

Comprehensive Review on *Withania coagulans* Dunal: Unveiling Pharmacognosy, Phytochemistry and Pharmacological Potentials

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ABSTRACT

Background: The Solanaceae family plant *Withania coagulans* (Stocks) Dunal is also known by the names vegetable rennet, paneer doda, paneer ka phool and rishyagandha. It is widely used in traditional medicines in countries like Pakistan, Iran, Afghanistan and East-West India. Since ancient times, herbs have been effective such as sedative, nervous system, depressant, hepatoprotective and treatment for various illnesses like diabetes, heart problem, cancer and asthma. The smoke from the plant is inhaled to ease toothaches and the twigs are chewed to clean teeth. This overview study analyses scientific and therapeutic prospects for further research on *Withania coagulans* and offers extensive information on the morphological, biochemical and pharmacological effects. **Materials and Methods:** ScienceDirect, Pub Med, Google Scholar, Scopus, or Research Gate are the scientific research databases has been utilized for gathering their information for the study of *Withania coagulans* Dunal. The pharmacological, pharmacognostical and phytochemical properties of *Withania coagulans* are summarized in this article. **Results:** Various parts and its pharmacological properties have been reported in *Withania coagulans* including anti-hyperglycemic, anti-inflammatory, anti-fungal, anti-bacterial, anti-asthmatic, hepatoprotective, immunosuppressive, sedative, diuretic and depressant medication. In additionally bioactive compounds has been isolated like withanolide, fatty acid, aromatic ester, 1-methyl-octadecanoic acid, hexanoic acid, n-hexadecenoic acid, Vitamin E. **Conclusion:** A comprehensive survey literatures concerning the morphological, microscopy, traditional uses, phytochemical and pharmacological effects for a wide variety of herbal extract presented in this review. Since numerous aspects plant extract have not yet been explored, some traditional uses still require validation in order to discover the unexplored opportunities of this plant.

Keywords: Bioactive compounds, Ethnobotanical aspects, Natural products, Ethnopharmacology.

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INTRODUCTION

For thousands of years, *Withania* has been used to treat illnesses, preserve food, stop epidemics and address other health issues. This shrub grows widely in Afghanistan, Nepal and East India. It happens in Shimla, Punjab, Rajasthan, Kamaun and Garhwal,^[1] India. Indian cheese maker, or *W. coagulans* Dunal belonging to Family Solanaceae, is a stiff, grey under shrub that grows 60-120 cm high in arid regions of India.^[2-5] It has been stated that this plant has a diversity of biological functions in its different portions.^[6] The sweet-taste fruits of *W. coagulans* are commonly applied to wounds. Additionally, the fruits are utilised to treat liver and asthma conditions. The seeds are used to cure liver problems, piles, ophthalmia and as an emmenagogue and diuretic. They are

used as blood purifier and used in nervous exhaustion, insomnia, impotence, dyspepsia, flatulent and intestinal infections.^[7] Milk coagulation can be achieved by the berries of the shrub. Milk coagulation is only caused by aspartic protease, as determined by mass spectrometry 2 analysis of purified protease and enzyme assays carried out in the presence of protease inhibitors.^[8,9]

Chewing on twigs can help with tooth cleaning and inhaling the plant's smoke can ease toothache pain. *W. coagulans* flowers are used to cure diabetes; locally, leaves and roots are utilised to cure a range of diseases.^[10] Anti-mutagenic, antioxidant, antidiabetic, anti-microbial, anti-fungal, anti-bacterial, anti-hyperglycemic and anti-cancer effects have been found for *W. coagulans* fruit extracts.^[11,12] The main active chemical constituents of plant are alkaloids, carbohydrates, phenolic compounds, steroids, tannins, amino acids, organic acids, withacoagin, withaferin, essential oils, flavonoids, vitamin, triterpenes etc.^[13,14] *Withania coagulans* as a coagulant for tofu production by assessing its impact on quality and sensory properties.^[12] The results may provide information on



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the potential of *Withania coagulans* in tofu manufacturing and its acceptability among consumers.^[15] The wild *Withania coagulans* fruits possess various nutraceutical and biological attributes, making them potentially valuable for health and wellness.^[16]

RESULTS AND DISCUSSION

Pharmacognostical study of *Withania coagulans*

Morphological Characters

The entire plant is a 60-120 cm tall, upright, greyish shrub. With densely packed grey or yellow-white branches, the leaves are 25-75 mm in length and 1500 mm in width, possessing a tendency to thin at the base. The dioecious, polygamous, 7-12 cm yellowish flowers are dioecious. The filament length of the stamen is 2 mm and its anther measures 3-5 mm. The stamen is level with the corolla tube.^[17,18] The ovary has no stigma and is oval in shape. It has a mushroom-shaped, 2-lamellate stigma, a glabrous style and is glabrous throughout. The smooth, globose berry has a diameter of 6 to 8 mm. The glabrous, 2.5-3 mm-diameter seeds have an ear-like structure.^[7,19] The fruits are superior, indehiscent, berries with numerous seeds. It is pedicellate, 4-6 mm in diameter, spherical to globular in shape and yellow to brown in colour showing in Figure 1. The fruits have a faint aroma and a slightly unpleasant taste.^[8]

Microscopic characters

The pedicel's outer layer, the epidermis, consists of rectangular to slightly elongated cells with a smooth cuticle. Below the epidermis lies the cortex, composed of parenchymatous cells. These cells are thin-walled and store various nutrients. The vascular bundles are arranged in a ring and include both xylem and phloem. The xylem vessels are thick-walled and lignified, while the phloem consists of thin-walled sieve elements and companion cells. At the center of the pedicel is the pith, made up of large parenchymatous cells shown in Figure 2 (i). The calyx's outermost layer consists of polygonal cells with a thick cuticle. Trichomes (hair-like structures) are often present and can be unicellular or multicellular. The internal tissue of the calyx, the mesophyll, is divided into palisade and spongy parenchyma shown in Figure 2 (iii). The palisade cells are elongated and arranged tightly, while the spongy parenchyma cells are more loosely packed. The vascular bundles are scattered throughout the mesophyll and contain xylem and phloem tissues. The xylem

vessels are thick-walled, and the phloem elements are thin-walled. The outer layer of the seed is the testa, which consists of several layers of cells. The outermost layer is composed of thick-walled sclerenchymatous cells that provide protection. The endosperm is a nutritive tissue inside the seed, composed of thin-walled parenchymatous cells. It is rich in starch and oils. The embryo is the young plant inside the seed, consisting of embryonic root (radicle), shoot (plumule), and cotyledons (seed leaves). The cells of the embryo are meristematic, meaning they have the capacity to divide and differentiate shown in Figure 2 (iv). The outermost layer of the pericarp is the epicarp, made up of polygonal cells with a thick cuticle. It may also have trichomes. The middle layer of the pericarp, the mesocarp, consists of parenchymatous cells that are thin-walled and store nutrients. Vascular bundles are present within this layer. The innermost layer of the pericarp, the endocarp, is composed of thick-walled sclerenchymatous cells shown in Figure 2 (ii) that provide protection to the seed shown in Table 1.

