CHAPTER

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Ashwagandha: Multiple Health Benefits

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INTRODUCTION

Medicinal plants are rich in secondary metabolites and essential oils of therapeutic importance. The important advantages claimed for therapeutic uses of medicinal plants in various ailments include their safety, economic feasibility, effectiveness, and ease of availability (Atal and Kapoor, 1989; Siddiqui, 1993). Ashwagandha (*Withania somnifera*) is a perennial plant belonging to the family Solanaceae. Ashwagandha, A popular Ayurvedic herb, is commonly known as "Indian winter cherry." The root smells like a horse ("*ashwa*"), and that is why it is named Ashwagandha (on consuming it gives the power of a horse). The species name *somnifera* means "sleep-inducing" in Latin, indicating its sedating properties. Some herbalists refer to Ashwagandha as Indian ginseng, because it is used in Ayurvedic medicine in a way similar to Chinese ginseng (*Panax ginseng*) in traditional Chinese medicine (TCM). It has been used as an antibacterial, antioxidant, adaptogen, aphrodisiac, liver tonic, and an anti-inflammatory agent (Mehrotra et al., 2011). *W. somnifera* has been used in different medicinal systems for centuries. Writings indicate that the therapeutic use of plants is as old as 4000–5000 BC and the Chinese used the first natural herbal preparations as medicines. In India, however, earliest references to the use of plants as medicine appear in Rigveda, which is said to have been written between 3500 and 1600 BC. Later, the properties and therapeutic uses of medicinal plants were studied in detail and recorded empirically by the ancient physicians in Ayurveda, which is a basic foundation of ancient medical science in India (Sirkar, 1989). This chapter describes various aspects of Ashwagandha, including its multiple health effects.

BOTANY OF *W. SOMNIFERA*

W. somnifera, commonly known as Ashwagandha, is an important medicinal plant that has been used in Ayurvedic and indigenous medicine for more than 3,000 years. Ashwagandha (*W. somnifera*) belongs to the genus *Withania* and family Solanaceae. Two species, such as, *Withania coagulans* Dunal and *W. somnifera* Dunal, are found in India. *W. coagulans* is a rigid gray under shrub 60–120 cm high. *W. somnifera* is an erect, evergreen, tomentose shrub 30–75 cm in height. Its roots are stout, fleshy, cylindrical, 1–2 cm in diameter, and whitish brown in color. Leaves are simple, ovate, glabrous, and opposite. Flowers are bisexual, inconspicuous, greenish or dull yellow in color, born on axillary umbellate cymes, and comprise five sepals, petals, and stamens each; the two-celled ovary has a single style and a bilobed stigma. The petals are united and tubular. The stamens are attached to the corolla tube and bear erect anthers that form a close column or cone around the style. Pollen production is poor. The fruit is a small, globose, orange-red berry when mature and is enclosed in a persistent calyx. The seeds are small, flat, yellow, and reniform in shape and very light in weight. The cultivated plants have sizeable differences from the wild forms not only in their morphological characteristics but also in their therapeutic action, although the alkaloids present are the same in both (Kaul, 1957; Atal and Schwarting, 1961; Schonbeck-Temesy, 1972; The Ayurvedic Pharmacopoeia of India, 1990a,b,c; Hepper, 1991; Mozaffarian, 2003).

The 23 known *Withania* species are widely distributed in the drier parts of tropical and subtropical zones, ranging from the Canary Islands, the Mediterranean region, Northern Africa, India, Sri Lanka, Afghanistan, Baluchistan, and Sindh (Schonbeck-Temesy, 1972;

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FIGURE 52.1 World distribution of *Withania somnifera*.

Hepper, 1991; Warrier et al., 1996; Hunziker, 2001). It is found in high altitudes, ascending to 5,500 feet in the Himalayas (Figure 52.1). It has various names, such as Kaknaj-e-Hindi (Arabic), winter cherry (English), Asgandh or Punir (Hindi), Kaknaj-e-Hindi or Asgand Nagaori (Persian, Urdu), and Ashwagandha (Sanskrit).

IMPORTANT BIOACTIVE MOLECULES PRESENT IN *W. SOMNIFERA*

The pharmacological effects of the roots of *W. somnifera* are attributed to the presence of withanolides, a group of steroidal lactones (Budhiraja et al., 1987). This plant is commonly used in formulations for its wide range of health benefits. In Ayurveda, *Withania* is widely claimed to be a potent aphrodisiac, sedative, and rejuvenative, and to have life-prolonging properties. It is also used as a general energy-enhancing tonic known as Medharasayana, which means that "it promotes learning and a good memory" (Nadkarni, 1976; Williamson, 2002).

Laboratory analysis has revealed more than 35 chemical constituents contained in the roots of *W. somnifera* (Rastogi and Mehrotra, 1998). The biologically active chemical constituents are alkaloids (isopellertierine, anferine), steroidal lactones (withanolides, withaferins), saponins containing an additional acyl group (sitoindoside VII and VIII), and withanoloides with a glucose at carbon 27 (sitonidoside XI and X). *W. somnifera* is also rich in iron. The roots of *W. somnifera* consist primarily of withanolides, which are believed to account for its extraordinary medicinal properties. Withanolides are steroidal and bear a resemblance, both in their action and appearance, to the active constituents ginsenosides present in Asian ginseng (*Panax ginseng*). Ashwagandha's withanolides have been researched in a variety of animal studies examining their effect on numerous conditions, including immune function and even cancer (Grandhi et al., 1994). Chemical analysis of Ashwagandha shows its main constituents to be alkaloids and steroidal lactones. Among the various alkaloids, withanine is the main constituent. The other alkaloids are somniferine, somnine, somniferinine, withananine, pseudo-withanine, tropine, pseudo-tropine, 3-a-gloyloxytropine, choline, cuscohygrine, isopelletierine, anaferine, and anahydrine. The withanolides within the leaves have C28 steroidal nucleus with C9 side chain and a six-member lactone ring. Twelve alkaloids, 35 withanolides, and several sitoindosides from *W. somnifera* have been isolated and studied. A sitoindoside is a withanolide containing a glucose molecule at carbon 27. Much of Ashwagandha's pharmacological activity has been attributed to two

main withanolides, withaferin A and withanolide D (Bone, 1996; Elsakka et al., 1990). Further chemical analysis has shown the presence of the following:

