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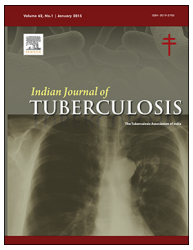

Original Article

Comparative study of effect of *Withania somnifera* as an adjuvant to DOTS in patients of newly diagnosed sputum smear positive pulmonary tuberculosis

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ABSTRACT

Background: Ashwagandha (*Withania somnifera* Linn.) a rejuvenative herb has long been used as an immunomodulator in Indian subcontinent. As immunity plays an important role in pathogenesis and treatment of tuberculosis (TB), so role of *W. somnifera* as an adjuvant has been studied on selected parameter.

Method: A randomized, double-blind placebo-control study was conducted in two groups of 60 newly diagnosed sputum smear positive pulmonary TB patients on Directly Observed Treatment – short course (DOTS) regime. *W. somnifera* root extract or placebo capsules were given as add-on therapy for duration of 12 weeks. Effects on sputum conversion, Hemoglobin (Hb), body weight, Erythrocyte Sedimentation Rate (ESR), RBC counts, WBC counts, CD4 and CD8 counts, Serum Glutamic-Oxaloacetic Transaminase (SGOT), Serum Glutamic-Pyruvic Transaminase (SGPT), serum uric acid and HRQL (Health Related Quality of Life) Index scores were studied.

Results: At the end of 8 weeks, sputum conversion was seen in 86.6% patients in study group and 76.6% in placebo group. At the end of 12 weeks a highly significant increase was seen in both CD4 and CD8 counts in study group. A raised SGOT and SGPT levels (>35 IU/L) were observed in 16.6% and 33.3% patients in study group; 43.33% and 53.33% in the placebo group of patients. Elevated serum uric acid levels (>6 mg/dl) were observed in 20% and 33.33% in study and placebo group respectively. Average gain in HRQL score was better in patients of study group.

Conclusion: Use of *W. somnifera* as an adjuvant in conjunction with anti-TB drugs used as DOTS showed a favorable effect on symptoms and immunological parameters in patients with pulmonary TB.

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1. Introduction

Tuberculosis (TB) has been a leading cause of death in the world for centuries. Today it ranks as the second leading cause of death from an infectious disease worldwide, after the human immunodeficiency virus. An estimated one third of the world population has been infected. India remains the highest TB burden country giving an estimated incidence of 2.2 million cases out of a global incidence of 9.6 million cases. Most of these people do not show signs of TB disease (termed latent infection). Approximately 1.5 million patients are put on antitubercular therapy every year, while approximately 0.3 million tubercular patients remain untreated.[1] Further, approximately 66,000 MDR-TB cases were diagnosed and put on treatment during the last three years.[2] It has also been reported that one infectious patient can infect 10–15 persons in a year unless effectively treated.

After entry into the lungs, tubercular bacilli have a series of encounters with different host defense mechanisms. Cell mediated immune responses play a pivotal role in host resistance to Mycobacterium tuberculi infection.[3,4] Cellular immunity against tubercular infection predominantly consists of T-lymphocytes that activate macrophages to produce agents such as reactive nitric oxide intermediates that are toxic to the harbored pathogens.[5,6] The progression and the final outcome of infection depend on the balance between outgrowth and killing of *Mycobacterium tuberculosis*. In most individuals, however, the immune response of the host usually merely manages to confine rather than eradicate the harbored microorganisms.[7] It is believed that the CD4+ T-cells releases interleukin-2 (IL-2), IL-4 and IFN-y and are believed to play an important role in immunity to intracellular infections and drive the secondary humoral response. The loss of CD4+ T cells in TB greatly increases susceptibility to both acute and reactivation TB.[8,9] In addition, CD8+ T cells are proved to be efficient in lysing infected cells and in reducing the number of intracellular bacteria.[11] The mechanisms of control of the bacterial load seem to be associated with granular exocytosis involving perforin and granzymes. So both CD4+ and CD8+ T cells provide protection against *M. tuberculosis*.[10,11] Efforts made to improve immunological status of the patient along with antitubercular drugs can have desired effect on treatment outcome.