Taxonomic Classification^[20]

- Kingdom-Plantae
- Subkingdom-Tracheobionta
- Division-Spermatophyta
- Class-Dicotyledons
- Order-Tubiflorae
- Family -Solanaceae
- Genus- *Withania*
- Species-coagulans

Vernacular Names^[20]

- Sanskrit-Rishyagandha
- Hindi-Paneer doda, Binputakah, Akri
- English-Indian cheese maker, India rennet, Vegetable rennet
- Bengal -Asva Gandha
- Sindhi- Punirjafota, Punirband
- Persian -Kaknajehindi, Punirbad
- Arabic-Javzulmizaja, kaknajehindi

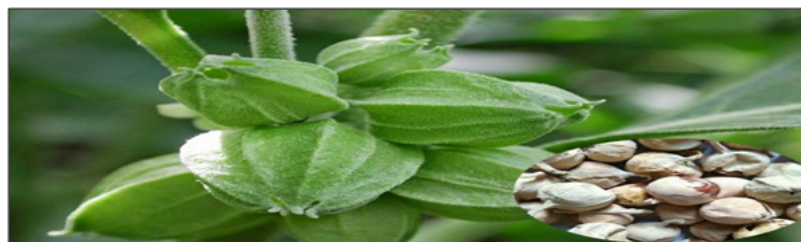


Figure 1: *Withania coagulans* Plant and Fruits.

Table 1: Microscopic Characters of *Withania coagulans*.

Part Used	Microscopic Characters	References
Pedicele	A single layer of tabular cells with many branching and unbranched trichomes covers the epidermis in the transverse section of the pedicel. This is followed by a cortex consisting of five to ten layers of collenchymatous cells. The pericycle has parenchymatous cells interspersed with pericyclic threads. The pericycle has parenchymatous cells interspersed with pericyclic threads. The xylem in the central region is bordered by a narrow band of phloem, which is enclosed by a ring of intra-xylary phloem. Parenchymatous cells encircle the hollow pith in the core and a few lignified fibres with robust walls that point in the direction of the phloem are visible.	[8,14]
Calyx	The calyx's bottom epidermis is made up of a single layer of thin-walled cells, while the upper epidermis has a few branching and unicellular covering trichomes. The mesophyll is made up of spongy parenchyma that is crossed by several tiny veins and wrapped in bundle sheath cells made of thin-walled parenchymatous cells.	[8,14]
Pericarp	The transverse section reveals a large zone of parenchymatous cells with significant cellulose thickening may be seen in the mesocarp of the pericarp (fruit wall). The exocarp, which is composed of a single layer of cells, is also visible. An isolated layer of cells makes up the endocarp.	[8,14]
Seed	A single layer of sub-epidermal cells with flattened, thin walls is seen after the epidermis in the transverse section of a seed. A layer of strongly lignified sclerenchyma cells with a constrictive lumen lies beneath the sub-epidermis. A seed coat's inner epidermis is made up of one to three layers of parenchymatous cells with weak walls, some of which are collapsing. Cells with prominent cellulose thickening and aleurone grains serve as a representation of the endosperm. Thin-walled, radially elongated cells in the cotyledon surround a significant zone of polyhedral, round, oval and round parenchymatous cells.	[14]

- Telugu-Panneru gadda
- Urdu-Habkajn

Ethnomedicinal uses

Withania coagulans is the popular name for the medicinal herb known as Rishyagandha. Numerous conditions include dyspepsia, diabetes mellitus, liver abnormalities, blood purification, controlling plasma glucose levels and avoiding kidney problems are treated with it.^[18] The fruit of *W. coagulans* has long been utilised as a milk coagulant.^[21,22] In Pakistan, Afghanistan, Iran and East India, it is a traditional medicinal remedy.^[23] The edible fruits of this plant are sweet and have sedative, emetic, diuretic and milk-coagulating properties. In order to treat burns, arthritis and rheumatism, this plant's fruit and root are employed.^[24]

The fruit is also frequently called "tukhm-e-hayat" (fruit of life). There is also evidence that the plant has a variety of other functions, including cardiovascular, hepatoprotective, immunosuppressive, cytotoxic, antifungal, antibacterial, anti-inflammatory, promotes healing of wounds and scavenges free radicals.^[25]

Phytochemical Activities

The main phytoconstituents isolated from *Withania coagulans* by using n-hexane fraction were withanolide. Withanolide are chemically lactone steroids and the basic structure of withanolide shown in Figure 20.^[26,27] The pale-yellow color

volatile oil (0.12% yield) was isolated from the fruits of *W. coagulans*. 40 known compounds were isolated from oil. The main volatile oils were veramol, eugenol, Caprylic, capric, caproic and lauric acids. Ninety-five percent of known chemical compound were oil-based.^[28] *W. coagulans* entire plant yielded three new withanolides, including 20,27-dihydroxy-3 β -(O- β -D-glucopyranosyl)1-oxo-(20S, 22R) O- β -D-glucopyranosyl-5,14,24-trienolide and 1 α ,20-dihydroxy-3 β -(20S,22R)-containing 5,24-dienolide and 3 β ,17 β -dihydroxy-14,20-epoxy-1-oxo-(22R)Alongside 5,24-dienolide.^[29] Two novel withanolides, withacogulin and 20 β -hydroxy-1-oxo-(22R)-witha-2,5,24-trienolide, were found from the entire *W. coagulans* plant. 17 β -hydroxy-14 α , 20 α -epoxy-1-oxo-(22R)-witha-3,5,24-trienolide was another identified withanolide.^[29] The ethanolic extract of *W. coagulans* revealed the presence of carbohydrates, proteins, flavonoids, steroids, anthraquinone, tannin, triterpenoids and phenolic compounds.^[30] The phytoconstituents that were separated from *W. coagulans* fruits was Cetyl palmitate shown in Figure 3, (3R,4R)-Dihydroxyadipic- γ , γ '-dilactone shown in Figure 4, Withacoagulanide A shown in Figure 5, Withacoagulanide B shown in Figure 6, Withacoagulanide C shown in Figure 7, Withacoagulanide D shown in Figure 8, Withacoagulanide C6-arabinosyl 2'-O-anisate shown in Figure 9, 3-O-Digalactosyl withacoagulanide B shown in Figure 10, Glyceryl-1,2-dipalmityl 3-phosphate shown in Figure 11, 3-Seco-withacoagulanolide 6 β -olyl galacturonoside shown in Figure 12, Withacoagulanide