Alkaloids: Anaferine, Anahygrine, Cuscohygrine, Scopoletin, Withanine, Withaninine, Somniferine, Tropeltigloate, Somniferinine, Somninine, Nicotine, Visamine, Withasomine, and Pseudotropine.
Salts: Cuscohygrine, Anahygrine, Tropine, Pseudotropine, and Anaferine.
Steroidal Lactones: Withaferin-A, Withanone, WS-1, Withanolide E, Withanolide F, Withanolide G, Withanolide H, Withanolide I, Withanolide J, Withanolide K, Withanolide L, and Withanolide M.
Nitrogen containing compounds: Withanol, Somnisol, and Somnitol.
Steroids: Cholesterol, β-sitosterol, Stigmasterol, Diosgenin, Stigmastadien, Sitoinosides VII, Sitoinosides VIII, Sitoinosides IX, and Sitoinosides X.
Flavonoids: Kaempferol and Quercetin (Nadkarni, 1954).

The plant contains carbohydrate-D-glucose, maltose, rhamnose, sucrose, and starch. It contains proteins, amino acids, and the alkaloid shankhpushpine ($C_{17}H_{25}NO_2$), with a melting point of 162–164°C. The most notable constituents are tropine alkaloids. Only convolamine has been identified, but other alkaloids (convoline, convolidine, convolvine, confoline, convosine, etc.) found in other species from this family are most likely present as well (Prasad et al., 1974; Lounasmaa, 1988; Singh and Bhandari, 2000). The fresh plant contains volatile oils, fatty acids, fatty alcohols, and hydrocarbons, such as myristic acid (30.9%), palmitic acid (66.8%), linoleic acid (2.3%), and straight chain hydrocarbon hextriacontane (Deshpande and Srivastava, 1975). A study was performed for a chemical examination of the whole plant (*C. pluricaulis*) and reported the presence of scopoletin, β-sitosterol, and ceryl alcohol. The chloroform fraction of this plant extract contains 20-oxodotriacontanol, tetratriacontanoic acid, and 29-oxodotriacontanol. The flavonoid kaempferol and steroids phytosterol and β-sitosterol were also found in significant amounts (Singh and Bhandari, 2000). An estimation of scopoletin (Nahata and Dixit, 2008) content was determined by spectrofluorimetry (Zafar et al., 2005) and HPTLC (Kapadia et al., 2006).

Ashwagandha roots contain alkaloids, starch, reducing sugar, hentriacontane, glycosides, dulcital, withaniol acid, and a neutral compound. Wide variation (0.13–0.31%) is observed in alkaloid content. Majumdar (1955) isolated eight amorphous bases (withanine, somniferine, somniferinine, somnine, withananine, withananinine, pseudowithanine, and withasomnine). Other alkaloids reported are nicotine, tropine, pseudotropine, 3,a-tigloyloxytropine, choline, cuscudohygrine, anaferine, anahygrine, and others. Free amino acids in the roots include aspartic acid, glycine, tyrosine, alanine, proline, tryptophan, glutamic acid, and cystine. The leaves contain 12 withanolides, alkaloids, glycosides, glucose, and free amino acids. The berries contain a milk-coagulating enzyme, two esterases, free amino acids, fatty oil, essential oils, and alkaloids. Methods for the analysis of alkaloid in Asgandh roots have also been reported (Majumdar, 1955; Mishra, 1989; Maheshwari, 1989; Table 52.1).

MAJOR MEDICINAL VALUE IN ANIMALS AND HUMANS

Withaferin A and withanolide D are the two main withanolides that contribute to most of the biological actions of *Withania* (Matsuda et al. 2001; Sharma et al. 2011). The active ingredients of WS are alkaloids (isopelletierine, anaferine, cuscohygrine, anahygrine, etc.), steroidal lactones (withanolides and withaferins), and saponins (Mishra et al., 2000). Sitoindosides and acylsterylglucosides in Ashwagandha are antistress agents. Active principles of Ashwagandha, for instance, sitoindosides VII–X and Withaferin A, have been shown to have significant antistress activity against acute models of experimental stress (Bhattacharya et al., 1987). The arial parts of WS yield 5-dehydroxy withanolide-R and withasomniferin-A (Rahman et al., 1991).

The biological activities of *W. somnifera* are anxiolytic, antidepressant, antifungal (Bhattacharya et al., 2000b), antimicrobial (Girish et al., 2006), antimalarial (Dikasso et al., 2006), apoptotic (Senthil et al., 2007), chondroprotective (Sumantran et al., 2007), cardioprotective (Hamza et al., 2008), immunomodulator (Davis and Kuttan, 2000), and neuroprotective (Sankar et al., 2007), promote inhibition of COX-2 enzyme (Jayaprakasam et al., 2003), and promote learning and memory in Alzheimer's disease (AD) (Bhattacharya et al., 1995). Numerous studies indicated that Ashwagandha possesses antioxidant, antitumor, antistress, anti-inflammatory, immunomodulatory, hematopoietic, antiaging, anxiolytic, antidepressive, and rejuvenating properties, and that it also influences various neurotransmitter receptors in the central nervous system (CNS) (Pattipati et al., 2003).

Animals

Use of medicinal plants for the treatment of various diseases has been a part of human culture since ancient times. Medicinal properties of plants were mostly discerned through trial and error, but they were also influenced by the belief systems of the people involved and often became entangled with religious and mythical practices (Mathias et al., 1996). Medicinal plant use evolved into an art and a science practiced according to the experience, traditions, and disease theory of the healer.

