Introduction
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Plant materials have long been used by numerous cultures for the treatment of various diseases. Since the advent of antibiotics from fungal sources the use of plant products as antimicrobials has been virtually non-existent. However in the face of limited life span of antibiotics due to drug resistance and emergence of newer viral diseases intractable to antibiotics, the pendulum is beginning to swing back towards an appreciation that plant products can serve as a source of novel therapeutic agents (Cowan M.M., 1999).

The field of Ethnopharmacology, which deals with the use of plant products as therapeutics, is therefore again gaining importance in the recent years and methods in Ethnopharmacology are being standardized (Waller W.P., 1993). The great interest in the use of medicinal plants by World Health Organisation in many developing countries has led to intensified efforts on the documentation of ethnomedical data of medicinal plants [Brantner and Green., 1994, Perumal Samy R and Ignacimuthu., 2000, Moskalenko S.A., 1986].
Even in advanced countries like United States, herbs have become commercially available in the dietary supplement industry as well as holistic medicine. Approximately one third of the population of United States has tried some form of alternative medicine at least once. Phytochemicals show promise as possible therapies for a range of diseases including AIDS and cancer (Paul Alan Cox and Michael J. Ballick, 1994). On a global basis at least 30 drugs, all single entities extracted from higher plants or modified further synthetically, are in use (Sukh Dev, 1997).

The rationale for using plants as a source of medicines is that plants produce a host of bioactive molecules most of which have probably evolved as chemical defences against infection, predation or physical agents (Richard A. Dixon, 2001).

The groups of compounds in plants that have been implicated to possess antimicrobial activity and their mode of action (Cowan M.M., 1999) are as follows.
(A) **Simple phenols and phenolic acids**

Effective against viruses, bacteria, and fungi. The mechanism of action seems to be by enzyme inhibition probably through reaction with sulphydryl groups or non-specific interaction with proteins.

(B) **Quinones**

They possess bactericidal and bacteriostatic activity. Quinones complex irreversibly with nucleophilic amino acids in proteins leading to inactivation.

(C) **Flavones, flavanols, and flavanoids**

They exhibit good inhibitory activity against multiple viruses. They have the ability to complex proteins. More lipophilic flavanoids may disrupt microbial membrane (Barnabas, C.G, and Nagarajan, S., 1988).

(D) **Tannins**

Tannins are toxic to filamentous fungi and yeasts. It forms complexes with proteins by non-specific forces.
(E) Terpenoids and Essential oils

Out of the essential oil derivatives, 60% are inhibitory to fungi and 30% are inhibitory to bacteria. The mechanism of action is not fully understood. It may involve membrane disruption.

(F) Alkaloids

They are effective against trypanosomes and plasmodia. It has the capacity to intercalate with DNA.

(G) Polypeptides

Peptides are active against yeast, gram negative and gram positive bacteria. They form ion channels in microbial membranes. It may also competitively inhibit adhesion of microbial proteins to host polysaccharide receptors.

(H) Lectins

Lectins are inhibitory to viruses. They inhibit viral interaction with critical host cell components.
The various steps involved in the development of a drug from plants are:

(a) Selection of a suitable part of the plant and preparation of the extract. Acetone is considered to be the best solvent for extraction.

(b) Separation of pure compounds from the extract and their characterisation.

(c) Testing their activity *in vitro*.

(d) Testing the activity in infected experimental animals.

(e) Clinical trials with human volunteers.

All the compounds exhibiting activity in laboratory tests may not necessarily become new drugs. Some will turn out to be identical or less potent than existing agents, Others may prove too toxic for commercial use. Nevertheless demonstrating activity in a bioassay is the first step in drug development process. A similar synthetic version may be examined instead. Even if that cannot serve as a drug, its discovery may suggest previously unconsidered avenues for attacking

Due to the doubts pertaining to the stability and shelf life of isolated pure compounds, using single herbs as such or using mixtures of herbs also for treatment is gaining importance in the recent years. The herbs used may act as

(A) Principal herb - Treats the cause or main symptoms of a disease

(B) Assistant herb - Strengthens the effect of Principal herb and produces leading effect in the treatment of accompanying symptoms.

(C) Adjuvant herb:

1) Enhances therapeutic effects or treats tertiary symptoms.
2) Eliminates toxicity.
3) Acts on the complementary target tissues not acted upon by the principal herb.

(D) Guiding herb - Directs the other herbs to the affected site.
The plant products may also be used in therapy along with the synthetic drugs for the following reasons.

(a) The phytochemicals may by themselves possess antimicrobial activity (Barnabas, C.G and Nagarajan, S., 1988), (Malcom, S.A and Sofowara, 1969). It may contribute to a cumulative effect when administered with synthetic drug.