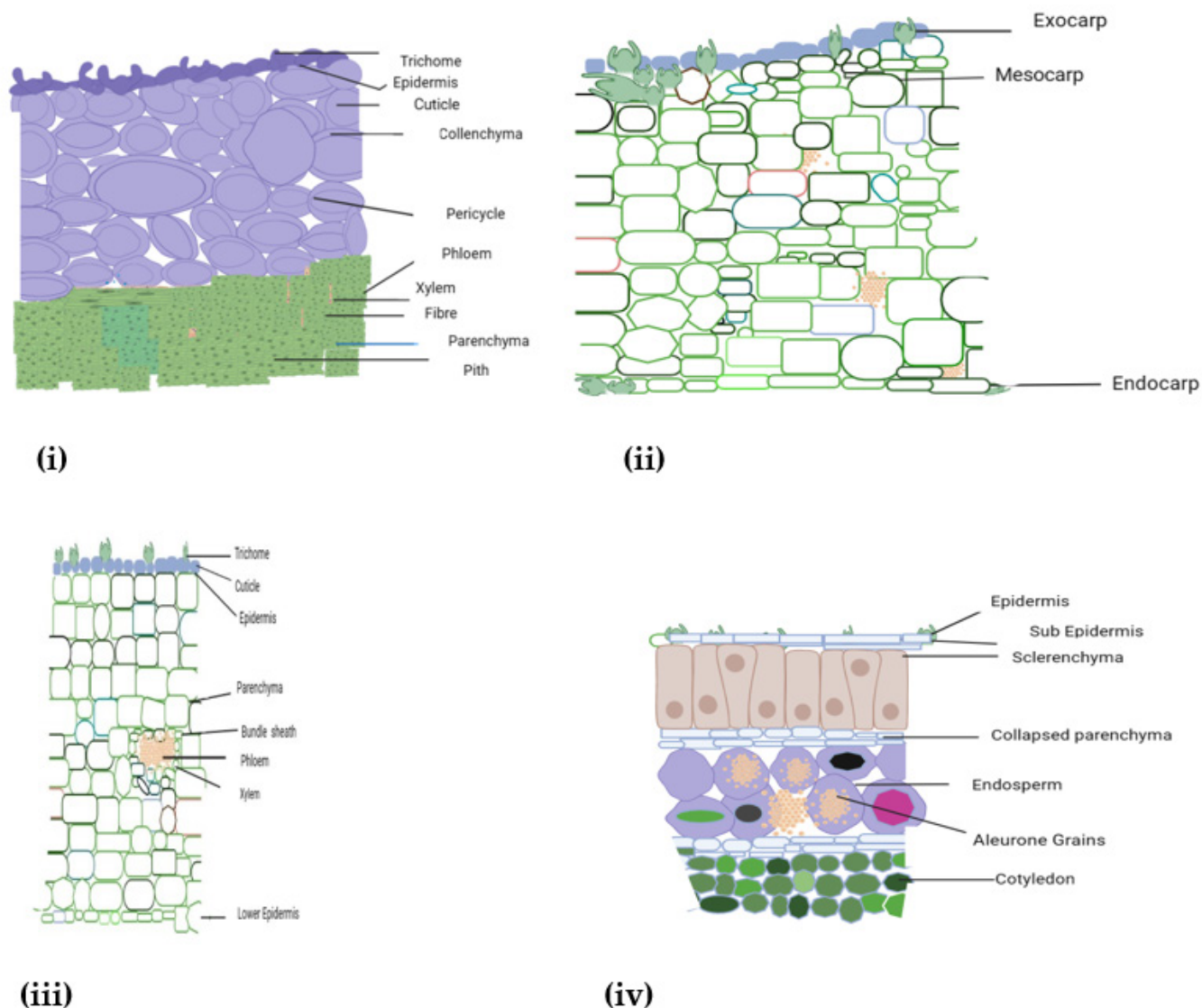


Figure 2: (i) Transverse section of Pedicle. (ii) Transverse section of Pericarp (Fruit wall). (iii) Transverse section of calaxy. (iv) Transverse section of Seed.



Figure 3: Cetyl palmitate dilactone.

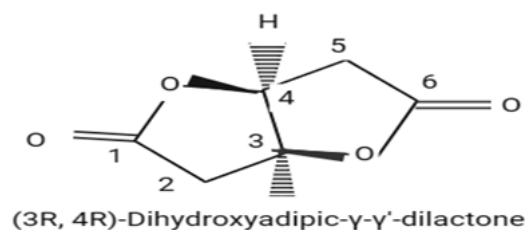


Figure 4: (3R,4R)-Dihydroxyadipic- γ , γ' -.

C 6 β -Olyl diarabinosyl 2''-(O)-anisate shown in Figure 13 and Caproyl trixyloside shown in Figure 14.^[31]

Six steroidal lactones, also referred to as withanolides or asteroids, were produced from extracts of *Withania coagulans*.^[32] These lactones are called withaferin A shown in Figure 15,^[33] withanolide H shown in Figure 16, withanolide A shown in Figure 17, with coagulin H shown in Figure

18 and withanolide J shown in Figure 19.^[34,35] Additionally, an aromatic ester, a monoterpenes benzyl glucoside and a novel fatty acid were identified as n-octatriacont-17-enoic acid, geranilan-10-olyl dihydrocinnamoate and geranilan-8-oic acid-10-olyl salicyloxy-2-O- β -d-glucofuranosyl-(6 \rightarrow 1'') Together with two known fatty acids, n-dotriacont-21-enoic acid and n-tetra triacontanoic acid, -O- β -d-glucofuranosyl-6-n-octadec-9',11'''-dienoate.

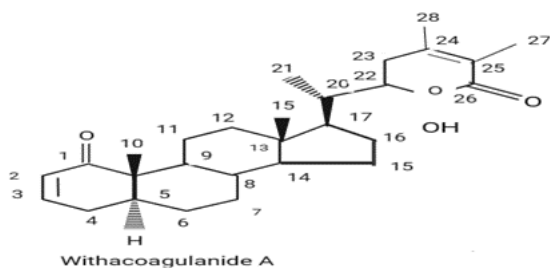


Figure 5: Withacoagulanide A.

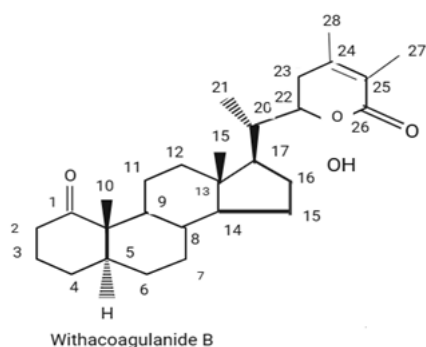


Figure 6: Withacoagulanide B.