TABLE 52.1 Sources of Bioactive Molecules from Different Parts of *Withania Somnifara* and Their Pharmacological Importance on Animals

Sl. no.	Type of bioactive molecules	Bioactive molecules	Plants parts	Medicinal value of the bioactive molecules	Benefited/experimented animals	References
1.	Steroidal lactones	Withanolides	Leaves (Atta-ur-Rahman et al., 1991; Choudhary et al., 1996; Bandyopadhyay et al., 2007)	Antioxidant activity	Rat	Bhattacharya et al. (1997a,b)
				Anxiolytic and antidepressant actions	Rat	Bhattacharya et al. (2000b)
				Treat Alzheimer's disease (AD) and associated problems	Isolated rabbit jejunum	Choudhary et al. (2005)
			Leaves (Atta-ur-Rahman et al., 1991; Choudary et al., 1996; Bandyopadhyay et al., 2007)	Antimicrobial activities	Balb/C mice	Owais et al. (2005)
		Withaferin A	Leaves (Jayaprakasam et al., 2003)	Stimulating tumor cell apoptosis	MCF-7 breast cancer cells	Zhang et al. (2011, 2012)
			Leaves (Jayaprakasam et al., 2003)	Causes G2 and M phase cell cycle arrest	Human breast cancer cell linesMDA-MB-231 and MCF-7	Stan et al. (2008)
			Leaves (Jayaprakasam et al., 2003)	Chemoprevention	Golden Syrian hamsters	Manoharan et al. (2009) and Panjamurthy et al. (2008, 2009)
			Leaves (Jayaprakasam et al., 2003)	Chemosensitization	Nu/nu mice	Fong et al. (2012)
			Leaves (Jayaprakasam et al., 2003)	Radiosensitization	Swiss albino mice	Ganasoundari et al. (1997)
			Leaves (Jayaprakasam et al., 2003)	Chemotherapeutic	Nu/nu mice, Balb/c mice, SCID mice.	Samadi et al. (2010), Thaiparambil et al. (2011), and Lahat et al. (2010)
			Leaves (Jayaprakasam et al., 2003)	Antiangiogenesis	Human umbilical vein endothelial cells	Mohan et al. (2004)
			Leaves (Jayaprakasam et al., 2003)	Anti-inflammation	Swiss albino mice	Sabina et al. (2008)
			Leaves (Jayaprakasam et al., 2003)	NF-kB inhibiting activity cell line	Spinal cord tissue	Swarup et al. (2011)
			Leaves (Jayaprakasam et al., 2003)	NF-kB inhibiting activity cell line	Lung epithelial cell line (A549)	Oh and Kwon (2009)
			Leaves (Jayaprakasam et al., 2003)	NF-kB inhibiting activity cell line	Macrophage cell line (RAW 264.7)	Oh et al. (2008b)

			Leaves (Jayaprakasam et al., 2003)	Antiproliferative activity	Leukemia cell line	Oh et al. (2008a)
			Leaves (Jayaprakasam et al., 2003)	Antiproliferative activity	Renal carcinoma cell line	Swarup et al. (2011)
			Leaves (Jayaprakasam et al., 2003)	Antiproliferative activity	Ovarian carcinoma cell line	Zhang et al. (2012)
			Leaves (Jayaprakasam et al., 2003)	Antiproliferative activity	Breast carcinoma cell line	Zhang et al. (2011) and Hahm et al. (2011)
			Leaves (Jayaprakasam et al., 2003)	Antiangiogenic activity	Primary endothelial cells HUVEC and HCEC	Yokota et al. (2006), Mohan et al. (2004), and Bargagna-Mohan et al. (2006)
			Leaves (Jayaprakasam et al., 2003)	Activation of caspase-3, increase translocation of cytochrome C from mitochondria to cytosol	Human leukemia U937 cells	Oh et al. (2008a,b)
			Leaves (Jayaprakasam et al., 2003)	Tumor-inhibitory potential in both *in vitro* and *in vivo* studies	Balb/c nude mice	Widodo et al. (2008)
			Leaves (Jayaprakasam et al., 2003)	Cell cycle arrest	U2OS cells	Widodo et al. (2008)
		Withaferin A	Root (Sinha and Ostrand-Rosenberg, 2013)	WA reduces macrophage production of pro-inflammatory cytokines, withaferin A reduces MDSC accumulation in tumor-bearing mice, WA minimizes MDSC production of the pro-tumor cytokine IL-10	BALB/c mice	Sinha and Ostrand-Rosenberg (2013)
2.	Alkaloides	Nicotine, Somniferine, Somniferinine, Withanine, Withananine, Pseudowithanine, Tropine, Pseudotropine, 3α-tigloyloxytropane, Choline, Cuscohygrine, *dl*-isopelletierine	Roots (Gupta and Rana, 2007)	Prolonged hypotensive, bradycardic, and respiratory-stimulant action	Dogs	Malhotra et al. (1981)
3.	Glycosides	Sitoindosides VII and VIII	Roots (Bhattacharya et al., 1987)	Antistress and antistress adaptogenic activity	Wistar rats	Bhattacharya et al. (2003), Dhuley (2000), and Singh et al. (2001)
4.	Glycowithanolide	Sitoindosides VII–X	Roots (Bhattacharya et al., 1995)	Significantly reversed ibotenic acid-induced cognitive defects in Alzheimer's disease (AD) model	Rats	Bhattacharya et al. (1995)
		Glycowithanolides and sitoindosides IX and X	Whole plant	Significant antistress activity	Albino mice and rats	Ghosal et al. (1989)
		Sitoindosides VII–X, and withaferin-A	Roots (Schliebs et al., 1997)	Attenuate cerebral functional deficits, including amnesia, in geriatric patients	Rat	Schliebs et al. (1997)

