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Ethnobotanical importance, phytochemical constituents, and pharmacological properties of *Withania somnifera*

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ABSTRACT

Withania somnifera belongs to the family of Solanaceae. It is widely used by the locals, especially in India, as a medicinal plant. *W. somnifera* is rich in alkaloid and steroidal lactone that account for various pharmacological activities. The present study aimed to review all the evidence on the ethnobotanical perspective of *W. somnifera* in some countries. This review also analyses the bioactive compounds that account for the pharmacological activities. The online medical literature databases such as ScienceDirect, PubMed, and Google Scholar were used to search articles up to March 2022. *W. somnifera* is widely used in Asian and African countries like India and South Africa, Pakistan, Egypt, Jordan, and Lesotho. In India, *W. somnifera* is prepared by boiling and crushing the leaves and roots to make a tonic poultice, juice, and paste to treat bacterial infections and bruises. Numerous *in vivo* and *in vitro* studies have demonstrated that *W. somnifera* exerts pharmacological effects such as anti-Parkinson's, anti-Alzheimer's, cardioprotective, antidiabetic, antiarthritic, and antibacterial properties. Withaferin A and withanolide are the major bioactive compounds contributing to the pharmacological effects. *W. somnifera* is a valuable plant that has been used in traditional medicine systems for a long time and is supported by its wide range of pharmacological activities. The extensive medicinal uses of *W. somnifera* are a sign of its great potential.

Implication for health policy/practice/research/medical education:
This contribution is to construct a literature review that discusses the importance of *W. somnifera* to various ethnics in different countries and continents. This article also reports the latest discovery of the phytochemicals and pharmacological properties of the plant, which may be taken into consideration in future clinical studies and therapies involving this plant.

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Introduction

Withania somnifera, known as ashwagandha in India, is a medicinal plant used for almost three centuries (1). Ashwagandha belongs to the Solanaceae family (2). The plant is 150 cm high with ovate and smooth leaves. The flower is 1 cm long, with greenish to bright yellow. The fruits are 6 mm long with red-orange colour when mature. The seeds are yellow with a 2.5 mm diameter. The cylindrical roots are 10 to 17.5 cm long and 6 to 12 mm in diameter. The roots possess a bitter and strong smell (3). In India, this popular herbal medicine is known as "Indian winter cherry" and "Indian ginseng" (4). It is named ashwagandha due to its roots' odour, which smells like a horse (ashwa), and is assumed to give power like a horse. In Latin, *somnifera* means "sleep-inducer," which indicates its sedating properties (5). *W. somnifera* are widely distributed in the drier region, usually in India, Sri Lanka, and North Africa (6). The plant extract contains many bioactive compounds contributing to its pharmacological activities. The main constituents of *W. somnifera* are alkaloid and steroidal lactone. The roots of *W. somnifera* are mostly accounted for its pharmacological effects. The main bioactive compounds in the root of *W. somnifera* are withanolides, which are steroidal lactones. They are believed to contribute to its medicinal uses, including antioxidant activity, anti-Alzheimer's, and antimicrobial properties.

The roots of *W. somnifera* contribute to most of its medicinal applications. However, other parts may also treat diseases based on the chemical constituents in each

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specific plant part. The ethnobotanical knowledge of *W. somnifera* is at the risk of disappearing as people only focus on conventional modern medicines such as drugs and surgery procedures. Thus, this review is conducted to present the ethnobotanical properties of *W. somnifera* based on the bioactive constituents contributing to its clinical applications. This study aimed to review the ethnobotanical perspective of *W. somnifera* and its relationship with pharmacological activities based on bioactive compounds.

Methods

This study reviewed reports from literature published from 2010 to March 2022. This narrative review article was based on the searches of Science Direct, PubMed, and Google Scholar databases using the term of plant name (*W. somnifera* OR ashwagandha), combined with the terms, bioactive compound, pharmacological activity, or ethnobotany. Findings from the reports were included in this review only if they reported the outcomes, such as pharmacological effects, bioactive compounds, and the ethnobotanical perspective of *W. somnifera*. The exclusion criteria included the studies unrelated to the research questions and review articles. Non-primary research articles were also excluded from this study. For the pharmacological studies, the research articles used were from the primary resources. This article includes the experimental studies, *in vivo* and *in vitro* studies relevant to the objective of the present review.

