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Natural products and human health— A special focus on Indian Ginseng *Withania somnifera* (L.) Dunal

Sunil Kayesth[1]*, Kamal Kumar Gupta[2], Kavita Tyagi[3], Roshani Raja Mohan[4], Jyoti Arora[5] and Veeranoot Nissapatorn[6]

[1]Medicinal Plant and Health Research Lab., Department of Zoology, [2]Department of Zoology, [4]Department of Botany, Deshbandhu College, University of Delhi, New Delhi 110019, India

[3]National Medicinal Plant Board, Ministry of Ayush, Govt. of India, New Delhi 110001, India

[5]USAID's Infectious Disease Detection and Surveillance (IDDS), ICF, New Delhi 110073, India

[6]School of Allied Health Sciences and World Union for Herbal Drug Discovery (WUHeDD), Walailak University, Nakhon Si Thammarat 80160, Thailand

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The burden of infectious and non-communicable diseases is increasing globally. The emerging and reemerging bacterial and viral diseases are posing major threats to human health and causing considerable socio-economic problems. The expansion of resistance development in pathogens against the present therapeutic drugs leads to new health challenges worldwide. Similarly, certain environmental and lifestyle factors that promote systemic chronic inflammation are also leading to numerous diseases and health problems. In addition, various social factors are also challenging the health system in India and other developing nations. To achieve Sustainable Development Goals (SDGs), prevent the development of more superbugs, and achieve universal health coverage in India and outside, natural ways to fight against deadly pathogens are more reliable. Currently, cutting-edge technologies like nanotechnology and omics in natural product research are opening new avenues in drug discovery to foster the challenges in developing novel drugs. For better health, it is essential to give equal weightage to the social aspects of health through education and research focusing on social factors and interventions that can improve people's health as well. In this direction, the immense potential of natural products can be explored and used as a forefront strategy to manage these burning health issues to achieve sustainable developmental goals. The AYUSH (Ayurveda, Yoga, Naturopathy, Unani, Siddha, and Homeopathy) medicines can play a fruitful role in rural and urban areas to increase the health care system in these directions. Indian Ginseng, *Withania somnifera* (L.) Dunal (Solanaceae), popularly known as 'Ashwagandha', has tremendous potential for use in the treatment of various ailments. It has been used in the Indian Ayurvedic system since ancient times, and present-time scientific research work validates its use not only for therapeutic purposes but also as a health promoter for people of all age groups. In this paper, we have reviewed work done on natural products in human health, highlighting cutting-edge technologies that boost drug development from natural products with special reference to *W. somnifera*.

Keywords: Health promoter, Human health, Natural products, *Withania somnifera*

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Introduction

The enormous burden of infectious and non-communicable diseases is a serious global concern, and it is leading to high mortality in humans. In addition, over-the-counter drugs in the medical sector, rampant usage of insecticides and pesticides in agricultural sectors, adulteration and preservatives in food items, and use of toxic chemicals in various industrial processes are aggravating the health challenges. The non-judicial use of antibiotics by humans through self-medication and health practitioners in the veterinary sector and food industries has led to the emergence of antimicrobial resistance manifolds. Environmental antimicrobial resistance, a silent upcoming biggest global multisectoral challenge, remained unnoticed. Factors like social inequalities, gender differences, gene and environmental interactions, and the role of epigenetics are some important social factors that are not addressed properly and are the biggest gap in the Indian health system. To mitigate such risks in the present and future, extensive research is needed to find alternative means that may reduce or prevent the curtailment of life on the only habitable planet, Mother Earth.

*Correspondent author
Email: skayesth@db.du.ac.in

It has been well reported that essential oils (EOs) derived from many aromatic plants have potent antibiotic, antioxidant, and insecticidal properties[1]. For example, terpene and its derivatives are effective against bacteria like *Staphylococcus aureus*, *Salmonella typhimurium*, *Enterobacter aerogenes*, and *Escherichia coli*[2]. Similarly, the anticancer properties of *Catharanthus roseus* (vinblastine, and vincristine) against different types of cancers[3]; Taxol, from the bark of Pacific yew (*Taxus brevifolia*) against ovarian and breast cancers[4]; tomato and cruciferous vegetables (e.g., broccoli, cauliflower, cabbage, brussel sprout) against prostate cancer[5] have been well reported. Hence, the potential of natural products needs to be fully explored for the prevention and cure of various diseases and also to prevent the development of resistance in pathogens to achieve SDGs.

This paper reviews the research on natural products in human health and the technology that boosts drug development from natural products. Special emphasis is given to *Withania somnifera* (L.) Dunal (Solanaceae), known as Ashwagandha or Indian Ginseng, is a true health promoter that can narrow down various health challenges worldwide. It has been used in the Indian Ayurvedic system since ancient times. Recently, scientific research has validated its use as a health promoter along with therapeutic uses for all age groups.

Natural products and immune-related health challenges

The sporadic upsurges in inflammation are critical for survival during injuries and infections. However, certain social, environmental, and lifestyle factors can promote systemic chronic inflammation, which may lead to numerous diseases and health problems such as *Diabetes mellitus*, heart diseases, chronic kidney diseases, non-alcoholic fatty liver disease, cancer, and autoimmune and neurodegenerative disorders, worldwide[6].