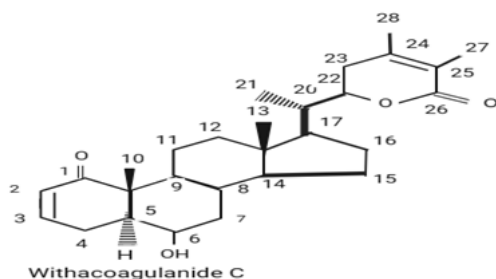


Figure 7: Withacoagulanide C.

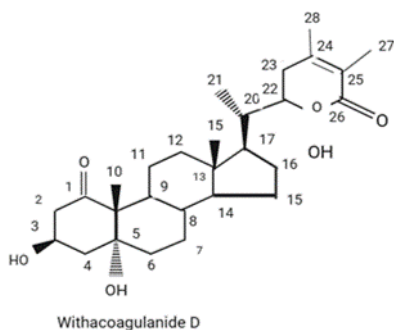


Figure 8: Withacoagulanide D.

Withania coagulans was extracted methanologically to provide two withanolides, 20(β)-hydroxy-1-oxo-(22R)-witha-2,5,24-trienolide and with coagulin, as well as a known steroidal lactone.^[36] The identification of new compounds in *Withania coagulans* particularly ergostane-type steroidal lactones, contributes to the understanding of its chemical composition and potential pharmacological activities. Ergostane-type steroidal lactones are known for their diverse

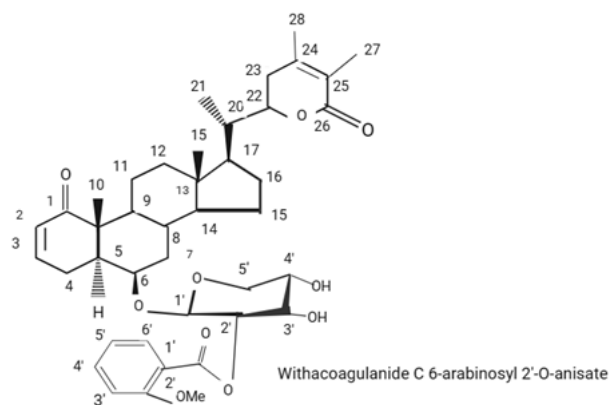


Figure 9: Withacoagulanide C 6-arabinosyl 2'-O-anisate.

bioactivities, including anti-inflammatory, immunomodulatory and anticancer properties.^[37]

Withania coagulans fruits were extracted one at a time using organic solvents. Following the extraction process, the extracts underwent a number of chromatographic methods, such as High-Performance Liquid Chromatography (HPLC) and column chromatography. Spectroscopic methods, including mass spectrometry and Nuclear Magnetic Resonance (NMR), were utilised to characterise the isolated chemicals. Three new types of chemicals were discovered through the chemical examination of the fruit extracts: Menthyl glycosides, Acyl withanolides and Novel withanolides.^[38]

A class of naturally occurring substances called withanolides is mostly present in plants belonging to the Solanaceae family, such as *Withania coagulans*. These substances' many pharmacological actions, such as their anti-inflammatory, antioxidant, immunomodulatory and anti-tumor qualities, have attracted a lot of interest. *Withania coagulans* is known to contain several withanolides^[39] and these compounds are considered the major bioactive constituents responsible for the plant's medicinal properties.^[29]

The concentration of the various *W. coagulans* components was ascertained using three distinct extracts: methanolic, hydroalcoholic and chloroform. According to the research report, the methanolic extract had higher overall phenolic content (55.9 mg/g), total tannins (76.6 mg/g), total flavonoids (0.88 mg/g) and total flavanol (0.25 mg/g) than the hydroalcoholic and chloroform extracts.^[8]

The HPTLC analysis will reveal the phytochemical profile of *Withania coagulans* from different geographical regions, emphasizing variations in beta-sitosterol content. It provides valuable insights into the phytochemical variability of *Withania coagulans* Dunal, specifically focusing on the quantification of beta-sitosterol across different geographical regions. The outcomes contribute to our understanding of the chemical diversity within this medicinal plant, aiding in its optimal

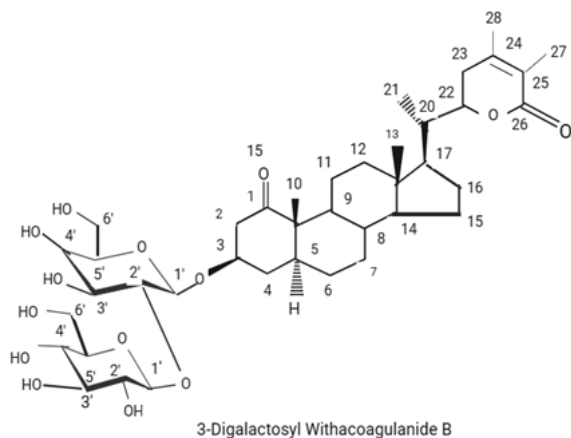


Figure 10: 3-Digalactosyl Withacoagulanide B.

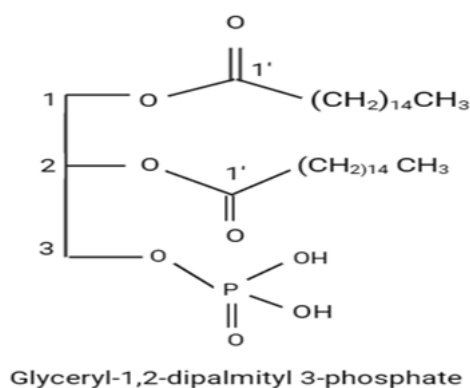


Figure 11: Glycerol-1,2-dipalmitoyl 3-phosphate.

