International Journal of Academic Research and Development
ISSN: 2455-4197; Impact Factor: RJIF 5.22
Received: 20-06-2019; Accepted: 22-07-2019
www.academicjournal.in
Volume 4; Issue 5; September 2019; Page No. 82-84

Pharmacological and Phytochemistry studies of *Withania somnifera* Dunal plant in Indian Ayurvedic system of medicine

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Abstract
Withania somnifera Dunal is a highly acclaimed species in the Indian Ayurvedic system of medicine. In Ayurvedic, it is known to promote physical and mental health and used to treat almost all the disorder that affect the human health and having high medicinal significance. It had natural sources of withanolids known as steroidal lactones which are used as ingredients in many formulations for a variety of diseases. Many pharmacological studies have been conducted to investigate the properties of multipurpose medicinal agent. Present investigation to revealed a consolidated account of pharmacology and Phytochemistry studies in *Withania somnifera* Dunal plant.

Keywords: *Withania somnifera*, pharmacology and Phytochemistry, withanolides, anticancer

Introduction
Withania somnifera Dunal plant [1] belongs to family-Solanaceae, order- Solanales and commonly called as *Ashwagandha*, *Ginseng* and *Wintercherry*. It is grown as a short shrub upto 30-150cm in height with a central stem from which branch extend radially and covered with dense matte of wooly hairs. Flowers are small and green, while the ripe fruit is orange-red and has milk coagulating properties. Plant also has long brown tuberous roots are used for medicinal purposes. This species is a highly acclaimed genus of medicinal plants in the Indian Ayurvedic system of medicine because of its valuable pharmaceutical and nutraceutical properties. It is a small group of herbs distributed in Canary Islands, Northern Africa, drier part of India, South West of Asia, Egypt, Morocco, Jordan, Pakistan and Afghanistan [2]. Among the 23 known species of *Withania* only while *Withania somnifera* Dunal is economically significant [3]. In commercial cultivation of *Ashwagandha* is mainly associated with two major problems. First the plant variation in alkaloid quantity and yield and secondly the long gestation period between planting and harvesting [4]. This manuscript represent the comprehensive information of the research work conducted on pharmacology and Phytochemistry of *Withania somnifera* Dunal plant.

Materials and methods
Pharmacological studies of *withania somnifera* dunal plant
Chemical constituents of *Withania somnifera* Dunal plant have been of great interest to the scientific community. The biological active chemical constituents are alkaloids as : Ashwagandhaine, cuscohygrine, anahydrine, tropine, etc. and steroidal compounds including ergostane-type steroidal lactones, withaferin-A, withanolides-A-Y, withsomniferin-A, withasomidenone, withasomniferols-A-C, withanone, etc [5, 6]. Withaferin-A (4-β-27-dihydroxy-5β-6β-epoxy-I-exowitha-2, 24-dienolide) as shown in Figure-1 and withanolide-A (5a, 20a-dihydroxy-6a, 7a-epoxy-1-oxowitha-2, 24-dienolide) as shown in Figure-2, are the main withanolidal active princioles, isolated from the plant parts. These alkaloids are chemically similar but differed in their chemical constituents [7].

Anti-inflammatory activities
The anti-inflammatory potential of *Withania somnifera* Dunal has been studied in details [8] which showed that the aqueous extracts of seeds possesses efficient anti-inflammatory activity as compared with hydrocartisons, a common anti-inflammatory drug [9]. The effect of *Ashwagandha* on glycosaminoglycan synthesis in the granulation tissue of carrageenan induced air pouch granuloma was studied [10]. The oral administration of 1000 mg kg^{-1} root powder decreased the glycosaminoglycan content (92%) which was much higher than that of the hydrocortisone and phenylbutazone. The granuloma tissue formation inhibiting activity of various fractions of an aerial parts extract using subcutaneous cotton-pellet implanation in roots [11]. The methanolic fraction of extract showed high anti-inflammatory activity as compared to that of 5 mg kg^{-1} dose of hydrocortisone sodium succinate. *Ashwagandha* plant was attributed to the high content of biologically active steroids in the plant of which withaferin-A is shown to be a major component. Withaferin-A alkaloid is potent inhibitor of the proinflammatory transcription factors and a promising agent for the treatment of the inflammatory cascade of cardiovascular diseases [12].