(*Continued*)

TABLE 52.1 Continued

Sl. no.	Type of bioactive molecules	Bioactive molecules	Plants parts	Medicinal value of the bioactive molecules	Benefited/experimented animals	References
5.	Withanolides	Withanolide A, withanoside IV, and withanoside VI	Leaves (Chaurasiya et al., 2008)	Anticarsinogenic effect	Human BJ-5ta fibroblasts, MCF-7 cells	Grin et al. (2012)
		Ashwagandhanolide	Roots (Subaraju et al., 2006; Mirjalili et al., 2009)	Abrogation of TNF-induced NF-κB activation	Human tumor cells	Mulabagal et al. (2009)
		Withanoside I	Root (Jeyanthi and Subramanian, 2009)	Ameliorate neuronal dysfunction in Alzheimer's disease (AD)	Rat	Kuboyama et al. (2006)
		Withanoside	Root (Jeyanthi and Subramanian, 2009)	Improved memory deficits in β amyloid-injected mice (to induce dendritic and axonal atrophy) and prevented loss of axons, dendrites, and synapses in the cerebral cortex and hippocampus	Mice	Kuboyama et al. (2005, 2006)
		Withanolide sulfoxide	Roots (Mulabagal et al., 2009)	Inhibit COX-2 enzyme and to suppress human tumor cell proliferation	Human tumor cells	Mulabagal et al. (2009)
		L-asparaginase	Fruits (Oza et al., 2010)	Inhibitory effect against lymphoblastic leukemia	Human leukemia cells	Oza et al. (2010)
		Withaferin A and withanolide D	Root (Leyon and Kuttan, 2004)	Significant antitumor and radio-sensitizing withanolides	Mice	Leyon and Kuttan (2004)
6.	Withanolides	Withanolide A	Root (Bani et al., 2006)	Increases the expression levels of T-helper 1 (Th1) cytokines, as well as CD4 and CD8 counts, enhances natural killer (NK) cell activity	Mice	Bani et al. (2006)
		Withanoside IV	Root (Kuboyama et al., 2006)	Attenuated the axonal, dendritic, and synaptic losses and memory deficits induced by amyloid peptide Aβ(25–35)	Mice	Kuboyama et al. (2006)
		Withanolide A, withanoside IV, and withanoside VI	Whole plants (Zhao et al., 2002)	Induce neurite outgrowth in human neuroblastome SHSY5Y	Human	Zhao et al. (2002)
		5-dehydroxy withanolide-R, withasomniferin-A, 1-oxo-5*b*, 6*b*-epoxy-witha-2-ene-27-ethoxy-olide, 2,3- dihydrowithaferin A, 24,25-dihydro-27-desoxy withaferin A, 27-α-*b*-D-glucopyranosyl physagulin D, physagulin D, withanoside I–VII,27-O-*b*-D-glucopyranosylviscosalactoneB, 4,16-dihydroxy-5*b*,6*b*-epoxyphysagulinD, viscosa lactone B, and diacetyl withaferin A	Root (Chaurasiya et al., 2008; Jeyanthi and Subramanian, 2009)	Nephroprotective effect	Rats	Jeyanthi and Subramanian (2009)

Treatment of animal diseases developed in parallel with the treatment of human diseases. This knowledge was passed on verbally, by example, and sometimes through writing (Mathias et al., 1996). Ethnoveterinary medicine (EVM) is important in animal health care in developing countries (Cunningham and Zondi, 1991). It has become a recognized field of research that includes traditional veterinary theory, medicines, surgical methods, diagnostic procedures, and animal husbandry practices (Mathias et al., 1996). Veterinary aspects of ethnobotany are included in the field of EVM.

Humans

Withania roots are astringent, bitter, acrid, somniferous, thermogenic, stimulant, aphrodisiac, diuretic, and tonic. The leaves contain antibiotic, antitumorous, antihepatotoxic, and anti-inflammatory properties. The seed contains milk-coagulating, hypnotic, and diuretic properties.

W. somnifera has been used as an antibacterial, antioxidant, adaptogen, aphrodisiac, liver tonic, and anti-inflammatory agent (Mehrotra et al., 2011). It is a reputed health food and herbal tonic that is used for cardiovascular diseases in ethnomedicine. It is available for human use either as a single herb or an ingredient of polyherbal or herbomineral formulations. The human doses of *Ashwagandha* are generally in the range of 4–6 g/day and are expected to be safe and nontoxic. Stress, as a major cardiovascular risk factor, leads to activation of sympathoadrenal and hypothalamic pituitary adrenal (HPA) axis and causes oxidative stress. Ashwagandha possesses a potent antistressor effect and is reported to alleviate stress-induced changes and provide cardioprotection in ischemic rats similar to the properties ascribed to adaptogens such as *Panax ginseng*. It also increases heart weight and glycogen in the myocardium and liver, indicating intensification of the anabolic process, and enhances the duration of contractility as well as coagulation time (Dhuley, 1998, 2000).

EXPERIMENTAL STUDIES SUPPORTING MEDICINAL VALUE OF *W. SOMNIFERA*

The leaves and roots of this plant are used as an abortifacient, aphrodisiac, diuretic, nerve tonic, narcotic, sedative, astringent, growth promoter, and anthelmintic. It has antiarthritic, antibacterial, antistress, antitumor, and anticancer activities. It is an antidote for scorpion stings. It is used for toning the uterus, consumption, dropsy, leucoderma, impotence, rheumatism, debility from old age, ulcer, sexual and genital weakness, assumption, rheumatic swelling, loss of memory, loss of muscular energy, spermatorrhea, syphilis, sterility of women, blood discharge, leucorrhea, anemia with emaciation, multiple sclerosis, neoplasia, cancer, and fatigue. Fruits and seeds are diuretics and are used in the coagulation of milk (Nadkarni, 1954).

