

PHARMACEUTICAL IMPORTANCE OF WITHANIA COAGULANS IN HEALTH AND DISEASES

¹NEELAM B. BARE, ²PRATIMA S. JADHAV

^{1,2}Department of Biochemistry, Institute of Science, Mumbai, Maharashtra, India

Abstract - Many plants have been reported to cure various health problems and diseases from ancient times. Medicinal plants play a vital role for the development of new drug. Considering all the medicinal properties, the species of genus 'Withania' of Solanaceae family are also of great medicinal value. Withania coagulans, commonly known as Indian cheese maker, paneer dodi or panner doda, vegetable rennet. The berries of the shrub are used for milk coagulation. They are also used in dyspepsia, flatulent colic and other intestinal infections. Withania coagulans (Stocks) Dunal is used to treat nervous exhaustion, disability, insomnia, wasting diseases, failure to thrive in children, impotence. Its fruits are used for liver complaints, asthma and biliousness. In particular withanolide isolated from the plants are considered to have Antimicrobial, antiinflammatory, antitumor, hepatoprotective, antihyperglycemic, cardiovascular, immunosuppressive, free radical scavenging, antimutagenic and central nervous system depressant activities of the plant have been reported. This review gives a aerial view mainly on the biological activities of some of the Withania coagulans compounds isolated and a comprehensive view of its pharmaceutical importance's in the mentioned diseases.

Keywords - Solanaceae, Withania coagulans, phytochemistry, Withanolides, antihyperglycemic.

I. INTRODUCTION

Ayurveda is the science of life. The plants are the key source of medicine in Ayurveda for treatment and prevention of diseases and maintenance of healthy life (Kitikar K.R. and Basu B.D., 1933). Using of herbal drugs is the traditional system in India for healing and curing. Due to many adverse effect of modern drugs people used to prefer herbal drugs. The traditional medicines are increasingly solicited through the traditional practitioners and herbalists in the treatment of infectious disease. Medicinal plants play a vital role for the development of new drugs (Mishra J. et al., 2013). World Health Organization (WHO) has defined medicinal plants as plants that contain properties or compounds that can be use for therapeutic purposes or those that synthesize metabolites to produce useful drugs (WHO 2008). The importance of traditional medicinal plants is increasing now a day because of various advantages over the synthetic drugs. (Mishra J. et al., 2013). Considering all the medicinal properties, the species of genus 'Withania' are also of great medicinal value. The Solanaceae family is comprised of 84 genera that include about 3,000 species, scattered throughout the world (Mirjalili M.M., et al., 2009). Members of this family are generally annual shrubs. The genera Withania and Physalis play an important role in the indigenous medicine of South East Asia, e.g. in the Unani and Ayurvedic systems. The twenty-three known species of genus Withania are widely distributed in the drier parts of tropical and subtropical zones, ranging from the Canary Islands, the Mediterranean region and northern Africa to Southwest Asia (Hepper F.N., 1991 and Warrier P.K., 1996). Among them, only two species, Withania somnifera (Ashwagandha) and Withania coagulans (Rishyagandha), are economically and medicinally

significant, being used and cultivated in several regions (Javanshir K., 2000 and Sharma R., 2004).

Withania coagulans commonly known as Indian cheese maker, paneerdodi or pannerdoda, vegetable rennet (Gupta V. et al., 2013). The berries of the shrub are used for milk coagulation. It is popularly known as Indian cheese maker. In Punjab, the fruit of Withania coagulans are used as the source of coagulating enzyme for clotting the milk which is called 'paneer'. They are also used in dyspepsia, flatulent colic and other intestinal infections. In some parts of Pak-Indian sub-continent, the berries are used as a blood purifier. The twigs are chewed for cleaning of teeth and the smoke of the plant is inhaled for relief in toothache (Dymock W. et al., 1972 and Anonymous, 1969). Withania coagulans (Stocks) Dunal is used to treat nervous exhaustion, disability, insomnia, wasting diseases, failure to thrive in children, impotence. Its fruits are used for liver complaints, asthma and biliousness. Flowers of coagulans (Stocks) Dunal are used in the treatment of diabetes (Bowm D., 1995). The root is harvested in autumn and dried for later use (Chevallier A., 1996 and Purohit S., et al. 2004). Antimicrobial, antiinflammatory, antitumor, hepatoprotective, antihyperglycemic, cardiovascular, immunosuppressive, free radical scavenging and central nervous system depressant activities of the plant have been reported (Maurya R., et al. 2010). Antimutagenic potential of fruits extracts of Withania coagulans have been reported by (Mathur D. and Agrawal R., 2011).