Anticancer and chemoprotective activities
The anticancer effect of *Ashwagandha* root extract has been studied extensively [13, 14] and it was found that the most effective agent in preventing cancer through its ability to reduce the tumor size. The treatment of root extract on induced skin cancer in mice exhibited significant decreases in the incidence and average number of skin lesions compared to control group [15]. Withaferin-A showed tumor-

inhibitory activity against cells derived from human carcinoma of nasophargx [16] and it also inhibited the growth of roots of *Allium cepa* Linn. by arresting the cell division at metaphase [17]. *Ashwagandha* root extract was evaluated for its antitumor effect in urethane induced lung adenomas in adult male Albina mice. Simultaneous administration of root extract (200mg kg^{-1} body weight daily orally for seven month) and urethane (125 mg kg^{-1} weekly for 7 months) reduced tumor incidence significantly [18]. Aqueous extract of root was used for anti-cytotoxic effect in chicken lymphocytes and remarkable inhibiting activity of dimethyl sulphoxide (DMSO) induced cytoxicity with a decrease in TMF-9 production was reported [19].

Ashwagandha root extract is reported to have anti-carcinogenic effect in animal and cell cultures by decreasing the expression of nuclear factor-kappa-B, suppressing intercellular tumor necrosis factor and potentiating apoptotic signalling in cancerous cell lines [20].

Hepatoprotective activity

The hepatoprotective effect of *Withania somnifera* Dunal root powder was studies [21] showed the influenced levels of lipid peroxidation and thereby provided the hepatoprotection. The effect of aqueous root extract on the hepatic cell of *Clarias batrachus* and reported that the root extract contains different flavonoids and neurodranemithers that stimulated the neuro endocrine system. It leading to hyperactivity of the endomembrane and the exit of molecules through the surface via exocytosis.

Immunomodulatory activity

Withaferin-A has specific immunosuppressive effects on human-B and T lymphocytes viz. antigen recognition and proliferative capacity of B and T lymphocytes [23]. *Ashwagandha* root extract was able to suppess the cytophosphamide induced potentiation of delayed type hyper sensitivity (DTH) ocation in mice. A protecticve effect on cytophosphamide induced myclosuppression was observed in animal treated with this extract [24]. In another study the aqueous root powder inhibited the mitogen induced lymphocyte proliferation and DTH reaction in rats [23]. Root extract also enhanced total white blood cells count, inhibited delayed type hypersensitivity reactions and enhanced phagocytic activity of macrophages [26]. Significant increases in haemoglobin concentration, red blood cell count, white blood cell count, platelet count and body weight were observed in *Ashwagandha* root extracted treated mice compared to untreated control mice.

Antifungal and antibacterial activities

The antifungal and antibacterial properties have been demonstrated in withanolides isolated from the ethanolic extract of whole plant and leaves of *Ashwagandha.* The methanolic extract possessed maximum inhibitory activity against a spectrum of bacteria. The aqueous fruit extract successfully treated *Salmonella* infection in mice as revealed by increased survival rate, as well as less bacteria load in various vital organs of the treated animals [27]. The methanol, hexane and diethyl ether extracts from both leaves and roots were evaluated for the antibacterial and synergistic activity by agar plate disc. Diffusion assay against *Salmonella typhimurium* and *Escerichia coli* [28].