From time to time, studies have been done where use of adjuvant like liquorice (*Glycyrrhiza glabra*), vitamin A (as retinyl acetate), zinc (as zinc sulphate), sylimarin, peppermint (*Mentha piperita*) essential oil inhalations, adaptogen (Spirulina), with Anti Tubercular Treatment (ATT) reported to have attenuated the side effects of ATT, hence increasing cure rate and improving drug compliance.[12–15] *Withania somnifera* or Ashwagandha (in Sanskrit), is a traditional herbal drug also called as ''Queen of Ayurveda'' and ''Indian ginseng''. The dried root is used in the traditional medicine systems of Ayurveda, Siddha, Sowa-Rigpa (Amchi), and Unani, medicine.[16] *W. somnifera* standards monographs published in the *Ayurvedic Pharmacopoeia of India* (Vol. I, 1989), *Unani Pharmacopoeia of India* (Vol. I, 2007), *Siddha Pharmacopoeia of India* (Vol. I, 2008), the World Health Organization (WHO) Monographs (Vol. 4, 2009), as well as in the currently valid editions of the *British Pharmacopoeia* (BP 2012), *Indian Pharmacopoeia* (IP 2014), and *United States Pharmacopoeia* (USP 36).[17,18] It contains a variety of pharmacologically and medically important constituents like withanolides, sitoindosides and other alkaloids which act on various systems of human body such as nervous system, immune system, reproductive system and endocrine system.[19–21] It has been used for multiple health benefits to get adaptogenic, aphrodisiac, immunomodulatory and anti-inflammatory effects.[22–27] It has also been studied in animals as a cytotoxic agent and has different Central Nervous System (CNS) applications.[28] The safety and efficacy of *W. somnifera* has been described in classical Ayurvedic texts and also in various preclinical and clinical studies.[29–32]

As immune system plays a key role in tubercular infection and response to drug therapy, the traditional and modem uses of this herb as an immunomodulator have prompted to use it in present study as an adjuvant in tubercular patients on DOTS (Directly Observed Treatment – short course).[33] The present research work was undertaken to study the effect of *W. somnifera* as an adjuvant to DOTS regime on immunological parameters and other health status indicators in sputum smear positive pulmonary TB.

2. Materials and methods

The study was conducted in accordance with the Indian Council for Medical Research Guidelines in humans (ICMR-GCP) and Declaration of Helsinki (2008) and was approved by the Institutional Ethics Committee (IEC).

2.1. Patient selection and study design

Present study was prospective, double blind, randomized, placebo controlled and a single-center study. It was conducted at Chest and TB hospital, Amritsar (Punjab) which is a university-affiliated, urban, tertiary care medical institute. The study included 60 (32 males and 28 females) newly diagnosed sputum smear positive patients of pulmonary TB of category I in DOTS under RNTCP (Revised National Tuberculosis Control Program – which is the state-run TB control initiative of the Government of India) within the age group of 15–65 years on first line antitubercular therapy in DOTS strategy (Fig. 1). Diagnosis was made on the basis of clinical examination and laboratory investigations including sputum for acid-fast bacilli. Detailed clinical history of all the patients regarding symptoms of TB such as cough, fever, expectoration, bodyaches and loss of weight were taken.

Patients on corticosteroids, barbiturates, hormones and having thyroid disorders, diabetes mellitus, cardiac disorders, obesity, pregnancy and lactation were excluded from the study. The written consent of patients was obtained after fully explaining them the details of study procedures in their vernacular language. They were strictly advised to complete their ATT course even after completion of this 12 week study.

2.2. Randomization and treatment allocation

The patients were divided into two groups, according to a pre-generated computerized randomization table. 30 patients were given *W. somnifera* root extract capsule 500 mg twice

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