Asgand (*W. somnifera*) has been recommended for the treatment of various ailments, which include polyarthritis (*Waja-ul-Mafasil*), rheumatoid arthritis (*Hudar*), lumbago (*Wajaul- Qutn*), painful swellings (*Tawwarum-e-Alami*), spermatorrhea (*Jaryan-e-Mani*), asthma (*Zeeq-un-Nafas*), leucoderma (*Bars*), general debility (*Zof-e-Aam*), sexual debility (*Zof-e-Bah*), (Ali, 1997, Anon, 2007a,b, Khare, 2007, Kirtikar and Basu, 1980, Nadkarni, 1982), amnesia (*Nisyan*) (Ali, 1997, Ghani and Khazainul, 1920), anxiety neurosis (*Qalaq-e-Usabi*), (Ali, 1997, Khare, 2007), scabies (*Jarb*), ulcers (*Qurooh*), marasmus (*Saghal*), and leucorrhea (*Sailan-ur-Rahem*) (Anon, 2007a,b; Table 52.2–52.4).

POTENTIAL MEDICINAL APPLICATION IN AMELIORATING HIGH-ALTITUDE STRESS

Administration of the active principles of *W. somnifera* at equimolar concentrations of sitoindosides VII–X and withaferin A was found to increase superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx) activity in rat brain frontal cortex and striatum. The antioxidant effect of active glycowithanolides of *W. somnifera* (WSG) may explain, at least in part, the reported anti-inflammatory, immunomodulatory, antistress, antiaging, and cognition-facilitating effects produced in experimental animals and in clinical situations (Bhattacharaya et al., 1997a,b).

Another study reported by Bhattacharya et al. (2000a,b, 2001) investigated the antioxidant activity of WSG in chronic foot shock stress-induced changes in rat brain frontal cortex and striatum. The stress procedure, administered once daily for 21 days, induced an increase in SOD and lipid peroxidation (LPO) activity, with concomitant decrease in CAT, and GPx activities in both the brain regions. WSG administered orally 1 h prior to the stress procedure for 21 days (10, 20, and 50 mg/kg) induced a dose-related reversal of the stress effects. Thus, they concluded that WSG tended to normalize the augmented SOD and LPO activities and enhance the activities of CAT and GPx. Their results indicate that at least part of the chronic stress-induced pathology may be due to oxidative stress, which is mitigated by WSG, lending support to the clinical use of the plant as an antistress adaptogen (Bhattacharya et al., 2000b).

The brain is relatively more susceptible to free radical damage than other tissues because it is rich in lipids and iron, both of which are known to be important in

TABLE 52.2 *In Vivo* Study of Different Bioactive Molecules of *Withania Somnifera* with Their Special Medicinal Value

Sl. no.	Extract name	Dosages	Route of Dosages	Duration	Experimental Animals	Pharmacological Effects	References
1.	Glycowithanolides	20 and 50 mg/kg	Oral	5 days	Wistar rats	Antidepressant effect, induced an anxiolytic effect, antianxiety effects	Bhattacharya et al. (2000b)
2.	Glycowithanolides	10, 20, and 50 mg/kg	Oral	10 days	Wistar rats	Antioxidative effect	Bhattacharya et al. (2000a)
3.	*W. somnifera* root extract	25 and 50 mg/kg	Oral	21 days	Wistar rats	Significant antistress adaptogenic activity	Bhattacharya and Muruganandam (2003)
4.	*W. somnifera* root extract (Withaferin A, sitoindosides VII–X, 5-dehydroxy withanolide-R, withasomniferin-A, 1-oxo-5b, 6b-epoxy-witha-2-ene-27-ethoxy-olide, 2,3- dihydrowithaferin A, 24,25-dihydro-27-desoxy withaferin A, 27-O-b-D-glucopyranosyl physagulin D, physagulin D, withanoside I–VII,27-O-b-D-glucopyranosylviscosalactoneB, 4,16-dihydroxy-5b,6b-epoxyphysagulinD, viscosa lactone B, and diacetyl withaferin A)	250, 500, and 750 mg/kg	Oral	14 days	Rats	Nephroprotective effect	Jeyanthi and Subramanian (2009)
5.	Withaferin A	2–4 mg/kg	Intraperitoneal (IP)	10 days	Mice	Prolonged survival of S-180 ascites	Lahat et al. (2010)
6.	Withaferin A	10–60 mg/kg		24 h	Swiss albino mice	Inhibited growth of mouse Ehrlich ascites carcinoma cells and increased tumor-free survival	Byun et al. (2001)
7.	*W. somnifera* root extract	100 mg/kg	Oral	28 days	Mice	Improves catecholamines and physiological abnormalities seen in Parkinson's disease (PD)	RajaSankar et al. (2009)
8.	*W. somnifera* root extract	100 and 200 mg/kg)	Intraperitoneal (IP)	14 days	Rat	Improves Huntington's disease (HD)	Kumar and Kumar (2009)
9.	*W. somnifera* leaf extract	100 mg/kg	Oral administration	7 days	Balb/C mice	Antimicrobial activities	Owais et al. (2005)