Ethnobotanical importance of *W. somnifera*

The study of ethnobotany includes the indigenous awareness of plants used as a shelter, medicine, and food (7). The ethnobotanical knowledge has contributed to drug discovery and development. Up to 25% of current pharmaceutical drugs are interrelated to the naturally occurring compounds in plants (8).

Withania somnifera (Figure 1) is classified as one of the important plants used to treat various ailments. The plant has been widely used traditionally in the Indian continent and African countries.

In Palamalai, one of the remarkable hills in Tamil Nadu, India, the root of *W. somnifera* is prepared in powder form before being taken orally. The local people use this plant to stimulate sexual ability in men (9). In the Javadhu hills of Tamil Nadu, local people consume the juice of *W. somnifera* leaves to treat diabetes (10). In the Pachamalai hills of Tamil Nadu, the rhizomes of *W. somnifera* are used for the treatment of neurasthenia and to enhance body strength. The preparation is usually taken orally (11). In Udumalpet Block, Tiruppur District, Tamil Nadu, all parts of the plant are used for the treatment of various ailments. The roots are pounded into powder and cooked with rice. The preparation is taken orally to increase lactation after delivery and treat rheumatism. The leaves juice is mixed with palm jaggery and calcium carbonate to treat throat

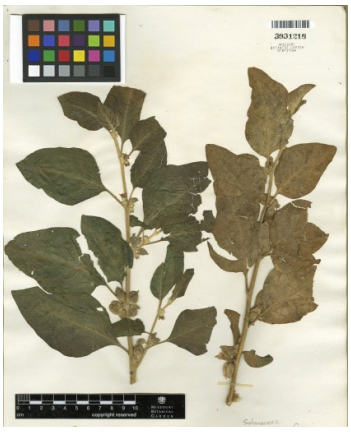

Figure 1. Voucher specimen of W. somnifera. (Retrieve from: https://ntbg.org/database/herbarium/detail/PTBG1000070076).

infection. The preparation is applied to the throat. Fruits are ground with milk and given orally to children to help with indigestion. Ripe fruits are cooked as a vegetable (12).

Withania somnifera is one of the most preferred plant species used by the people in the Taungya community in Terai Arc Landscape, India. They prepare poultices from the leaves to treat the swelling bodies. The plant is prepared as juice and consumed as a tonic to improve the health. In another preparation, root pastes of *W. somnifera* are mixed with powder of the whole plant of *Argyreia speciosa* to cure leucorrhoea (13). In Paschim Medinipur district, West Bengal, India, *W. somnifera* is used as antivenom. The root decoction is administered to the snakebite victim to prevent snake venom from binding to tissues and causing severe conditions (14). The indigenous community in the Shimago district of Karnataka, India, consumes *W. somnifera* to treat asthma. The root decoction is taken orally with garlic or cow's milk, two to four times daily (15). An experimental study showed that *W. somnifera* had a vasorelaxant capacity as it increased nitric oxide generation (16).

People in Ethiopia, East Africa, consume the roots of *W. somnifera* orally to prevent typhoid. In addition, the fumigation of dried plant leaves in the house of a sick person reduces the risk of infectious disease transmission to others (17). In Berbere District in Southeast Ethiopia, the local people use the roots of *W. somnifera* to treat the evil eye. They consume the decocted roots orally, and the residue is used as a dry bath (18). In the Shinile district of Ethiopia, the people use the roots of *W. somnifera* to treat malaria. The dried roots are ground and boiled before being taken with goat or camel milk (19). The presence of withanolides A-Y may be attributed to its antimalarial activity (20). Further phytochemical tests are necessary to identify the specific type of withanolide compounds for the best antimalarial effects. In another preparation, the leaves are pounded and boiled before being taken with goat milk orally. Milk decoction is the common traditional way of the *W. somnifera* preparation. The preparation is

prepared by mixing *W. somnifera*, milk, and water with a ratio of 1:8:32 in an earthenware pot. The milk increases the nutrition effects of *W. somnifera* (21). The local people in Omo River Valley, Ethiopia, used *W. somnifera* leaves to treat diarrhea and stomachache. The root infusion is being taken orally to treat these diseases (22).

