Review Article

Withania somnifera as a potential nanomedicine: A review

Anam Amin Shami*, Emmania Abid, Laiba Tanveer

Department of Biotechnology, University of Central Punjab

***Corresponding author's email:** anam.shami61@gmail.com

Abstract

Withania somnifera, commonly known as Ashwaganda, is an important medicinal plant for a long time. Roots, seeds and other parts of Ashwaganda have clinically important pharmacological properties. The phytochemicals present in the plant include flavonoids, alkaloids, phenols and withanolids which make it useful in treatment of cancer, cardiovascular diseases and diabetes. *Withania somnifera* possess anti-inflammatory, anticancer, antioxidant, antimicrobial and anti-aging activities. Nanobiotechnology is an emerging field as nanoparticles allow targeted and controlled drug delivery. Green synthesis of nanoparticles involves the use of plants for their ability to reduce harmful impacts associated with chemically synthesized nanoparticles. The green synthesis approach has been applied for the synthesis of nanoparticles form plant extracts obtained from *Withania somnifera*. Silver, gold, selenium, platinum and many more nanoparticles have been synthesized by mixing the root extracts of Ashwaganda and metal salts. Another approach involves the use of plant extracts encapsulated in niosomes and in combination with solid lipid nanoparticles which is pharmacologically helpful. The nanoparticles from *Withania somnifera* utilize anti-inflammatory, anticancer, antioxidant, antimicrobial and anti-aging activities of Ashwaganda and help in targeted delivery of the drug. The plant-based nanoparticles show better characteristics including bioavailability, solubility and improved shelf life. This approach can be developed further for agricultural and technological uses like sensors and imaging technology.

Keywords: *Withania somnifera*, Ashwaganda, Green synthesis, Flavonoids, Withanolids, Alkaloids.

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Introduction

Withania somnifera, a well-known medical herbal plant commonly known as Winter Cherry and Ashwaganda, belongs to the family Solanaceae and is widely distributed worldwide [1 - 3]. The ancient doctors utilized different parts of *Withania somnifera* in Ayurvedic medicine to treat various diseases because of its pharmacological properties like anticancer, immunomodulatory, antioxidant, anti-inflammatory, putative anti-diabetic and anti-stress [1, 4 - 5]. *Withania somnifera* nanoparticles have gained attention due to its wide range of pharmacological properties to describe the precise cellular, physiological and molecular processes [6].

A nanoparticle is a small material with a diameter of 1 to 100 nm, invisible to the naked eye [7]. Nano-sized particles possess enhanced physiochemical and structural characteristics, making them a potential marker for the detection and diagnosis of a particular disease [8].

Withania somnifera nanoparticles play an important role for the protection of neurons, reduction in oxidative stress and enhancement of cognitive mechanisms in Alzheimer and Parkinson diseased patients [9]. In insomnia patients, it helps to reduce the induction of sleep by lowering the stress and improves the quality of sleep [10]. The different parts of Ashwaganda such as roots, seeds and fruit or berries have gained recognition for their pharmacological activities [9 - 10].

The root extracts of *Withania somnifera* are extensively explored for its pharmacological properties, such as antioxidant, immunomodulatory, anticancer, anti-inflammatory properties and adaptogenic actions [5, 11]. The plants anticancer activity inhibits the growth of new blood vessels, leading to the suppression of tumor growth [14]. It also has a cytotoxic impact on cancer cells by triggering apoptosis resulting in death of cancer cells. *Withania somnifera* could be used for treating different cancer as it has proved to be safe for human use and has demonstrated potential therapeutic effectiveness in pre-clinical studies involving different molecular pathways [15].

The antioxidant activity of the extracts helps to reduce the oxidative stress and protects the DNA from the damage caused by cancer cells [16]. Moreover, the adaptogenic action of the roots assists in stress management and enhancing the overall wellness by regulating the HPA (hypothalamic-pituitary adrenal) axis, which controls the body's response to stress [17]. Adaptogenic action helps to maintain hormonal balance, minimize the harmful effects of prolonged stress and reduce levels of stress chemicals like cortisol [13]. Inflammatory effect reduces joint inflammation, decreases the release of pro-inflammatory cytokines and can be used to treat the various inflammatory diseases [18]. Root powder of *Withannia somnifera* has the potential to control the level of hormones in diseases linked to hypothyroidism [19].

Withania somnifera has been found to exhibit excellent anti-inflammatory, anti-arthritic and analgesic activities in both in vitro and in vivo models through mechanisms such as inhibition of pro-inflammatory cytokines, reduction of ROS (reactive oxygen species) and metalloproteinase-8 levels and inhibition of NF-kB activity [20]. The aqueous root extract of *Withannia somnifera* (WSAq) showed anti-inflammatory activity in Collagen induced Arthritic (CIA) rats which was demonstrated by decrease in the concentration of pro-inflammatory cytokines and increase in IL-10 concentration [21]. The roots of *Withania somnifera* contain biological compounds such as flavonoids, alkaloids and withanolides which contribute to the anti-inflammatory and anticancer properties [22]. The two phytochemicals, flavonoids and alkaloids causes apoptosis of cancer cells, inhibiting their division and proliferation [23].

The fruit of the *Withania somnifera* plant have gained attention for their immunomodulatory, anti-inflammatory, hepatoprotective, anticancer, and antioxidant properties [20, 22]. Bioactive compounds such alkaloids, flavonoids, sterol, withanolides and phenolic compounds contribute to the attractive properties of *Withania somnifera* [25]. The antioxidant property of the fruit helps to reduce the oxidative damage to cells by acting as a free radical scavenger and Reactive Oxygen Species (ROS) protector

[26]. Different antioxidant assays, such as the Ferric Reducing Antioxidant Power (FRAP), thydroxyl radical scavenging assay and the 2,2-diphenyl-1-picrylhydrazy radical (DPPH) scavenging assay aid in the antioxidant potential of the fruit of *Withannia somnifera* plant [27].

The seeds of the *Withansia somnifera* plant are well-known for their medicinal properties [28]. They contain bioactive substances such as fatty acids, sterols, alkaloid and withanolides which provide adaptogenic and anti-stress properties [29]. Withanolides work on enzymes and receptors, overcoming the symptoms of stress and enhancing general wellbeing [30]. Adaptogens increases resistance to stress, promote homeostasis and control the production of hormones, and neurotransmitter associated with stress [31]. Andtogens help to initiate adaptive stress response by stimulating cellular and organismal defense systems [32]. *Withania somnifera* seeds have anti-diabetic and immunomodulatory properties [4]. The seeds have been found to improve insulin sensitivity, blood sugar levels and lesson's diabetes-related problems.

Withania somnifera has been used for treating diabetes mellitus (DM) [33]. *Withania somnifera* seeds can stimulate the immune system by stimulating the production of immune cells like macrophages and T-lymphocytes [32, 33].

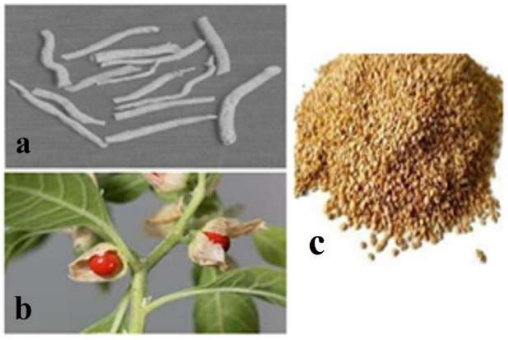

Figure 1. Parts of *Withannia* plant having various medical properties. (A) Plant Roots (B) Plant Flower (C) Plant Seeds

Withania somnifera extracts can boost the immune response by modulating both the innate and adaptive immune systems [36]. The seed extracts modulates the synthesis of immune mediators such cytokines, thereby controlling immune responses and immune function [37]. Due to potential applications and uses of *Withania somnifera*, it is a potential plant for green synthesis of nanoparticles for various advantages. This review is based on the study of stable nanoparticle synthesis from *Withania somnifera* plant and various nanoparticles using phytochemicals from *Withania somnifera*.