Many anti-inflammatory compounds are extracted from medicinal plants, viz. *Acanthopanax senticosus* harms[7], *Actinidia arguta*[8], *Ainsliaea fragrans* Champ[9], *Ampelopsis grossedentata*[10], *Cassia occidentalis* roots[11], are used for obstructing major signalling pathways. The polyphenol metabolite of *Curcuma longa* has been reported to act as a reducer for inflammatory cytokines IL-6 and TGF-β[12].

The metabolites present in the natural products are potent immunomodulators and do not cause any side effects[13,14]. The polysaccharides of *Aloe vera* caused a reduction of proinflammatory cytokines[15] and increased levels of tumour necrosis factor-alpha (TNF-α) and immunoglobin G (IgG), which influences the immune system[16,17]. The *Allium sativum* and *Azadirachta indica* have been used as immunomodulators; *A. sativum* enhanced the activities of IFN-γ, IL-2, TNF-α, and interleukin 4 (IL-4) and improved the upregulating activity of natural killer (NK) cells and *A. indica* increased the phagocytic index and synthesis of nitric oxide[15,18]. These studies indicate that natural products have huge potential in managing immune-related disorders and thus can replace chemical-based therapeutic agents.

Recent advances in disease control

Newly emerging and re-emerging bacterial and viral diseases (Ebola, SARS, COVID-19) pose major threats to human health and cause considerable socioeconomic problems globally. These diseases are capable of human-to-human transmission and have the most significant pandemic potential. During such a pandemic, developing efficient antiviral drugs, vaccines, pharmaceuticals, and therapeutics is crucial. These outbreaks need speedy and applicable solutions specifically for limited-resource settings in the public health system for infection prevention, control, and management. In recent times, artificial intelligence, new computational methods, and other machine learning technologies are expected to make the hunt for new pharmaceuticals faster, inexpensive, and more effective[19]; for example, cheminformatics and bioinformatics can play a lead role in drug discovery[20].

The design and discovery of a new drug is a very extensive, overpriced, and challenging procedure that involves an average period of 10–15 years[21,22]. Over the past few decades, natural products have gained a major impetus for drug discovery. Natural products consist of an enormous number of bioactive compounds, and some of them can be easily extracted from fruits, vegetables, and other plant parts.

AYUSH and universal health coverage

AYUSH workforce, therapeutics, and principles can improve the present healthcare system. Therefore, AYUSH may play a significant role along with the allopathic system of medicine to achieve universal health coverage (UHC) in India[23]. At present, allopathic practitioners also feel that the acquaintance of the

allopathic system or medicine with AYUSH therapies will strengthen the healthcare system in India[24].

Many conventional herbal and plant medicines have antioxidant and anti-inflammatory properties and an anti-amyloid aggregation effect. These are found to improve acetylcholine esterase (AChE) levels or limit AChE within the brain, which helps treat Alzheimer's disease and other neurological disorders[25]. Homeopathic treatments have shown positive results in patients with A/H1N1 influenza (swine flu)[26]. Patients with a high-risk case of COVID-19 and SARS-CoV-2 have been treated with an integrated approach of Yoga and Ayurveda[27]. It has been reported that practising yoga is very helpful in curing psychosomatic diseases such as depression[28] and anxiety[29]. Furthermore, cancer[30,31], heart disease[32,33], diabetes[34,35], dyslipidemia[36], and dementia associated with diabetes[37] can be treated and managed with an integrative AYUSH system. Unani system of medicine has been reported to provide a management strategy for diseases like ulcers[38] and hypothyroidism[39].

Advances and challenges in natural product research

Bioactive compounds from the extracts of fruits, vegetables, spices, and medicinal plants contain antioxidant, antimicrobial, anti-inflammatory, cardioprotective and anti-cancerous activities[21]. Such phytoconstituents can overcome the limitations of chemotherapy and the multidrug resistance problem[19]. Apart from this, natural compounds act directly on their specific molecular targets or indirectly by stabilising conjugates that affect metabolic pathways[40]. Many herbal plants, plant preparations, and phytoconstituents have a long history in antiviral therapy and can be used in preventing viral infections, including COVID-19 transmission.

Dietary supplements or functional and superfoods are also useful in preventing and managing COVID-19 viral infection. In a recent study on glycyrrhizin, a key active of *licorice* root has been shown to inhibit the replicating of the SARS virus. Likewise, Chalcones from *Angelica keiskei* possess inhibitory activity against SARS-CoV proteases[41]. These herbs decrease the severity of disease symptoms, increase recovery rates and improve patients' psychological well-being. Still, the treatment of COVID-19 is a huge burden for public health care. Therefore, herbal products in clinical practice may be used for treatment.

Nanotechnology and natural product research

In recent times, the drug development industry has been using nanotechnology, which was used only in cosmetic industries. Nanoscience advancements can address the technical problems related to formulation and bring a revolution. Along with improvising the solubility factor and the stability of active components, nanoparticles also help in extending the combination of action and various degrees of hydrophilicity/lipophilicity with the formulation. Nanotechnology can also be implemented in the target-based delivery of substances in a particular organ or tissue.