In Eastern Cape, South Africa, the locals use *W. somnifera* for the treatment of wounds. The leaves of *W. somnifera* are prepared into poultice before being applied to the open cuts, abscesses, and wounds (23). In Nkonkobe Municipality, Eastern Cape, South Africa, the fruits of *W. somnifera* are used in food preparations as flavouring and preservative agents (24). In Capricorn, Sekhukhune, and Waterberg districts, the roots of *W. somnifera* are used to treat chronic cough. The dried roots are pounded and taken orally three times daily (25). People who live in the mountain regions of Southern Africa have a higher prevalence of cold. They consume the decoction of *W. somnifera* to treat the disease (26). In Kannaland, local people treat wounds and sores by applying *W. somnifera* directly to the affected area. The infusion of the plant's roots has been used to treat fatigue due to its tonic effects. They also consume the leaves infusion for stomach disease (27). The local people of Western Cape of South Africa use the *W. somnifera* leaves as soap due to the saponin content in the leaves (28). In KwaZulu-Natal, South Africa, the local people use *W. somnifera* as an antimicrobial agent to treat head sores. The plant preparation is consumed as a tonic. In paediatric care, plant infusion is used for baby baths (29). In Venda, South Africa, the indigenous people use *W. somnifera* for candida infections. The leaves are boiled with a few leaves of *Ensete ventricosum* and the decoction is consumed orally three times daily (30). In Lesotho, indigenous people in the Maseru district consume the roots and leaves of *W. somnifera* for the treatment of tuberculosis (TB), internal tumours, skin sores, and breast cancer (31). In Djobouti, the indigenous people in the region of Randa use *W. somnifera* for the treatment of bronchitis. The crushed roots are soaked in water, and then the water is taken orally (32).

In Pakistan, the locals mix the crushed *W. somnifera* leaves with wheat flour and wrap on swelling joints. The leaves are heated on fire before being wrapped around the painful body part to alleviate the pain (33). In Malakand Pass Hills, Khyber Pakhtunkhwa, Pakistan, the indigenous people consume *W. somnifera* seed for aphrodisiac, a sexual instinct simulant. They also consume the seeds for wound treatment and temperature maintenance (34). A study of traditionally used plants for musculoskeletal disorders in Northern Pakistan found that *W. somnifera* has been used for the treatment of joint pain. The roots and leaves are prepared in powder and paste, respectively. The roots are ground to make powder before being taken in small quantities to treat joint pain and swelling (35). In Yemen, the locals use the leaves of *W. somnifera* to treat ear infections and ear pain. The leaves are squeezed, and the juice is used as ear drops. The paste from the pressed leaves is used to smear on the area of the skin tumour, to treat boils, bruises, and fungal skin infections. The leaves are crushed and mixed with *Fagonia indica* and *Senna italica* leaves as a paste before being applied topically on the affected area (36). In Egypt, the indigenous people in the Sinai Peninsula apply the seeds of *W. somnifera* as an analgesic to treat painful areas such as inflamed skin, boils, and scabies (37). People in Shobak, Jordan, consume the decoction of *W. somnifera* leaves and stem for the treatment of smallpox and cancer (38). In Kerman province, Iran, *W. somnifera* has been used traditionally as a nerve tonic. The decoction of aerial parts, including stems, leaves, flowers, and fruits, are consumed orally by the indigenous people (39) (Table 1).