Pharmacological activities of *Withania somnifera*

Withania somnifera has the ability to synthesize various phytochemicals, which are biologically active and advantageous substances [38]. *Withania somnifera* produces a variety of phytochemicals including terpenoids, alkaloids, lignans, saponins and flavonoids [39]. *Withania somnifera* is benefitted from these phytochemicals by protection from environmental stressors including infections, insects and UV radiation, and providing attractive properties including flower color and many more [40].

Withania somnifera linked therapeutic effect is also linked to phytochemicals synthesized by the plant [41]. [42] studied and reported the efficacy of *Withania somnifera* produced phytochemicals against *Myocbacterium tuberculosis*. A study reported the presence of withanoside IV, 12-Deoxywithastramonolide, withaferin A and withanolide A which were responsible for biological activity of *Withania somnifera* [43]. Another study reported the presence of caffeic, ferulic and benzoic acids along with withaferin A, withanone, and withanolide A in the leaves, roots and stem of *Withania somnifera* with a concentration of 4 grams [44]. Withaferin A demonstrates a broad spectrum of

pharmacological actions, such as anti-inflammatory, anti-stress and antioxidant [45]. Withaferin A also modulates that how the body responds to stress by controlling hormones associated with stress and nervous transmitters [46]. Withanolide D has demonstrated to suppress the growth and proliferation of a variety of cancer cells in different tissues including colon, lungs, prostate and breast [47].

Flavonoids including Rutin and Quercetin produced by *Withania somnifera* contribute to the antifungal and antibacterial activity of the plant [48]. Flavonoids in conjugation with phenolic compounds show scavenging of free radicals, hence, giving *Withania somnifera* antioxidant activity [49]. Rutin in *Withania somnifera* has shown some protective effects against neurodegenerative disorders by lowering oxidative stress-related brain inflammation and damages [50]. Recent studies have shown that *Withania somnifera* can provide neuroprotection by altering numerous cellular and molecular pathways involved in neurodegenerative diseases [50]. *Withania somnifera* nanoparticles have the ability to removes protein clumps such as beta-amyloid plaques in Alzheimer's and alpha-synuclein aggregates in Parkinson disease, which are clinical hallmarks of neurodegenerative disorders that cause neuronal malfunction and cell death [51]. It also shows prospective cardiovascular advantages by enhancing endothelial function and lowering blood pressure [52].

Alkaloids produced by *Withania somnifera* belong to organically produced nitrogen containing chemicals [53]. Numerous alkaloids in *Withania somnifera* has been investigated for its potential neuroprotective properties [5, 7]. Somnferine is an important alkaloid which has neuroprotective properties and withanine has antioxidant activity, hence, decrease the buildup of amyloid-beta peptides that develops the Alzheimer's disease [7, 52]. Different phytochemicals show various therapeutic activities, which makes *Withania somnifera* a successful medical compound and a potential nanoparticle approach for improved therapies. Table 1 summarizes different phytochemicals present in *Withania somnifera* and their individual therapeutic effects.

Green synthesis of nanoparticles from *Withania somnifera*

Nanotechnology involves the manipulation of substances at nanoscale, ranging from one to hundred nanometers, to create nanoparticles with unique characteristics [55]. Nanoparticles have a small size and large surface area-to-volume ratio compared to the bulk materials, resulting in improved physicochemical properties [56].

Table 1: Phytochemical composition of *Withania somnifera*

Phytochemical	Compound	Therapeutic Effect	Reference
Withanolids	Withanolide D	Anticancer	[47]
	Withaferin A	Anti-inflammatory	[43]
		Anti-stress	
		Anti-toxic	
Flavonoids	Rutin	Antioxidant	[50]
		Anti-inflammatory	
	Quercitin	Anti-stress	[48]
		Anti-toxic	
		Biological Modifier	
Phenolic Compounds	Caffeic acid	Anticancer	[44]
	Gallic acid	Anti-toxic	[44]
Alkaloids	Withanine	Anti-inflammatory	[54]
	Somniferine	Neuroprotection	[54]

Green synthesis of nanoparticles refers to the use of natural plant extracts for the synthesis of nanoparticles for further applications [57]. Nanoparticles synthesized by green synthesis offer a reduced risk which is posed by artificial chemicals [58]. Phytochemicals produced by *Withania somnifera* are used in therapeutic nanoparticles produced by the plant and also allows stable synthesis of nanoparticles [56 - 57]. Plant extracts are used as reducing and stabilizing agents during a process called plant extract-mediated synthesis to create nanoparticles [60].

Plant-extracted nanoparticles are stabilized by the biomolecules of the plant which include proteins, polyphenols and flavonoids [61]. The stabilizing biomolecules constitute of variety of functional groups including amino group, hydroxyl group and carboxyl group which interact with the surrounding molecules and form stable nanoparticles [62]. The stabilizing interactions between biomolecules and surrounding molecules include electrostatic attraction forces, hydrogen bonds and Van der Waal forces [61 - 62].

Characterization of green synthesized nanoparticles

The characterization of nanoparticles after plant-based synthesis is important todetermine the size and surface area : volume ratio of the nanoparticles to ensure their efficacy [65]. For nanoparticle characterization various techniques are used: Transmission Electron Microscopy (TEM), X-Ray Diffraction (XRD), Scanning Electron Microscopy (SEM), Fourier-Transform Infrared Spectroscopy (FTIR) [65]. Transmission Electron Microscopy (TEM) helps in the analysis of nanoparticle morphology and distribution [66]. X-Ray Diffraction (XRD) is an important technique which helps in the understanding of crystalline structures and determines the arrangement of atoms within the structure of nanoparticles [65 - 66]. Along with the physical arrangement of atoms in the nanoparticles, XDR allows the chemical behavior prediction of the nanoparticles [69]. Scanning electron microscopy (SEM) is a potent imaging method used to examine the surface topography and morphology of nanoparticles [70]. Fourier-Transform Infrared Spectroscopy (FTIR) method is frequently used to examine the functional groups that are present on the surface of nanoparticles, it offers important details about the molecular makeup, bonding properties and chemical makeup of the nanoparticles [71]. Table 2 shows the basic nanoparticle characterization techniques and their resulting predictions.

Table 2: Techniques for characterization of plant extracted nanoparticles

Technique	Prediction	References
TEM (transmission electron microscopy)	Morphological characteristics	[66]
XRD (X-ray diffraction technique)	Atomic arrangement	[65 - 67]
	Chemical behavior	
SEM (Scanning Electron Microscopy)	Topological characteristics	[70]
	Morphological characteristics	
FTIR (Fourier-transform infrared spectroscopy)	Topography	[71]
	Morphological characteristics	

Properties of *Withania somnifera*-based nanoparticles

As reported in numerous studies, *Withania somnifera* possesses a number of phytochemicals which make it a useful therapeutic plant. These therapeutic properties help in the green synthesis of efficient nanoparticles from *Withania somnifera* which pose reduced risk to the body. The nanoparticles exhibit anticancer, antioxidant, anti-inflammatory, antimicrobial and antiaging activites of *Withania somnifera* plant. Table 3 summarizes some important nanoparticles derived from *Withania somnifera* and their therapeutic properties.

