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ISSN 0973-9777
Volume-7 , Number-1
January - February 2013
GISI Impact Factor 0.2310

Science

Volume-7 Number-1 January - February 2013

The Indian Journal of Research

ANVIKSHIKI

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Maneesha Publication

(Letter No.V-34564,Reg.533/2007-2008)

B-32/16-A-2/1,Gopalkunj,Nariya,Lanka

Varanasi,U.P.,India

Anvikshiki
The Indian Journal of Research
Volume 7 Number 1 January 2013

Science
Papers

PRINT ISSN 0973-9777,WEBSITE ISSN 0973-9777

Letter No.V-34564,Reg.533/2007-2008 INDIAN JOURNAL OF RESEARCH(2013)**7,1-6**
ANVIKSHIKI ISSN 0973-9777 Advance Access publication 22 Dec. 2012

WITHANIA COAGULANS – AN OVERVIEW WITH SPECIAL REFERENCE TO DIABETES MELLITUS

DR AMIT VAIBHAV*, DR O. P. SINGH** AND DR S.K. TIWARI***

Declaration

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Abstract

Diabetes is a chronic disease which affects all groups of people of different sections of the society. Modern, hectic lifestyle is contributing to increasing number of diabetics, some even in the age group of 30 to 40 years. The reasons are many and include increased tension, faulty eating habits with increasing dependence of junk foods. Smoking and increased use of tobacco, pollution, hereditary causes, can be inducted as the other factors which are increasing the incidence of diabetes in the young. Oral hypoglycemic agents like sulphonylureas and biguanides are still the major players in the management of the disease but there is growing interest in herbal remedies due to the side effects associated with the oral hypoglycemic agents.. One such herb which has been studied is Withania coagulans (Doda Paneer) which has been found to have profound hypoglycemic activity. Withania coagulans (Doda Paneer) has been used since time immemorial in Indian Ayurvedic medicines. The details of this plants morphology, medicinal property and its role in the management of diabetes mellitus are compiled here and discussed in this review.

Key words: Diabetes, hypoglycemic agents, herbal medicines, Withania coagulans, Doda Paneer.

Introduction

In Indian systems of medicine, a large number of drugs of either herbal or mineral origin have been advocated for various types of diseases and other different unwanted conditions in humans[1,30]. Ayurvedic medicines are largely based upon herbal and herbomineral preparations and have specific diagnostics and therapeutic principles [2]. Traditional medicine is the synthesis of the therapeutic experience of

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generation of practicing Physicians of indigenous system of medicine throughout the history of mankind as many infectious diseases have been treated with herbals. The traditional medicines are increasingly solicited through the traditional practitioners and herbalists in the treatment of infectious diseases. Medicinal plants play a vital role for the development of new drugs. The bioactive extract should be standardized on the basis of active compounds. Currently 80% of the world population depends on plant derived medicine for the first line of primary health care for human alleviation because it has no side effects. Withania coagulans Dunal is common throughout Pakistan. It is also found in North-West India and Afghanistan. The plant is known by different names in different local languages, such as 'Akri' or 'Puni-ke-bij' in Hindi, 'Tukhme- Kaknaje-hindi' in Persian. Spicebajja in Afghan, Khamjira in Punjabi and Punir band or Punirja- fota in Sindhi [3]. Withania coagulans Dunal belongs to family Solanaceae. Withania is a small genus of shrubs, which are distributed in the East of the Mediterranean region and extend to South Asia. The berries of the shrub are used for milk coagulation. It is popularly known as Indian cheese maker. In Punjab, the fruit of W.coagulans are used as the source of coagulating enzyme for clotting the milk which is called 'paneer' so it is also known as "Doda 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. 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. W. 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. The root is harvested in autumn and dried for later use. Some caution is advised in the use of these plants since it is toxic. Antimicrobial, anti- inflammatory, antiumor, hepatoprotective, anti-hyperglycemic, cardiovascular, immuno-suppressive, free radical scavenging and central nervous system depressant activities of the plant have been reported. The use of medicinal plants by humans is as old as the origin of the human race. Withania coagulans is an important medicinal herb as large numbers of phytochemicals have been isolated from this, which are in use in different herbal formulations and pharmaceutical products[30].

Taxonomical Classification

Kingdom	:	Plantae
Division	:	Magnoliophyta
Order	:	Solanales
Family	:	Solanaceae
Genus	:	Withania
Sindhi Name	:	Paneer

Botanical Description

Shrub branched, 2-3m in length, ridge and furrows are present, slightly hairy stem cylindrical, 0.5-0.16cm length, hair curved. Lamina oval to oblong, 1-6 cm length ,0.3-2.6 cm width, margin smooth, thick apex obtuse, more than one leaf arise from one point, base oblique, mid-rib wavy. Inflorescence axillary cymose, globose, flowers yellow, 0.7-0.9 cm in length 0.4-0.5 cm width, oblong to lanceolate, pubescent ,sepals green, densely hairy ovate, completely adnate except tips. Petals 5, yellow margin serrulate, apex, obtuse, 0.8-1.2 cm long, 0.3 0.4cm wide. Stamens 5, filament thin and straight, 0.4-

