A Review on Anti-Tubercular Plants And Current Trends

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Abstract:
Tuberculosis (TB), an old disease caused by the bacteria Mycobacterium tuberculosis is still responsible for more deaths worldwide each year than any other infectious disease, including human immunodeficiency virus (HIV) in spite of availability of effective treatment that has existed for over 50 years since the 1940s. The development of resistance to antibiotics is only one of the many challenges facing the fight to stem this deadly epidemic. Practical factors including a lack of community awareness, access to diagnostic tools, healthcare facilities, and patient supervision and follow-up are compounded by the disease's wide geographic range. A failure of communication and coordination between local and international control units is equally problematic. As we continue to make great strides in medical technology and research, there is the need for a greater effort to mobilize resources and make lasting, focused investments of funding and professional training in areas of endemic TB in order to finally see an end to this bacteria's lasting reign of devastation. This review article looks at the current global trends of the disease from a broader perspective. The present paper involves various plant drugs along with their chemical constituents responsible for anti-tubercular activity. This review work stimulates various researchers for further research on the potential use of medicinal plants having anti-tubercular activity

Keywords: Tuberculosis, anti-tubercular, natural, ayurveda, Multiple-drug resistant (MDR-TB); Extensively-drug resistant (XDR-TB).

Introduction: Tuberculosis (TB) has consistently shown a much higher annual mortality rate than HIV or any other infection. This is due to an array of events that begins with the virulence of Mycobacterium tuberculosis, the highly contagious and persistent bacterium responsible for TB infection. Another contributing factor is the ability of these bacteria to develop genetic mutations that confer resistance to a number of formerly effective antibiotics. The World Health Organization (WHO) estimated about 480,000 cases of multiple-drug resistant (MDR-) TB detected worldwide in 2013. MDRTB and its more resistant sibling, extensively-drug resistant (XDR-) TB, have become increasingly common since successful antibiotic treatments of TB were discovered. Ominously, some experts predict that MDRTB will replace non-resistant TB as the most common form of the disease in the next 50 years. Tuberculosis is the major opportunistic infection of HIV/AIDS in developing countries Anti-tuberculosis drugs are a two-edged sword. While they destroy pathogenic M. tuberculosis they also select for drug resistant bacteria against which those drugs are then ineffective. Global surveillance has shown that drug resistant tuberculosis is widespread and is now a threat to tuberculosis control programs in many countries . The drugs now available for the treatment of tuberculosis were discovered in a period of two decades (1944-1965), during which a relatively intensive search was carried out in various industrial and nonindustrial laboratories. There are many reasons for the decreased interest in research on new antituberculosis drugs. First, success attained with short course chemotherapy involving combinations of the available powerful drugs led to the incorrect assumption that there was no real need for other products. Second, large-scale screening systems for the detection of new anti-tuberculosis agents are particularly time-consuming and entail some problems related to the handling of the pathogen

Upper Respiratory Infection : Types of upper respiratory infection include the common cold (head cold), the mild flu, tonsillitis, laryngitis, and sinus infection. Of the upper respiratory infection symptoms, the most common is a cough. Lung infections may also lead to a stuffy or runny nose, sore throat, sneezing, achy muscles, and headache.

Lower Respiratory Infection : Lower respiratory infections may be found in your lungs or breathing airways. They can be caused by viral infections like the severe flu or bacterial infections like tuberculosis. Lower respiratory infection symptoms include a severe cough that may produce mucus (phlegm), cause shortness of breath, chest tightness, and wheezing when exhaling.

Whooping cough (pertussis), is caused by the *Bordetella pertussis* bacterium. Uncontrollable, violent coughing that can make it difficult to breathe is characteristic of this lung infection. The whooping sound comes from an ill person sucking in air after a coughing fit. Anyone, including adults, can get pertussis, but infants stand a particularly severe, even life-threatening, risk.The pertussis vaccine is recommended for both adults and children. This vaccine helps prevent the spread of infection of whooping cough in infants and others. Vaccines are available beginning at 2 months old

Natural products as Anti-TB agents : Natural products including plants, animals and minerals have been the basis of treatment of human diseases. History of medicine dates back practically to the existence of human civilization. The current accepted modern medicine or allopathy has gradually developed over the years by scientific and observational efforts of scientists . Natural products as crude materials with efficacy against various diseases have been selected by humans over many generations of practical experience. Such experiential evaluation is different from the scientific Medicinal plants, since times immemorial, have been used in virtually all cultures as a source of medicine. The widespread use of herbal remedies and healthcare preparations, as those described in ancient texts such as the Vedas and the Bible, and obtained from commonly used traditional herbs and medicinal plants, has been traced to the occurrence of natural products with medicinal properties. Ayurveda, literally meaning the "Science of life and longevity" in ancient Sanskrit, is the one of the oldest healing system of India based on lifestyle, diet and herbs18. In Ayurveda tuberculosis is known as Rajayakshma, Yakshma, Shosha, Kshaya . List of plants from Ayurveda has been discussed in Table 2 given below. Anti-tubercular plants from foreign origin Not only in India, anti-tubercular plants were found all over the world including South Africa, New Zealand, Malaysia, Nigeria, Tibet etc. A list of anti-tubercular plants from foreign origin has been shown in Table 3 given below .