Table 3. Therapeutic properties exhibited by *Withania somnifera*-derived nanoparticles

Nanoparticle	Therapeutic properties	References
Selenium	Anticancer	[72]
	Antioxidant	
Zinc and Zinc Oxide	Anticancer	[73]
		[74]
	Anti-diabetic	[75]
Silver	Cytotoxic	[76]
	Antioxidant	[77]
	Antimicrobial	[78]
		[79]
Gold	Anticancer	[80]
Titanium dioxide	Anticancer	[81]
	Cytotoxic	
Copper and Copper Oxide	Antioxidant	[82]
	Antibacterial	[83]
Withania somnifera in conjugate with lipid nanoparticles	Anti-aging	[84]
Carbon quantum dots	Antimicrobial	[85]
Platinum	Anti-diabetic	[86]

Anti-cancer activity

Nano-particle derived from *Withania somnifera* has demonstrated tumor-suppressing potential and metastasis in various types of cancer such as liver, breast, lung and colon [6]. *Withania somnifera*-associated nanoparticles activate apoptosis-linked signaling pathways, including cell death and preventing cancer cell growth [45]. These nanoparticles have the ability to alter the expression of the B-cell lymphoma 2 family of proteins, which control apoptosis [87]. *Withania somnifera* nanoparticles lead towardscell cycle arrest at G0/G1, S, and G2/M phases, preventing cancer cells from uncontrolled multiplication and division [88]. *Withania somnifera*-linked nanoparticles can also block angiogenesis, a process crucial for tumor growth, by inhibiting the activity of Vascular Endothelial Growth Factor (VEGF), a key regulator of angiogenesis [89].

Withania somnifera has been used for the synthesis of selenium nanoparticles, which exhibit anticancer activity [72]. *Withania somnifera*-associated selenium (Se) nanoparticle synthesis was carried out by mixing plant leave extract with selenious solution. Recent study reported that selenium nanoparticles derived from *Withania somnifera* improves the sperm quality in diabetic mice [90]. Zinc oxide (ZnO) nanoparticles produced from roots of *Withania somnifera* have been reported to be efficient against breast cancer cell lines because of their anti-tumor potential [73]. [80] reported and studied *Withania somnifera* coated gold (Au) nanoparticles to treat triple-negative breast cancer cell line MDA-MB-231. [81] synthesized phytomediated green titanium dioxide (TiO2) NPs from *Withania somnifera* root extract, which significantly reduced the viability of HepG2 in invitro and can be used to treat liver cancer. Green synthesized zinc nanoparticles from *Withania somnifera* extract showed

anticancer properties when tested on Hela cell lines [74].

Antioxidant activity

The antioxidant activity of *Withania somnifera* nanoparticles has been investigated due to its importance in preventing damage caused by oxidative stress [91]. *Withania somnifera* nanoparticles have been found to neutralize free radicals and decrease oxidative damage, while also increasing enzyme antioxidant activity [90 - 91]. Animal studies have shown that *Withania somnifera* can significantly reduce oxidative stress markers and strengthen the cellular antioxidant defense mechanism [94]. *Withania somnifera* in combination with *Camellia sinensis* shows synergetic antioxidant activity [95].

Withania somnifera exhibit antioxidant and antibacterial activity which makes it helpful in the synthesis of copper (Cu) nanoparticles [83]. Copper oxide (CuO) nanoparticle treated plants showed significantly higher polyphenols and corresponding antioxidant activity at 20 DAT [82]. [83] with the help of DPPH assay found that synthesized copper nanoparticles exhibit good antioxidant potential. *Withania somnifera* alone and in combination Rodiola imbricata have been used for green synthesis of silver (Au) nanoparticles because of their cytotoxic, antioxidant and catalytic activities [74 - 75]. Selenium (Se) nanoparticles has significant antioxidant activity and antibacterial potential to treat diseases caused by bacteria [72].

Anti-aging activity

Withania somnifera nanoparticles have also found to show anti-aging effects [34]. Oxidative stress occurs when the production of ROS exceeds the body's antioxidant defense mechanisms, leading to cellular deterioration and accelerated aging [96]. These nanoparticles stimulate collagen production,improve cell viability and proliferation, reduce DNA damage, and reduced oxidative stress [97]. As a result, *Withania somnifera* nanoparticles may have potential benefits for skinhealth and anti-aging.

[98] found that extracts of *Withania somnifera* can improve skin conditions as well as the quality of life in photoaged healthy individuals. A study was carried out with niosomes encapsulating *Withania somnifera* extract and solid lipid nanoparticles which showed the delivery of important phytochemicals including withaferin A and withanolide A to important layers of skin [84].

Anti-inflammatory and anti-microbial Activity

Withania somnifera-derived nanoparticles are gaining interest due to their potent anti-inflammatory and immunomodulatory properties as a therapeutic agent [99]. These nanoparticles can modulate mediators and pro-inflammatory cytokines, controlling their production and dissolution [100]. Nano- particles have the ability to decrease the levels of pro-inflammatory cytokines, which are linked to avariety of inflammatory illnesses [101]. By targeting the nuclear factor-kappa B (NF-κB), a transcription factor involved in inflammation, *Withania somnifera* can suppress its activation and subsequently reduce the expression pro-inflammatory genes [100, 101]. Cytotoxic properties of *Withania somnifera* have been used in Titanium dioxide (TiO2) nanoparticles against HepG2 cell lines [81].

The antimicrobial activity is mainly associated with damaging the cell wall components of microbial cell [104]. Silver (Ag) nanoparticles extracted from *Withania somnifera* have shown antimicrobial activity by binding with penicillin-binding protein class IV of bacterial cell wall [78].

The green synthesized silver (Ag) nanoparticles demonstrated a wide range of antibacterial activity against both gram-positive and gram-negative bacteria [79]. The silver nanoparticles interfered with multiple cellular functions, including growth, cell membrane damage, ROS generation and inhibiting biofilm. A recent investigation reported the efficacy and antiviral activity of carbon quantum dots extracted from *Withania somnifera* against SARS-CoV-2 pseudovirions [85]. [83] studied and reported that copper oxide (CuO) derived from the root extracts of *Withania somnifera* have a good antibacterial activity against *Staphylococcus aureus*.

Anti-diabetic

Withania somnifera possess anti-diabetic effect when studied on rats and plant extract obtained from the roots of *Withania somnifera* shows antidiabetic activity [105]. *Withania somnifera* root powder showed anti-diabetic activity in Streptozotocin-induced diabetic rats [106]. A systematic review of 25 reported studies showed effectiveness of *Withania somnifera* extract against diabetes mellitus as demonstrated in an in-vivo study by [107, 33]. Metal nanoparticles derived from *Withania somnifera,* hence, also exhibit anti-diabetic potential. [75] experimentally demonstrated that zinc oxide nanoparticles could be used to treat diabetic patients. A study conducted on streptozotocin-induced diabetic rats to investigate the effects of *Withania somnifera* nanoparticles on pancreatic β-cell dysfunction [108]. It was found that nanoparticles of *Withania somnifera* regulated blood glucose levels by improving insulin secretion and sensitivity of β-cells. Use of platinum nanoparticles synthesized from *Withania somnifera* against diabetes in rats have been reported [86].

Advantages of *Withania somnifera*-derived nanoparticle over chemically-derived nanoparticles

Withania somnifera nanoparticles has recently gained significant attention for its potential in nanomedicine [109]. This medicinal herb has been found to offer various benefits for biomedical applications as well as other industries [110]. *Withania somnifera*-based nanoparticles exhibit good biocompatibility as they are synthesized from natural plant extracts and have little to no negative impact on the body [109]. *Withania somnifera* nanoparticles can extend the shelf life of pharmaceuticals and other bioactive chemicals by protecting them from environmental factors such as deterioration and oxidation [22]. Nanoparticle of *Withania somnifera* can also increase the bioavailability of bioactive substances due to their small size and large surface area, which enhances their dispersion and absorption [111]. This in turn, boosts the efficacy of bioactive substances.