Many nanotechnological approaches, including precursors systems for liquid crystals (PSLCs), liquid crystal (LC) systems, solid lipid nanoparticles (SLNs), polymeric nanoparticles, microemulsions, and liposomes have been successful in delivering the various substances having diverse properties used in the common formulation[42]. Nanotechnology also allows for the changing properties and behaviour of these substances in a biological atmosphere. Moreover, nanotechnology enhanced the effectiveness of active constituents and reintroduced many other constituents that had been abandoned in the earlier formulation[43]. It can enhance selectivity, efficiency, thermal and photo-degradation resistance, with minimal side effects, and coordinate the action and release of active components[44].

Omics in natural product research application

Herbal medicine research can employ omics (such as genomics, transcriptomics, proteomics, or metabolomics) as a research tool, for example, herbs gene/protein functions and herb/host interactions as functional genomics, transcriptomics, and proteomics. In addition, various tools and techniques of metabolomics, pharmacogenomics, and toxico-genomics can be used to understand the chemical processes, which involve medicinal herb metabolites, as well as differences in the host genome and herbs, and assessment of harmful effects of herbs[45]. Some complicated diseases and disorders, such as cancer, Alzheimer's disease, and Parkinson's disease, though better understood, do not have simple or single targets. Multi-compound drugs are necessary to treat these complex illnesses. Herbal medications are multi-compound pharmaceuticals which can be studied utilising a metabolomics technique for multi-compound screening. Most new herbal medications

are derived from the secondary metabolites of plant metabolism (alkaloids, terpenoids, and phenolic chemicals)[46]. Interdisciplinary herbal genomics research, in conjunction with large-scale sequencing technologies, metabolomics, and proteomics, is critical for the rapid discovery of metabolic pathways/enzymes. New herbal genomics research, such as the medicinal plant genomics collaboration, as well as advances in other omics data, may aid in the speedy discovery of unknown metabolic pathways/enzymes. Because of its high throughput, sensitivity, accuracy, specificity, and reproducibility, transcriptomics employing DNA microarray has become a useful and popular method for herbal medicine research. Proteomics techniques can be used to investigate the function, organisation, diversity, and dynamics of a cell or a whole tissue at the same time. Proteomics technology can be used to screen traditional medicine's target molecules, isolate, and characterise novel active components, as well as assess hazardous compounds.

Social science education and research in health: A prerequisite

There are numerous social factors that can affect human health, but social inequalities, gender differences, genes, environmental interactions, and the role of epigenetics are some of the most important. Health equity is an important challenge[47], and if it is taken care of, it can reduce the health challenge within a population[48]. Urban slums, data related to them, poverty, hygiene, and complex social dynamics are other challenges. The slums foster the emergence of new diseases and resistant organisms and challenge the eradication of old diseases in society[47,49]. The burden of malnutrition in India is another setback and persistent health challenge[50]. Similarly, mental health is emerging as a new challenge worldwide, and populations with lower socioeconomic status, and specifically among youth, are affected more[51]. There are 20 suicide attempts for every fatality worldwide, and suicide nevertheless results in more than one death per 100. It is a leading cause of death among the youth population[52].

Literature-based evidence shows that early childhood adversities can drastically influence brain structure and cognitive, academic, and behavioural performance[53]; hence, early childhood development should be considered strictly for a better outcome[48]. Necessary changes like the participation of people in activities related to health for empowerment[54], effective communication between patients and healthcare[55], community-based participatory research[56], and a systemic approach to health can predict better outcomes[57].

Indian Ginseng, *W. somnifera*: A therapeutic and health promoter

The leaves, stems, and fruits of *W. somnifera* have medicinal properties, but its roots are primarily used in traditional medicine. Ashwagandha is derived from the word "Ashwa", meaning horse, and "gandha", the typical smell of the horse[58]. Although native to India, this herb is also grown in other parts of the world[59].

Since olden times, it has been used as Ayurvedic medicine to strengthen the nervous system. Also, the roots of *W. somnifera* have been used as a tonic, an aphrodisiac, narcotic, diuretic, anthelmintic, and stimulant[60]. Globally, people are developing an interest in *W. somnifera* due to its potential health benefits, mainly in stress management, cognitive function, and physical performance. It is well reported that *W. somnifera* supplementation may show neuroprotective activity. For example, neuroplasticity, antioxidant, and anti-inflammatory properties of this herb have been recently reported[61,62]. Also, patients with other related neuropsychiatric diseases such as anxiety, depression, and insomnia benefit from using this plant species[63,64]. It is helpful in obsessive-compulsive disorder (OCD) and shows anti-inflammatory, immunomodulatory, and antibacterial properties[65]. In addition, it may also be helpful in conditions like infertility, sleep disorders, cancer, diabetes, cardiac problems, anxiety, hypothyroidism, muscle weakness, and stress[66–69] (Fig. 1). Some of major phytoconstituents of *W. somnifera* and their role in human health are presented in Table 1. Many of the phytocnstituents are derived from Withanolides