Phytochemical constituents of *W. somnifera*

The pharmacological effects of *W. somnifera* are contributed to its bioactive compounds. The main bioactive compounds found in *W. somnifera* are alkaloids and steroidal lactones. An HPLC analysis showed the presence of withanolides, including withanolide A **[1]**, 12- deoxywithastamonolide **[2],** and withaferin A **[3]** in the roots of *W. somnifera*. In this study, withanolide A had a higher concentration compared to 12-deoxywithastramonolide (40). Another study on *W. somnifera* found five more compounds, withanone **[4]**, withastramonolide **[5]**, 27-hydroxywithanone **[6]**, including two withanolide glycosides, withanoside **[7]** and physagulin D **[8]**, besides three known withanolides. In this study, withanone and withaferin A were the highest compositions (41). Other than withanolides and alkaloids, saponin **[9]**, coumarins **[10]**, flavonoid **[11]**, terpenoids **[13],** and a phenolic compound, ellagitannin **[12]** is also present (42).

The methanolic extract of *W. somnifera* was separated using thin layer chromatography, yielded two withanolides, 5-dihydroxywithanolide-R **[14]** and withasomniferin-A **15].** The plant roots contain withanolide glycoside, withanoside I **[16]**, withanoside II **[17]**, withanoside III **[18]**, withanoside IV **[19]**, withanoside V **[20]**, withanoside VI **[21]**, and withanoside VII **[22]**. Withanoside IV showed the highest concentration in the roots of *W. somnifera* compared to others (43). In another study, withanolides and withanolide glycosides, including withaferin A, 12-deoxywithastramonolide, withanoside IV, withanoside V, withanolide A, and withanolide B **[23]** co-existed in an extract (44) (Figures 2-4).

Pharmacological properties of *W. somnifera*

Neuroprotective activity

A study on the effects of *W. somnifera* extract on cognitive function of the human subject showed to have anti-Alzheimer's activity. Healthy human subjects who received two 250 mg capsules twice daily of an encapsulated dried aqueous extract of the roots and leaves of *W. somnifera*,

Table 1. The Summary of Ethnomedicinal Uses of *W. somnifera*

Region	Disease	Plant part	Preparation/administration	References
India	Sexual performance	Roots	The roots are pounded into powder and taken orally	(10)
	Diabetes	Leaves	The leaves are ground and prepared as juice to be drank	(10)
	Neurasthenia	Rhizome		(11)
	Lactation	Roots	The root powder is cooked with rice	(12)
	Rheumatism	Roots	The root powder is cooked with rice	(12)
	Throat infection	Leaves	Leaves juice is mixed with palm jaggery and calcium carbonate and applied externally to the throat	(12)
	Indigestion	Fruitss	Fruits are ground with milk and administered orally	(12)
	Swollen body	Leaves	The plant is prepared as juice to be consumed as a tonic	(13)
	Leucorrhoea	Roots	The root paste is mixed with powder of the whole plant of *Argyreia speciosa* and taken orally	(13)
	Antivenom	Roots	The decoction is administered orally to the snakebite victim	(14)
	Asthma	Roots	The decoction is consumed orally with garlic or cow's milk	(15)
Ethiopia	Typhoid	Roots	The fumigation of dried leaves of *W. somnifera* in the house of sick person to reduce the risk of infection	(17)
	Evil eye	Roots	Decocted roots are consumed orally, and the residue is used as a dry bath	(18)
	Malaria	Roots	The dried roots are ground and boiled before being taken with goat or camel milk	(19)
	Diarrhoea and stomachache.	Roots	The root infusion is taken orally	(22)
South Africa	Wounds	Leaves	The poultice is applied to the open cuts	(23)
	Chronic cough	Roots	The dried roots are pounded and taken orally three times daily	(25,26)
	Wounds and sores		Applying directly to the affected area.	(27)
	Fatigue	Roots	The infusion of the plant is consumed as a tonic.	(27)
	Stomach disease	Leaves	The infusion is taken orally	(27)
	Head sores		Is used as a tonic	(29)
	Paediatric care		The plant is crushed in water and used as a baby bath	(29)
	Musculo-skeletal pain		Is used as a tonic	(29)
	General health		Is used as a tonic	
	Candida infections	Leaves	The leaves are boiled with a few leaves of *Ensete ventricosum* before the decoction is consumed orally	(30)
Lesotho	Tuberculosis, internal tumours, skin sores, breast cancer	Roots and leaves		(31)
Djobouti	Bronchitis	Roots	The roots are crushed are soaked in water and taken orally	(32)
Pakistan	Swelling joints	Leaves	The leaves are heated on fire, crushed with wheat flour, and wrapped around the painful body part to alleviate the pain	(33)
	Aphrodisiac	Seeds	Is consume orally	
	Wound	Seeds		(34)
	Joint pain	Roots and leaves	The roots are ground to powder and being taken in small quantities to treat joint pain and swelling. The leaves are prepared into paste and applied to the affected body part	(35)
Yemen	Ear infections and ear pain	Leaves	The leaves are squeezed, and the juice is used as ear drops	(36)
	Skin infections	Leaves	The leaves are crushed and mixed with *Fagonia indica* and *Senna italica* leaves to form a paste, and is applied topically to the affected area	(36)
Egypt	Analgesic and inflammation	Seeds		(37)
Jordan	Smallpox, cancer	Leaves and stem		(38)
Iran	Nerve disease	Aerial parts	The decoction is consumed orally as tonic	(39)