Withania somnifera nanoparticles have the potential to be used in a wide range of industries, including nanomedicine, industrial, and agriculture [112]. They can act as operational materials in industrial processes as well as provide effective delivery of drugs, imaging and diagnostics [113]. The bioactive substances found in *Withania somnifera* have range of therapeutic benefits, making it a widely recognized medical herb [11]. By formulating the bioactive substances into nanoparticles, their transport to the target areas is more efficient and their medicinal potential is maximized [114].

Emerging potential of *Withania somnifera* derived nanoparticles

Plant-based nanomedicines have been a rising interest for many researchers because of their improved and targeted delivery [115]. *Withania somnifera* nanoparticles have apotential to improve drug stability, solubility, bioavailability and targeted drug

delivery to their specific target tissues, reducing the side effects [114 - 115]. Immunomodulatory, antioxidant, anticancer, anti-diabetic, anti-inflammatory and many other properties of *Withania somnifera* makes it an important medicinal plant against cancer, cardiovascular diseases and immune diseases [4]. Due to therapeutic use of *Withania somnifera*, it exhibits an emerging potential as nanomedicine and green-synthesized nanoparticles [118].

To maximize their synergistic benefits, nanoparticles of *Withania somnifera* can be coupled to other medicinal products, such as chemotherapeutic medicines [5]. This combination will reduce the damaging side effects of chemotherapy against cancer. Since most of the therapeutic properties of *Withania somnifera* lies in roots, the root extract can be encapsulated in nanoparticles like niosomes for enhanced therapeutic effect because of its controlled release [119]. The human-based trials of various therapeutic *Withania somnifera*-based nanoparticles will lead to development of effective and cheaper medical therapies [120].

For the quick and sensitive detection of biomolecules like DNA, proteins or enzymes, nanoparticles of *Withania somnifera* can be used in biosensor technology [121]. *Withania somnifera*-derived nanoparticles also possess technological potential. For the detection of various environmental contaminants, heavy metals or biological analytes, nanoparticle of *Withania somnifera* can be used as nano-sensors [122]. In contrast to MRI (magnetic resonance imaging) and fluorescence imaging, nanoparticle of *Withania somnifera* are able to be functionalized with imaging agents like fluorescent dyes or magnetic nanoparticles [61].

Nanoparticles can be derived from *Withania somnifera* to achieve various crop management functions including crop growth, productivity and stress resistance [123]. Nanoparticles can enhance nutrient uptake, encourage plant growth, and offer defense against pests, diseases, and abiotic stressors when used as nano pesticides as well as nano fertilizers [124]. The soil can be decontaminated and its quality improved as a result of the nanoparticles' ability to attach to pollutants and aid in their extraction or breakdown [125]. Nanoparticle of *Withania somnifera* have antibacterial and antifungal characteristics that can be used to combat plant diseases [126].

Conclusion

Withania somnifera is a biologically important plant having various pharmacological, technological and agricultural applications. Nanobiotechnology is emerging in all the fields because of their ability of targeted and controlled delivery. Plant-derived nanoparticles are the best approaches to neutralize the harmful effect of chemically synthesized metal and non-metal nanoparticles. *Withania somnifera* root extracts have been used as anti-inflammatory, antioxidant, anticancer and antimicrobials for a long time. These properties of *Withania somnifera* can be combined with nanoparticles for treatment of various diseases and disorders. In future this approach can also be used for the synthesis of regenerative medicines and personalized medicines which can reduce the harm to individuals.

References

1. Paul S, Chakraborty S, Anand U, Dey S, Nandy S, Ghorai M, Saha SC, Patil MT, Kandimalla R, Proćków J, Dey A. *Withania somnifera* (L.) Dunal (Ashwagandha): A comprehensive review on ethnopharmacology, pharmacotherapeutics, biomedicinal and toxicological aspects. Biomedicine Pharmacotherapy. 2021; 143:112-175.

2. Dinesh P, Rasool M. Herbal formulations and their bioactive components as dietary supplements for treating rheumatoid arthritis. InBioactive Food as Dietary Interventions for Arthritis and Related Inflammatory Diseases 2019 Jan 1 (pp. 385-399). Academic Press. Management of Alzheimer's Disease: Recent Trends and Future Perspectives," *Molecules*. 2021;26(12): 3696.
3. Shaheen HM, Alsenosy AA. Nuclear Factor Kappa B Inhibition as a Therapeutic Target of Nutraceuticals in Arthritis, Osteoarthritis, and Related Inflammation. InBioactive Food as Dietary Interventions for Arthritis and Related Inflammatory Diseases 2019 Jan 1;437-453. Academic Press.
4. Alanazi HH, Elfaki E. The immunomodulatory role of *Withania somnifera* (L.) dunal in inflammatory diseases. Frontiers in pharmacology. 2023 Feb 22; 14:1084757.
5. Mikulska P, Malinowska M, Ignacyk M, Szustowski P, Nowak J, Pesta K, Szeląg M, Szklanny D, Judasz E, Kaczmarek G, Ejiohuo OP. Ashwagandha (*Withania somnifera*)—Current research on health-promoting activities: a narrative review. Pharmaceutics. 2023;15(4):1057.
6. Kashyap VK, Peasah-Darkwah G, Dhasmana A, Jaggi M, Yallapu MM, Chauhan SC. *Withania somnifera*: progress towards a pharmaceutical agent for immunomodulation and cancer therapeutics. Pharmaceutics. 2022 Mar 10;14(3):611.
7. Khan I, Saeed K, Khan I. Nanoparticles: Properties, applications and toxicities. Arabian journal of and 2019 Nov 1;12(7):908-931.
8. Yagublu V, Karimova A, Hajibabazadeh J, Reissfelder C, Muradov M, Bellucci S, Allahverdiyev A. Overview of physicochemical properties of nanoparticles as drug carriers for targeted cancer therapy. Journal of Functional Biomaterials. 2022 Oct 20;13(4):196.
9. Das R, Rauf A, Akhter S, Islam MN, Emran TB, Mitra S, Khan IN, Mubarak MS. Role of withaferin A and its derivatives in the management of Alzheimer's disease: Recent trends and future perspectives. Molecules. 2021 Jun 17;26(12):3696.
10. Cheah KL, Norhayati MN, Yaacob LH, Rahman RA. Effect of Ashwagandha (*Withania somnifera*) extract on sleep: A systematic review and meta-analysis. PloS one. 2021;16(9): e0257843.
11. Gaurav H, Yadav D, Maurya A, Yadav H, Yadav R, Shukla AC, Sharma M, Gupta VK, Palazon J. Biodiversity, biochemical profiling, and pharmaco-commercial applications of *Withania somnifera*: A review. Molecules. 2023 Jan 26;28(3):1208.
12. Habeeb Rahuman HB, Dhandapani R, Narayanan S, Palanivel V, Paramasivam R, Subbarayalu R, Thangavelu S, Muthupandian S. Medicinal plants mediated the green synthesis of silver nanoparticles and their biomedical applications. IET nanobiotechnology. 2022 ;16(4):115-144.
13. Priyanka G, Anil Kumar B, Lakshman M, Manvitha V, Kala Kumar B. Adaptogenic and immunomodulatory activity of Ashwagandha root extract: An experimental study in an equine model. Frontiers in veterinary science. 2020 Sep 29; 7:541112.
14. Bhat JA, Akther T, Najar RA, Rasool F, Hamid A. *Withania somnifera* (L.) Dunal (Ashwagandha); current understanding and future prospect as a potential drug candidate. Frontiers in Pharmacology. 2022; 13:1029123.
15. Dutta R, Khalil R, Green R, Mohapatra SS, Mohapatra S. *Withania somnifera* (Ashwagandha) and withaferin A: Potential in integrative oncology. International journal of molecular sciences. 2019 Oct 25;20(21):5310.
16. Dar NJ, Hamid A, Ahmad M.