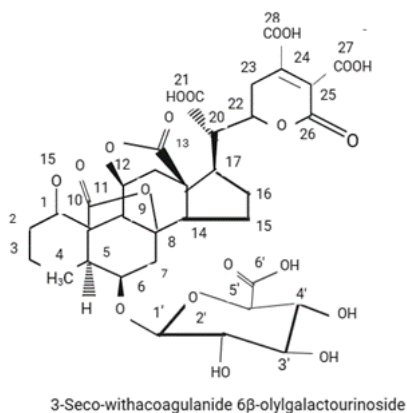


Figure 12: 3-Seco-withacoagulanide 6β-olylgalactourinoside.

utilization for therapeutic purposes.^[40] The fatty acid composition of *Withania coagulans* fruits can provide insights into the nutritional value and potential health benefits associated with the consumption of these fruits. Additionally, certain fatty acids, such as linoleic acid, are precursors to bioactive compounds with potential health-promoting effects.^[41] The presence of diverse phytoconstituents in the oil extracted from seeds of *Withania*

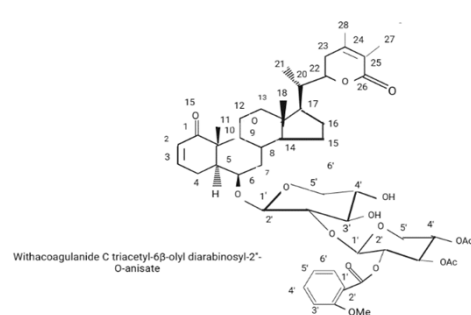


Figure 13: Withacoagulanide C 6β-olyl diarabinosyl 2''-(O)-anisate.

coagulans suggests a rich chemical composition with potential pharmacological activities.^[42]

Pharmacological Activities

Many pharmacological studies have been conducted utilising both *in vitro* and *in vivo* test paradigms, employing different standardised extracts from different *W. coagulans* sections. The phytoconstituents in the plant mediate the details of the standardised extracts that show notable biological actions like antidiabetic, anti-inflammatory, hypolipidemic, hepatoprotective, anti-oxidant, anti-microbial and anti-cancer characteristics.

Hepatoprotective Activity

This plant aqueous methanolic extract (800 mg/kg, orally) has been demonstrated to have hepatoprotective effects on rats liver damage caused by CCl_4 and it has also been found that the gallic acid and rutin levels in the extract enhance *W. coagulans* hepatoprotective properties.^[43] In BALB/c mice, the *Withania coagulans* n-hexane fraction and crude methanolic extract showed encouraging hepatoprotective properties. Levels of Liver Enzymes: To measure liver function, hepatic enzyme markers such as Alkaline Phosphatase (ALP), Aspartate Transaminase (AST) and Alanine Transaminase (ALT) were measured showed that, in comparison to the control group, the groups treated with the n-hexane fraction and crude methanolic extract of *Withania coagulans* had significantly lower liver enzyme levels. Histopathological analysis supported *Withania coagulans* hepatoprotective benefits by showing a decrease in liver necrosis and inflammation.^[44]

Anti-diabetic activity

Withanolide-A was isolated from n-hexane fraction of *Withania coagulans* plant and evaluated for anti-diabetic activity by determining enzyme inhibitory activity.^[45] By assessing the effect of glycosylation of haemoglobin and the inhibition of α-glycosidase and α-amylase enzymes, the methanolic extract of *W. coagulans* fruits was assessed for its potential to prevent diabetes.^[46,47] The phytochemical screening and characterization of phytoconstituents was isolated from hydroalcoholic extract of fruits of *W. coagulans* significantly inhibited α-glucosidase activity

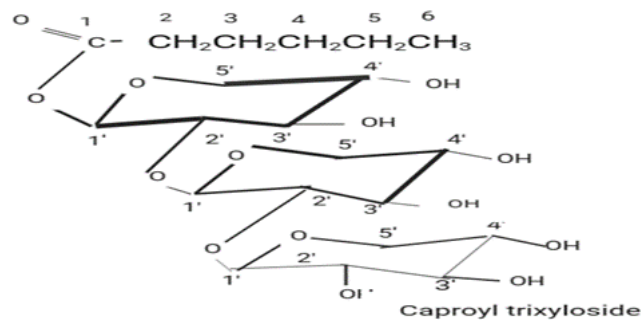


Figure 14: Caproyl trixyloside.

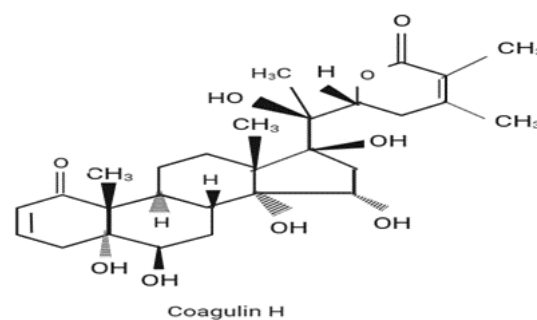


Figure 18: Coagulin H.

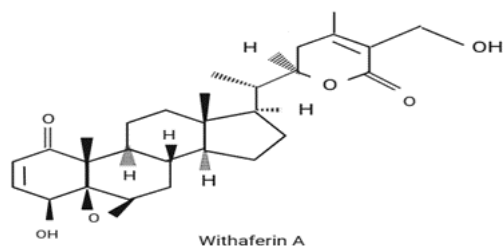


Figure 15: Withaferin A.

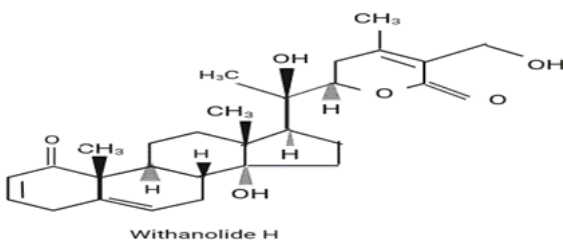


Figure 16: Withanolide H.

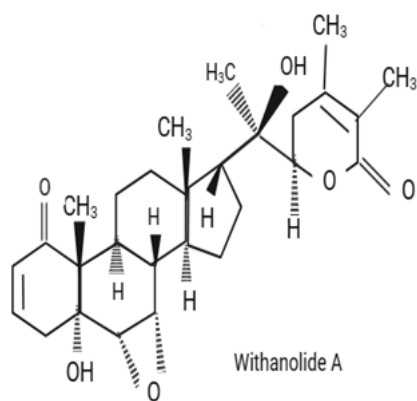


Figure 17: Withanolide A.

and delayed the peak blood glucose level.^[48] The aqueous extract of *W. coagulans* fruits helps in the identification of trace minerals that have hypoglycemic and antidiabetic properties, such as calcium and magnesium.^[49] The aqueous extract of *W. coagulans* flower (150 and 200 mg/kg, orally) significantly improved insulin sensitivity index and reduced high blood glucose levels in rats with type 2 diabetes mellitus induced by Poloxamer-407 (PX-407).^[50] The hydroalcoholic extract of *W. coagulans* dried fruit (1000 mg/