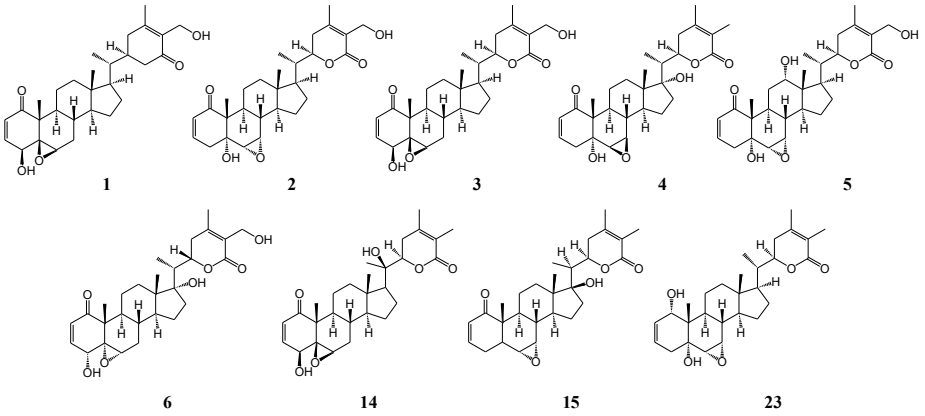

Figure 2. Chemical structures of withanolide compounds of *W. somnifera.*

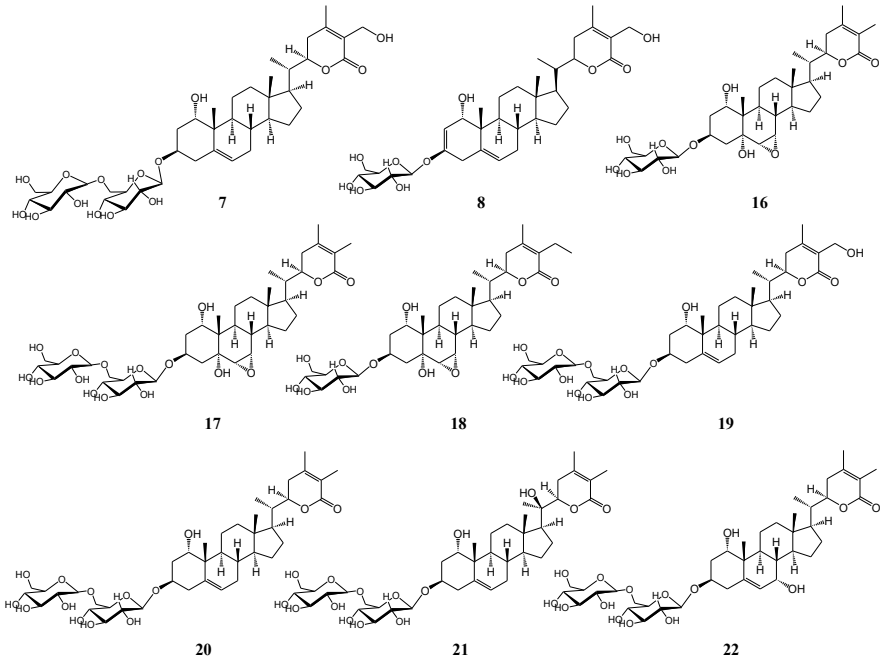

Figure 3. Chemical structures of withanolide glycosides of *W. somnifera.*

showed to have an improvement in cognitive and psychomotor performance (45).

In a study involving the accumulation of β-amyloid peptides (Aβ) in transgenic mice, root extraction of *W. somnifera* corrected the behavioural deficit by activating the lipoprotein receptor-related protein in the liver (46). Withanamide A **[24]** and withanamide C **[25]** in *W. somnifera* bond to β-amyloid protein (BAP) and prevented the BAP formation (47), thus protecting the cell from Aβ toxicity. Another experimental study showed that the presence of withaferin A **[3]** was attributed to the amelioration of Alzheimer's disease (48). Withaferin A **[3]** may inhibit the β-amyloid aggregation, thus alleviating the symptoms of the patients with Alzheimer's disease (Figure 5).

In a study that examined the effects of a proprietary *W. somnifera* root and leaf extract supplement, cognitive abilities, cortisol levels, and self-reported mood, stress, food cravings, and anxiety levels were tested in healthy adults. The study demonstrated that daily administration of *W. somnifera* supplement resulted in improvements in the physiological, cognitive, and psychological stress response over a 30-day period (49).