Adverse effects of Anti-TB drugs

Drug	Adverse effects
Isoniazid	Skin rash, hepatitis
Rifampicin	Abdominal pain, nausea, vomiting, hepatitis, thrombocytopenic purpura
Pyrazinamide	Arthralgia, hepatitis
Streptomycin	Vestibular and auditory nerve damage, renal damage
Streptomycin	Retrobulbar neuritis, ocular side effects
Thioacetazone	Skin rash, Exfoliative dermatitis
Paraaminosalicylic acid	Anorexia, nausea, vomiting, hypersensitivity reactions
Kanamycin	Vertigo, auditory nerve damage, nephrotoxicity
Ethionamide	Diarrhoea, abdominal pain, hepatotoxicity
Cycloserine	Dizziness, headache, depression, psychosis, convulsions

Etiology agent

Mycobacteriumtuberculosis

M. tuberculosis infection has been known throughout human history. The bacterium is believed to have originated from East Africa. As early humans moved out of East Africa, settling in Europe and Asia, TB infection moved with them and continued to wreak devastation for centuries throughout the known world . Evidence of tubercular decay was seen on the spines of mummies from the Egyptian pre-dynastic era and the Peruvian pre-Columbian era, around 2400 B.C. . Ancient Greeks termed the illness “phthisis.” Later, the “Great White Plague” of TB infection raged across Europe for over a century. Throughout this time, the disease was considered almost inevitably fatal, and no effective treatment or cure existed. A milestone occurred when Hermann Heinrich Robert Koch discovered and expounded the etiology of tuberculosis in his presentation “Die Aetiologie der Tuberculose” to the Berlin physiological society. He presented his discoveries on March 24th, 1882, and later received the Nobel Prize in 1905. This was the start of an era of unprecedented advances in the treatment and prevention of this deadly disease . In 1943 another milestone was marked: the first known effective cure for the infection, antibiotic called streptomycin, was discovered in a laboratory at Rutgers University in New Jersey. The first large-scale clinical trial of streptomycin took place at the British Medical Research Council in 1948 and was the first published drug trial to randomize participants. This study set the methodological standard for modern-day randomized, controlled trials. It also was the first time patients showed resistance to streptomycin. Also in 1948, two new anti-tuberculosis agents, thiacetazone and paraaminosalicylic acid, entered the market. When either of these agents was administered with streptomycin, cure rates dramatically increased and acquired resistance in the bacteria decreased . Isoniazid was successfully tested and added to the TB regimen in 1951. This was followed by the development of a plethora of new drugs:

Pathogenesis : Mycobacterium tuberculosis is an airborne pathogen. Once inhaled, droplets bearing the mycobacteria settle throughout the airways. Most of the bacilli are trapped in the upper parts of the airways where the mucussecreting goblet cells are located. The mucus catches the invading bacilli, and the cilia on the surface of the cells constantly undulate to move the mucus and trapped foreign particles upward for removal. This system provides the body with an initial physical defense that prevents infection in most persons exposed to tuberculosis.

The Bacteriology : Mycobacterium tuberculosis is a large, non-motile, slow-growing obligate aerobic bacterium. As an obligate aerobe, it has a predilection for the oxygenated environment of the upper lobes of the lungs. M tuberculosis has a doubling time of 18 hours and clinical cultures can take approximately 6–8 weeks. It is resistant to dehydration and so can survive in expectorated sputum. Morphologically the bacterial cell wall contains an array of complex lipids such as mycolic acids, long-chain fatty acids facilitating the acid-fast characteristics; Wax D; and Phosphatides, which contribute to the clinically relevant feature of caseating necrosis Traditionally cord formation has been related to virulence since avirulent M. tuberculosis strains do not form cords.

However recent findings suggest similar cord formation in non-pathogenic, opportunistic Mycobacterium species, i.e. M. abscessus, M. chubuense, M. gilvum, M. haemophilum, M. marinum, M. obuense, M. parafortuitum, and M. vaccae. The cord patterns among species are not easily distinguished by light microscopy, an important diagnostic implication in minimizing the potential for false negatives and unnecessary exposure to an ineffective and arduous drug regimen In 1998 the complete gene sequence of M. tuberculosis variant (H37Rv) was determined, comprising of 4,411,529 base pairs and 4000 genes [18]. The genome has an extremely high guanine + cytosine content and is remarkably different than most bacteria in that it possesses dedicated enzymes specialized for lipogenesis and lipolysis. It has been suggested that these fatty acid-utilizing enzymes are potentially associated with the ability of M. tuberculosis to survive in host tissues, using fatty acids as a carbon source.

