

## **EXPLORING THE THERAPEUTIC POTENTIAL OF PANEER DODI FOR DIABETES MANAGEMENT**

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### **ABSTRACT**

Diabetes mellitus is a chronic metabolic disorder affecting carbohydrate metabolism. It has become a global health concern. *Withania coagulans* commonly known as "Paneer Dodi," holds significant promise in diabetes management. The present review explores the pharmacological potential of *W. coagulans*, emphasizing its traditional uses and diverse biological activities. The plant is rich in bioactive compounds like withanolides, demonstrates anti-diabetic, anti-inflammatory, antioxidant, and antimicrobial effects. Coagulins unique peptides derived from *W. coagulans* exhibit therapeutic potential. The plant's cultivation, chemical constituents and various types of diabetes are discussed. This overview underscores the relevance of *W. coagulans* in natural product-based drug discovery by providing insights into its diverse therapeutic applications. It explores the extraction methods, pharmacological actions, and therapeutic potential of *Withania coagulans*. Hydroalcoholic and hot water extraction processes are detailed with emphasizing factors affecting efficiency. The pharmacological actions encompass hepatoprotective, antihyperglycaemic, anti-inflammatory, anti-cancer, wound healing, anti-mutagenic, antibacterial, antihelmintic, cardiovascular, diuretic effects and potential applications in Alzheimer's disease. Withanolides play a pivotal role in its diverse therapeutic effects. The findings suggest *Withania coagulans* as a promising research and development of novel therapeutic agents. This succinctly captures the key aspects by providing a concise overview of *Withania coagulans*' multifaceted medicinal properties.

**Keywords :** *Withania Coagulans*, Antihyperglycaemic, Diabetes mellitus, Coagulin.

### **1. INTRODUCTION**

#### **Diabetes**

Diabetes mellitus is a chronic metabolic condition affecting the processing of proteins, lipids and carbohydrates. A key feature of this disorder is a compromised insulin response, leading to impaired carbohydrate utilization, particularly glucose<sup>1</sup>. The predominant endocrine disorder, diabetes mellitus (DM) often stems from insufficient insulin production or activity, also known as insulin resistance. Commonly referred to as "sugar" in popular culture, diabetes has a substantial impact with the International Diabetes Federation projecting a rise in cases from 40.9 million to 69.9 million in India by 2025<sup>2</sup>. The pancreas plays a pivotal role in diabetes producing both insulin and glucagon. Insulin released by beta (β) cells in the islets of Langerhans aids in glycogenesis and glucose delivery to tissues by reducing blood sugar levels<sup>3</sup>. Conversely, alpha (α) cells in the same organelles release glucagon by elevating blood glucose through glycogenolysis. Notably, insulin is not necessary for erythrocytes and neural tissue to utilize glucose<sup>4</sup>. The offspring of individuals with diabetes face an increased risk of obesity, metabolic disorders, cardiovascular diseases, and cancer. Type 2 diabetes mellitus (T2DM) accounts for 80-90% of cases with varying severity and consequences<sup>5</sup>. Engaging in modest physical exercise is associated with a decreased mortality risk for individuals with diabetes. Genetic factors are recognized as contributors to the occurrence of diabetes. The escalating burden of non-communicable diseases like diabetes poses a significant health challenge, affecting the economic growth of WHO African Region members<sup>6</sup>. Diabetes manifests either through abnormal insulin synthesis or secretion. Seen in Type 1 diabetes mellitus (T1DM) and pancreatic duct stenosis, or through the emergence of insulin resistance and abnormal production, observed in Type 2 diabetes (T2DM) and specific secondary diabetes<sup>7</sup>.