(b) When administered along with the synthetic drug they may serve as bio enhancer in vitro (Veena Balakrishnan et al., 2001).

(c) The plant products may also act as bioavailability enhancer in vivo. (Rashmeet, K. Reen and Jaswant Singh, 1991).

Bioavailability, which is an important pharmacokinetic parameter, can be defined as the rate at which the drug becomes available to the body and the extent to which the dose is absorbed after administration. There is a great need for improvement of bioavailability of a large number of drugs which are (1) poorly bioavailable (2) given for long periods (3) toxic
and expensive. Maximizing oral bioavailability is therapeutically important because the extent of bioavailability directly influences plasma concentration and consequently therapeutic efficacy. Poorly bioavailable dose remains subtherapeutic, because a major portion of the dose never reaches the plasma or exerts its pharmacological effect until very large doses are given which may lead to serious side effects. Any significant improvement in bioavailability will result in lowering the dose frequency or dose of that particular drug (Usha zutshi and K.L. Bedi., 1996).

(d) The plant product may also be administered as an adjuvant to eliminate toxicity of the synthetic drug used (S.D.Saraswathy et al., 1998).

The growing field of Ethnopharmacology thus holds immense promise.
History of tuberculosis can be traced before the period of Christ. The first demonstration of tuberculosis as a contagious disease was made in 1865 by Jean Antoine Vиллемин. Tuberculosis persists as a global public health problem of a serious magnitude requiring urgent attention. It still remains as the single largest cause of death even though eleven years have elapsed since WHO declaring tuberculosis a global health emergency. Two million people die every year due to tuberculosis. India has about fourteen million cases of tuberculosis and contributes to one fourth of the global incidence of tuberculosis. Someone gets infected with tuberculosis every second. Through the ages, the contribution of tuberculosis to the misery of mankind has been immeasurable.

Tuberculosis is caused by bacteria belonging to the genus Mycobacterium. There are at least 54 species of Mycobacterium (Wayne, L.G and Kubica.G.P., 1986). Mycobacteria are slender rods that sometimes show branching filamentous forms resembling fungal mycelium. Hence, the name ‘Mycobacterium’, meaning fungus like bacteria. In humans M.tuberculosis is the most important pathogen. M.tuberculosis is a straight or slightly curved rod occurring singly in pairs or in small clumps. Closely related species are M.africanum,
M. bovis and M. microti. These four together are referred to as the MTB complex.

Inhalation is the most frequent route of infection, less often by ingestion and rarely by inoculation into the skin (Barksdale, L. and Kim, K.S., 1977). When infection occurs, the bacilli are ingested by alveolar macrophages to keep the reaction localized. The bacilli multiply intracellularly (Dannenberg, A. M. Jr., 1989). The disease derives its name from the characteristic lesion that is formed—the tubercle. This is an avascular granuloma composed of central zone containing giant cells, with or without caseation necrosis, surrounded by epithelioid cells and a peripheral zone of lymphocytes and fibroblasts. Tuberculoprotein induces the formation of monocytes, macrophages, epithelioid cells and giant cells in tissues. The bacterial polysaccharide causes exudation of neutrophils from blood vessels into tissues. Lipids cause the accumulation of macrophage and neutrophils. Phosphatides induce the formation of tubercles consisting of epithelioid cells and giant cells.

The development of specific cellular immunity sets in about six to eight weeks after infection (Bates, J. H., 1982). The immune response is dominated by CD4+ lymphocytes (Orme, I. M. et al., 1993). This
coincides with the development of delayed type hypersensitivity which could be demonstrated by the reaction to purified protein derivative of the organism given intradermally. Erythema and an induration measuring more than 10mm develops usually between 48-72 hours after the injection (Youmans.G.P., 1975). CD4+ lymphocytes release cytokines resulting in the production of activated macrophages. The activated macrophages release lytic enzymes and toxic radicals which are mycobactericidal. In most cases the infection stops at this point and the pulmonary lesion may heal by resorption, fibrosis and occasionally by calcification leaving a characteristic scar (Lowrie.D.B and Andrew.P.S.,1988).

If the host response is unable to halt the infection, the bacteria multiply within the macrophages and may progress to chronic tuberculosis with tubercle formation, cavitation and shedding of tubercle bacilli in sputum (Open tuberculosis). By about three weeks the macrophage laden with mycobacteria spread along the lymphatics to the draining lymph node. Though tuberculosis may affect any organ, lungs is the organ most frequently affected. When the infection is confined to the peripheral and subpleural part of the lungs, it is referred to as **Pulmonary tuberculosis**. When the draining lymphatics are involved it is called **Lymphangitis**. When the regional lymph
nodes are also involved it is called **Lymphadenitis**. An infection involving all these regions is referred to as Primary complex.

