Chapter I

Introduction
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Tuberculosis has been present in humans since antiquity, the earliest unambiguous detection of *Mycobacterium tuberculosis* is in the remains of bison dated 18,000 years back. And now it is worldwide health problem as it is a common menace for the human population world wide and to India in particular. WHO has declared it as a global emergency. As resistant strains of *Mycobacterium tuberculosis* have increasingly being emerged, treatment failure is too often, a fact, especially in countries lacking the necessary health care organizations to provide the long and costly treatment adapted to patients. Because of lack of treatment or compliance, Tuberculosis (TB) in India, is a major public health problem, nearly 2 million new cases recorded in 2009. Out of an estimated 1.3 million people who died of Tuberculosis in 2008. India’s case detection was around 67 %, while the estimated number of Tuberculosis cases that had become multi-drug resistant was 99,000 in 2009. Even though the Tuberculosis mortality rate has fallen by 35% since 1990, the disease claimed 1.7 million lives last year of which 3.8 lakh were women. The Tuberculosis mortality rate has dropped from 30 in 1990 to 20 per 100,000 in 2009. 1.7 million died of Tuberculosis in 2009. (The Times of India, New Delhi, Nov.15,2010) 4.4 Lakh new cases of multi drug resistant Tuberculosis (MDR-TB) are emerging each year, and less than 5% of those cases being properly treated. 9.4 million new TB cases including 3.3 million women in 2009, and 5.8 million cases were notified through DOTS program.

According to World Health Organization's annual report, “Global Tuberculosis Control 2010,” around 4,700 die of Tuberculosis daily. An estimated 9.4 million contracted the disease in 2009-the same number as the previous year (The Times of India, New Delhi, Nov.15,2010). However, “the biggest challenge as per the World Health Organization is multi drug resistant(MDR) strains of TB per year, which are both hard to detect and treat.

Regimens were optimized along with the implementation of the directly observed therapy short course (DOTS) initiative. The Government of India has been implementing the WHO-recommended DOTS strategy via the Revised National Tuberculosis Control Programme (RNTCP) nationwide in 1993 (Park K. Park’s, 2009).
Due to rapid industrialization, population explosion and hazardous profession, our atmosphere has become house of pathogenic agents. The epidemiological triad i.e. agent, host and environment have become favourable for flourishing the diseases.

It is caused by acid fast, slender, rod shaped, aerobic, weakly Gram-positive bacilli Mycobacterium tuberculosis. Tuberculosis is of two types, pulmonary and extra pulmonary.

Persons having features such as narrow chest, long neck, protruded larynx, less muscular arms and Akhlat Fasida (morbid matter) in upper respiratory tract and CNS are more susceptible to this disease. In most cases infections are acquired by person-to-person transmission of air borne droplet from an active case to susceptible host.

General characteristic symptoms of TB are persistent cough of about 3 or 4 weeks, intermittent fever, chest pain, haemoptysis, breathlessness, loss of appetite etc. Important signs are sunken and sleepy eyes, prominent bones, wasting of muscles, oily urine, facial cyanosis and Sulb, Daqeeq and Zaeef pulse.

In Unani system of medicine, it is classified into three stages based on dryness of Rutoobaat. Rutoobaat Oola, Sania and Salisa are dried in first, second and third stage respectively.

Effective TB treatment is difficult, due to the unusual structure and chemical composition of the mycobacterial cell wall, which makes many antibiotics ineffective and hinders the entry of drugs. The two antibiotics most commonly used are rifampicin and isoniazid. TB requires much longer periods of treatment (around 6 to 24 months) to entirely eliminate mycobacteria from the body. Latent TB treatment usually uses a single antibiotic, while active TB disease is best treated with combinations of several antibiotics.

However, the occurrence of multidrug resistant (MDR) strains of M. tuberculosis is a public health issue, as treatment is longer and requires more expensive drugs. Multi-Drug resistant tuberculosis (MDR-TB) is defined as resistance to two most effective first-line TB drug, rifampicin and isoniazid. Extensive drug-resistant TB (XDR-TB) is resistant to three or more of the six classes of first and second-line drugs. Drug resistant
tuberculosis is transmitted in the same way as regular TB. Primary resistance occurs in persons who are infected with a resistant strain of TB. A patient with fully susceptible TB develops secondary resistance (acquired resistance) during TB therapy because of inadequate treatment, not taking the prescribed regimen appropriately, or using low quality medication. In year 2000, an estimated 3.2% of all the tuberculosis new cases (between 185,000 and 414,000) were multiresistant. Treatment guidelines for these cases have much less easily been established and are complicated by drug side effects and co-infections with HIV-1. The clinical isolates' cross resistance monitoring provides insights in designing regimen strategies. A recent survey of cohort studies, or more recent clinical data, has led to some recommendations, although as mentioned by these authors, a full comparison of all the clinical data is not possible. This survey recommends the use of a regimen of at least five adequate anti tubercular drugs.

However ATT-induced toxicities show potentially serious adverse effect. Most antitubercular drugs, particularly pyrazinamide, rifampicin, and isoniazid, can cause hepatotoxicity, while ethambutol is seldom responsible for the same adverse effect. If a patient develops hepatitis, and no other cause is likely, drug-induced hepatitis must be presumed and the drugs stopped. Drug induced toxicities are a major form of iatrogenic disease. The pediatric, geriatric and female patients, chronic alcoholics and chronic liver diseases, acetylator status and under and malnutritional status have all been incriminated as possible predisposing factors. Continuation of ATT after development of toxicities is associated with a high fatality rate.

Apart from the other factors (including non compliance of patient), immunity related factors are the major causes of emergence of MDR Tuberculosis. In Tuberculosis the nature of protective immunity has been found to be of the cell-mediated type which confers partial protection against M. tuberculosis, while humoral immunity has no defined role in protection. Two type of cell are essential: Macrophages, which directly phagocytize tubercle bacilli, and T cells (mainly CD4+Lymphocytes), which induce protection through the production of lymphokines, especially interferon (IFN-\(\gamma\)). For these reasons, it is vital that a potent immunomodulator and adjuvant drug is developed to prevent the MDR and the toxicities induced by ATT. Unani therapy has a helpful role to
play in the prevention of toxicities induced by ATT drugs. These properties may also enhance the bioavailability of modern chemotherapy to maintain their sensitivity and overcome the drug compliance and Multi drug resistance.

Unani drugs are having a holistic approach in the management of disease, potentiates the Tabiat and modulate the immunity of the subject in general. Though Unani drugs may have anti mycobacterial property, but not scientifically studied so far. The immunomodulatory property of Unani drugs is well known and therefore these can be given as supportive and adjuvant therapy. These Unani drugs hence may be added as adjuvant drugs for enhancement of efficacy & in the prevention of MDR TB which is growing rapidly.

It is felt that this Unani formulation (UNIM-104) may be evaluated as an adjuvant in order to prevent MDR-TB by an immunostimulation property or direct antibacterial property on modern scientific parameters through clinical studies.

The study was Placebo controlled randomized bi-centric clinical trial. It was conducted on 20 cases in control group and 20 cases in test group. The total of 30 AFB positive cases in control group and 30 AFB positive in test group were registered. Out of which 20 cases in control group and 20 cases in test group completed the protocol (3 Months protocol therapy). The diagnosed cases were selected as per inclusion and exclusion criteria. All the relevant informations of the patients were recorded in especially designed case record form (CRF).

The statistical analysis were done by paired ‘t’ test. The findings of both the test and control groups were evaluated and compared to conclude the study.