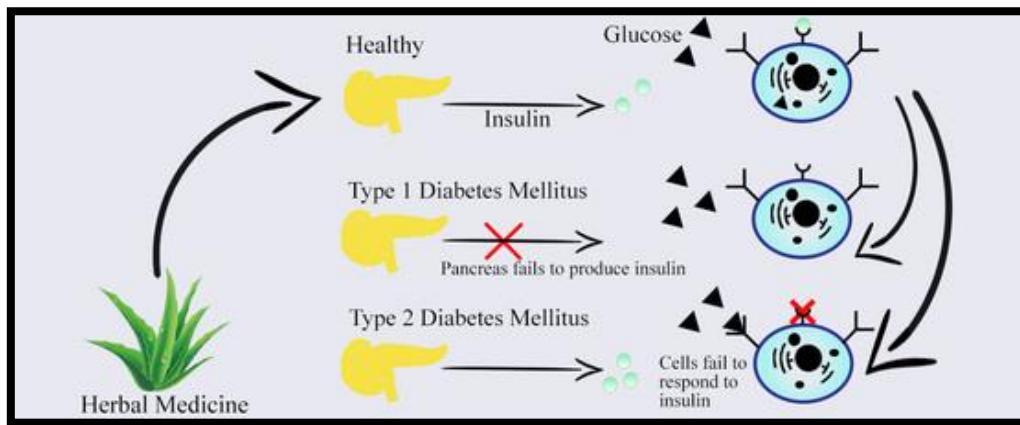
### **2. TYPES OF DIABETES**

#### **1. Type 1 diabetes :**

Type 1 diabetes blood glucose (sugar) level is too high because body can't produce a hormone called Insulin. It is also known as Juvenile diabetes<sup>8</sup>. It happens because body attacks the cells in pancreas that make the insulin, lacking the production at all. Insulin is necessary to live. It does an essential job. It allows the glucose in blood to enter cells and fuel bodies. Type 1 diabetes, breaks down the carbohydrate from food and drink and turns it into glucose. But when the glucose enters bloodstream, there's no insulin to allow it body cells. More and more glucose then builds up in bloodstream, leading to high blood sugar levels<sup>9</sup>.

## 2. Type 2 diabetes :

In type 2 diabetes, the insulin in pancreas can't work properly, or pancreas can't produce enough insulin. This means blood glucose (sugar) levels keep rising<sup>10</sup>. Around 98% of people with diabetes in India have type 2. It is serious condition and can be lifelong. Having type 2 diabetes without treatment means that high sugar levels in blood can seriously damage parts of body, including eyes, heart and feet. These are called the complications of diabetes. But with the right treatment and care, type 2 diabetes reduce risk of developing problem<sup>11</sup>.



**Fig.1**

## 3. Gestational diabetes :

Gestational diabetes is diabetes that can develop during pregnancy. It affects women who haven't been affected by diabetes before. It means you have high blood sugar and need to take extra care of yourself and your bump. This will include eating well and keeping active. It usually goes away again after giving birth. It is usually diagnosed from a blood test 24 to 28 weeks into pregnancy<sup>12</sup>.

## 4. Maturity Onset Diabetes of the Young (MODY) :

MODY is a rare form of diabetes which is different from both type 1 and type 2 diabetes, and runs strongly in families. MODY is caused by a mutation (or change) in a single gene. If a parent has this gene mutation, any child they have, has a 50 % chance of inheriting it from them. If a child does inherit the mutation, it will generally develop MODY before 25 years, whatever their weight, lifestyle, ethnic group etc<sup>13</sup>.

## 5. Neonatal Diabetes :

Neonatal diabetes is a form of diabetes that is diagnosed under the age of six months. It's a different type of diabetes than the more common type 1 diabetes as it's not an autoimmune condition (where the body has destroyed its insulin producing cells)<sup>14</sup>.

## 6. Wolfram Syndrome :

Wolfram Syndrome is a rare genetic disorder which is also known as DIDMOAD syndrome after its four most common features (Diabetes Insipidus, Diabetes Mellitus, Optic Atrophy and Deafness)<sup>15</sup>.

## 7. Alstrom Syndrome :

Alstrom Syndrome is a rare genetic disorder characterized by retinal degeneration leading to vision impairment, early-onset hearing loss, cardiomyopathy affecting heart function, increased risk of obesity, type 2 diabetes and potential renal failure. Individuals may experience orthopedic and rheumatologic issues, including spinal curvature, arthritis, and short stature. Other associated problems involve reproductive system defects, undescended testes, low testosterone, polycystic ovaries, underactive thyroid, and acanthosis nigricans (dark skin patches)<sup>16</sup>.

## 8. Latent Autoimmune Diabetes in Adults (LADA) :

LADA is a type of diabetes which seems to straddle type 1 and type 2 diabetes. Bits of it are more like type 1, and other bits are more like type 2. That's why some people call it type 1.5 diabetes or type 1 ½ diabetes. It's not actually classified as a separate type of diabetes at the moment, but there's some medical research going on to try and pinpoint exactly what makes it different from type 1 and type 2 diabetes<sup>17</sup>.

## 9. Type 3c diabetes :

Type 3c diabetes is a type of diabetes that develops when another disease causes damage to the pancreas. The conditions related to type 3c are pancreatic cancer, pancreatitis, cystic fibrosis or haemochromatosis. Removal of pancreas can develop it<sup>18</sup>.

#### **10. Steroid-Induced Diabetes :**

Some people who take steroids can go on to develop diabetes. This is known as steroid-induced diabetes. It is more common in people who are at higher risk of type 2 diabetes<sup>19</sup>.

#### **11. Cystic Fibrosis Diabetes :**

Cystic fibrosis diabetes is the most common type of diabetes in people with cystic fibrosis. Although it has features of both type 1 and type 2, it is a different condition<sup>20</sup>.