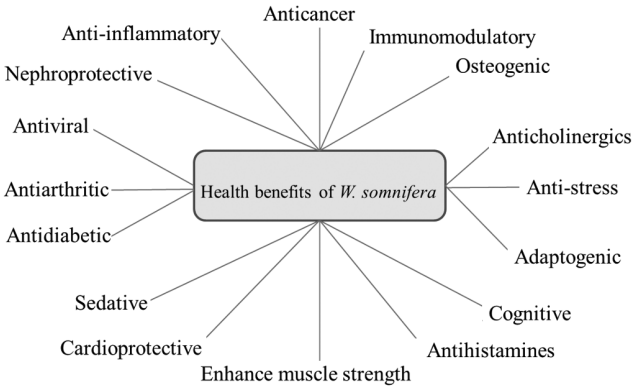

Fig. 1 — Health benefits of *W. somnifera*[65].

Table 1 — Chief Phytoconstituents of *W. somnifera* and their role in human health

Molecule	Activities	Reference
Withaferin A	Anticancer, Antidiabetic	70–72
Withanolides A-Y	Anti-inflammatory activity	70,73
Withasomniferin A	Nephroprotective effect	70,74
Withanone	Anti-inflammatory, Antiarthritic, Antiviral against SARS-CoV-2 Neuroprotection	70,75–77
Withasomniferols A-B	Immunomodulatory activity promotes osteogenic differentiation	70,78,79
Withasomniferols C	Anti-viral	70,80
Withasomidienone	Potent inhibitor of HIV-1gp120.	70,81
Withanine	Anticancer and antidiabetic.	82,83
Somniferine	Most potent anti-SARS-CoV-2 molecules with inhibitory activity against Mpro, PLpro and RdRp.	84
Tropine	Anticholinergics and Antihistamines	85
Choline	Choline is a source of methyl groups needed for many steps in metabolism.	86
Isopelletierine	Anthelminthic activity	87
Anaferin	Anti-inflammatory, anti-stress, immunomodulatory, adaptogenic, anticancer and neuroprotective activities	88,89

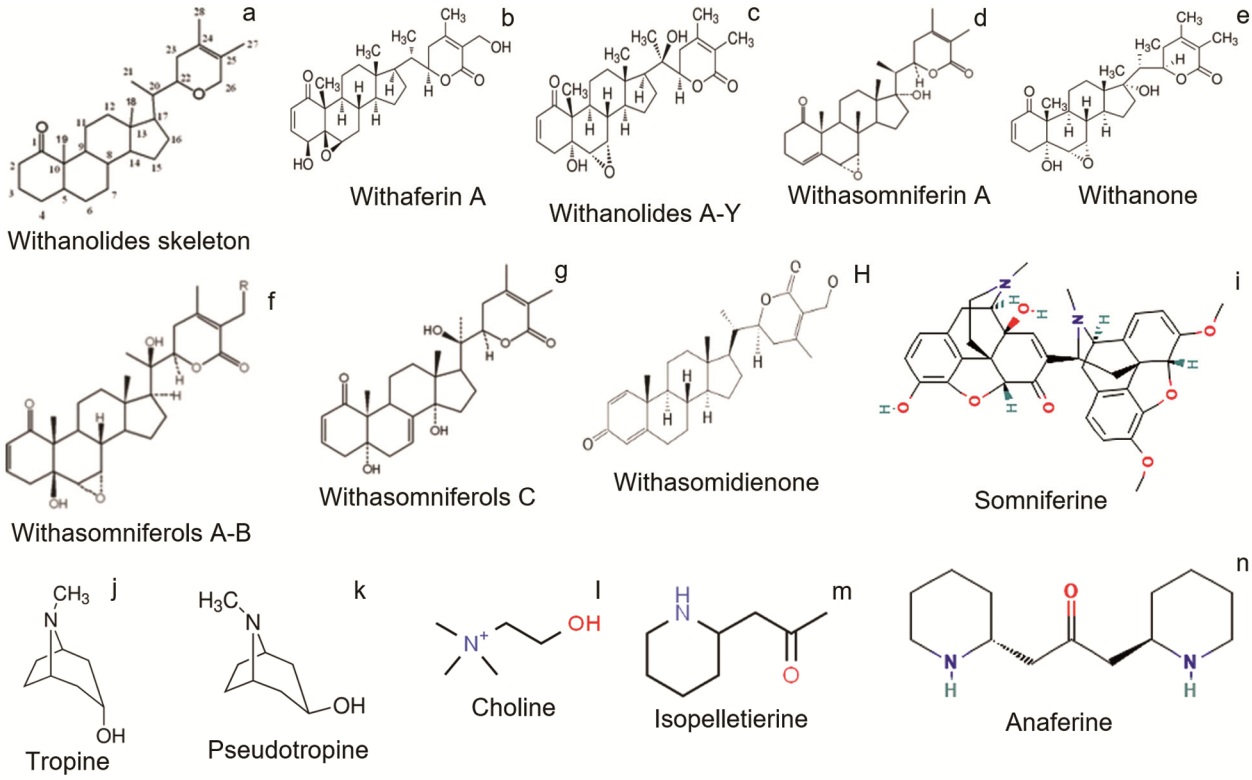

Fig. 2 — Major phytoconstiyuents of *W. somnifera*.