Pharmacologic overview of *Withania somnifera*, the Indian Ginseng. Cellular and molecular life sciences. 2015 Dec; 72:4445-4460. N.
17. Hosseini N, Moharari F, Soltanifar A. Evaluation of the effectiveness of *Withania somnifera* root extract on the anxiety symptoms among children with ADHD in Mashhad. Pak J Med Health Sci. 2019;13(1):210-216.
18. Kany S, Vollrath JT, Relja B. Cytokines in inflammatory disease. International journal of molecular sciences. 2019 Nov 28;20(23):6008.
19. Andallu B, Radhika B. Hypoglycemic, diuretic and hypocholesterolemic effect of winter cherry. *Withania somnifera*. 2000:607-609.
20. Bashir A, Nabi M, Tabassum N, Afzal S, Ayoub M. An updated review on phytochemistry and molecular targets of *Withania somnifera* (L.) Dunal (Ashwagandha). Frontiers in Pharmacology. 2023; 14:1049334.
21. Khan MA, Ahmed RS, Chandra N, Arora VK, Ali A. In vivo, extract from *Withania somnifera* root ameliorates arthritis via regulation of key immune mediators of inflammation in experimental model of arthritis. Anti-Inflammatory & Anti-Allergy Agents in Medicinal Chemistry (Formerly Current Medicinal Chemistry-Anti-Inflammatory and Anti-Allergy Agents). 2019 Feb 4;18(1):55-70.
22. Polumackanycz M, Petropoulos SA, Śledziński T, Goyke E, Konopacka A, Plenis A, Viapiana A. *Withania somnifera* L.: phenolic compounds composition and biological activity of commercial samples and their aqueous and hydromethanolic extracts. Antioxidants. 2023 Feb 22;12(3):550.
23. Kopustinskiene DM, Jakstas V, Savickas A, Bernatoniene J. Flavonoids as anticancer agents. Nutrients. 2020 Feb 12;12(2):457.
24. Banik B, Das S, Das MK. Medicinal Plants with Potent Anti-inflammatory and Anti-arthritic Properties found in Eastern Parts of the Himalaya: An Ethnomedicinal Review. Pharmacognosy Reviews. 2020;14(28).
25. Mizwicki MT, Norman AW. Vitamin D Sterol/Vitamin D Receptor Conformational Dynamics and Nongenomic Actions. Vitamin D. 2018 Jan 1:269-292.
26. Meitha K, Pramesti Y, Suhandono S. Reactive oxygen species and antioxidants in postharvest vegetables and fruits. International journal of food science. 2020;2020(1):8817778.
27. El Jemli M, Kamal R, Marmouzi I, Zerrouki A, Cherrah Y, Alaoui K. Radical-scavenging activity and ferric reducing ability of Juniperus thurifera (L.), J. oxycedrus (L.), J. phoenicea (L.) and Tetraclinis articulata (L.). Advances in Pharmacological and Pharmaceutical Sciences. 2016;2016(1):6392656.
28. Pandey V, Ansari WA, Misra P, Atri N. *Withania somnifera*: Advances and implementation of molecular and tissue culture techniques to enhance its application. Frontiers in Plant Science. 2017 Aug 9; 8:1390.
29. Saleem S, Muhammad G, Hussain MA, Altaf M, Bukhari SN. *Withania somnifera* L.: Insights into the phytochemical profile, therapeutic potential, clinical trials, and future prospective. Iranian journal of basic medical sciences. 2020;23(12):1501.
30. Speers AB, Cabey KA, Soumyanath A, Wright KM. Effects of *Withania somnifera* (Ashwagandha) on stress and the stress-related neuropsychiatric disorders anxiety, depression, and insomnia. Current neuropharmacology. 2021 Sep 9;19(9):1468.
31. Panossian A. Understanding adaptogenic activity: specificity of the pharmacological action of adaptogens and other phytochemicals. Annals of the New York Academy of Sciences. 2017 Aug;1401(1):49-64.
32. Panossian A, Seo EJ, Efferth T. Novel molecular mechanisms for the

adaptogenic effects of herbal extracts on isolated brain cells using systems biology. Phytomedicine. 2018 Nov 15; 50:257-284.
33. Durg S, Bavage S, Shivaram SB. *Withania somnifera* (Indian ginseng) in diabetes mellitus: a systematic review and meta-analysis of scientific evidence from experimental research to clinical application. Phytotherapy research. 2020 May;34(5):1041-1059.
34. Sharifi-Rad J, Quispe C, Ayatollahi SA, Kobarfard F, Staniak M, Stępień A, Czopek K, Sen S, Acharya K, Matthews KR, Sener B. Chemical Composition, Biological Activity, and Health-Promoting Effects of *Withania somnifera* for Pharma-Food Industry Applications. Journal of Food Quality. 2021;2021(1):8985179.
35. Iuvone T, Esposito G, Capasso F, Izzo AA. Induction of nitric oxide synthase expression by *Withania somnifera* in macrophages. Life sciences. 2003 Feb 21;72(14):1617-1625.
36. Tharakan A, Shukla H, Benny IR, Tharakan M, George L, Koshy S. Immunomodulatory effect of *Withania somnifera* (Ashwagandha) extract—a randomized, double-blind, placebo-controlled trial with an open label extension on healthy participants. Journal of clinical medicine. 2021 Aug 18;10(16):3644.
37. Di Sotto A, Vitalone A, Di Giacomo S.Plant-derived nutraceuticals and immune system modulation: an evidence-based overview. Vaccines. 2020 Aug 22;8(3):468.
38. Dhama P, Ding X, Sharma A. Exploring phytochemicals of *Withania somnifera* from different vicinity for functional foods. Journal of Future Foods. 2023 Sep 1;3(3):278-287.
39. Munir N, Mahmood Z, Shahid M, Afzal MN, Jahangir M, Ali Shah SM, Tahir IM, Riaz M, Hussain S, Akram M, Yousaf F. *Withania somnifera* chemical constituents' in vitro antioxidant potential and their response on spermatozoa parameters. Dose-Response. 2022 Feb 5;20(1): 15593258221074936.
40. Roy A, Khan A, Ahmad I, Alghamdi S, Rajab BS, Babalghith AO, Alshahrani MY, Islam S, Islam MR. Flavonoids a bioactive compound from medicinal plants and its therapeutic applications. BioMed Research International. 2022;2022(1):5445291.
41. Ramli S, Wu YS, Batumalaie K, Guad RM, Choy KW, Kumar A, Gopinath SC, Rahman Sarker MM, Subramaniyan V, Sekar M, Fuloria NK. Phytochemicals of *Withania somnifera* as a future promising drug against SARS-CoV-2: pharmacological role, molecular mechanism, molecular docking evaluation, and efficient delivery. Microorganisms. 2023 Apr 12;11(4):1000.
42. Singh A, Kumar S, Gupta VK, Singh S, Dwivedi VD, Mina U. Computational assessment of *Withania somnifera* phytomolecules as putative inhibitors of Mycobacterium tuberculosis CTP synthase PyrG. Journal of Biomolecular Structure and Dynamics. 2023 Jul 24;41(11):4903-4916.
43. Nile SH, Nile A, Gansukh E, Baskar V, Kai G. Subcritical water extraction of withanosides and withanolides from ashwagandha (*Withania somnifera* L) and their biological activities. Food and Chemical Toxicology. 2019 Oct 1; 132:110659.
44. Tomar V, Beuerle T, Sircar D. A validated HPTLC method for the simultaneous quantifications of three phenolic acids and three withanolides from *Withania somnifera* plants and its herbal products. Journal of Chromatography B. 2019 Aug 15; 1124:154-160.
45. Kumar S, Mathew SO, Aharwal RP, Tulli HS, Mohan CD, Sethi G, Ahn KS, Webber K, Sandhu SS, Bishayee A. Withaferin A: A pleiotropic anticancer agent from the Indian medicinal plant *Withania somnifera* (L.) Dunal.