#### **12. Monogenic Diabetes :**

Monogenic diabetes is a rare condition different from both type 1 and type 2 diabetes. It's caused by a mutation in a single gene. If a parent has this mutation, their children have a 50% chance of inheriting it. Since monogenic diabetes is so rare, people can often get misdiagnosed. And in some cases of monogenic diabetes, the condition can be managed with specific tablets and doesn't require insulin treatment. That's why it's incredibly important to understand rare forms of diabetes and diagnose them correctly. (There are two types of monogenic diabetes - Neonatal and MODY)<sup>21</sup>.

#### **Paneer Dodi**

The exploration of natural products through pharmacological screening has yielded numerous drug discoveries with plants being a predominant source of lead compounds. Throughout history, plants have provided valuable therapeutic compounds such as morphine, cocaine, digitalis, and quinine. In the realm of ancient medicine, various plants have been documented for their efficacy in addressing diverse health issues. Among these plants, *Withania coagulans* (W. coagulans) is commonly known as 'Indian Cheese Maker' or 'Vegetable Rennet,' holds significance as an essential medicinal plant<sup>22</sup>. Belonging to the Solanaceae family, W. coagulans is a gray-whitish shrub native to the east Mediterranean region, extending to South Asia. Widely distributed in parts of Pakistan and India, W. coagulans is extensively utilized in Ayurvedic medicine particularly in diabetic cases<sup>23</sup>. Its applications also extend to addressing nervous exhaustion, disability, insomnia, wasting diseases, failure to thrive in children and impotence<sup>24</sup>. The fruits of W. coagulans exhibit sedative, emetic, alterative, and diuretic properties. Additionally, these are employed in treating liver complaints, asthma, and biliary problems<sup>25</sup>. Notably, the plant's active compounds, particularly withanolides display a range of therapeutic activities including antimicrobial, anti-inflammatory, antitumor, hepatoprotective, anti-hyperglycemic, cardiovascular, immuno-suppressive, free radical scavenging, and central nervous system depressant effects<sup>26</sup>. It provides a comprehensive overview of the biological activities associated with specific compounds isolated from W. coagulans and delves into the plant's phytochemistry. The diverse therapeutic potentials of W. coagulans, the review emphasizes its significance in the realm of natural product-based drug discovery.

#### **Botanical description of *Withania coagulans*:**

- **Botanical Name:** *Withania coagulans* Dunal
- **Family:** Solanaceae
- **Subfamily:** Solanoideae.
- **Tribe:** Physaleae.
- **Subtribe:** Withaninae.
- **Sanskrit Name:** Rishyagandha1&2
- **Hindi Name:** Punir, Punir bandh, Akri, Binputakah, Paneer Doda.
- **English Name:** Indian Cheesemaker, Indian Rennet, Vegetable Rennet.
- **Trade Name :** Paneer dodi, Panner, doda, Panir bed, Paneer dhodi.

#### **Scientific name :**

- **Kingdom:** Plantae, plants
- **Subkingdom:** Tracheobionta, vascular plants
- **Superdivision:** Spermatophyte, seeds plants
- **Division:** Angiosperm
- **Class:** Dicotyledons
- **Order:** Tubiflorae
- **Family:** Solanaceae
- **Genus:** *Withania*
- **Species:** *Coagulans*

**Vernacular Name :**

<b>Language</b>	<b>Vernacular Names</b>
Bengal	Asvagandha
Bombay	Kaknaj
Gwalior	Asgandha
Panjab	Khamjaria, Khamjira
Sindhi	Punirjafota, Punirband
Persian	Kaknajehindi, Punirbd
Arabic	Kaknajehindi
Telgu	Panneru-gadda
Urdu	Hab kaknaj

**Plant Description :**

**Biological source:**

Paneer Phool also called *Withania coagulans* is a small shrub and belongs to the family Solanaceae. It is commonly known as 'Paneer Dodi' or 'Indian Cheese Malor<sup>27</sup>'.

**Origin and Distribution :**

*Withania coagulans* Dunal, a compact grey under shrub ranging from 60-120 cm in height is found in the arid regions of Punjab with additional sightings near Simla, Garhwal and Kumaun. Flowering from November to April, its berries ripen from January to May and natural regeneration occurs through seeds. The dioecious flowers appear in auxiliary clusters, featuring a campanulate calyx covered in fine stellate grey tomentum. Male flowers have stamens at the corolla top, while female flowers exhibit shorter stamens. The berry is 6-8 mm globose, encircled by a scurfy-pubescent enlarged calyx. Seeds are ear-shaped and glabrous, measuring 2.5-3.0 mm in diameter<sup>23</sup>.

It is found in the Eastern Mediterranean and extends to North Africa and Southeast Asia. It is growing throughout India in dry areas such as Punjab, Gujarat, Rajasthan, Shimla, Kumaon, and Gujarat.