Susceptibility to tuberculosis is multifactorial. The various factors suggested are:

1. **Constitutional factors** – Racial differences in susceptibility have been reported. The Jews have a high level of resistance. Negroes and Red Indians have been found to be more susceptible than whites in the USA and the Welsh and Irish than the English.

2. **Hormonal factors** – Increased susceptibility of diabetics to develop tuberculosis is known. This may be due to the excessive multiplication of tubercle bacilli in the tissue of an uncontrolled diabetic as a result of increased availability of glycerol. There is a low incidence of tuberculosis in hyperthyroidism. It is believed that destruction of bacilli is enhanced by increased physiological activity of phagocytes in hyperthyroidism. Corticosteroids provoke activation of latent lesions and lead to increased multiplication of bacilli in the lesions.
(3) Environmental factors- The Environmental factors include Economic status, Occupation, Hypersensitivity and other diseases.

Low socioeconomic status and malnutrition are important predisposing factors. With improvements in the standards of living, its incidence has come down in the affluent countries. It has been aptly called ‘a barometer of social welfare’.

Dusty occupations, especially exposure to silica dust favours tuberculosis. Doctors, nurses and laboratory workers who have contact with patients and infectious materials are prone to develop the disease.

Numerous studies have also emphasized the importance of host resistance and hereditary susceptibility. Recently the disease has formed a formidable alliance with HIV and remains a leading killer in the world.

The diagnosis of tuberculosis can be done by a lung X-ray. Examining the sputum is a more reliable tool. Sputum is best collected early in the morning before any meal. If the sputum is scanty, a 24hr
collection may be examined. In early or convalescent cases, bacillary shedding may be intermittent and three consecutive samples should be examined for better results. Where sputum is not available, laryngeal swabs may be examined. In children who tend to swallow the sputum, stomach washings may be tested. The sputum should be collected directly into sterile wide mouthed container free from antiseptics.

Sputum smear in new glass slides can be examined by fluorescence microscopy using fluorescent dyes like auramine O, rhodamine etc for acid fast bacilli. Mycobacteria are called acid fast bacilli because once stained they resist decolourisation by dilute mineral acids. Acid fastness has been variously ascribed to the presence of unsaponifiable wax (mycolic acid) in the bacilli or to a semipermeable membrane around the cell. Mycobacteria can also be detected by Ziehl Neelsen stain (carbol fuchsin). The bacilli is stained red and it can be identified under oil immersion lens (100X) against a background stained with methylene blue. They possess waxy cell walls and hence do not readily take up Gram’s stain. It has been estimated that at least 5,000 acid fast bacilli should be present per ml of sputum for them to be readily demonstrable in direct smears.
Cultures are very sensitive for detection of tubercle bacilli and may be positive with as few as 10-100 bacilli per ml of sputum. Routine culture of mycobacteria in solid Lowenstein Jensen medium takes around 6-8 weeks. A negative report is given if no growth appears after 8-12 weeks.

The best known immunological test for tuberculosis is a well controlled Mantoux test. The standard tuberculin test consists of the intracutaneous injection of 0.1 ml of 5TU PPD. A single test is more accurate if read early and again at one week. The transverse diameter of the induration is usually taken as positive from 10mm upwards (A.G. Ghoshal and P.P. Roy., 2000).

Other techniques which may be employed are BACTEC method which takes three weeks and polymerase chain reaction method (PCR) which takes 24 hours. BACTEC 460 TB Automated radiometric technique which uses 14C labelled palmitic acid as substrate and depends on the detection of radiolabelled carbon dioxide as a measure of growth of mycobacteria, takes three weeks. PCR technique which takes 24 hours amplifies a short sequence of DNA within the 38K Da
protein gene of Mycobacterium tuberculosis. This technique is so sensitive that presence of 3-4 organisms is sufficient for detection.

In the prevention of tuberculosis, general measures such as adequate nutrition, good housing and health education are as important as specific antibacterial measures. Immunoprophylaxis is by intradermal injection of the live attenuated vaccine introduced by Calmette and Guerin (1921), the bacilli Calmette – Guerin or BCG. This is a strain of M.bovis attenuated by 239 serial subcultures. The efficacy of the BCG vaccine ranges from 80 % to a total absence of protection. The consensus opinion at present is that BCG does protect against tuberculosis in infants and children. The protection is not absolute but the disease in immunized children runs a milder course.

Chemotherapy has revolutionized the management of tuberculosis. The first line drugs currently used in the chemotherapy of tuberculosis are Rifampicin, Isoniazid, Pyrazinamide ,Ethambutol and Streptomycin (Prema Gurumurthy, 1997).