II. BOTANICAL DISTRIBUTION

Withania coagulans Dunal is a rigid, gray-whitish small shrub, about 60-120 cm tall. The leaves are about 2.5-7.5 cm long and 1.5 cm broad, usually

lanceolate oblong, sometimes ovate, obtuse, narrow at the base and very short stalked. The flowers are about 7-12 mm across, yellowish, and are dioecious and polygamous in nature. The flowers are found in axillary cymose clusters. The berries are about 7-12 mm in diameter, red, smooth and enclosed in leathery calyx. The seeds are dark brown, ear shaped, glabrous with sharp fruity smell.

III. PHYTOCHEMISTRY AND PHARMACEUTICAL PROPERTIES

Withania coagulans contain the milk-coagulating enzyme, two esterases, free amino acids, fatty oil, an essential oil and alkaloids. *Withania coagulans* is a rich reservoir of pharmaceutically active steroidal lactones known as withanolides. Chemical profiling of *Withania coagulans* shows wide spectrum of chemical compounds like withanolides, withacoagin and coagulan. Withaferin A (steroidal lactones of withanolide series) had been isolated from fruits of *Withania coagulans* (Khare C.P., 2007). In recent years there has been a surge in pharmacological studies on withanolides, with increasing evidence of antitumor, antiarthritic, antiageing, and neuroprotective properties (Gupta V. and Keshari B.B., 2013). Substantial pharmacological activities have been accredited to two main withanolides, withaferin A (WS-3) and withanolide D (WS-D).

Some of the examples of pharmacological activities as per view of literature are, Withaferin A and withanolide E were reported to have specific immunosuppressive effects on human B and T lymphocytes as well as on mice thymocytes (Shohat et al, 1978)20. *Withania coagulans* has wound healing activities in streptozotocin-induced diabetic rats. The hydroalcoholic fraction of the methanolic extract (standardized by withaferin A) of *Withania coagulans* in both topical and oral form showed a significant increase in the rate of wound contraction. The withaferin-A is responsible for significant increase in the collagen levels, protein, DNA, SOD, CAT and decreased level of hexosamine (Prasad et al 2010). A withanolide, named coagulanolide isolated from *Withania coagulans* fruits has antihyperglycemic activity in rats (Maurya, et al 2008). A withanolide from *Withania coagulans* showed significant anti-inflammatory effects in acute inflammation (Budhiraja, et al., 1984). A steroidal lactone, Withanolide isolated from the aqueous extract of fruits of *Withania coagulans*, has cardiovascular effect. A new withanolide, with a unique chemical structure similar to the aglycones of the cardiac glycoside, isolated from the fruits of *Withania coagulans*. This withanolide produced a moderate fall of blood pressure in dogs which has blocked by atropine and not mepyramine or propranolol. In rabbits Langendorff preparation and

ECG studies, produced myocardial depressant effects but in perfused frogs hearts it caused mild positive inotropic and chronotropic effects (Budhiraja et al 1983).

IV. RESEARCH DONE ON WITHANIA COAGULANS ANTI-HYPERGLYCAEMIC ACTIVITY

Hypoglycemic activity of *Withania coagulans* was exhibited in streptozotocin induced rats (Hemalatha et al 2004). Significant improvements in symptoms and signs were observed and euglycemia was attained in diabetes mellitus type 2 (Jaiswal et al 2009). A withanolide, named coagulanolide isolated from *Withania coagulans* fruits has antihyperglycemic activity in rats (Maurya et al 2008). The median effective dose of isolated coagulanolide from fruits of *Withania coagulans* was determined about 25 mg/kg in streptozotocin-induced diabetic rats, which is comparable to the standard antidiabetic drug metformin (Maurya et al 2008)

4.1 Anti-Hyperlipidemic Activity

The aqueous extract of *Withania coagulans* fruits in high fat diet induced hyperlipidemic rats, significantly reduced elevated serum cholesterol, triglycerides, lipoprotein and the LPO levels. The coagulanolide isolated from fruits of *Withania coagulans* has antidyplipidemic effect on mice (Maurya et al 2008). The hydroalcoholic extract of *Withania coagulans* dried fruits was effective and comparable to atorvastatin in controlling the high cholesterol diet-induced hyperlipidemia in rats.

4.2 Anti-Inflammatory Activity

The alcoholic extract of *Withania coagulans* showed significant anti-inflammatory effect in acute inflammation induced with egg albumin (Budhiraja et al 1977). A withanolide from *Withania coagulans* showed significant anti-inflammatory effects in acute inflammation (Budhiraja et al 1984).

4.3 Cardiovascular Effects

A withanolide similar to aglycones of the cardiac glycones isolated from *Withania coagulans* produced a moderate fall of blood pressure in dogs which has blocked by atropine and not mepyramine or propranolol. In rabbits Langendorff preparation and ECG studies, produced myocardial depressant effects but in perfused frogs hearts it caused mild positive inotropic and chronotropic effects (Budhiraja et al 1983).