kg, orally) reported antidiabetic and antihyperlipidemic activity in streptozotocin (55 mg/kg, intraperitoneally) induced diabetic rats.^[51] Total phenol (5.2 mg/g), flavonoid (5.5 mg/g) and alkaloid 9.5 mg/kg) content of methanolic *W. coagulans* fruit extract significantly reported antimicrobial and antidiabetic activity.^[52] When administered orally, the ethanolic extract of *W. coagulans* fruit (500, 750 and 1000 mg/kg) demonstrated hypoglycemic and antidiabetic effects against diabetic rats caused by streptozotocin (55 mg/kg, intraperitoneally).^[53] *W. coagulans* fruit aqueous extract (125, 250 and 500 mg/kg, orally significantly reduce nicotinamide (230 mg/kg), insulin and other related enzyme activity.^[54] In streptozotocin-induced diabetic mice, one novel withanolide called coagulanolide and four previously identified withanolides extracted from *W. coagulans* fruit shown antihyperglycemic action.^[55] Rats with normal and streptozotocin-induced diabetes (45 mg/kg intraperitoneally) had reduced blood glucose levels when *W. coagulans* fruit aqueous extract was given orally at 100, 200 and 300 mg/kg.^[56] In streptozotocin-induced diabetic mice administered intraperitoneally at a dose of 70 mg/kg, withaferin-a hydroalcoholic fraction of the methanolic extract of *W. coagulans* fruits-increases the pace of wound contraction.^[57] When compared to the placebo group, the *Withania coagulans* intervention group showed a statistically significant decrease in fasting blood glucose levels. Postprandial blood glucose levels, HbA_{1c} levels and lipid profile showed favorable changes in the *Withania coagulans* group.^[58,59] *Withania coagulans* extract-loaded nano-formulation holds promise in mitigating diabetes-induced renal stress and inflammation. The combination of anti-diabetic and anti-inflammatory properties of *Withania coagulans* amplified by nanotechnology, presents a potential therapeutic strategy for addressing diabetes-related complications.^[60,61]

Anti-cancer Activity

W. coagulans extracts, derived from its fruit, root, leaf and leaf stalk, exhibit promising anticancer properties against various human (Hela, MCF-7 and RD) and rat (RG2 and INS-1) cancer cell lines. This suggests the potential therapeutic relevance of *W. coagulans* in combating cancer.^[62] Methanolic extract *W. coagulans* dried fruit berries reduces MDA-MB-231 cell lines' susceptibility to breast cancer by around 50%.^[25] Berries from *W. coagulans* were extracted using ethanol and the results showed

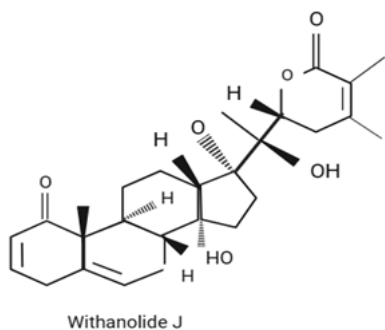


Figure 19: Withanolide J.

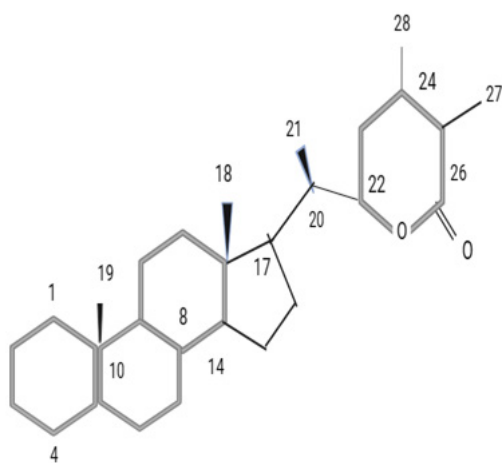


Figure 20: Basic skeleton of withanolide.

anticancer activity against MCF7 cells.^[63] Withanolides, including Coaguloside A, Withanolide G, Withanolide A, Withanolide B, Withanolide D, Withanolide E, Withanolide F and Withanolide H, isolated from diverse parts of *W. coagulans* (roots, leaves, fruits), demonstrate significant anticancer activity against human prostate cancer cells.^[64,65] Intraperitoneal administration of methanolic extracts from *W. coagulans* fruits at doses of 500, 1000 and 1500 mg/kg significantly inhibits micronucleus formation in mice bone marrow cells. This suggests a potential protective effect against genotoxicity, highlighting the extract's anti-mutagenic properties and its possible relevance in preventing DNA damage *in vivo*.^[66] The hydro-methanolic extract (3:1 v/v) of *W. coagulans* (250, 500 and 1000 mg/kg, orally) reported antioxidant and anti-proliferative activity in Benign Prostate Hyperplasia (BPH) in rats and reduced Malondialdehyde (MDA) level and increase Total Antioxidant Capacity (TAC).^[67] The fruit extracts of *Withania coagulans* demonstrated a dose-dependent reduction in the frequency of micronuclei formation in peripheral blood cells with reference to the group under positive control. The fruit extracts of *Withania coagulans* possess significant antimutagenic potential, as evidenced by the reduction in mutagen-induced micronuclei formation.^[66] Significant reduction in the incidence and size of papillomas in mice treated with *W. coagulans* fruit extract compared to the control group. Molecular analyses indicated modulation of signaling pathways implicated in skin

carcinogenesis. *Withania coagulans* extract exhibited inhibitory effects on inflammation, oxidative stress and angiogenesis, providing mechanistic insights into its anticarcinogenic potential.^[68]

Anti-oxidant activity

The methanolic extract of *W. coagulans* leaves has demonstrated the greatest levels of antioxidant and free radical scavenging activity of DPPH and phosphormolybdenum methods.^[69] Two substances, withaferin A and withanolide A, were extracted from *W. coagulans* leaf and stem explants and were shown to have the ability to scavenge free radicals in cell suspension culture.^[70,71] The hydro-alcoholic extract (1000 mg/kg, orally) of roots of *W. coagulans* reported significant antioxidant activity by lowering the apoptosis of cerebellar Purkinje neurons caused by oxidative stress post reperfusion or ischemia in wistar rats.^[72] The hydro-methanolic extract (1000 mg/kg, orally) of roots of *W. coagulans* has neuroprotective effect against oxidative stress and improved anti-oxidant enzyme activity by decreasing Malondialdehyde (MDA) level and decrease neuronal death in rats striatum.^[73] A variety of assays, such as the DPPH (2,2-Diphenyl-1-Picrylhydrazyl) radical scavenging activity, the ABTS (2,2'-Azino-Bis(3-ethylbenzothiazoline-6-Sulphonic acid)) radical scavenging activity and the Ferric Reducing Antioxidant Power (FRAP) assay, were used to assess the antioxidant potential of aqueous and organic solvent extracts (such as methanol and ethanol). The extracts from leaves, stem and roots exhibited significant antioxidant activity in all tested assays. Dose-dependent scavenging of free radicals and efficient reducing power were observed.^[74]

Anti-inflammatory activity

W. coagulans methanolic/chloroform (1:1) fruit extract-loaded microemulsions that are applied topically has potent anti-inflammatory properties.^[75]