(1) Isoniazid - This remains the corner stone of TB treatment and no standard drug regimen is formulated without Isoniazid. It is bactericidal at all pH values and acts against actively multiplying tubercle bacilli. The mechanism of action is poorly
understood. It may involve depletion of NAD and inhibition of mycolic acid synthesis. It is well absorbed from the alimentary tract and is distributed throughout the body water, readily crossing tissue barriers. It is metabolized or inactivated by acetylation to acetyl isoniazid which is hydrolysed to monoacetyl hydrazine and isonoicotinic acid. The rate at which acetylation of isoniazid occurs is genetically determined and based on rate of acetylation two phenotypes have been identified – rapid and slow acetylators. The t1/2 in fast acetylators is 1hr and in slow acetylators is 41/2 hrs. The adverse effects are rashes, fever, jaundice, peripheral neuritis etc.

(2) Rifampicin- It is the most potent drug which acts against actively and slowly multiplying bacilli which are intracellular or extracellular. It acts by inhibiting bacterial DNA dependent RNA polymerase leading to suppression of initiation of transcription. The drug is readily absorbed from the gastrointestinal tract and is uniformly distributed. About 80% of the administered drug is bound to plasma proteins and is excreted through the bile as well as urine. Rifampicin is mainly metabolized to des acetyl rifampicin in the body. The serum half
life of rifampicin (after the first dose) is about three hours. The adverse effects are jaundice and chronic liver disease.

(3) **Pyrazinamide** – It is bactericidal at acidic pH. The exact mode of action is not known. It is effective against semi dormant bacteria. The drug is completely absorbed from the gastrointestinal tract. There is an evidence of protein binding to the extent of 30-35%. The main metabolite is pyrazinoic acid and is poorly excreted through the kidney. The adverse effect is arthralgia.

(4) **Ethambutol** - It is baceriostatic in nature and is more suitable as a companion drug. It inhibits cell wall synthesis by interfering with the incorporation of mycolic acid into the cell wall. Absorption of ethambutol is rapid and it is slowly eliminated. The adverse effect is optic neuritis and decrease of visual acuity.

(5) **Streptomycin** - It is bactericidal at alkaline pH and acts against actively multiplying tubercle bacilli. It acts by inhibiting protein synthesis by binding to 30S ribosomal subunit. It is not absorbed from the gastrointestinal tract and has to be administered parenterally. About 30% of the drug is bound to plasma
proteins. No metabolites of streptomycin have been identified and the drug is excreted by the kidney. The half life is about 2-3 hours. The adverse effect is ototoxicity.

The second line drugs are Ofloxacino (Quinolones)- which acts against both replicating and dormant micro organisms by specifically inhibiting DNA gyrase. , Amikacin , Cycloserine , Kanamycin , Viomycin , Capreomycin etc.

Due to the problem of drug resistance, a combination of drugs is preferred for treatment. Drug resistance may be of two types.

(1) Primary-Presence of drug resistance in a patient who has never received prior treatment with anti TB drugs

(2) Secondary- Resistance to one or more anti TB acquired during the course of treatment due to poor quality of drugs, poor patient compliance, use of single drug, reduced dosage etc.

The mode of treatment currently followed is DOTS (Directly Observed Therapy Short Course-2 Months) involving the four first line drugs in a dosage corresponding to the RNTCP (Revised National
Tuberculosis Control Programme) regimen. Long term therapy (6months) is involved in the treatment. Multidrug therapy is usually followed since the patient may develop resistance against any of the drugs.

But the problems encountered are (a) there is poor patient compliance with the physician’s advise and dosage regimen. (b) Over use of antibiotics also leads to the development of new drug resistant strains (c). Long term use of these drugs also leads to toxicity in some cases. Most of the anti TB drugs are toxic.

As mentioned earlier, use of plant products along with the drug may reduce the toxicity. Apart from possessing antibacterial activity, they may also serve as a bioenhancer or bioavailability enhancer.

Around 351 Indian plants have been screened for antitubercular activity.

Lawsonia Inermis has been tested for activity against Mycobacterial strains M.Phlei, M.607, M.Tuberculosis H37RV. (Bhatnagar et al., 1961) The tuberculostatic activity of Lawsonia inermis in animal models has been demonstrated. (Sharma., 1990) The antitubercular activity of root bark extract of Morinda
citrifolia against M.Phlei and M.607 has been established (Bhatnagar et al., 1961). Compounds isolated from Morinda citrifolia also possess antimycobacterial activity. The inhibition of in vitro growth of Mycobacterium tuberculosis by a phytosiderophore, Tephrosia purpurea has been demonstrated (Rajiv. J et al., 2001). The in vitro antimycobacterial activity of Physalis angulata has been studied (Pietro et al 2000)

Out of the various plants tested for their anti tubercular activity, Piper longum holds special interest.