Pharmaceuticals. 2023 Jan 22;16(2):160.
46. Chaves T, Fazekas CL, Horváth K, Correia P, Szabó A, Török B, Bánrévi K, Zelena D. Stress adaptation and the brainstem with focus on corticotropin-releasing hormone. International journal of molecular sciences. 2021 Aug 23;22(16):9090.
47. Lacombe J, Cretignier T, Meli L, Wijeratne EK, Veuthey JL, Cuendet M, Gunatilaka AL, Zenhausern F. Withanolide D enhances radiosensitivity of human cancer cells by inhibiting DNA damage non-homologous end joining repair pathway. Frontiers in oncology. 2020 Jan 8; 9:1468.
48. EL-Hefny M, Salem MZ, Behiry SI, Ali HM. The potential antibacterial and antifungal activities of wood treated with *Withania somnifera* fruit extract, and the phenolic, caffeine, and flavonoid composition of the extract according to HPLC. Processes. 2020 Jan 16;8(1):113.
49. K. J. J. D. J. W. S. L.R. *et al.*, "Original contributions Antioxidant and Phytochemical composition of Leaves, Stem and Root Extracts of Withania coagulans and *Withania somnifera*," *J. Med. Spice Plants*.2021; 647(1): 1-29.
50. Wongtrakul J, Thongtan T, Kumrapich B, Saisawang C, Ketterman AJ. Neuroprotective effects of *Withania somnifera* in the SH-SY5Y Parkinson cell model. Heliyon. 2021 Oct 1;7(10).
51. Limanaqi F, Biagioni F, Busceti CL, Ryskalin L, Polzella M, Frati A, Fornai F. Phytochemicals bridging autophagy induction and alpha-synuclein degradation in parkinsonism. International journal of molecular sciences. 2019 Jul 3;20(13):3274.
52. Silva IV, de Figueiredo RC, Rios DR. Effect of different classes of antihypertensive drugs on endothelial function and inflammation. International journal of molecular sciences. 2019 Jul 14;20(14):3458.
53. K. S. Teja, G. T. Sivaram, K. M. Yuvaraj, and L. Kadiri, "Effect of different dates of sowing, organic manures on protein , fiber and alkaloid content in leaves and roots of ashwagandha (*Withania somnifera*)," 2002;11(9), 522–524.
54. Hatami M, Mortazavi M, Baseri Z, Khani B, Rahimi M, Babaei S. Antioxidant compounds in the treatment of Alzheimer's disease: Natural, hybrid, and synthetic products. Evidence-Based Complementary and Alternative Medicine. 2023;2023(1):8056462.
55. Nasrollahzadeh M, Sajadi SM, Sajjadi M, Issaabadi Z. An introduction to nanotechnology. InInterface science and technology 2019 Jan 1; 28: 1-27.
56. Joudeh N, Linke D. Nanoparticle classification, physicochemical properties, characterization, and applications: a comprehensive review for biologists. Journal of Nanobiotechnology. 2022 Jun 7;20(1):262.
57. Hussain I, Singh NB, Singh A, Singh H, Singh SC. Green synthesis of nanoparticles and its potential application. Biotechnology letters. 2016 Apr; 38:545-560.
58. Jeevanandam J, Kiew SF, Boakye-Ansah S, Lau SY, Barhoum A, Danquah MK, Rodrigues J. Green approaches for the synthesis of metal and metal oxide nanoparticles using microbial and plant extracts. Nanoscale. 2022;14(7):2534-2571.
59. Vijayaram S, Razafindralambo H, Sun YZ, Vasantharaj S, Ghafarifarsani H, Hoseinifar SH, Raeeszadeh M. Applications of green synthesized metal nanoparticles—a review. Biological Trace Element Research. 2024 Jan;202(1):360-386.
60. Adeyemi JO, Oriola AO, Onwudiwe DC, Oyedeji AO. Plant extracts mediated metal-based nanoparticles: synthesis and biological applications. Biomolecules. 2022 Apr 24;12(5):627.

61. Nguyen NT, Nguyen LM, Nguyen TT, Nguyen TT, Nguyen DT, Tran TV. Formation, antimicrobial activity, and biomedical performance of plant-based nanoparticles: a review. Environmental Chemistry Letters. 2022 Aug;20(4):2531-2571.
62. Abarca-Cabrera L, Fraga-García P, Berensmeier S. Bio-nano interactions: binding proteins, polysaccharides, lipids and nucleic acids onto magnetic nanoparticles. Biomaterials research. 2021 Apr 21;25(1):12.
63. Vladilo G, Hassanali A. Hydrogen bonds and life in the universe. Life. 2018 Jan 3;8(1):1.
64. Zhou HX, Pang X. Electrostatic interactions in protein structure, folding, binding, and condensation. Chemical reviews. 2018 Feb 28;118(4):1691-1741.
65. Mourdikoudis S, Pallares RM, Thanh NT. Characterization techniques for nanoparticles: comparison and complementarity upon studying nanoparticle properties. Nanoscale. 2018;10(27):12871-12934.
66. Malatesta M. Transmission electron microscopy as a powerful tool to investigate the interaction of nanoparticles with subcellular structures. International Journal of Molecular Sciences. 2021 Nov 26;22(23):12789.
67. Upadhyay S, Parekh K, Pandey B. Influence of crystallite size on the magnetic properties of Fe3O4 nanoparticles. Journal of Alloys and Compounds. 2016 Sep 5; 678:478-485.
68. Li W, Zamani R, Rivera Gil P, Pelaz B, Ibáñez M, Cadavid D, Shavel A, Alvarez-Puebla RA, Parak WJ, Arbiol J, Cabot A. CuTe nanocrystals: shape and size control, plasmonic properties, and use as SERS probes and photothermal agents. Journal of the American Chemical Society. 2013 May 15;135(19):7098-7101.
69. Kim BH, Heo J, Park J. Determination of the 3D atomic structures of nanoparticles. Small Science. 2021 Jan;1(1):2000045.
70. Nikolić V, Ilić-Stojanović S, Petrović S, Tačić A, Nikolić L. Administration routes for nano drugs and characterization of nano drug loading. InCharacterization and biology of nanomaterials for drug delivery 2019 Jan 1: 587-625.
71. Faghihzadeh F, Anaya NM, Schifman LA, Oyanedel-Craver V. Fourier transform infrared spectroscopy to assess molecular-level changes in microorganisms exposed to nanoparticles. Nanotechnology for Environmental Engineering. 2016 Dec; 1:1-16.
72. Alagesan V, Venugopal S. Green synthesis of selenium nanoparticle using leaves extract of *Withania somnifera* and its biological applications and photocatalytic activities. Bionanoscience. 2019 Mar 15; 9:105-116.
73. Prasad KS, Prasad SK, Veerapur R, Lamraoui G, Prasad A, Prasad MN, Singh SK, Marraiki N, Syed A, Shivamallu C. Antitumor potential of green synthesized ZnONPs using root extract of *Withania somnifera* against human breast cancer cell line. Separations. 2021 Jan 18;8(1):8.
74. S. Dhabian and R. Jasim, "Anticancer and Antioxidant Activity of the Greenly Synthesized Zinc Nanoparticles Composites using Aqueous Extract of *Withania somnifera* plant," *Egypt. J. Chem.*, pp. 0–0, May 2021, doi: 10.21608/ejchem.2021.75114.3686.
75. Malaikozhundan B, Vinodhini J, Kalanjiam MA, Vinotha V, Palanisamy S, Vijayakumar S, Vaseeharan B, Mariyappan A. High synergistic antibacterial, antibiofilm, antidiabetic and antimetabolic activity of *Withania somnifera* leaf extract-assisted zinc oxide nanoparticle. Bioprocess and biosystems engineering. 2020 Sep; 43:1533-1547.
76. Kapoor S, Sood H, Saxena S, Chaurasia