A study demonstrated the neuroprotective effects of *W. somnifera* on 6- hydroxydopamine induced Parkinsonism in Wistar rats. The rats were pre-treated with 100, 200, and 300 mg/kg of the *W. somnifera* extract orally for 3 weeks. An increase in striatal dopamine content and other metabolites was attributed to the anti-oxidation activity of alkaloid and steroidal lactone contained in *W.*

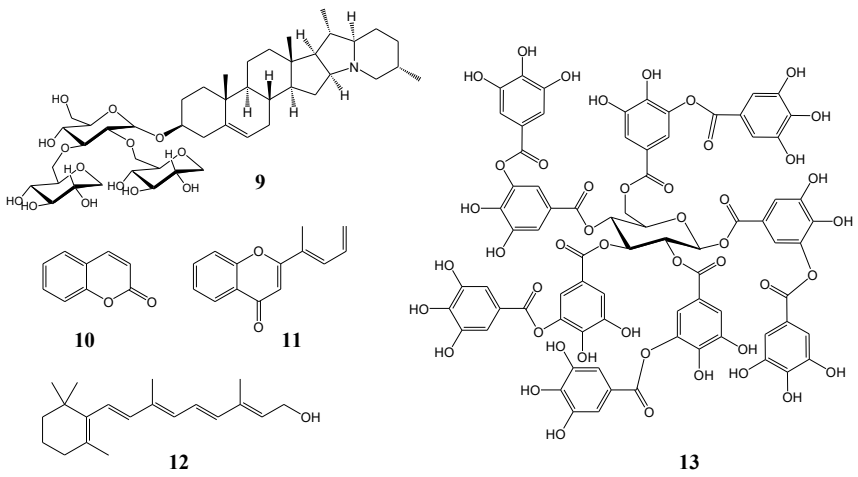

Figure 4. Chemical structures of non-withanolide compounds of *W. somnifera*.

somnifera. The increased dopamine content improves the rat's locomotor activity and muscle coordination and highlights its anti-Parkinson effects (50).

In a randomized open-label clinical study, *W. somnifera* root powder was administered orally to elderly male patients along with *Brimhana nasya* nasal drop, a classic ayurvedic treatment for amnesia. *W. somnifera* root powder reported significant benefits in all components of Pittsburgh Sleep Quality Index (PSQI). None of the adverse effects of drug and therapy was noted during this study. The result of this study suggests the use of this combined therapy in primary insomnia in the elderly, which is cost-effective and can be adopted as therapeutic remedy as well as preventive measures for geriatric insomnia (51).

