification under toxic plants that cause abortion and sterility [122, 123]. In this way, some researchers addressed the concern by orally administering *W. somnifera* root extract to pregnant rats during a period of major organogenesis and histogenesis (days 5 to 19 of gestation). Briefly, pregnant rats received a dose of 500, 1000, and 2000 mg/kg/day and were monitored for a range of clinical symptoms, although no evidence of maternal or fetal toxicity was stated. The root extract provoked no changes in body weight of parental females, the number of corpora lutea, implantations, viable fetuses, and external, skeletal, and visceral malformations. Thus, the authors proposed evidence of safety related to *W. somnifera* root extract at least at 2000 mg/kg/day [124]. Regardless, caution must be exercised concerning the use of *W. somnifera* during pregnancy given the limited number of published studies addressing the issue [122, 123]. According to the National Institutes of Health [125], *W. somnifera* contains several compounds that may cause miscarriage, premature birth, or uterine contractions [124]. *W. somnifera* is commonly safely used by adults in doses up to 1000 mg per day, for up to 12 weeks, but pregnant and breastfeeding women should not consume [125].

Collectively, the wealth of research suggests that oral intake of *W. somnifera* is safe with a possible exception during pregnancy. In addition, given that *W. somnifera* is being formulated into a wide range of commercially available food and beverages, the total day consumption by consumers of such products may need to be more closely considered. In this sense, future research may focus on differences in bioavailability of the various forms (leaf and root powder, extracts, and essential oils) related to safety and adverse effects.

8. Conclusion

The *Withania* genus has been traditionally used for its therapeutic potential in numerous diseases, of which insomnia, depression, and immunostimulant effects stand out. However, remarkable anti-inflammatory and rejuvenating activities have also been stated, with in vitro and in vivo studies highlighting excellent antioxidant, antiproliferative, cytotoxic, anti-inflammatory, and antimicrobial activity. However, not all species present the same activity, with the most studied and economically important one being the roots of *W. somnifera*. More importantly, the clinical studies performed so far have progressively affirmed the *W. somnifera* therapeutic effects, namely, its excellent ability to increase vitality, physical performance, and hematopoietic capacity and to treat insomnia. Moreover, *W. somnifera* is being valued for its ability to promote longevity and strengthen the immune system without stimulating the body's reserves. Nonetheless, despite the advances stated so far, further clinical trials and more precise and deeper studies, namely, addressing the bioavailability and effect of pure compounds and the occurrence of synergistic effects when used in combination, along with the development of methods to standardize the percentage composition of active compound(s) in marketed products, are the fields that most

need to be intensively explored. Actually, although it is possible to find various products containing *W. somnifera* at variable amounts and safety studies do not report adverse effects, it is of utmost importance to have deeper knowledge on synergistic effects that may possibly occur with other food components and to know what are the effects when high doses are used and even what are the effects in pregnancy.

Data Availability

The data supporting this review are from previously reported studies and datasets, which have been cited. The processed data are available from the corresponding author upon request.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Authors' Contributions

All authors contributed equally to the manuscript. Conceptualization was done by Javad Sharifi-Rad, Hari Prasad Devkota, Beraat Özçelik, Miquel Martorell, William C. Cho, and Natália Cruz-Martins; Cristina Quispe, Seyed Abdulmajid Ayatollahi, Farzad Kobarfard, Mariola Staniak, Anna Stępień, Katarzyna Czopek, Surjit Sen, Krishnendu Acharya, Karl R. Matthews, Bilge Sener, Celale Kırkın, Montserrat Victoriano, Deepak Chandran, Manoj Kumar, and Hafiz Ansar Rasul Suleria contributed to validation, investigation, data curation, and writing the draft of the manuscript; review and editing of the manuscript were performed by Javad Sharifi-Rad, Hari Prasad Devkota, Beraat Özçelik, Miquel Martorell, William C. Cho, and Natália Cruz-Martins. All authors read and approved the final manuscript.

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