**3. MORPHOLOGY**

**Seeds:** Seeds of Dodipaneer 2.5-3.0 mm in diameter, dark brown, slightly pear-shaped, pale. Natural regeneration occurs from seeds<sup>28</sup>.



**Fig No.2**

**Leaves:** The Leaves of the Paneer Dodi 2.5-5.7 by 1-2.2cm long, lanceolate-oblong, complete, obtuse, uniform color on both sides, thick, small, or more rugose with acute base<sup>28</sup>.



**Fig No.3**

**FLOWER :**

Paneer Phool flowers are described as long, campanulate structures covered with fine stellate grey hair and featuring triangular teeth, each 2.5 mm long. The plant is dioecious displaying axillary clusters of flowers measuring 0.6 mm characterized by inflexible and slender stems. The calyx is 6 mm long. The corolla measures 8 mm externally divided by about a third down with oval and subacute lobes. In male flowers, the stem is about the same width as the upper part of the corolla tube featuring a 2 mm long glabrous filament and 3 mm long anthers. The ovoid ovary lacks style or stigma. Female flowers have stamens reaching the 12<sup>th</sup> height of the corolla tube with 2 mm long glabrous filaments and small sterile anthers. Ovaries are ovoid and glabrous with a glabrous style, mushroom-shaped stigma, and 2-lamellate structure. The plant blooms from November to April with fruits maturing from January to May<sup>29</sup>.



**Fig No.4**

**Fruits:**

Berry 6-8 mm. Globose, smooth, closely curved by the enlarged membrane calyx, the outside-pubescent scurfy-pubescent<sup>29</sup>.



**Fig No.5**

**Cultivation of Plant**

Cultivation of *Withania coagulans* is commonly known as Indian Cheese Maker or Vegetable Rennet involves specific steps to ensure optimal growth and yield. Here's a detailed explanation of the cultivation process<sup>30</sup>:

**1. Climate and Soil Requirements**

*W. coagulans* thrives in arid to semi-arid climates with well-drained soil. The plant can tolerate a wide range of soils but prefers sandy-loam to sandy-clay soils. Adequate sunlight is essential for the growth of this plant.

**2. Land Preparation**

Clear the cultivation area of weeds, debris, and rocks to create a clean and well-prepared field. Incorporate well-rotted organic matter into the soil to enhance its fertility and water-holding capacity.

### **3. Propagation**

*W. coagulans* is typically propagated through seeds. Seeds should be collected from mature fruits during the harvesting season. The seeds are small and should be sown at a shallow depth in rows or raised beds.

### **4. Sowing**

Sow the seeds during the early spring or at the onset of the monsoon season. Maintain proper spacing between the rows to facilitate easy access for cultivation and harvesting.

### **5. Irrigation**

Adequate and timely irrigation is crucial, especially during the germination and early growth stages. Once established, *W. coagulans* is moderately drought-tolerant, but regular watering promotes better growth and yield.

### **6. Weeding and Mulching**

Keep the cultivation area free from weeds, especially during the early stages of plant growth. Mulching helps in conserving soil moisture, suppressing weed growth and maintain a stable temperature around the plants.

### **7. Support Structures**

As *W. coagulans* grows, it may benefit from support structures to prevent lodging and facilitate air circulation. Simple stakes or trellises can be installed to support the plants.

### **8. Pruning:**

Regular pruning helps to maintain the shape of the plant and encourages lateral branching, leading to a bushier and more productive plant.

### **9. Harvesting:**

Harvesting typically occurs when the berries are ripe, usually between January and May. Harvest the entire plant or selectively pick the berries as needed for medicinal or commercial purposes.

### **10. Post-Harvest Processing :**

After harvesting, the berries are processed to extract the active compounds, particularly withanolides, for medicinal purposes.

Successful cultivation of *W. coagulans* requires attention to soil quality, water management, and proper care throughout the growth stages. Additionally, adherence to good agricultural practices contributes to the overall health and productivity of the plant.

### **Chemical Constituents :**

Aqueous and methanolic extractions of *Withania coagulans* fruits reveal a diverse array of constituents. The berries house the milk-coagulating enzyme, proteins, phenolic compounds, tannins, saponins, carbohydrates, organic acids, two esterases, free amino acids, fatty oil, essential oil, and alkaloids. Notable amino acids include proline, hydroxyproline, valine, tyrosine, aspartic acid, glycine, asparagine, cysteine, and glutamic acid. Alcoholic extraction yields fourteen alkaloidal fractions from the fruits<sup>31</sup>. The plant contains 17.8% free sugars, predominantly D-galactose and D-arabinose in a 1:1 ratio, with traces of maltose. Enzymatic studies reveal the absence of a  $\beta$ -galactosidic linkage in the polysaccharide.