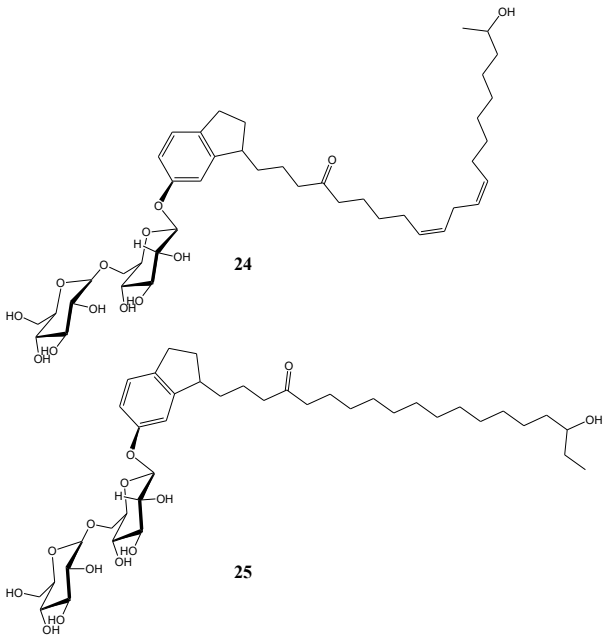

Figure 5. Chemical structure of withanamide A and withanamide C.

Cardioprotective effect

Withania somnifera has been shown to possess cardioprotective properties in the animals. The ability of rats to adapt with physical ability indicates the cardioprotective activity of *W. somnifera*. An increase in glycogen content of the heart shows the animals adapted to physical work and hypoxia (52). A standardized extraction of *W. somnifera* showed protective effects against doxorubicin-induced cardiac toxicity by its antioxidant activity (53). Another experimental study was conducted on *Escherichia coli*-infected broilers (54). *E. coli* infections caused cardiac injury with a subsequent increase in serum lactate dehydrogenase (LDH) activity. Administration of aqueous *W. somnifera* root extract restored the LDH activity. Another study conducted on neonatal cardiomyocytes of rats revealed that the presence of withaferin A **(3)** might protect cardiac ischemic reperfusion injury (55). Withaferin A **(3)** may inhibit the cell apoptosis induced by hydrogen peroxide (H2O2) with a subsequent increase in various antioxidant molecules such as SOD2, SOD3, and Prdx-1.

Antidiabetic

Both leaves and roots of *W. somnifera* exhibited antidiabetic activity by increasing the glucose uptake in myotube and adipocyte. The leaves extract was more active in increasing the glucose uptake as compared to the roots. Moreover, the leaves extract increased the secretion of insulin in the basal pancreatic beta cell. The compound responsible for the antidiabetic activity *W. somnifera* was withaferin A **(3),** as it showed the highest glucose uptake in myotubes (56). Furthermore, in alloxan-induced diabetes rats, both leaves and roots extraction of *W. somnifera* played a role in reducing blood glucose levels through their antioxidation activities. Administration of these extractions showed a significant decrease in the size of pancreas injuries through the regeneration of beta-cells. This may lead to

an increase in insulin production and secretion (57).

Antiarthritic

Withania somnifera showed a role as an antiarthritic agent by effectively inhibiting *Clostridium histolyticum* collagenase activity (58). Moreover, the root extract of *W. somnifera* demonstrated a protective effect against collagenolytic degradation of collagen. Thus, the *W. somnifera* extract can aid in protection against arthritis and other diseases that involve the activity of collagenase. Additionally, the root extraction of *W. somnifera* showed a sustained decrease in nitric oxide levels secreted by knee cartilage from osteoarthritis patients (59). *W. somnifera* acts as antiarthritic and anti-inflammatory remedy. An experimental study showed that the anti-inflammatory effects were attributed to the nitric oxide scavenging activity of *W. somnifera* (60). Another study revealed that withaferin A and withanolide D were the essential compounds for inhibiting pro-inflammatory mediators such as TNF-α, IL-1β, and proteases (61). Both compounds inhibited Ikappa B phosphorylation with subsequent suppression of the inflammatory response. This effect will further alleviate the symptoms of arthritic patients as it reduces inflammation and stiffness.