Diagnosis : **Culture and Sensitivity :** The permeability of the aforementioned barrier enables the bacterium to resist conventional gram staining, causing gram stains to show a weak positive, or to show up white; so typically an alternative (acidfast) stain is used instead. Acid-fast, also known as the Ziehl-Neelsen stain refers to the ability of M. tuberculosis to retain carbolfuchsin stain, despite decolorization treatment with ethanol-hydrochloric acid . Preparation prior to staining involves NaOH treatment, which destroys unwanted bacteria, human cells, and fluid, followed by centrifugation. This is followed by culture on Lowenstein-Jensen media for up to 8 weeks. Lowenstein-Jensen media contains complex nutrients and dyes, i.e. egg yolk and malachite green dyes; dyes inhibit normal flora present in sputum samples. Clinically, tuberculosis can be diagnosed by signs and symptoms, characteristics on chest radiography, and positive skin reactivity findings from the tuberculin (Mantoux) skin test . Sign and symptoms suggestive of TB include: significant cough that lasts 3 weeks or longer, chest pain, hemoptysis, coughing up sputum (productive cough), fatigue, weight loss, anorexia, chills, pyrexia, night sweats . On chest radiograph, TB disease activity is evidenced by any parenchymal, nodal, or pleural abnormality with or without associated calcification . Confirmation of these findings and tests are supported by the microscopic identification of acid-fast rods and the culture of the bacteria.

Treatment and Prognosis :

Patients with latent tuberculosis infection have the bacteria in their bodies but do not typically present with symptoms because the bacteria are not active. If the bacteria become active and multiply, then the symptoms of TB will become evident in the patient. For this reason, patients with known latent TB are prescribed preventative pharmacological interventions. The current medications that are used for the treatment of latent tuberculosis are isoniazid, rifampin, and rifapentine . Non-resistant TB is usually treated by a regimen of several drugs taken for a period of 6 to 9 months. Currently, there are 10 drugs that are approved by the FDA for the treatment of active TB. Of these approved drugs, the first-line pharmacological intervention that forms the core treatment regimen includes isoniazid, rifampin, ethambutol, and pyrazinamide Treatment regimens for non-resistant TB have an initial phase of 2 months, followed by a continuation phase of usually 4-7 months. The 6-month regimen consists of isoniazid, rifampin, and pyrazinamide given for 2 months followed by isoniazid and rifampin for 4 months. Ethambutol or streptomycin is added in the first 2 months in patients with advanced disease. The success rate with the 6-month regimen in sputum conversion (conversion defined as a negative culture in 3 consecutive samples taken 1 day apart) is far beyond 90% within the first two months of therapy. The relapse rate after 3-5 years is about 0-3% . It is very important to complete the treatment regimen because bacteria could still be active and become resistant to these first-line drugs if the treatment is stopped prematurely. For this reason, physician supervision and follow-up become important to ensure patient compliance . Shortening anti-tuberculosis treatment regimens is one strategy expected to improve patient adherence to treatment, resulting in better case management and disease control and minimizing the risk of drug resistance. Gatifloxacin, normally a second-line drug, was selected for a recent phase 3 trial to evaluate the efficacy of a 4-month regimen compared to the standard 6 months. This trial assessed the effect of shortening rifampin-sensitive TB treatment by using a fluoroquinolone-based approach. The results of the study failed to show that 4-month treatment with gatifloxacin, which was substituted for ethambutol, was non-inferior to the standard 6-month regimen. There was a higher recurrence rate observed with the 4- month regimen. MDR-TB and XDR-TB are inherently more difficult to treat because the treatment must be individualized and closely monitored. Depending on the susceptibility of the infection, treatment regimens for resistant strains can last up to 36 months or more. An additional complication of this treatment is that, while first-line TB drugs are relatively nontoxic, second-line treatments like fluoroquinolones carry the risk of more serious side effects. Second-line treatments also tend to be more expensive than first-line drugs, and they may not be available in areas where access to health care is limited. These factors all complicate the treatment of an illness that is already difficult to defeat. There are also a few new drugs in development with novel mechanisms of action against TB. These include bedaquiline, a diarylquinoline which inhibits ATP synthesis in mycobacteria, and delamanid, which inhibits bacterial mycolic acid (an important cell-wall component) synthesis. As these drugs and others proceed through trials, their efficacy and safety for patients will become more evident.