Furthermore, the seeds boast a fatty oil content of 12–14%. This comprehensive chemical profile underscores the pharmacological potential of *Withania coagulans* suggesting its utility in various applications from traditional medicine to potential industrial uses<sup>32</sup>.

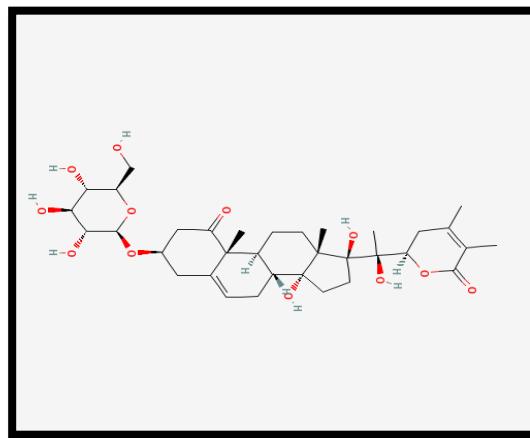
The oil is rich in linoleic acid and  $\beta$ -sitosterol, known for hypocholesterolaemic effects. *W. coagulans* is abundant in steroid lactones, specifically withanolides, characterized by a polyhydroxy C28 steroid lactone structure attached to an ergostane skeleton. Withanolides are not exclusive to Solanaceae but extend to marine organisms and other plant families, such as Taccaceae and Leguminosae<sup>33</sup>.

### **Coagulin:**

coagulins are a group of peptides derived from the fruit of *Withania coagulans*. These are composed of amino acids linked together by peptide bonds.

#### **1. Coagulin L:**

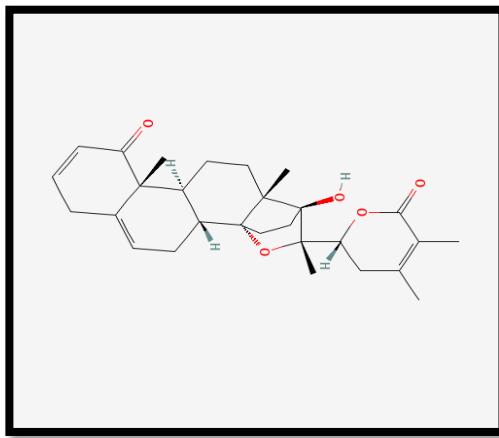
Coagulin L is a peptide derived from the fruit of *Withania coagulans*, a plant known for its medicinal properties. This peptide has been studied for its potential biological activities and therapeutic applications. While specific details about Coagulin L may vary based on research findings, peptides like Coagulin L are known to exhibit various pharmacological effects including anti-diabetic, antimicrobial, antioxidant and immunomodulatory activities. However, further research may elucidate the structure, function, and therapeutic potential of Coagulin L<sup>34</sup>.



**Fig No.6** Coagulin L (14,17,20-trihydroxy-3 $\beta$ -(O- $\beta$ -D-glucopyranosyl)-1-oxowitha-5,24-dienolide))

## 2. Coagulin C :

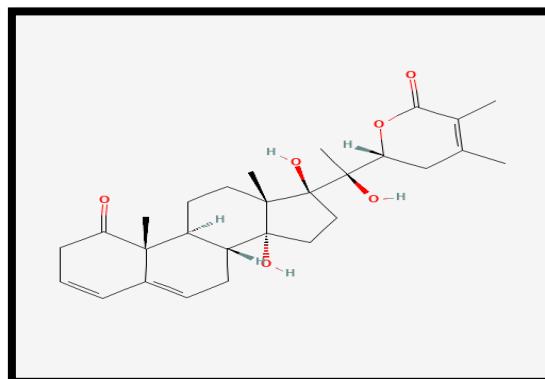
Coagulin-C is a peptide isolated from the fruit of *Withania coagulans*, while specific details about Coagulin-C may vary based on research findings, peptides like Coagulin-C are known to exhibit various pharmacological effects, including antihyperglycemic, antimicrobial, antioxidant, and immunomodulatory activities. Further research can elucidate the structure, function, and therapeutic potential of Coagulin-C<sup>35</sup>.



**Fig No.7**

## 3. Withanolide F:

Withanolide F is a specific withanolide compound isolated from *Withania coagulans*, a plant with medicinal properties. Withanolides are a group of naturally occurring steroidal lactones found in plants of the Solanaceae family. Withanolide K, like other withanolides may possess various pharmacological activities, including antidiabetic, anti-inflammatory, antioxidant, and potentially anticancer effects. It shows antidiabetic activity by enhancement of insulin sensitivity, stimulation of insulin secretion, inhibition of carbohydrate absorption, protection of pancreatic beta cells<sup>36</sup>.