skeleton (Fig. 2a). These include Withaferin A (Fig. 2b), Withanolides A-Y (Fig. 2c), Withasomniferin A (Fig. 2d), Withanone (Fig. 2e), Withasomniferols A-B (Fig. 2f), Withasomniferols C (Fig. 2g), Withasomidienone (Fig. 2h), Somniferine (Fig. 2i), Tropine (Fig. 2j), Pseudotropin (Fig. 2k), Choline (Fig. 2l), Isopelletierine (Fig. 2m), and Anaferine (Fig. 2n)

Adaptogenic effect of *W. somnifera*

W. somnifera has shown adaptogenic effects[90]. A statistically significant decrease in cortisol, epinephrine, glucose, triglycerides, creatinine, IL-6, alanine aminotransferase, and aspartate aminotransferase was observed when a group of horses subjected to various stressors were given *W. somnifera* root extract. This indicates the adaptogenic, antioxidant, and immunostimulating effects. In a similar study, *W. somnifera* root and *Panax ginseng* showed adaptogenic effects when the rats were given extract prior to the chronic stressor. These herbal treatments could alleviate glucose intolerance, plasma corticosterone levels, hyperglycaemia,

gastric ulcers, cognitive deficits, sexual dysfunction, immunosuppression, and mental depression, which is a good indication of the adaptogenic effects of the extracts[90,91].

Antibacterial and antifungal properties of *W. somnifera*

W. somnifera showed a broad range of antimicrobial actions; it is safe, non-toxic, and has no reported side effects; therefore, it can be considered an alternative to antibiotics[92]. In a study, *W. somnifera* revealed growth inhibitory activities against methicillin-resistant *Staphylococcus aureus* and *Enterococcus* spp.[93]. *W. somnifera* root extract has also proved its growth inhibitory activities against the Gram-negative bacteria *Escherichia coli*, *Proteus mirabilis*, *Pseudomonas aeruginosa*, *Salmonella typhi, Citrobacter freundi*, and *Klebsiella pneumonia*[94–96]. The possible mechanism behind the antibacterial properties of *W. somnifera* lies in its immunomodulatory, cytotoxic, and gene-silencing activities[97]. *W. somnifera* was also effective against *Streptococcus mutant* and *Streptococcus sobrinus,* which causes dental caries[98]. Another animal study model found that *W. somnifera* could be used effectively to treat salmonellosis[99]. Along with the antibacterial properties, *W. somnifera* exhibits antifungal actions against *Candida albicans*[96]. The *W. Somnifera* glycoprotein extracted from its root showed antifungal properties against *Aspergillus flavus*, *Fusarium oxysporum, Fusarium verticilloides*, and antibacterial action against *Clavibacter michiganensis* subsp. *michiganensis*[100]. *W. somnifera* also showed antibacterial activity against *P. aeruginosa*[101]. The probable mechanism behind the antimicrobial action is damage to the cell membrane. In another study, the fatty acids in fluid extracted from fixed oil obtained from *W. somnifera* seeds showed antibacterial action against the Gram-negative *Salmonella enterica*[102].

Anti-inflammatory/Immunomodulatory effects of *W. somnifera*

Inflammatory-related diseases like pulmonary, cardiovascular, diabetes, autoimmune, cancer, and neurodegenerative diseases can be managed by *W. somnifera*[103,104]. In certain preclinical studies, *W. somnifera* could regulate mitochondrial function and apoptosis and reduce inflammation by inhibiting IL-6, TNF-α, nitric oxide, and reactive oxygen species[103]. In a mouse model with lupus, *W. somnifera* root powder inhibited proteinuria and nephritis[105]. In another study, *W. somnifera* showed its positive effect against rheumatoid diseases[106]. In the rat model, inflammation induced by injecting complete Freund's adjuvant was significantly reduced by *W. somnifera* due to changes in the concentrations of two glycoproteins, i.e., acute phase protein 1 and pre-albumin[107]. In another study, by using the HaCaT (human keratinocyte cellline), an aqueous solution from *W. somnifera* root could inhibit the NF-kB and MAPK (Mitogen-Activated Protein Kinase) pathways by declining the levels of cytokines, interleukin (IL)-8, IL-6, (TNF-α), IL-1, and IL-12, and enhancing the levels of the anti-inflammatory cytokines. These studies conclude that *W. sominfera* can be used in skin-related inflammation[108]. In a preclinical study of lipopolysaccharide-induced systemic neuroinflammation, the anti-neuroinflammatory effects of *W. sominfera* water extract were reported. The animals treated with *W. sominfera* ASH-WEX showed inhibition which appears due to inhibition of lipopolysaccharide (LPS)-activated NF-kB, P38, and JNK/SAPKMAPK pathways. These results indicate that *W. somnifera* can manage inflammation associated with neurological disorders as well[109]. *W. somnifera* extract was also reported in managing arthritis symptomsin patients[110].