10.	Withaferin A	1, 2, 4, 8 mg/kg body weight	Oral administration	7 days	Balb/C mice	WA reduces macrophage production of pro-inflammatory cytokines, withaferin A reduces MDSC accumulation in tumor-bearing mice, WA minimizes MDSC production of the pro-tumor cytokine IL-10	Sinha and Ostrand-Rosenberg (2013)
11.	Sitoindosides VII and VIII	25 and 50 mg/kg	Oral administration	21 days	Wistar rats	Antistress and antistress adaptogenic activity	Bhattacharya and Muruganandam (2003)
12.	Withaferin A	4 or 8 mg/kg	Intraperitoneal (IP)	24 days	PC-3 (prostate)	↓Tumor growth	Yang et al. (2007)
13.	Withaferin A	8 mg/kg	Intraperitoneal (IP)	21 days	DRO81-1 (medullary thyroid)	↓Tumor growth	Samadi et al. (2010)
14.	Withaferin A	2 and 4 mg/kg	Intraperitoneal (IP)	30 days	4T1 (mouse breast)	↓Tumor growth	Thaiparambil et al. (2011)
15.	Withaferin A	5 mg/kg	Intraperitoneal (IP)	17 days	AB12 (mesothelioma)	↓Tumor growth	Yang et al. (2012)
16.	Withaferin A	3 and 6 mg/kg	Intraperitoneal (IP)	28 days	Panc-1 (pancreatic)	↓Tumor growth	Yu et al. (2010)
17.	Withaferin A	20 mg/kg	Intraperitoneal (IP)	105 days	DMBA (oral)	↓Oral cancer (100%)	Manoharan et al. (2009)
18.	Withaferin A	100 µg/mouse	Intraperitoneal (IP)	196 days	MMTV-neu (breast)	↓Macroscopic and ↓microscopic tumor burden	Hahm et al. (2014)
19.	Glycowithanolides	1 mL/kg	Intraperitoneal (IP)	21 days	Rat	Increase the antioxidant activity	Bhattacharya et al. (1997a,b)
20.	Leaf powder	1.1 µg/mL	Oral	20 days	Mice	↓Tumor growth	Widodo et al. (2008)
21.	Leaf extract	0.3 mL of 24 µg/mL leaf extract	Subcutaneous	20 days	BALB/c nude mice	↓Tumor growth	Widodo et al. (2007)
22.	Withaferin A	10–60 mg/kg	Intraperitoneal (IP)	120 days	Mice	↓Tumor growth	Devi et al. (1992)
23.	Sitoindosides IX and X	50–200 mg/kg	Oral and intraperitoneal	4 days	Mice	↑Immunomodulatory and CNS effects	Ghosal et al. (1989)
24.	Root extract of *W. somnifera*	20 mg/kg	Intragastric	45 days	Mice	Antioxidative effect	Hussain et al. (2013)

TABLE 52.3 *In vitro* Study of Different Bioactive Molecules of *Withania Somnifera* with Their Special Medicinal Value

Sl. no.	Extract name	Dosages	Duration	Experimental cell lines	Pharmacological effects	References
1.	27-acetoxy-4b, 6a-dihydroxy-5b-chloro-1-oxowitha-2, 24-dienolide. 5b,6b,14a,15a-diepoxy-4b,27-dihydroxy-1-oxowitha-2,24-dienolide & Withaferin A	40 mg/mL, 9.4 mg/mL	4 days	Human lung cancer cell line (NCI-H460)	Growth inhibition and cytotoxic activity against human lung cancer cell line	Choudhary et al. (2010)
2.	L-asparaginase	0.01, 0.05, 0.1, 0.2, 0.5, 1, 2, 3, and 5 IU	3 days	Human leukemia cells	Inhibitory effect against lymphoblastic leukemia	Oza et al. (2010)
3.	Withanolides	0.003–1.0 lg/mL	3 h	Isolated rabbit jejunum	Treat Alzheimer's disease (AD) and associated problems	Choudhary et al. (2005)
4.	Withanolides	200 μg/mL	3 h	Isolated human neutrophils	Treat Alzheimer's disease (AD) and associated problems	Choudhary et al. (2005)
5.	Withaferin A	0, 0.156, 0.313, 0.625, 1.25, 2.5, 5 μM.	72 h	MCF-7 breast cancer cells	Stimulating tumor cell apoptosis	Zhang et al. (2011, 2012)
6.	Withaferin A	2 μM	24 h	Human breast cancer cell lines MDA-MB-231 and MCF-7	Causes G2 and M phase cell cycle arrest	Stan et al. (2008)
7.	Withaferin A	0.25, 0.5, 1.0, 1.5, 2.0 μM	24 h	Human leukemia U937 cells	Activation of caspase-3, increase translocation of cytochrome C from mitochondria to cytosol	Oh et al. (2008a)
8.	Withaferin A	0.5 μM	24 h	Human STS cell lines	Anticancerous effect	Lahat et al. (2010)
9.	Withaferin A	2 mg/kg	24 h	HT-1080, SKLMS-1 (soft tissue sarcoma)	↓Tumor growth	Lahat et al. (2010)
10.	Withaferin A	8 mg/kg	48 h	CaSki (cervical)	↓Tumor growth	Munagala et al. (2011)

11.	Withaferin A	8 or 12 mg/kg	72 h	Human uveal melanoma cell lines	Induce apoptosis	Samadi et al. (2012)
12.	Withaferin A	2 μM	24 h	Human umbilical vein endothelial cells	Antiangiogenic activity	Mohan et al. (2004)
13.	Withaferin A	1.5 μM	48 h	Osteogenic sarcoma (U2OS) and fibrosarcoma (HT1080) cells	Anticancerous effect	Widodo et al. (2008)
14.	Leaf extract, withaferin A, Withanone, Withanolide A	(0.8–5.0 μg/mL), (0.1–0.5 μM), (5–10 μg/mL), (5–10 μg/mL)	48–72 h	Glioma cell lines C6 (rat) and YKG1 (human)	Effective glioma therapy	Shah et al. (2009)
15.	Withaferin A	4.0 and 5.0 μM	3 h	Human lung cancer cells, A549	Alters intermediate filament organization, cell shape and behavior	Grin et al. (2012)
16.	Withaferin A	1.0 to 4.0 μM	3 h	MCF-7 cells		
17.	Withaferin A	2 μM	24 h	BJ-5ta cells		
18.	Withaferin A	2.5 and 5.0 μM	16 h	Human breast cancer cells (MCF-7 and SUM159 cells)	Induct the apoptotic process	Hahm et al. (2014)
19.	Withaferin A	5 and 10 μM	48 h	Leukocyte-depleted erythrocytes	Suicidal effectiveness on erythrocyte	Jilani et al. (2013)
20.	Water extract of *W. somnifera* leaves	0.1–2.5% of the crude extract	72 h	Rat C6 glioma cell line Human glioma cell lines (YKG1, U118MG and A172)	Useful for complimentary therapy for glioma	Kataria et al. (2011)
21.	Ashwagandha leaf extracts	0.3 μg/mL	24 h	Human neuroblastoma (IMR32) and rat glioblastoma (C6) cells	Protect brain-derived cells against oxidative stress and induce differentiation	Shah et al. (2015)