**Fig No.8**

#### **4. METHOD OF EXTRACTION**

There are different methods by which extraction of *Withania coagulans* can be carried out<sup>37</sup>. 1. Hydroalcoholic Extraction

2. Hot water Extraction

##### **1. Hydroalcoholic Extraction :**

The dried fruits of *Withania coagulans* were finely powdered and extracted by hot percolation method using Soxhlet apparatus. The solvent used was 50% methanol. After extraction the extract was dried in a water bath at a temp 35-40 °C<sup>38</sup>.

Step-by-step method for hydroalcoholic extraction of *Withania coagulans*:

##### **A. Materials Needed:**

1. Dried *Withania coagulans* plant material (leaves, roots, or fruits)
2. Ethanol and water (hydroalcoholic solvent)
3. Grinder or blender
4. Glass containers or extraction vessel
5. Filter paper or cheesecloth
6. Rotary evaporator or distillation setup
7. Analytical balance
8. Amber glass bottles for storage
9. Lab equipment (e.g., beakers, pipettes, stirring rods)

##### **B. Procedure:**

**1. Preparation of Plant Material:** Ensure that the *Withania coagulans* plant material is thoroughly dried to reduce moisture content and preserve the integrity of bioactive compounds. Grind or chop the dried plant material into small pieces using a grinder or blender. This increases the surface area for extraction and facilitates to release bioactive compounds.

**2. Extraction Setup:** Place the ground plant material in a glass container or extraction vessel. Prepare the hydroalcoholic solvent by mixing ethanol and water in the desired ratio. The choice of ratio depends on the target compounds and extraction preferences. Common ratios range from 1:1 to 9:1 (ethanol:water). Cover the plant material with the hydroalcoholic solvent, ensuring that the solvent completely immerses the plant material.

**3. Extraction Process:** Seal the container to prevent evaporation of the solvent and loss of volatile compounds. Allow the mixture to macerate or steep for a specified period, typically ranging from 24 to 72 hours, depending on the extraction protocol and desired compounds. Agitate the mixture periodically to enhance extraction efficiency. This can be done by stirring the mixture manually or using a magnetic stirrer.

**4. Filtration:** After the extraction period, filter the mixture to separate the liquid extract (hydroalcoholic solution) from the solid plant material. Use a filter paper or cheesecloth to remove plant debris and particulate matter. The filtered extract should be clear and free from visible solids.

**5. Concentration:** Transfer the filtered extract to a rotary evaporator or distillation setup for solvent removal and concentration. Apply gentle heat and vacuum to evaporate the solvent, leaving behind a concentrated extract. Monitor the temperature and vacuum levels to prevent degradation of heat-sensitive compounds.

**6. Analysis and Storage:** Analyze the concentrated extract for the presence of desired bioactive compounds using analytical techniques such as HPLC or spectrophotometry. Determine the yield and concentration of target compounds in the extract. Store the extracted solution in amber glass bottles or airtight containers to minimize degradation and maintain stability. Label the bottles with the extraction date and contents for future reference.

**2. Hot Water Extraction:** The dried fruits *Withania coagulans* were finely powdered and extracted by boiling with water for 2 hr. After extraction the extract was dried in a water bath at a temp 35-40 °C<sup>38,39</sup>.

##### **A. Methodology:**

**1. Preparation of Plant Material:** Harvest mature *Withania coagulans* plant parts, typically the leaves, roots or fruits. Clean the plant material to remove dirt and debris. Dry the plant material to reduce moisture content which helps in preservation and improves extraction efficiency.

**2. Extraction Process:** Grind or chop the dried plant material into smaller pieces to increase the surface area for extraction. Add the plant material to a container or extraction vessel. Cover the plant material with distilled water or a

specified solvent-to-water ratio based on the extraction protocol. Allow the mixture to steep or boil, depending on the extraction method chosen (maceration, decoction, or infusion). Maintain appropriate temperature and time conditions to optimize extraction efficiency without degrading heat-sensitive compounds. Stir or agitate the mixture periodically to ensure uniform extraction.

**3. Filtration:** After the extraction period, filter the mixture to separate the liquid extract (aqueous solution) from the solid plant material. Use a filter paper, cheesecloth or fine mesh sieve to remove plant debris and particulate matter.

**4. Concentration:** Concentrate the aqueous extract by evaporating excess water using techniques such as rotary evaporation, freeze-drying, or spray-drying. Adjust the extract concentration as needed for further analysis or application.

**5. Analysis and Storage:** Analyze the concentrated extract for the presence of desired bioactive compounds using analytical techniques such as HPLC (High-Performance Liquid Chromatography) or spectrophotometry. Store the extracted solution in appropriate containers (amber glass bottles or airtight containers) to minimize degradation and maintain stability.