Muscular strength enhancing property of *W. somnifera*

W. somnifera supplementation has been reported to significantly increase muscle strength, muscle mass, and muscle renewal processes by stabilising the plasma creatine kinase levels, increasing testosterone levels, and a significant decrease in body fat[111,112]. In a study, *W. somnifera* supplementation in athletes was reported to significantly improve cardiorespiratory endurance, increase maximal aerobic capacity, time to exhaustion, ventilatory threshold, and lower levels of serum cortisol, a hormone associated with stress[113]. In a similar type of study, a group of adult athletes was given a strictly defined dose of *W. somnifera*, and the control group received a placebo. The study concluded a significant increase in maximum aerobic capacity than the placebo group. The athletes treated with *W. somnifera* had significantly higher 'Total Quality Recovery Scores'. Along with these changes, a significant increase in antioxidant levels was observed in the treated group. Very interestingly, no side effects were noted during the entire study[114]. In another study, *W. somnifera* extracts and its Withaferin A (Fig. 2b) and Withanone (Fig. 2e) were tested on muscle cell differentiation using C2C12 myoblasts. The results demonstrated that *W.*

somnifera Withanone and Withanone-rich extracts cause a stronger differentiation of myoblasts to myotubes, deaggregation of heat and metal-stress-induced aggregated proteins, activation of hypoxia and autophagy pathways, hence, can be useful in muscle repair and strengthening activity[115].

Antidiabetic activity of *W. somnifera*

W. somnifera has shown its ability to lower blood glucose levels in an animal model[116–120]. In a study, it was confirmed that Withaferin A (Fig. 2b) could effectively control diabetes in rats through modulation of Nrf2/NF-kB signalling and, therefore, has significant potential for therapy[121]. The *in silico* studies have confirmed that Withaferin A obtained from *W. somnifera* can control diabetes successfully[122]. *W. somnifera* has shown a blood-glucose-lowering effect[123]. In another study performed on white albino rats having high levels of cholesterol, *W. somnifera* significantly lowered the levels of cholesterol along with its antioxidant effects[118,120,124]. In another clinical trial, this herb was reported to improve the lipidemic profile, body weight, and blood pressure[125,126]. Similarly, *W. somnifera* showed a significant reduction in elevated blood glucose levels, glycosylated haemoglobin, insulin, and glucose tolerance improved insulin sensitivity index in non-insulin-dependent diabetes mellitus (NIDDM) rats. These results suggest that the aqueous extract of *W. somnifera* can be used in the management of diabetes[127].

Anticancer properties of *W. somnifera*

W. somnifera root, stem, and leaves, exhibit anti-cancer properties and can be used to treat cancer[128]. The secondary metabolite Withanolides, alkaloids of *W. somnifera*, show great anti-cancer potential due to the induction of apoptosis. *W. somnifera* is quite effective against breast, lung, colon, prostate, and even blood cancers[129]. It acts as a chemotherapeutic agent against breast cancer, especially ER/PR-positive breast cancer and triple-negative breast cancer[130]. Along with therapeutic action in breast cancer, it helps in cancer prevention and improving the quality of life[130]. Withaferin A (Fig. 2b) derived from *W. somnifera* is also effective in melanoma. Withaferin A induces apoptosis reduces cell proliferation, and inhibits melanoma cell migration[131]. The antitumor mechanisms of Withaferin A in glioblastoma multiforme (GBM) investigated through RNA-seq analysis, Western blot, immunofluorescence staining, qRT-PCR, and siRNA gene silencing showed significant inhibition of GBM growth *in vitro* and *in vivo* that triggered intrinsic apoptosis of GBM cells. These changes arrested GBM cells in the G2/M phase of the cell cycle by dephosporylating Thr161 CDK1. These results indicate that Withaferin A can be used for the treatment or prevention of glioblastoma multiforme[132]. *W. somnifera* extract is also effective against the harmful effects of radiation. It reduces oxidative stress and inflammation in the liver and spleen tissues and can be used to protect these vital organs against radiotherapy-induced damage[133]. In another study, different parts of *W. somnifera* particularly the roots, and the most active components Withanolides and Withaferins in addition to Withanone (Fig. 2e) (WN) and Withanosides reported effective against different kinds of cancer cell lines[134]. Similarly, *in vitro* cytotoxicity of *W. somnifera* 50% ethanol extract of root, stem, and leaves was reported against five human cancer cell lines of four different tissues viz., PC-3, DU-145 (prostrate), HCT-15 (colon), A-549 (lung), and IMR-32 (neuroblastoma)[135].