Antibacterial activity

The antibacterial activity of *W. somnifera* is due to the presence of withanolide A. The leaves extract of *W. somnifera* has a strong zone inhibitory activity against gram-positive bacteria from the pus sample of methicillin-resistant *Staphylococcus aureus* and *Enterococcus* spp. with the size of zone inhibition of 20.6 and 19.8 mm, respectively (63). The roots, flowers, and leaves extract of *W. somnifera* showed antimicrobial activity against gram-negative bacteria such as *E. coli, Salmonella typhi, Citrobacter freundii, Pseudomonas aeruginosa,* and *Klebsiella pneumoniae*. The leaves extract exhibits a more significant size of zone inhibition against the bacteria such as *E. coli, Salmonella typhi,* and *Pseudomonas aeruginosa* compared to other extracts (63).

COVID-19 related activities

Since the coronavirus disease 2019 (COVID-19) pandemic started with the outbreak of a highly pathogenic human coronavirus, the world has been facing a challenge, and there has been a pressing need for efficient drugs. Presently, there is no defined COVID-19 intervention, and clinical trials of prospective therapeutic agents are still in the nascent stage. In the absence of a specific drug for COVID-19, treatment with plant extracts could be an option worthy of further investigation and has motivated to evaluate the safety and anti-SARS-CoV-2 activity of plant extracts.

A study has revealed a potential for *W. somnifera* compounds, withaferin A, withanone, and caffeic acid phenethyl ester, to block SARS-CoV-2 entry into the host cells via the binding capacity to inhibit transmembrane protease serine 2 (TPMRSS2). TMPRSS2 is a serine protease on the host cell surface with which SARS-CoV-2 interacts to replicate and induce invasion (64). A few virtual screenings were done as preliminary studies for this newly discovered disease. An *in silico* evaluation of major withanolides found in *W. somnifera,* withanolide A, withanolide B, and withanone showed the plausible inhibitory potential of the compounds for curbing COVID-19 infection (65). A molecular docking analysis identified withanoside V and somniferine compounds from *W. somnifera* had potential inhibition and high affinities towards SARS-CoV-2 main protease (M^{pro}). The analysis predicted to restrain the action of SARS-CoV-2 M^{pro} thereby obstructing further translation of viral protein that assists in damaging the vital organs of the host (66).

Conclusion

Withania somnifera is a valuable plant due to its wide range of pharmacological activities. *W. somnifera* has been used in a traditional medicine system for a long time to treat illnesses. As highlighted in this review article, the extensive medicinal uses of *W. somnifera* are a sign of its great potential. Ethnobotanical study and pharmacological research conducted over the last decade confirmed many traditional uses of *W. somnifera* in many countries such as India, Ethiopia, Pakistan, and South Africa. Several phytochemical studies have been conducted to isolate many bioactive compounds. Extraction of *W. somnifera* shows that the plant contains a high number of alkaloids and steroidal lactones such as withaferin A and withanolide A. Other bioactive compounds found are flavonoids, coumarins, tannins, and terpenoids. Few pharmacological studies have been done to evaluate the potential mechanism of the reported pharmacological activities. *W. somnifera* has been approved to treat Alzheimer's and Parkinson's diseases, diabetes, arthritis, microbial infections, and cardiovascular problems.

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Authors' contributions

All authors have equally contributed to the literature survey and collected the data from the various published articles to be included in the manuscript. NBJ conceived the presented idea, developed the article, wrote, and prepared the manuscript; NM supervised the research and critical revision of the article. All authors read the manuscript and confirmed the publication of the final version.

Conflict of interests

The authors declare there is no conflict of interest concerning this study.

Ethical considerations

Ethical issues regarding authorship, data acquisition, review and analysis have been carefully observed by authors.

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