TABLE 52.4 Different Types of Curable Disease After Application of Different Bioactive Molecules of *Withania Somnifera*

Sl. no.	Curable disease	Bioactive molecules	References
1.	Oxidative stress	Withanolides	Bhattacharya et al. (1997a,b)
2.	Alzheimer's disease	Withanolides	Choudhary et al. (2005)
		Sitoindosides VII–X	Bhattacharya et al. (1995)
		Withanoside I	Kuboyama et al. (2006)
		Withanoside	Kuboyama et al. (2005, 2006)
		Withanolide sulfoxide	Mulabagal et al. (2009)
3.	Neurodegenerative disease	Withanoside IV	Kuboyama et al. (2006)
		Withanolide A, withanoside IV, and withanoside VI	Zhao et al. (2002)
4.	Microbial disease	Withanolides	Owais et al. (2005)
5.	Cancer	Withaferin A	Zhang et al. (2011, 2012), Stan et al. (2008), Fong et al. (2012), Panjamurthy et al. (2009), Samadi et al. (2010), Thaiparambil et al. (2011), and Lahat et al. (2010)
		Withanolide A, withanoside IV, and withanoside VI	Grin et al. (2012)
6.	Bacterial disease	Withaferin A and withanolide D	Leyon and Kuttan (2004)
		Withaferin A and 3-b-hydroxy-2,3-dihydrowithanolide F	Budhiraja et al. (1987)
7.	Stress relief	Sitoindosides VII and VIII	Bhattacharya and Muruganandam (2003), Dhuley et al. (2000), and Singh et al. (2001)
		Glycowithanolides and sitoindosides IX and X	Ghosal et al. (1989)
8.	Amnesia	Sitoindosides VII–X, and withaferin-A	Schliebs et al. (1997)
9.	Lymphoblastic leukemia	L-asparaginase	Oza et al. (2010)
10.	Poor immunity	Withanolide A	Bani et al. (2006)
11.	Nephronic disease	5-dehydroxy withanolide-R, withasomniferin-A, 1-oxo-5*b*, 6*b*-epoxy-witha-2-ene-27-ethoxy-olide, 2,3-dihydrowithaferin A, 24,25-dihydro-27-desoxy withaferin A, 27-α-*b*-D-glucopyranosyl physagulin D, physagulin D, withanoside I–VII,27-O-*b*-D-glucopyranosylviscosalactoneB, 4,16-dihydroxy-5*b*,6*b*-epoxyphysagulinD, viscosa lactone B, and diacetyl withaferin A	Jeyanthi and Subramanian (2009)

generating reactive oxygen species (ROS). The brain also uses nearly 20% of the total oxygen supply. Free radical damage to the brain may contribute to neuronal loss in cerebral ischemia and may be involved in normal aging and neurodegenerative diseases (epilepsy, schizophrenia, PD, AD, and others). Because traditional Ayurvedic use of WS has included many diseases associated with free radical oxidative damage, it has been considered likely that the effects may be due to a certain degree of antioxidant activity. Decreased activity of these enzymes leads to accumulation of toxic oxidative free radicals and resulting degenerative effects. An increase in these enzymes would represent increased antioxidant activity and a protective effect on neuronal tissue. Active WSG (10 or 20 mg/kg, intraperitoneal) was given once daily for 21 days to groups of six rats. Dose-related increases in all enzymes were observed; the increases comparable to those seen with deprenyl (a known antioxidant) administration (2 g/kg/day, intraperitoneal). This implies that WS does have an antioxidant effect in the brain that may be responsible for its diverse pharmacological properties. Further studies on other parts of the brain (e.g., cerebellum, medulla, and hypothalamus) may provide information with respect to the effects of WS on cognitive behavior and other functions of the brain in both healthy and diseased individuals.

In another study, an aqueous suspension of WS root extract was evaluated for its effect on stress-induced lipid peroxidation (LPO) in mice and rabbits (Dhuley, 1998). LPO blood levels were increased by

intravenous administration of 0.2 mg/kg of lipopolysaccharides (LPS) from *Klebsiella pneumoniae* and 100 mg/kg of peptidoglycans (PGN) from *Staphylococcus aureus*. Simultaneous oral administration of WS extract (100 mg/kg) prevented an increase in LPO. The authors indicated that the almost innocuous doses of LPS and PGN used in this study were comparable to a mild bacteremia that may follow tooth extraction or streptococcal angina.

Antistressor effects of Asgand were investigated in rats using a cold water swimming stress test. The treated animals showed better stress tolerance (Archana and Namasivayam, 1999). A withanolide-free aqueous fraction isolated from the roots of *W. somnifera* exhibited antistress activity in a dose-dependent manner in mice (Khare, 2007). Asgand has been evaluated for its adaptogenic activity. Administration of Asgand with other drugs in experimental animals exposed to a variety of biological, physical, and chemical stressors was found to offer protection against these stressors (Bhattacharya, 1992; Rege et al., 1999).