#### **B. Factors Affecting Extraction Efficiency:**

**Particle Size:** Finely ground plant material increases surface area and improves extraction efficiency.

**Extraction Time and Temperature:** Longer extraction times and higher temperatures generally lead to increased extraction efficiency but should be optimized to avoid degradation of heat-sensitive compounds.

**Solvent-to-Plant Ratio:** The ratio of water to plant material affects the concentration of extracted compounds.

**pH:** Adjusting the pH of the extraction medium can influence the solubility and stability of target compounds.

**Agitation:** Stirring or agitation helps in enhancing mass transfer and improving extraction efficiency.

#### **C. Advantages of Water Extraction:**

- Environmental friendly and safe for consumption.
- Suitable for extracting a wide range of polar and non-polar compounds.
- Low cost and easy scalability.
- Minimal risk of solvent residues in the final extract

**Pharmacological Actions :** The berries of *W. coagulans* play a vital role in milk coagulation and hold a significant place in Ayurvedic, Unani, and ancient Indian medicinal traditions. Withanolides extracted from *W. coagulans* exhibit diverse biological activities. The sweet fruits are known for their sedative, emetic, alterative, and diuretic effects valuable in chronic liver conditions and as a blood purifier. Additionally, these fruits are utilized to address dyspepsia, flatulent colic and various intestinal infections. The therapeutic applications extend to the treatment of asthma, biliary and stranguary, highlighting its multifaceted role in traditional medicine.

**Hepatoprotective activity :** The aqueous extract of *W. coagulans* fruits demonstrates hepatoprotective activity, particularly through 3-β-hydroxy-2,3 dihydrowithanolide F, a steroidal compound with anti-inflammatory properties. In a study on adult albino rats, the withanolide exhibited significant hepatoprotective effects against CCl4-induced hepatotoxicity at a dose of 10 mg/kg (i.p.). Evaluation included observing pentobarbitone-induced hypnosis, assessing serum levels of SGOT and SGPT and histopathological examination of hepatic tissues. Concomitant treatment with 10 mg/kg withanolide showed a substantial protective impact on the liver, emphasizing its potential therapeutic role in mitigating hepatic disorders ( $P < 0.05$ )<sup>40</sup>.

**Antihyperglycaemic and antihyperlipidemic effects:** Aqueous and chloroform extracts from *W. coagulans* fruits exhibited significant pharmacological effects on blood glucose, lipid profile and body weight in type 2 diabetic rats. Administered at 1 g/kg body weight for 14 days, these extracts caused a notable decrease in glucose, triglyceride, total cholesterol, LDL, and VLDL levels, along with an increase in HDL. The extracts also reduced serum and hepatic lipid peroxidation in diabetic rats and db/db mice. The most effective dose for reducing fasting blood glucose was identified as 1g/kg, with a maximum reduction of 33.2% in normal rats. Coagulanolide4, along with other withanolides demonstrated significant inhibition of postprandial hyperglycemia and improved glucose tolerance, suggesting its potential as an antidiabetic and antidiabetic agent. The efficacy of compound 5, comparable to metformin aligns with the traditional use of *W. coagulans* in managing hyperglycemia and dyslipidemia<sup>41,42</sup>.

**Anti-inflammatory:** The alcoholic extract and total alkaloids from *W. coagulans* demonstrated noteworthy anti-inflammatory effects in various models. In induced acute inflammation with egg albumin and subacute inflammation with formalin. As well as in granulation tissue formation using the cotton pellet method, significant anti-inflammatory activity was observed. Specifically, 3-b-Hydroxy-2,3-dihydrowithanolide F exhibited substantial anti-inflammatory effects at 10 mg/kg in subacute inflammation models including granuloma formation and formalin-induced arthritis in

rats. Its efficacy was comparable to 50 mg/kg phenylbutazone and 10 mg/kg hydrocortisone. However, this compound did not exhibit significant activity in acute inflammation models. These findings highlight the potential anti-inflammatory properties of *W. coagulans* constituents in specific inflammatory conditions<sup>43</sup>.

**Anti-Cancer Property:** Cancer, characterized by uncontrolled cell growth and tumor formation can spread throughout the body. *Withania coagulans* Dunal has been extensively studied for its anticancer effects showing efficacy in reducing tumor size. The plant contains anecdotes with reported antitumor effects and flavonoids demonstrating antimutagenic and anticarcinogenic properties. In mice with induced skin cancer, *Withania coagulans* root extract significantly decreased the incidence and average number of skin lesions. Withaferin A demonstrated tumor inhibition against human carcinoma cells and revealed its chemotherapy and immune stimulation effects in mice. Additionally, *Withania coagulans* exhibited anti-proliferative activity against head adenosquamous carcinoma and demonstrated antitumor effects on lung cancer in mice. The plant's water extracts have been utilized to inhibit cytotoxic effects and enzyme activity showcasing its potential in cancer treatment<sup>44</sup>.