4.4 Immunosuppressive Effects

Withaferin A and withanolide E were reported to have specific immunosuppressive effects on human B and T lymphocytes as well as on mice thymocytes (Shohat et al 1978). A known withanolide, coagulin-H, was evaluated for its effect on various cellular

functions related to immune responses including lymphocyte proliferation, interleukin-2 (IL-2) cytokine expression. These results were compared with prednisolone. Coagulin-H was found to have a powerful inhibitory effect on lymphocyte proliferation and the Th-1 cytokine production. The inhibition of the phytohaemagglutinin (PHA) activated T-cell proliferation by coagulin-H (Mesaik et al 2006).

4.5 Anti-mutagenic effects

The antimutagenic activity of *Withania coagulans* fruit extracts was investigated on cyclophosphamide induced micronucleus formation in mouse bone marrow cells. The results confirmed that a single intraperitoneal administration of *Withania coagulans* fruit extract at the doses of 500, 1000 and 1500 mg/kg body weight prior to 24 h significantly prevented the micronucleus formation in dose dependent manner in bone marrow cells of mice as compared to cyclophosphamide group (Prasad S.K et al.,2010).

4.6 Diuretic effect

The diuretic activity of the aqueous extract of fruits of *Withania coagulans* was studied by in vivo Lipschitz test model with slight modifications using furosemide as a standard. The results indicated significant increase in the urine volume by 79.12 % and 71.02 % at 500 mg/kg and 750 mg/kg body weight doses respectively compared to controls. Urinary electrolyte excretions were increased at both the doses compared to controls (Dabheliya J. et al., 2011).

4.7 Wound healing activity

The hydroalcoholic fraction of the methanolic extract of *Withania coagulans* was administered in the form of 10% w/w ointment topically and at a dose of 500 mg/kg body weight orally to streptozotocin-induced diabetic rats, it showed a significant increase in the rate of wound contraction compared to diabetic controls (Rajurkar S.M et al., 2011).

4.8 Anti-fungal activity

Two withanolides, 14,15 β -epoxywithanolide I and 17 β -hydroxywithanolide K, isolated from ethanolic extract of the whole plant of *W. coagulans*, have been found to be active against a number of potentially pathogenic fungi (Choudhary M.T. et al, 1995).

4.9 Anti-bacterial and anti-helminthic activities

The volatile oil obtained from alcoholic extract of fruits of *Withania coagulans* has antibacterial activity against *S. aureus* and *Vibrio cholera*, and it is also found to have antihelminthic activity (Khan M.T.J et al, 1993 and Grind K.N., et al 1967).

4.6 Hepatoprotective effects

Withanolide, 3 β -hydroxy-2,3-dihydrowithanolide F isolated from *Withania coagulans* was tested against CCl₄- induced hepatotoxicity, and the compound was found to possess marked protective effect, When compared, it is more active than hydrocortisone on a weight basis (Bhudhiraja S.K., et al 2010).

CONCLUSION

Medicinal plants play a vital role for the development of new drugs. *Withania coagulans* has been found to contain vast array of the pharmaceutical important compounds. The bioactive compounds isolated for *Withania coagulans* are chemically diverse and have the great potential against various diseases. At present, there insufficient information available on *Withania coagulans* bioactive compound and its biological activity and pharmacology hence extensive research is needed to produce the therapeutic use to cure various diseases.