OP. Green synthesis of silver nanoparticles using Rhodiola imbricata and *Withania somnifera* root extract and their potential catalytic, antioxidant, cytotoxic and growth-promoting activities. Bioprocess and Biosystems Engineering. 2022:1-6.

77. Jagadheeswari R, Lakshmi T, Balusamy S, David S, Raghunandha S. Biosynthesis of silver nanoparticles using *Withania somnifera* L. Dunal extract and its antibacterial activity against food pathogens. Ann. Phytomed. 2020;9(1):195-198.
78. Gaurav I, Singh T, Thakur A, Kumar G, Rathee P, Kumari P, Sweta K. Synthesis, in-vitro and in-silico evaluation of silver nanoparticles with root extract of *Withania somnifera* for antibacterial activity via binding of penicillin-binding protein-4. Current Pharmaceutical Biotechnology. 2020 Dec 1;21(15):1674-1687.
79. Abul Qais F, Samreen, Ahmad I. Broad-spectrum inhibitory effect of green synthesised silver nanoparticles from *Withania somnifera* (L.) on microbial growth, biofilm and respiration: a putative mechanistic approach. Iet Nanobiotechnology. 2018 Apr;12(3):325-335.
80. Meher K, Paithankar H, Hosur RV, Lopus M. Ashwagandha-polyphenols-functionalized gold nanoparticles facilitate apoptosis by perturbing microtubule assembly dynamics in breast cancer cells. Journal of Drug Delivery Science and Technology. 2022 Apr 1; 70:103225.
81. Al-Shabib NA, Husain FM, Qais FA, Ahmad N, Khan A, Alyousef AA, Arshad M, Noor S, Khan JM, Alam P, Albalawi TH. Phyto-mediated synthesis of porous titanium dioxide nanoparticles from *Withania somnifera* root extract: broad-spectrum attenuation of biofilm and cytotoxic properties against HepG2 cell lines. Frontiers in Microbiology. 2020 Jul 28; 11:1680.
82. Singh OS, Pant NC, Laishram L, Tewari M, Dhoundiyal R, Joshi K, Pandey CS. Effect of CuO nanoparticles on polyphenols content and antioxidant activity in Ashwagandha (*Withania somnifera* L. Dunal). Journal of Pharmacognosy and Phytochemistry. 2018;7(2):3433-3439.
83. Shanmugapriya J, Reshma CA, Srinidhi V, Harithpriya K, Ramkumar KM, Umpathy D, Gunasekaran K, Subashini R. Green synthesis of copper nanoparticles using *Withania somnifera* and its antioxidant and antibacterial activity. Journal of Nanomaterials. 2022;2022(1):7967294.
84. Chinembiri TN, Gerber M, Du Plessis LH, Du Preez JL, Hamman JH, Du Plessis J. Topical delivery of *Withania somnifera* crude extracts in niosomes and solid lipid nanoparticles. Pharmacognosy magazine. 2017 Oct;13: S663.
85. Nair A, Kuppusamy K, Nangan S, Natesan T, Haponiuk JT, Thomas S, Ramasubburayan R, Gnanasekaran L, Selvaraj M, Gopi S. Multifunctional natural derived carbon quantum dots from *Withania somnifera* (L.)–Antiviral activities against SARS-CoV-2 pseudoviron. Environmental Research. 2023 Dec 15; 239:117366.
86. Li Y, Zhang J, Gu J, Chen S. Biosynthesis of polyphenol-stabilised nanoparticles and assessment of anti-diabetic activity. Journal of Photochemistry and Photobiology B: Biology. 2017 Apr 1; 169:96-100.
87. Daei S, Ziamajidi N, Abbasalipourkabir R, Aminzadeh Z, Vahabirad M. Silver nanoparticles exert apoptotic activity in bladder cancer 5637 cells through alteration of Bax/Bcl-2 genes expression. Chonnam Medical Journal. 2022 Sep;58(3):102.
88. Khan MS, Qais FA, Ahmad I. Indian berries and their active compounds: Therapeutic potential in cancer prevention. InNew Look to Phytomedicine 2019:179-201.

89. Maarouf RE, Azab KS, El Fatih NM, Helal H, Rashed L. *Withania somnifera* Alter BCL2/Bax signaling and trigger apoptosis of MCF-7 and MDA-MB231 breast cancer cells exposed to γ-radiation. Human & Experimental Toxicology. 2023 May 31; 42:09603271231180849.
90. Mohammed Ali IA, AL-Ahmed HI, Ben Ahmed A. Evaluation of green synthesis (*Withania somnifera*) of selenium nanoparticles to reduce sperm DNA fragmentation diabetic mice induced with streptozotocin. Applied Sciences. 2023 Jan 4;13(2):728.
91. Logie E, Vanden Berghe W. Tackling chronic inflammation with withanolide phytochemicals—A withaferin a perspective. Antioxidants. 2020 Nov 10;9(11):1107.
92. Suganya K, Kayalvizhi E, Yuvaraj R, Chandrasekar M, Kavitha U, Suresh KK. Effect of *Withania somnifera* on the antioxidant and neurotransmitter status in sleep deprivation induced Wistar rats. Bioinformation. 2020;16(8):631.
93. Mehta SK, Gowder SJ. Members of antioxidant machinery and their functions. Basic principles and clinical significance of oxidative stress. 2015 Nov 11; 11:59-85.
94. Gómez Afonso A, Fernandez-Lazaro D, Adams DP, Monserda-Vilaro A, Fernandez-Lazaro CI. Effects of *Withania somnifera* (Ashwagandha) on hematological and biochemical markers, hormonal behavior, and oxidant response in healthy adults: A systematic review. Current Nutrition Reports. 2023 Sep;12(3):465-477.
95. Devi A, Dwibedi V, George N, Khan ZA. Response surface optimization for investigating antioxidant potential of Camellia Sinensis and *Withania somnifera* in synergistic manner. Proceedings of the National Academy of Sciences, India Section B: Biological Sciences. 2023 Jun;93(2):397-408.
96. Pizzino G, Irrera N, Cucinotta M, Pallio G, Mannino F, Arcoraci V, Squadrito F, Altavilla D, Bitto A. Oxidative stress: harms and benefits for human health. Oxidative medicine and cellular longevity. 2017;2017(1):8416763.
97. Manke A, Wang L, Rojanasakul Y. Mechanisms of nanoparticle-induced oxidative stress and toxicity. BioMed research international. 2013;2013(1):942916.
98. Narra K, Naik SK, Ghatge AS. A study of efficacy and safety of ashwagandha (*Withania somnifera*) lotion on facial skin in photoaged healthy adults. Cureus. 2023 Mar;15(3).
99. Sharma PK, Kumar L, Goswami Y, Pujani M, Dikshit M, Tandon R. The aqueous root extract of *Withania somnifera* ameliorates LPS-induced inflammatory changes in the in vitro cell-based and mice models of inflammation. Frontiers in Pharmacology. 2023 Jun 12; 14:1139654.
100. Pontes-Quero GM, Benito-Garzón L, Pérez Cano J, Aguilar MR, Vázquez-Lasa B. Modulation of inflammatory mediators by polymeric nanoparticles loaded with anti-inflammatory drugs. Pharmaceutics. 2021 Feb 23;13(2):290.
101. Brusini R, Varna M, Couvreur P. Advanced nanomedicines for the treatment of inflammatory diseases. Advanced drug delivery reviews. 2020 Jan 1; 157:161-178.
102. Liu T, Zhang L, Joo D, Sun SC. NF-κB signaling in inflammation. Signal transduction and targeted therapy. 2017 Jul 14;2(1):1-9.
103. Martorana F, Guidotti G, Brambilla L, Rossi D. Withaferin A inhibits nuclear factor-κB-dependent pro-inflammatory and stress response pathways in astrocytes. Neural plasticity. 2015;2015(1):381964.
104. Wang X, Shen Y, Thakur K, Han J, Zhang JG, Hu F, Wei ZJ. Antibacterial activity and mechanism of ginger essential oil against Escherichia coli and Staphylococcus aureus. Molecules.