0.5cm long. Ovary 2 loculed, fruit berry enclosed in enlarged calyx, dehiscent regularly. Anthers are elongated, 0.3-0.4 cm long, ribs prominent, rarely hairy. Fruit berry, globose, 1.5-1 cm long, 0.7-1 cm width, Sepals covers the fruit and ended into crown like structure. Seeds oval to rounded, yellowish brown, 41-59 in number, 0.1-0.3cm long, 0.2-0.3cm wide, dotted. Flowering period is from January to April. The pulp and husk of the berry, which is known to contain an enzyme. The main component of berries are esterases, fatty oil, amino acids such as proline, hydroxyproline,valine, tyrosine, aspartic acid, glycines, aspargines, cysteine and glutamic acid and alkaloids are the phytoconstituents [30]. The most of the activities of the plants is due to the presence of an active component as, *Withanolide*. *Withanolides* are steroidal lactones with an ergostane skeleton [4]. The fruits are diuretic [5,6,7] hypolipidemic[8]

Distribution : Drier parts of Punjab, Gujarat, Simla and Kumaon in In-dia, Baluchestan in Iran, Pakistan and Afghanistan.

Synonyms : English: Vegetable Rennet, Indian-Cheese-maker, Unani- Desi Asgandh, Kaaknaj-e-Hindi, Paneer, Paneer-band, Akri (fruit), Siddha/Tamil-Ammukkura. Local names: This plant is known by different names, in different local languages, such as 'Akri' or 'Puni-ke-bij' in Hindi, 'Tukhme-kaknaje-hidi' in Persian. 'Spiubajja' in Af-ghan, 'Khamjira' in Punjabi and 'Punirband' or 'Punir- ja –fota' in Sindhi .

Useable Part : Whole plant, roots, leaves, stem, green berries, fruits, seeds and bark are used.

Withanolides : The term "withanolide" is a structural term that has been used for "withan" from the genus Withania, and "olide" is chemical term for a lactone. To this date, about 400 witha-nolides or closely related congeners have been discovered in altogether 58 solanaceous species belonging to 22 genera. Withanolides have been discovered also in certain Tacca spp. of the Taccaceae (taccalonolides) and Ajuga spp., e.g., A. parviflora Benth. La-miaceae (ajugins)[30,9], as well as in some marine organisms. Nevertheless, their occurrence in the Solanaceae is predominating by far. Different withanolides, withacoagin and coagulan reported from W. coagulans. Withaferin A (Steroidal lactones of withanolide series) had been isolated from fruits of W. coagulans.

Structures [30]: Withanolides of ergostan steroids are four-ring triterpenes. The plant steroids are derived from sterols and comprise steroid saponins, steroid alkaloids, pregnanes, androstanes, estranes, ecdysteroids, withanolides and cardiac glycosides. "Withanolide" represents the term for the C28-skeleton 22-hydroxyergostan-26-oic acid -22, 26-olide; this γ-lactones residue containing the structure is a theoretical. The basic skeleton of withanolides is shown in Figure 1. Basically there are two major groups of withanolides as follows: A- Withanolides with an unmodified skeleton a) With a regular β -oriented side chain b) With an unusual α -oriented side chain. B- Withanolides with modified carbocyclic skeletons or side chains. These withanolides are initially classified on the basis of the chemotypes of the Withania species depending on the region of the collected plant. Chemically, these compounds may be classified as ergostane derivatives from their structural pattern; these can be broadly divided into seven groups. 1. 5β, 6 β -epoxides 2. 6 α, 7 α -epoxides 3. 5-enes 4. Intermediate compounds 5. 5 α, 6 α -epoxides 6. 6 β, 7 β -epoxides 7. Phenolic withanolides[10]. Among these, the 5β, 6β -epoxides are most common. Most of the compounds possess a 4β -hydroxy1 group. Pu-rushothaman and Vasanth (1989) extracted four-ring com-pound which possess α, β -unsaturated-γ-lactone system, in e.g. ixocarpa- lactone A. (Refer into Atta-ur-Rahman 1998e). Ray (1989) showed that the withanolides which possess 6α and 7α-epoxides generally contain 5α -hydroxyl and are believed to originate from 5β, 6β -epoxides (Refer to Atta-ur- Rahman 1998e).

Synthesis : Withanolides generally contain a polyoxygenated er-gostan skeleton[30]. One of the characteristics is the ability to introduce oxygen functions in almost every position of the carrbocyclic skeleton and side chain of compounds of this type (Naz 2002). Withanoloieds are synthesized via

the mevalonate pathway of terpenoids formation and arise from the initial cyclization of 3S-squalene-2, 3-epoxide (Kreis and Muller-Uri 2010).