REFERENCES

- [1] Bown D.: Encyclopedia of Herbs and their Uses. Dorling Kindersley, London (1995); 500.
- [2] Budhiraja R.D, Bala S, Craeg F N and Arora B. Protective effect of 3-beta-hydroxy-2-3 dihydrowithanolide-F against CCl₄ induced Hepatotoxicity. *PlantaMedica*, **52**(1): 1986, 28–29.
- [3] Budhiraja R.D, Sudhir S, Garg K.N, Arora BC (1984) Anti-inflammatory activity of 3 β -Hydroxy-2,3-dihydro-withanolide F. *PlantaMedica***50** (2): 134-136
- [4] Budhiraja RD, Sudhir S, Garg KN.; Cardiovascular effects of a withanolide from *Withania coagulans* Dunal fruits.: *Indian J. Physiol. Pharmacol* (1983). **27**(2), 129-134.
- [5] Chevallier A.: The Encyclopaedia of medicinal plants: Dorling Kindersley London (1996); 500.
- [6] Choudhary M.I, Dur-e-Shahwar, Zeba P, Jabbar A, Ali I and Rehman A. Antifungal steroidal lactones from *W. coagulans*. *Phytochemistry*, **40**(4): 1995, 1243–1246.
- [7] Dabheliya J, Khan S.A, Joshipura M, Vasoya M, Patel S and Vijaya S. Diuretic poteial of aqueous extract of fruits of *Withania coagulans* Dunal in experimental rats. *International Journal of Pharmacy and Pharmaceutical Sciences*, **2**(4): 2010, 51-53.
- [8] Dymock W., Waden C.J.H., and Hopper D: *PharmacographiaIndica*, reprinted by Institute of health and TB Research, Karachi (1972); 306.
- [9] Gaind K.N and Budhiraja R.D. Antibacterial and antihelminthic activity of *Withania coagulans* Dunal. *Indian J Pharmacol*, **29**: 1967, 185-186.
- [10] Gupta V., Keshari B.B.: *Withania coagulans* Dunal (PanneerDoda): A Review. *International Journal of Ayurvedic and Herbal Medicine* 2013; **3**(5) 1330-1336.
- [11] Hepper F.N.: In *Solanaceae III: taxonomy, chemistry, evolution*; Hawkes J.G., Lester R.N., Nee M., Estrada E., Eds.: Royal Botanic Gardens, Kew, UK, (1991); 211-227.
- [12] Jaiswal D., Rai P.K., Watal G., Antidiabetic effect of *Withania coagulans* in experimental rats. *Indian Journal of Clinical Biochemistry*, 2009;**24** (1) 88-93.
- [13] Javanshir K.: *Vegetation of Bashagerd*: University of Tehran Publication, Tehran, Iran, (2000); 156-162.
- [14] Khan M.T.J, Ashraf M, Tehniyat S, Bukhtair M K, Ashraf S and Ahmed W. Anti bacterial activity of *W. coagulans*. *Fitoterapia*, **64**: 1993, 367–378.
- [15] Khare C.P.: *Indian Medicinal Plants*: Springer-Verlag, Berlin/Heidelberg.
- [16] Kirtikar K.R., BasuB.D.: *Indian Medicinal Plants* (CM Basu,Allahabad) 1933, **2**:17777-1781.

- [17] Mathur D and Agrawal R.C.: Evaluation of in vivo antimutagenic potential of fruits extracts of *Withania coagulans* : Scholars Research Library (2011) **3(4)**:373-376.ed.
- [18] Maurya R. and Akansha J: Chemistry and pharmacology of *Withania coagulans* : An Ayurvedic remedy: J PharmaPharmacol (2010) **62**:153-160.
- [19] Maurya R., Akanksha, Jayendra, Singh A.B. Srivastava A.K., Coagulanoide, a withanolide from *Withania coagulans* fruits and antihyperglycemic activity, 2008, Bioorganic and Medicinal chemistry letters, **18**, 6534.
- [20] Mesaik M.A, HaqZu, Muradb S, Ismail Z, Abdullah N.R, Gill H.K, Atta-ur-Rahman, YousafM, Siddiqui RA, Ahmade A, Choudhary MI 'Biological and molecular docking studies on coagulin-H, Human IL-2 novel natural inhibitor.' MOL IMMUNOL 2006, **43**:1855–1863
- [21] Mirjalili M.H, Moyano E, Bonfill M, Cusido R.M. and Palazon J.: Steroidal Lactones from *Withaniasomnifera*, an Ancient Plant for Novel Medicine: Molecules (2009), **14**, 2373-2393, doi: 10.3390/molecules 14072373.
- [22] Mishra J., Dash A.K., Mishra S.N., and Gupta A.K.: *Withania coagulans* in treatment of diabetes and some other disease: A Review. Research journal of Pharmaceutical, Biological and Chemical Sciences 2013; **2(4)** 1251-1258.
- [23] Prasad S.K., Kumar R., Patel D.K., Hemlatha S., Wound healing activity of *Withania coagulans* in streptozotocine induced diabetic rats. Pharm. Biol. 2010 Dec, **48 (12)**: 1397-404.
- [24] Rajurkar S.M, Thakre P.N and Waddukar S.G. Phytochemical and pharmacological screening of *Withania coagulans* berries as anti-inflammatory. SciAbst CP38, New Delhi: 2001, pp. 215.
- [25] S. Hemlatha, A.K. Wahi, P.N. Singh, J.P.N. Chansouria, Hypoglycemic activity of *Withania coagulans* Dunal in streptozotocine induced diabetic rats, Journal of Ethnopharmacology **93** (2004)261-264.
- [26] Shohat B, Kirson I, Lavie D.: 'Immunosuppressive activity of two plant steroidal lactones withaferin A and withanolide E'. : Biomedicine. 1978, **28**:18–24.
- [27] World Health Organization(WHO), (2008).

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