Phytochemistry studies of *withania somnifera* dunal plant

The changes of environmental factors into plant tissues culture may also produce a new and sometimes unexpected, secondary metabolic profile [29]. Phytochemistry of *Ashwagandha* has been studied extensively by several workers and groups of chemical such as steroidal lactones, alkaloids, flavonoids, tannin, etc. have been identified, extracted, characterized and isolated [30]. Present investigation highlight more than 13 alkaloids 138 withanolides and several sitoindosides as withanolidis containing a glucose molecule at carbon-27, have been isolated and reported from aerial parts, roots and berries [31]. Major chemical constituents of this plant, withanolides are mainly localized in the leaves and roots and their concentration usually ranges from 0.001-0.5% dry weight [30]. Withanolidees are a group in which C-22 and C-26 are oxidized to form a six membered lactone ring and structure of *Withanolide* skeleton shown in Figure: 1-3. The withanolide skeleton may be defined as a 22-hydroxyergostan. 26-olic acid 26, 22, lactone. Modification of the carbocyclic skeleton or the side chain give rise to many novel structures variants of with anolides. It has been reported that plants accumulating these polyoxygenated compounds possess enzymes machinery capable of oxidizing all carbon atoms in the steroid nucleus. The characteristic feature of withanolides and ergostane-type steroids is one C8 or C9-side chain with a lactone or lactol ring. Lactone ring may be either six-membered or five-membered and fused with the carbocyclic part of the molecule through a carbon-carbon bond or through an oxygen bridge. The appropriate oxygen substituents may lead to bond formation of new bonds, aromatization of ring and many other kinds of rearrangements resulting in novel structures [32, 33].

Withanolides are the principal bioactive compounds found in *Ashwagandha* species, there are some withanolide specific of them. Withaferin-A is a major compound found in *Withania somnifera* Dunal. A unique thiodimer of withanolide named Ashwagandhanolide has been found in *Ashwagandha* [34]. The isolation of five new withanolide derivatives are from the roots of *Ashwagandha* together with 14 known compounds[35] are reported a novel chlorinated withanolide, 6a-chloro-5b, 17a-dihydroxy withaferin-A.

Many other chemical compound have also been reported and alkaloids are detected in all parts of plant in roots, fruits and leaves, with the highest content found in leaves. Another study also detected nicotine, somniferine, somniferinine, withanine, withananine, pseudowithanine, tropine, pseudotropine, 3-atigluxyoxy-tropane, choline, cuscohygrine, di-isopelletierine and new alkaloids anaferine and anhygrine in this medicinal plant [5]. Total alkaloid content varied between 0.12 and 0.31% [36]. Apart from these contetns, the plant also contains chemical constituents like cylsteryl glucosides, starch and a variety of amino acids including aspartic acid, protein, tyrostinealamine, glycine, glutamic acid and iron [5].

Results and discussion

Withania somnifera Dunal plant uses as a multipurpose traditional medicine has been resulted into several commercial drugs and therefore, its ranks a highly valued plant in the pharmaceutical industries. The pharmacology

and Phytochemistry of *Ashwagandha* has been widely investigated, but the toxicology studies of the extracts of the plant parts in different solvents are very few. In the case of *Ashwaganndha*, the studies are at a primary level, although it is required to identify the novel clinical properties of the plant. The identification and isolation of the particular compound responsible for the specific activity is more important. The further advancements in the analytical and separation chemistry will provide valuable insights on the toxicology and isolation of novel compounds alongwith the chemotypic variation of the ethnobotanically important species. The availability of micropropagation protocol will be supportive to conserve the elite germplasm of this genees. The transgenic protocols for either the plants are well established but the effects to enhances the withanolides or alkaloids contents in plant parts using this approach are lacking.

Roots of plant showed anticancer and radiosensitizing affects in animal module. Total alkaloid fraction of the root extract exhibits hypotensive, bradicardiac and respiratory ectivities in dogs. Withanolides possess remarkable antibacterial, anticancer, antiarthritic and immunosuppressive properties and protective effect against carbon tetrachloride induced toxicity. *Ashwagandha* could prove to be a good natural source of a potent and relativelt safe chemotherapeutic agent. Further studies are needed to explore the clinical potential of this plant for the cancer therapy.

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