Cardioprotective properties of *W. somnifera*

The effect of *W. somnifera* was studied in a group of albino rats in which myocardial necrosis was induced by isoprenaline treatment. A decrease in glutathione levels and a decrease in the activity of superoxide dismutase, catalase, creatinine phosphokinase, and lactate dehydrogenase were observed in the group of rats treated with *W. somnifera*. Lipid peroxidation levels also decreased significantly. These results indicate that *W. somnifera* has a cardioprotective effect in an experimental model of isoprenaline-induced necrosis rats[136]. Studies were also conducted on rats in which cardiac ischemia was induced. This caused significant myocardial necrosis, an oxidation–antioxidation imbalance, and an increase in lipoperoxidation. Histopathological studies have noted that the administration of *W. somnifera* significantly reduces damage to the heart caused by ischemia. *W. somnifera* has a cardioprotective effect due to its anti-apoptotic properties and due to its restoring of the oxidative balance[137]. The cardioprotective effect of Withaferin A (Fig. 2b) was also studied in rats model. It was found that low doses of Withaferin A elicit a cardioprotective effect by upregulating the

mitochondrial anti-apoptotic pathway due to an increase in AMP-activated protein kinase (AMPK) phosphorylation and an increase in the Bcl-2/Bax ratio (AMPK)[138]. This enzyme is involved in a number of processes responsible for maintaining energy homeostasis at both the cellular and whole-body levels. AMPK regulates glucose, protein and fat levels in the nervous system and peripheral tissues and responds to hormonal signals by modulating food intake and energy consumption. It is also known that AMPK is activated by caloric restriction and is involved in several processes correlated with ageing and diseases that often occur in older people. AMPK restores energy balance and is therefore thought to improve quality and length of life[139,140]. However, only low doses of Withaferin A (1 mg/kg) showed a cardioprotective effect, whereas the administration of higher doses (5 mg/kg) was not effective[138]. In another study, it was reported that ethanolic extract of *W. somnifera* caused the reduction in cholesterol, low-density lipoprotein, triacyle glycerol in isoproterenol-induced cardiac toxic rats. The antioxidants glutathione, glutathione peroxidase, and catalase were also reported to increase in the treated rats[141].

W. somnifera and neurological disorders

Alzheimer's disease

W. somnifera has been reported to neutralize the toxic effects of amyloids responsible for neurocognitive impairment during HIV infection[142]. In one study, Vitanon, extracted from *W. somnifera* significantly improved the cognitive function in rats due to the inhibition of amyloid-42, reduction in pro-inflammatory cytokines TNF-α, IL-1, IL-6, and Monocyte Chemoattractant Protein-1, nitric oxide, and lipid peroxidation, and secretase enzymes responsible for the formation of insoluble neurotoxic aggregates of amyloid[77]. Withaferin A (Fig. 2b) extracted from *W. somnifera* showed similar responses as it reduced the amyloid aggregation and inhibited oxidative and pro-inflammatory chemicals, regulated heatshock proteins[143], and inhibited the gene expression of neuroinflammatory molecules related to NF-kB[144]. In one more study on transgenic mice, which were given a half-purified extract of *W. somnifera* root containing withanolides, counterbalanced the negative effects of Alzheimer's disease by increasing the number of the LDL receptor-related protein LRP1 (low-density lipoprotein-related protein 1) in the liver[145]. The increasing LRP1 levels reduced amyloid and reversed the behavioural deficits in Alzheimer's disease[146].

According to various studies, the LRP1 functionally controls the steps required to form the amyloid precursor protein APP, which is critical for amyloid production and APP processing[147], and it is a key regulator of protein proliferation[148]. *W. somnifera* derivatives Withanolide A, Withanolide B, Witanoside IV and Witanoside V interact with the hydrophobic core of amyloid 1–42 in the form of an oligomer which prevents further interaction with monomers and decreases aggregation[149,150]. In another study, the adult mice administered with Vitanolide A intranasally significantly reduced the cerebral infarction, improved the blood-brain barrier function, and showed reduction in cerebral oedema[151]. A study conducted on human embryonal neuroblastoma SK-N-SH cells showed antioxidant properties of *W. somnifera* extract. It also modulated cholinergic transmission, potentially inhibiting acetylcholinesterase activity[152].

Parkinson's Disease

In a study, prior to an injection of 6-hydroxydopamine into the striatum in the rats to induce Parkinson's disease, oral administration of a *W. somnifera* extract at doses of 100, 200, and 300 mg/kg body weight for 3 weeks significantly reduced lipoperoxidation, increased glutathione concentration, increased glutathione S-transferase, glutathione reductase, glutathione peroxidase, superoxide dismutase and catalase activities, catecholamines, and dopamine D2 receptor binding and enhanced tyrosine hydroxylase expression in dose-dependent manner[153–155]. *W. somnifera* extract not only improved biochemical parameters but also reduced motor impairment compared to the control. In the fruit flies' model, administration of a standardized methanol extract of *W. somnifera* root also counteracts deficits associated with Parkinson's disease[156].

Huntington's Disease

The administration of *W. somnifera* extract had a significant effect on biochemical parameters and motor function due to its antioxidant properties in an artificially induced Huntington's Disease by applying 3-NP intraperitoneally in an animal model. The treated animal reported a dose-dependent decrease in lipo-peroxidation, a decrease in the levels of lactate and nitrate dehydrogenase, an increase in the levels of superoxide dismutase and catalase, an unblocking of

the mitochondrial complex, and thus a restoration of ATP synthesis[157]. In another study in mice, Withaferin A (Fig. 2b), isolated from *W. somnifera*, demonstrated amelioration of the impaired proteostasis by activating the heat shock response and delaying disease progression. The mouse model with Huntington's disease treated with Withaferin A lived significantly longer and restored behavioural and motor deficits. Biochemical studies confirmed the activation of heat shock, the reduction of mutant huntingtin aggregates, and the improvement of striatal function in the brain. In addition, Withaferin A significantly reduced inflammatory processes, as noted by reduced microglia activity[158,159].