**Wound Healing Activity :** The hydroalcoholic fraction of *W. coagulans* methanolic extract was applied topically as a 10% w/w ointment and orally at a dose of 500 mg/kg body weight to diabetic rats induced by streptozotocin. In both forms – topical (10% w/w ointment) and oral (500 mg/kg body weight, p.o.) – the hydroalcoholic fraction demonstrated a substantial increase in the rate of wound contraction compared to diabetic control groups. This suggests a potential therapeutic effect of *W. coagulans* in promoting wound healing in diabetic conditions whether administered topically or orally<sup>45</sup>.

**Anti-Mutagenic & Anti-Hypertensive Activity :** The study examined the antimutagenic activity of *Withania coagulans* fruit extracts on cyclophosphamide-induced micronucleus formation in mouse bone marrow cells.

The results affirmed that a single intraperitoneal administration of *Withania coagulans* fruit extract at doses of 500, 1000, and 1500 mg/kg body weight, given 24 hours prior, significantly prevented micronucleus formation in a dose-dependent manner in mouse bone marrow cells. This preventive effect was notably observed when compared to the group treated with cyclophosphamide alone. Overall, the findings suggest the potential antimutagenic properties of *Withania coagulans* fruit extract in protecting against micronucleus formation induced by cyclophosphamide<sup>46</sup>.

**Antibacterial & Anti helminthic Activities :** The volatile oil derived from the alcoholic extract of *W. coagulans* fruits exhibits antibacterial effects against *S. aureus* and *Vibrio cholera*. Additionally, this volatile oil demonstrates antihelminthic activity highlighting its potential as a multifunctional agent with antimicrobial properties<sup>47</sup>.

**Cardiovascular Diseases :** Cardiovascular diseases, encompassing heart, brain, and kidney vascular issues, result from various causes with atherosclerosis and high blood pressure being prevalent. *Withania coagulans* Dunal fruit extracts, particularly in high-fat diets induced hyperlipidemia in rats, significantly lowering serum cholesterol, triglycerides, lipoproteins, and LPO levels. This effect was comparable to Ayurvedic products demonstrating a hypolipidemic impact in Triton-induced hypercholesterolemia. Cocaolinolide from *W. coagulans* fruits displayed anti-distribution effects in mice. Water extracts of dried fruit exhibited hyperlipid activity in Triton-induced hypercholesterolemia in rats. Furthermore, antihyperlipidemic and antiatherosclerotic effects were observed in diabetic rats induced by streptozotocin. The hypolipid activity may involve interference with lipid synthesis, metabolism and excretion. *W. coagulans* Dunal fruit extracts rich in withanolides and lactones have reported cardiovascular benefits in dyslipidemia. These findings underline the potential of *W. coagulans* in managing cardiovascular issues providing a basis for further investigation into its active components<sup>48</sup>.

**Diuretic effect :** The diuretic activity of the aqueous extract from *W. coagulans* fruits was assessed using an in vivo Lipschitz test model with furosemide as the standard. The findings revealed a substantial increase in urine volume registering a 79.12% rise at a dose of 500 mg/kg and a 71.02% increase at 750 mg/kg body weight compared to the control group. Moreover, urinary electrolyte excretions exhibited a notable elevation at both dosage levels compared to the control group. It suggests that the aqueous extract of *W. coagulans* fruits possesses significant diuretic effects highlighting its potential for influencing urine volume and electrolyte excretion<sup>49</sup>.

**Alzheimer's Disease :** Alzheimer's Disease is a progressive neurological disorder leading to cognitive decline and neuronal death. Classified as a neurodegenerative dementia the condition initiates mildly and worsens over time. Studies suggest that withanolides, compounds found in certain plants like *Withania coagulans* exhibit inhibitory effects on metastatic activity and quinone reductase. Notably, specific withanolides show a favorable impact on events within the cholinergic signal transmission cascade in the cortical and basal forebrain. These findings hold promise for the potential use of withanolides in the treatment of Alzheimer's disease. However, further research is useful to explore and validate their therapeutic effectiveness in addressing the complexities of this neurodegenerative condition<sup>50</sup>.

## 5. CONCLUSION

In conclusion, the comprehensive review underscores the significant pharmacological potential of *Withania coagulans*, commonly known as "Panier Dodi," in managing diabetes mellitus and various other health conditions. Rich in bioactive compounds such as withanolides and coagulins, exhibits a wide range of therapeutic effects including anti-diabetic, anti-inflammatory, antioxidant, and antimicrobial properties. Its traditional uses, cultivation methods and diverse pharmacological actions make it a valuable resource in both traditional medicine and modern pharmacology. *Withania coagulans* holds promise as a natural product for drug discovery and the development of novel therapeutic agents, suggesting avenues for further research and exploration in the field of herbal medicine and pharmaceutical science.

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