AVAILABLE DRUG FORMULATION USING *W. SOMNIFERA*

Ashwagandha is advocated as a protective drug against atherosclerosis, hypertension, and coronary heart diseases (Mehra et al., 2009). It reduces the sensitivity of the heart to adrenergic stimulation and thereby protects the heart against sympathetic outbursts. Moharana (2008) reported that the roots and leaves of *Ashwagandha* are traditionally used in the form of powder, decoction, or oil. These have been used in folk medicine against general disability, hypertension, inflammation, and wounds. Thirunavukkarasu et al. (2006) found *Ashwagandha* to have energy boosting properties and recommended its use as a dietary supplement for cardioprotection. The effect of *Ashwagandha* root was evaluated for lipid peroxidation in stress. The herb was found to have very good antioxidant activity, which may partly explain the antistress, congestion-facilitating, anti-inflammatory, and antiaging effects of this herb (Moharana, 2008; Table 52.5).

TABLE 52.5 List of Some Available Drug Formulated by *Withania Somnifera*

Sl. no.	Product name	Manufacturer	Utility of the product
1.	Stresswin	Baidynath Ayurved Bhawan	→ Combating exertion, reduction in anxiety, strain, and stress, improvement of stamina, relief from disturbed sleep, mental alertness
2.	Stresscom	Dabur India Ltd.	→ Relieves anxiety neurosis, physical and mental stress, and relieves general debility and depression
3.	Brento	Zandu Pharmaceutical Works Ltd.	→ Nerve tonic
4.	Ashvagandha	Morpheme Remedies	→ Combating stress
5.	Dabur Ashwagandha Churna	Dabur	→ Combating stress
6.	Ashwagandha	Ayurceutics	→ Stress reliever
7.	Himalaya Massage oil	The Himalaya Drug Co.	→ Stress relief and relief from insomnia
8.	Ashwagandharista	Baidynath Ayurved Bhawan	→ Nerve tonic, memory and cognition improvement, better power of concentration, relieves mental tension, natural sleep induction, and recovery from nervous and general debility
9.	Arshadi pills	Dehlvi Remedies	→ Stress, depression, cardiac tonic
10.	Ashwagandha extract	Nanjing Zelang Medical Technology Co., Ltd.	→ It is called "Indian ginseng" and contains alkaloids, steroidal lactones, withanaloids, and iron; it has antiallergy, antihistamine, antibacterial, local anaesthetic, antipyretic, and pain-relieving functions → Alkaloids could be used in sedative and pain relief, lowering blood pressure. The function of anti-inflammation of withanolides can inhibit cancer cell growth, treat chronic inflammation, such as lupus and rheumatoid arthritis, reduce vaginal discharge, improve sexual function, etc.

(*Continued*)

TABLE 52.5 Continued

Sl. no.	Product name	Manufacturer	Utility of the product
11.	Ashwagandha/*W. somnifera* extract withanolides	Wuxi Gorunjie Natural-Pharma Co., Ltd.	→ Ashwaghanda extract can treat different diseases like inflammation, arthritis, stress and anxiety, and even mental disorders → Improves the white blood cell in the body in a way that increases the phagocytosis or the process of removing dead cells → Enhances the results of radiation and chemotherapy → Regulates the nerve signals and makes sure that it is balanced → A great source of energy; it develops stamina by managing the process of metabolism → Best source for antioxidants and hormonal forerunners → Maintains necessary bodily functions → Protects the immunity cells that are subjected to chemicals that may prevent the cells to work properly
12.	Nutramax-AE (100%)	Hunan Nutramax Inc.	→ Antiallergy → Antihistamine → Antipyretic and pain-relieving → Local anesthetic → Antibacterial
13.	Nutramax *W. somnifera* extract (10:1)	Hunan Nutramax Inc.	→ Winter cherry medicinally works as an adaptogen, antistress agent, aphrodisiac, and in all cases of general debility → Ashwangandha extract is traditionally used in case of spermatorrhoes, loss of strength, seminal debility, and as a growth promoter → The root extracts exhibits antistress, hypotensive, antispasmodic, bradicardic, and respiratory stimulant activities → The herb promotes sound sleep, provides protection against environmental free radicals, nourishment of the cells, and works as rejuvenate
14.	Natural 80 mesh American ginseng root extract	Qingdao Fraken International Trading Co., Ltd.	→ Withanolides possess remarkable antibacterial, antitumor, antiarthritic, anti-inflammatory, and immunosuppressive properties
15.	100% Natural *W. somnifera* extract Alkaloids, Withanolides Ashwagandha extract	Xi'an Saina Biological Technology Co., Ltd	→ Antiallergy, antihistamine, antipyretic, pain-relieving, local anesthetic, antibacterial

CONCLUDING REMARKS AND FUTURE DIRECTIONS

In Ayurveda, the use of medicinal plants for better health management has been performed up to the present time, and its utility has increased across the globe. Medicinal plants contain several types of medicinally and pharmacologically important bioactive molecules that maintain the health and vitality of individuals and also cure disease. Several studies on *W. somnifera* have indicated its use as an aphrodisiac, liver tonic, anti-inflammatory agent, and astringent, and to treat bronchitis, asthma, ulcers, emaciation, insomnia, and senile dementia. Clinical trials and animal research support the use of Ashwagandha for anxiety, immunomodulation, hematopoiesis, cognitive and neurological disorders, inflammation, tumors, and PD. This plant is also responsible for the exertion of an influence on the endocrine, nervous, and cardiopulmonary systems. The most well-known bioactive molecules of *W. somnifera* are withaferins and sitoindosides, which reduce the oxidative damage of the cells and help in the prevention of several diseases. Studies on *W. somnifera* have indicated that supplementing with this plant can reduce lipid peroxidation, possibly by scavenging free radicals, and can help to build up a potent antioxidant defense system. This chapter describes that *W. somnifera* contains several bioactive molecules that are important for good health and for maintaining life at high altitudes, because it is responsible for the reduction of oxidative stress. This plant can also be used as a multipurpose medicinal agent. More research is needed to determine a potential dosage range for achieving its multipurpose drug properties.

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