Anti-microbial activity

Biosynthesis of Iron nano rods by using *W. coagulans* which is more effective than chemically prepared nano rods. These green synthesized nano rods reported significant anti-bacterial activity against *S. aureus* and *P. aeruginosa*.^[76] Capric acid, caprylic acid, caproic acid, lauric acid, palmitic acid, eugenol and varamol, identified in the volatile oil extracted from *W. coagulans* fruits using microwave-assisted hydro-distillation, exhibit potent antibacterial activity against *Pseudomonas aeruginosa*, *Enterococcus faecalis* and methicillin-resistant *Staphylococcus aureus*. These compounds showcase the potential of *W. coagulans* as a source of antibacterial agents.^[28] Aqueous extract of *W. coagulans* seeds was subjected to phytochemical screening, which identified the following substances: proteins, amino acids, carbohydrates, flavonoids, glycosides, phenolic compounds, gums and mucilage. It is also reported antifungal and antibacterial

effect of plant extract against 10 bacterial strains (*Escherichia coli*, *Staphylococcus aureus*, *Bacillus cereus*, *Clostridium*, *E. coli* (Humans), *Xanthomonas*, *Salmonella typhi*, *Klebsiella pneumonia* and *Salmonella* and 5 fungal strains (*Penicillium*, *Alternaria alternata*, *Aspergillus niger* and *Aspergillus flavus*).^[77] Using standard disc diffusion and broth microdilution procedures, the antibacterial activity of the fruit extract was assessed against a panel of pathogenic microorganisms, including fungi and bacteria (both Gram-positive and Gram-negative). The fruit extract contained alkaloids, flavonoids, phenols, tannins, saponins and terpenoids, according to the phytochemical study. The fruit extract shown notable antibacterial action against strains of fungi, bacteria and both Gram-positive and Gram-negative bacteria.^[78] Fecal egg count analysis revealed a significant reduction in nematode eggs in the treatment group compared to the control group. Birds treated with *Withania coagulans* exhibited improved health parameters, including weight gain, feed consumption and feather condition.^[79] The ethanolic extract demonstrated significant anti-helminthic activity, with dose-dependent effects observed. The extract induced paralysis and mortality in the helminths, indicating its potential as an anthelmintic agent.^[80]

Diuretic activity

Aqueous extract (500 and 750 mg/kg, p.o.) of dried fruits of *W. coagulans* reported to possess diuretic activity by using Lipschitz method. The results showed significant excretion of electrolytes and increases urine volume.^[81] The diuretic activity of the hydroalcoholic extract was evaluated using standard diuretic indices, including urine volume, electrolyte concentration and creatinine clearance. It indicated a significant increase in urine volume in rodents treated with the hydroalcoholic extract of *Withania coagulans*. In comparison with the group under control. The observed diuretic activity of the hydroalcoholic extract of *Withania coagulans* may be attributed to its bioactive compounds, such as withanolides, flavonoids and alkaloids. These compounds have been previously reported for their nephroprotective and diuretic effects.^[82]

Hypolipidemic activity

Total phenolic and flavonoid components extracted from *W. coagulans* fruits aqueous extract reduce lipid levels, decrease oxidative stress in the hypercholesterolemic effect on rabbits and also ameliorate the condition of dyslipidemia caused by a high intake of fat or cholesterol.^[83] The hydroalcoholic extract (1000 mg/kg,p.o) of dried fruit of *W. coagulans* showed antihyperlipidemic activity and atorvastatin in high cholesterol diet induced hyperlipidemia in rats and reduce serum triglyceride, LDL and VLDL levels while elevating HDL levels with atorvastatin.^[51] Streptozotocin-induced diabetic mice showed antihyperlipidemic benefits from an aqueous extract of the dried fruits of *W. coagulan*.^[84] The poly-constituents found in *Withania coagulans* Dunal aqueous and chloroform extracts

have antihyperglycemic and antihyperlipidemic actions in a rat type 2 diabetes experimental model. The blood glucose levels of both the aqueous and chloroform extracts were significantly lower than those of the diabetes control group. The lipid profile values showed significant improvements with both aqueous and chloroform extracts. decreases in triglyceride and total cholesterol levels and increases in HDL cholesterol.^[85,86]

Immunomodulatory activity

The effects on the immune system and small intestinal morphology of broiler chickens by 1,25-dihydroxycholecalciferol [1,25(OH)2D3], *Withania somnifera* (WS) root and *Withania coagulans* (WC) fruit hydroalcoholic extracts. 42 days were spent raising 55 male Ross 308 grill chickens that were one day old. They were divided into fifty-five pens at random, with 10 birds in each pen (replica). Eleven dietary treatments were given to broiler chickens: a negative control diet with a 30% reduction in Ca concentration; a positive control diet with sufficient Ca; and a negative control diet supplemented with either WS or WC extracts at three different levels (0, 75 and 150 mg/kg diet) or 1, 25(OH)2D3 at two different levels (0 and 0.5 µg/kg diet). The investigation's findings showed that adding 150 mg/kg of WS or WC as a supplement enhanced the humoral immune response.^[87]

Cardiovascular activity

The impact of a coagulin isolated from the fruits of *Withania coagulans* on experimental rats myocardial injury caused by isoprenaline. Researchers have looked at how *Withania coagulin* affects the regulation of biochemical parameters like the heart enzymes lactate dehydrogenase and creatinine phosphokinase, the endogenous antioxidant glutathione and the antioxidant enzymes superoxide dismutase, catalase and glutathione peroxidase. After isoprenaline was administered, there was an increase in the level of malonyldialdehyde in the heart tissue. Furthermore, the treatment of isoprenaline reduces the reduced glutathione level and the activity of antioxidant enzymes in cardiac tissues, including glutathione peroxidase, catalase and superoxide dismutase. In the isoprenaline group, there was a notable decrease in lactate dehydrogenase and creatinine phosphokinase, two vital indicators of myocardial damage.^[88]

Anti-convulsant activity

The active compounds in *Withania coagulans*, including withanolides, have been examined for their impact on neurotransmitter systems involved in epilepsy and seizures. Withanolides, in particular, are believed to exert anticonvulsant effects through various mechanisms, including GABAergic modulation. GABA (Gamma-Aminobutyric Acid) is an inhibitory neurotransmitter crucial for regulating neuronal excitability and its dysregulation is implicated in seizure disorders.^[89] Studies on animal models have provided evidence of *Withania coagulans* potential to reduce seizure activity. The plant extract has shown

anticonvulsant effects in different experimental paradigms, suggesting a modulatory role in the underlying neurobiology of seizures.^[90]