Phytochemistry

Different phytochemistry studies have been done on *W. coagulans* and various compounds have been isolated from the plant. The phytochemical investigations on *W. coagulans* up to 2011 reported a number of phytoconstituents. The most important constitutions of *W. coagulans* is withanolides which can be chemically classified in to the following groups[30]

a. Withanolide glycoside
b. Withaphysalins
c. Physalins
d. Nicandrenones or ring D Aromatic Withanolides
e. Jaborols or aromatic ring Withanolides
f. Acnistins
g. Perculactones
h. Withajardines

Medicinal Uses of Withania Coagulans :

Withania coagulans: A remedial drug Withania coagulans is used in chronic complaints of liver. A composite Ayurvedic herbal hepatoprotective medicine 'Liv-52' contains extracts of Withania coagulans and W. somnifera. They are also used in dyspepsia, flatulent colic and other intestinal infections. In some parts of Pak-Indian subcontinent, 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 [12].Withania coagulans (Stocks) Dunal is used to treat nervous exhaustion, debility, 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 [13]. The root is harvested in autumn and dried for later use[14]. Some caution is advised in the use of these plants since it is toxic [15]. Antimicrobial, anti-inflammatory, antiumor, hepatoprotective, anti-hyperglycemic, cardiovascular, immunosuppressive, free radical scavenging and central nervous system depressant activities of the plant have been reported[16]. Phytochemical screening of hydro alcoholic fraction showed the presence of steroids, alkaloids, phenolic compounds, tannins, saponins, carbohydrates, proteins, amino acids and organic acids, whereas chloroform fraction showed the presence of mainly steroids and alkaloids. Pharmacological investigations have elucidated association of these activities with the specific steroidal lactones known as Withanolides present in Withania. Withaferin A and Withanolide A and Withanone are the major Withanolides present in Withania somnifera and Withania coagulans.

Active Compounds

Withanolides are a group of steroidal lactones found among members of Solanaceae. Withanolides are named after the name of the source plant Withania species. They are generally defined as C-28 steroidal lactones. The presence of a lactones ring with C-22 and C-26 oxygen functions to form a six or five membered lactones ring on an Ergostane skeleton, intact ergostane or rearranged, constitutes the basic structure of all Withanolides. The Withanolides skeleton may be defined as 22-hydroxy ergostane-26-

oic acid-26, 22-olide[30]. Modifications ofeither the carboxylic skeleton or of the side chains result in many novel structural variants of Withanolides which are described as modified Withanolides or ergostane-type steroids related to Withanolides[17]. It was reported that Withanolides posses anti-tumor, anti-angiogenic, chemopreventive and anti-inflammatory activities. Therefore, Withanolides may represent useful leads for the development of potential anti-cancer drugs. Withanolides are reported to have antitumor [18], antibacterial [19] anti-inflammatory[20] and immunosuppressive, cytotoxicity, antiulcer*Withanolide* (Component Withanolide, Withaferin A, inhibits angiogenesis (Mohan et al., 2004)[22]. Withanolides have also been reported to inhibit metastatic and quinine reductase activity. Some of them have been show to preferentially affect events in the cholinergic signal transduction cascade of the cortical and the basal forebrain, indicating their promise for the treatment of Alzheimer's disease[23]. Withanolides mediate their effects through suppression of the transcription factor nuclear factor-EB (NF-EB). The evidence is multifaceted. NF-EB is activated by various carcinogens, tumor promoters, and conditions in the tumor microenvironment (hypoxia and acidic pH),most inflammatory agents activate NF-EB. Chemopreventive agents have been shown to suppress NF- EB activation [24]. Withanolides are potent suppressors of NF-EB activation induced by various agents and that this suppression is mediated through inhibition of IKK. This mechanism accounts for the ability of Withanolides to suppress the expression of geneproducts that regulate apoptosis, proliferation, angiogenesis and invasion[30]. Anti proliferative, Preapoptotic, anti-invasive, anti-osteoclastogenic, antiangiogenic, anti-metastatic, radio sensitizing, antiarthritic and cardioprotective effects assigned to Withanolide may be mediated in part through the suppression of NF-EB and NF-EB regulated gene products (Haryuo et al., 2006). Diverse pharmacological activities reported that Withanolide, Withaferin-A includes anti-inflammatory, anti-tumor and anti-oxidant properties[25]. Some studies have demonstrated that Withaferin-A has potent anti-inflammatory, anti-oxidant and antitumorproperties [26,27,28,30].

Conclusion

The Withania coagulans has been shown to possess varied medicinal properties. The aqueous extract of the fruits has been shown to exert This has included therapeutic effects of the whole plant and its extracts, fractions and isolated withanolides. The hepatoprotective, anti-inflammatory, antihyperglycaemic, hypolipidaemic, free radical scavenging, antimicrobial, cardiovascular, central nervous system depressant, immunomodulating, antitumour and cytotoxic activities . The plant doda paneer is a very good drug to treat diabetes mellitus, It not only lowers the blood sugar level but it also minimizes the future complication of diabetes such as neuropathy, retinopathy, nephropathy and cardiovascular pathologies by its very potent antioxidant action. It also possess a very good hepato-protective, anti-tumor, anti-angiogenic, chemopreventive and anti-inflammatory activities. In spite of its very good medicinal properties it is very economical, easily available, easily consumable all these properties make it a best drug for Diabetes Mallitus.

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