2020 Aug 30;25(17):3955.
105. Das R, Afrin N. In vivo study of anti-diabetic activity and safety profile analysis of ethanolic extract of root of *Withania somnifera* on alloxan-induced diabetic rats. World Journal of Pharmaceutical Research. 2019 Oct 17;8.
106. Jafri AA, Aggarwal J, Batra J. Antidiabetic effect of *Withania somnifera* Root in STZ induced diabetic rats. Cardiometry. 2022 Dec 1(25):1278-1283.
107. Ashwini D, Mahalingam G. Green synthesized metal nanoparticles, characterization and its antidiabetic activities-a review. Research Journal of Pharmacy and Technology. 2020;13(1):468-474.
108. Vaiserman A, Koliada A, Zayachkivska A, Lushchak O. Nanodelivery of natural antioxidants: an anti-aging perspective. Frontiers in bioengineering and biotechnology. 2020 Jan 10; 7:447.
109. Kiani BH, Haq IU, Alhodaib A, Basheer S, Fatima H, Naz I, Ur-Rehman T. Comparative evaluation of biomedical applications of zinc nanoparticles synthesized by using *Withania somnifera* Plant Extracts. Plants. 2022 Jun 7;11(12):1525.
110. M. P. S. S, "A Comprehensive Review on Medicinal Herb *Withania somnifera* (L.) Dunal in Women's Health: a Rejuvenator From Siddha Medicine," *Curr. Pharmacol. Reports*. 2022; 8(1): 72-77.
111. Rana N, Singh SK, Banu NA, Hjazi A, Vamanu E, Singh MP. The ethnopharmacological properties of green-engineered metallic nanoparticles against metabolic disorders. Medicina. 2023 May 25;59(6):1022.
112. P. Maheswari, S. Harish, M. Navaneethan, C. Muthamizhchelvan, S. Ponnusamy, and Y. Hayakawa, "Bio-modified TiO2 nanoparticles with *Withania somnifera*, Eclipta prostrata and Glycyrrhiza glabra for anticancer and antibacterial applications," *Mater. Sci. Eng. C*, vol. 108, p. 110457, Mar. 2020, doi: 10.1016/j.msec.2019.110457.
113. Haleem A, Javaid M, Singh RP, Rab S, Suman R. Applications of nanotechnology in medical field: a brief review. Global Health Journal. 2023 Jun 1;7(2):70-77.
114. Martínez-Ballesta M, Gil-Izquierdo Á, García-Viguera C, Domínguez-Perles R. Nanoparticles and controlled delivery for bioactive compounds: Outlining challenges for new "smart-foods" for health. Foods. 2018 May 7;7(5):72.
115. Patra JK, Das G, Fraceto LF, Campos EV, Rodriguez-Torres MD, Acosta-Torres LS, Diaz-Torres LA, Grillo R, Swamy MK, Sharma S, Habtemariam S. Nano based drug delivery systems: recent developments and future prospects. Journal of nanobiotechnology. 2018 Dec; 16:1-33.
116. Koklesova L, Jakubikova J, Cholujova D, Samec M, Mazurakova A, Šudomová M, Pec M, Hassan ST, Biringer K, Büsselberg D, Hurtova T. Phytochemical-based nanodrugs going beyond the state-of-the-art in cancer management—Targeting cancer stem cells in the framework of predictive, preventive, personalized medicine. Frontiers in Pharmacology. 2023 Mar 23; 14:1121950.
117. Harish V, Tewari D, Gaur M, Yadav AB, Swaroop S, Bechelany M, Barhoum A. Review on nanoparticles and nanostructured materials: Bioimaging, biosensing, drug delivery, tissue engineering, antimicrobial, and agro-food applications. Nanomaterials. 2022 Jan 28;12(3):457.
118. Selvakesavan RK, Franklin G. Prospective application of nanoparticles green synthesized using medicinal plant extracts as novel nanomedicines. Nanotechnology, science and applications. 2021 Sep

23:179-195.
119. Fuladi S, Emami SA, Mohammadpour AH, Karimani A, Manteghi AA, Sahebkar A. Assessment of the efficacy of *Withania somnifera* root extract in patients with generalized anxiety disorder: a randomized double-blind placebo-controlled trial. Current Reviews in Clinical and Experimental Pharmacology Formerly Current Clinical Pharmacology. 2021 May 1;16(2):191-196.
120. Anand U, Carpena M, Kowalska-Góralska M, Garcia-Perez P, Sunita K, Bontempi E, Dey A, Prieto MA, Proćków J, Simal-Gandara J. Safer plant-based nanoparticles for combating antibiotic resistance in bacteria: A comprehensive review on its potential applications, recent advances, and future perspective. Science of The Total Environment. 2022 May 15; 821:153472.
121. Dhaka A, Mali SC, Sharma S, Trivedi R. A review on biological synthesis of silver nanoparticles and their potential applications. Results in Chemistry. 2023 Sep 11:101108.
122. Das R, Rauf A, Akhter S, Islam MN, Emran TB, Mitra S, Khan IN, Mubarak MS. Role of withaferin A and its derivatives in the management of Alzheimer's disease: Recent trends and future perspectives. Molecules. 2021 Jun 17;26(12):3696.
123. Azameti MK, Imoro AW. Nanotechnology: A promising field in enhancing abiotic stress tolerance in plants. Crop Design. 2023 Jun 28:100037.
124. El-Saadony MT, Saad AM, Soliman SM, Salem HM, Desoky ES, Babalghith AO, El-Tahan AM, Ibrahim OM, Ebrahim AA, Abd El-Mageed TA, Elrys AS. Role of nanoparticles in enhancing crop tolerance to abiotic stress: A comprehensive review. Frontiers in plant science. 2022 Nov 2; 13:946717.
125. Rajput VD, Minkina T, Upadhyay SK, Kumari A, Ranjan A, Mandzhieva S, Sushkova S, Singh RK, Verma KK. Nanotechnology in the restoration of polluted soil. Nanomaterials. 2022 Feb 24;12(5):769.
126. Adnan M, Akbar A, Mussarat S, Murad W, Hameed I, Begum S, Nazir R, Ali N, Ali EA, Bari A, Aziz MA. [Retracted] Phyto-Extract-Mediated Synthesis of Silver Nanoparticles (AgNPs) and Their Biological Activities. BioMed Research International. 2022;2022(1):9845022.