Wound healing activity

Research on streptozotocin-induced diabetic rats has revealed that *Withania coagulans* accelerates the healing of wounds. The plant extract promotes tissue regeneration, collagen synthesis and angiogenesis, essential processes in the wound repair cascade.^[91] The preparation and characterization of a topical gel containing both Pregabalin and *Withania coagulans* extract represent a novel approach to address burn injuries. Pregabalin, a medication commonly used for neuropathic pain and *Withania coagulans* known for its anti-inflammatory and wound-healing properties, synergistically contribute to potential therapeutic benefits in burn management. The topical gel formulation involves the integration of Pregabalin and *Withania coagulans* extract into a suitable gel base. The process includes selecting compatible excipients, ensuring proper dispersion of the active ingredients and optimizing the formulation for stability and efficacy.^[92]

Neuroprotective effect

The mechanisms underlying neuroprotection may involve the attenuation of oxidative stress, reduction of inflammatory responses and modulation of apoptotic pathways. *Withania coagulans* through its bioactive compounds potentially counteracts neuronal damage and promotes cell survival in the CA1 hippocampus. Various assessments, such as histological analysis, biochemical assays and behavioral tests, may be employed to gauge the extent of neuroprotection. The purpose of these analyses is to ascertain how *Withania coagulans* root extract affects neuronal integrity, cognitive function and the reduction of ischemia-induced hippocampal damage in the CA1 region.^[93] Investigating the role of *Withania coagulans* extract in reducing oxidative stress-induced cerebellar Purkinje neuron death after ischemia/reperfusion injury offers important new information about putative neuroprotective pathways. *Withania coagulans* rich in bioactive compounds like withanolides is recognized for its antioxidant and anti-apoptotic properties. In this study, the protective effects of *Withania coagulans* extract are examined in the context of cerebellar Purkinje neurons, which are susceptible to damage during ischemia/reperfusion events. After the extract is taken, its effects on apoptosis and oxidative stress are evaluated.^[72] The potential of *Withania coagulans* root extract as a medicinal agent is suggested by its observed effects on withdrawal syndrome in rats. The neuroprotective and modulatory properties of the extract may influence neurotransmitter systems implicated in withdrawal, offering a novel avenue for intervention.^[94]

Anti-depressant activity

Withania coagulans fruit alcoholic extract was tested for potential antidepressant efficacy in Swiss albino mice using the Tail

Suspension Test (TST), a recognised technique for evaluating antidepressant-like effects in rodents. The reduction in immobility time in the TST indicated by this study suggests that the alcoholic extract of *Withania coagulans* fruits may have antidepressant-like qualities in Swiss albino mice. Further investigations, including dose-response studies and elucidation of underlying neurobiological mechanisms, are warranted to validate and expand upon these preliminary results.^[95] Mice treated with an alcoholic extract of *Withania coagulans* fruits showed a decrease in immobility time and an increase in swimming time, which may indicate an antidepressant-like effect.^[96] The study explored the Central Nervous System (CNS) depressant and analgesic effects of the fruits of *Withania coagulans* (Stocks) Dunal, a plant traditionally used in folk medicine. The investigation involves preclinical assessments to elucidate the potential neuropharmacological properties of the fruit extract. The alcoholic extract of *Withania coagulans* fruits was administered to the experimental groups, while a control group received a vehicle. Behavioral parameters were recorded and analyzed. It suggested that *Withania coagulans* (Stocks) Dunal fruits may possess CNS depressant and analgesic activities, as indicated by the observed behavioral changes in the experimental models.^[97] It revealed a dose-dependent improvement in motor coordination, as evidenced by an increase in latency to fall from the rotarod in mice treated with the aqueous extract of *Withania coagulans* fruits compared to the control group. The observed improvement in motor coordination, indicated by increased latency to fall in the rotarod test, suggests a potential positive influence of the *Withania coagulans* fruit aqueous extract on neuromuscular function in Swiss albino mice.^[98] The motor coordination activity of the alcoholic extract obtained from *Withania coagulans* fruits using the Rotarod test in Swiss Albino mice. The results provide insights into the potential neurological effects of the extract, contributing valuable information for further pharmacological investigations.^[99]

Anti-hypertensive activity

The study explored the utilization of *Withania coagulans* a plant-derived protease, for the enzymatic hydrolysis of wheat gluten to produce bioactive peptides with antioxidant and antihypertensive properties. The aim is to harness the potential health benefits of bioactive peptides derived from gluten, a widely abundant protein source. A unique method for improving the functional characteristics of gluten peptides is provided by the combination of the enzymatic hydrolysis process with *Withania coagulans*. The feasibility of using *Withania coagulans* for the enzymatic hydrolysis of wheat gluten, leading to the production of bioactive peptides with antioxidant and antihypertensive activities. The outcomes contribute to the growing field of functional food ingredients with potential health-promoting effects.^[100]

CONCLUSION

Withania coagulans commonly known as "Paneer dodda" or "Indian Rennet," has been the subject of extensive pharmacognostical, pharmacological and phytochemical investigations. This medicinal plant has a rich history in traditional medicine and modern scientific studies have sought to unravel its therapeutic potential. The integration of multiple scientific approaches has provided a comprehensive understanding of the plant's botanical characteristics, chemical composition and pharmacological activities. Pharmacognostical investigations form the foundational aspect of understanding the plant at a macroscopic and microscopic level. The morphological and anatomical features revealed through these studies contribute to the identification and standardization of *Withania coagulans*. Such precision is essential for ensuring the quality and authenticity of herbal medicines derived from this plant. Additionally, pharmacognostical studies provide insights into the organoleptic properties, which can influence the organoleptic quality of herbal formulations. The phytochemical investigation of *Withania coagulans* has been pivotal in uncovering its diverse array of bioactive compounds. Various classes of phytoconstituents, including alkaloids, flavonoids, saponins and tannins, have been identified. These compounds not only contribute to the plant's therapeutic properties but also play a crucial role in its interaction with biological systems. The identification and quantification of specific phytoconstituents lay the groundwork for standardization and quality control in the production of herbal medicines derived from *Withania coagulans*. The pharmacological investigations have shed light on the wide spectrum of therapeutic activities exhibited by *Withania coagulans*. Studies have reported anti-inflammatory, antioxidant, antimicrobial, antidiabetic and immunomodulatory properties, among others. The diverse pharmacological activities underscore the potential of *Withania coagulans* in addressing various health conditions. These findings not only validate the plant's traditional uses but also open avenues for further exploration in drug development and complementary medicine.

In conclusion, the pharmacognostical, pharmacological and phytochemical investigations of *Withania coagulans* collectively contribute to a comprehensive understanding of this medicinal plant. The integration of traditional knowledge with modern scientific methods has unveiled its intricate botanical features, diverse chemical composition and wide-ranging therapeutic activities. As *Withania coagulans* continues to garner attention in the scientific community, further research and clinical studies will undoubtedly contribute to its integration into mainstream medicine, providing novel therapeutic options for various health challenges.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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