W. somnifera for the treatment of obsessive-compulsive disorder and alcohol withdrawal syndrome

W. somnifera root extract may be a helpful adjunct to selective seratonin reuptake inhibitors in the treatment of patients with obsessive-compulsive disorder[160]. A study demonstrated the administration of methanolic and aqueous extract of *W. somnifera* at 10, 25, 50, and 100 mg/kg doses significantly improved behavioural deficits in the mice without affecting motor activity. The obtained results were concordant with the standard treatment[161]. In another study, the oral administration of *W. somnifera* alleviated withdrawal anxiety and also improved locomotor activities in rats[162,163].

COVID-19 and *W. somnifera*

W. somnifera shows antiviral properties[164,165]. In an *in vitro* and in silico study, the antiviral property of *W. somnifera* against the hepatitis C virus was also reported[166]. *W. somnifera* extract's immune homeostatic inflammation regulatory, pro-inflammatory cytokines inhibitor, organ protective, stress preventing, anti-hypertensive, and anti-diabetic properties can be deployed against COVID-19 infections. *W. somnifera* Witanoside V and Somniferin, may potentially inhibit the major SARS-CoV-2M protease[167]. Similarly, Witanolides and Withanones (Fig. 2e) of *W. somnifera* can also have similar action against COVID-19[168,169].

Safety of *W. somnifera* uses

Herbal supplements are growing tremendously on a large scale; hence, the monitoring of their safety is very important. The first case of *W. somnifera* toxic effect on liver was reported in Japan in 2004, and the patient recovered from it after withdrawal with symptomatic treatment in just a couple of weeks[170]. Another case of hepatotoxicity was a 39-year-old woman, who was diagnosed with jaundice and nausea after consuming *W. somnifera* root extract over-the-counter[171]. Severe liver toxicity was observed in a 41-year-old woman when she consumed *W. somnifera* extract with progesterone[172]. Although these reports claim the hepatotoxicity of *W. somnifera,* these are not sufficiently indecisive for the toxicity claims of *W. somnifera.* On the contrary, there are scientific reports which claim no toxicity at all. In a study, 80 fully healthy individuals were subjected to the . *somnifera* toxicity test, and these individuals were monitored for all-desirable parameters. The test results were very satisfactory, and no toxicity was reported[173]. Another study on a group of eighteen volunteers confirms no significant changes in levels of health parameters. On the contrary, there was an increase in serum creatinine and a decrease in blood urea nitrogen levels, indicating an increase in muscle mass during the study[174]. Despite its many benefits, it is advised not to take *W. somnifera* during breastfeeding and pregnancy. In a study, the highest dose of 2000 mg/kg/day was administered to a pregnant female rat, and no toxic effects and no changes were observed in the body weight of the pregnant females, the number of corpus luteum, or embryo implantation. Furthermore, no external, skeletal, or visceral deformities of the foetuses were detected[175].

Contraindications

W. somnifera preparations are not recommended for all patients without controlling the other therapies they are receiving. Patients with hyperthyroidism should avoid *W. somnifera*. Although preparations containing *W. somnifera* root have proven efficacy in relieving the symptoms of hyperthyroidism, their use in these patients is contraindicated, as they may exacerbate the effects of the disease due to increases in the concentration of 3,3',5-triiodothyronine (T3) and tetraiodothyronine (T4)[176]. *W. somnifera* has been used in the treatment of male infertility; however, men with hormone-sensitive prostate cancer should avoid it due to an increase in testosterone production in the treated group, which may aggravate the problems[59]. The higher doses of *W. somnifera* root extract may also lead to miscarriage[177]. People who have been prescribed benzodiazepine and barbiturate group of drugs should avoid *W. somnifera* root

extracts due to their action on dopaminergic neurons[178]. *W. somnifera* root may interact with preparations for the anti-anxiety, sleep, myorelaxant, and sedatives and may exacerbate their effects due to synergism. *W. somnifera* should not be taken with anticonvulsants, barbiturates, and benzodiazepines due to its additive effects, as it shows impaired motor coordination, muscle weakness, headache, decreased libido, muscle tremors, and drowsiness[179]. Based on the above discussion and reports, it can be concluded that *W. somnifera* is a safe plant for both short-term and long-term use.

Conclusion and future prospects

Natural products, especially plant products, have many secondary metabolites used for health purposes in traditional medicine systems. In India, a rich legacy of the Ayurvedic system or other traditional systems has been in practice since ancient times. For sustainable development and a better healthcare system, more research should be promoted to understand the role of natural products or plants' secondary metabolites in the health, agriculture, environment, and food sectors. *W. somnifera* was used 3000 years ago in Ayurvedic medicine, and the research has proven its credibility in health science due to its multiple benefits for different body systems. Although much more is known about *W. somnifera*, more studies are needed to confirm its potential therapeutic uses and determine the optimal doses and durations of use.

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Conflict of interest

The author/s declares no conflicts of interest regarding the publication of this paper.

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