Epidemiology Current Global Distribution : The latest trends in the global distribution of tuberculosis were published in 2018 by the World Health Organization in their annual report on tuberculosis [32]. Globally, TB is one of the top 10 causes of death and the leading cause of death in HIV infection / AIDS. Many people continue to fall sick each year from TB infection. TB caused an estimated 1.3 million deaths among HIV-negative individuals and an estimated 300000 death among HIV-positive individuals in 2017. Worldwide, an estimated 10.0 million people developed TB disease in 2017 with a breakdown of 5.8 million men, 3.2 million women and 1.0 million children. Cases were reported in all countries and age groups; overall 90% were adults (aged ≥15 years), 9% were individuals living with HIV (72% in Africa) and two thirds were from eight countries: India (27%), China (9%), Indonesia (8%), the Philippines (6%), Pakistan (5%), Nigeria (4%), Bangladesh (4%) and South Africa (3%). The

listed 8 countries and 22 other countries in WHO's list of 30 high TB burden countries made up for 87% of the world's cases; while 6% of global cases were in the WHO European Region (3%) and WHO Region of the Americas (3%)

Global Initiatives : While tuberculosis infection spans the globe, the fight against it has been spearheaded by a few key organizations. The WHO has implemented far-reaching programs that work with local governments, other international aid organizations, NGOs, and other stakeholders to develop research and provide equipment and services to improve community management of this epidemic. In 1995, the WHO first began to standardize the collection of regular reports of global TB incidence and other statistics. The year 2015 marked the twentieth year of TB data collection, and the fifteenth year since the adoption of Millennial Development Goals (MDGs) signed by all 191 United Nations member states in 2000. These goals proposed specific metrics to track progress on a variety of issues, including reducing the incidence and improving treatment of infectious diseases. One of the declared MDGs was to reverse the then-increasing incidence of TB, a goal which has been met by its evaluation date of 2015. Another was to increase the TB cure rate, which has risen from less than 80% in 1990 to around 86% since 2013. However, as the time period encompassed by the MDGs comes to an end in 2015, the global fight against TB is far from over.

Prevention and Control : The major health-care interventions for preventing new infections and progression to TB disease are the treatment of latent TB infection and vaccination of children with the bacille Calmette-Guérin (BCG) vaccine. While preventive treatment for a latent TB infection is expanding, accessibility of care is still a problem to those that require it; this is unlike BCG vaccination coverage which is high . WHO has strongly recommended treatment for latent TB infection in two important groups' i.e. individuals living with HIV, and children aged less than 5 years who are household contacts of an individual with bacteriological confirmed pulmonary TB Progress is being made in the fight against TB infection on many fronts. One important strategy to control this disease is the development of tools to provide a quick, accurate diagnosis of drug-resistant strains of bacteria in the field. Another, equally critical element is coordination between healthcare providers. Infrastructure, up-to-date hospitals and clinics, and community education all play essential roles in the struggle to control this disease . A serious concern in modern TB treatment is the delay in diagnosis of drug-resistant strains of the bacteria, which require specialized treatment regimens. This is especially important because the areas where MDR-TB and XDR-TB are endemic are also largely underdeveloped areas with limited access to modern healthcare and laboratory equipment. In cases where TB is suspected but the bacteria's susceptibility is unknown, patients may receive ineffective treatment before the resistance of their infection is identified. This can increase the patient's risk of morbidity and mortality from TB, as well as encourage bacterial development of more extensive resistance mechanisms to a broader range of antibiotics. This delay may also prolong the window for transmission of the infection, perpetuating the reservoir of resistant microorganisms. It is clear that access to timely diagnosis is essential to providing appropriate treatment and reducing the prevalence of resistant organisms . Currently, a widely-used standard for drug susceptibility testing (DST) of TB is the BACTEC MGIT960, a fully-automated system created for the culture and identification of Mycobacterial strains through DNA analysis which has been in use since 1998. In a study by Catanzaro and associates, the BACTEC MGIT960 was compared with the three rapid diagnostic kits for performance and accuracy. The study included the Line Probe Assay (LPA) and Pyrosequencing (PSQ), which both produced results in an average of 1.1 days, and Microscopic Observation of Drug Susceptibility (MODS), which produced results in an average of 14.3 days. In contrast, the BACTEC MGIT960 took an average of 24.7 days to produce results. All three rapid test kits had very high specificity for detection of the most common types of drug resistance in MDR-TB and XDRTB, ranging from 97-100%. The sensitivity of the kits was somewhat lower but still significantly high: for resistance to isoniazid, rifampin, moxifloxacin, and ofloxacin, sensitivity was found to be 94-100%, for amikacin and capreomycin, it was 84-90%, and for kanamycin, it was 48-62%. This means that all three rapid test kits were able to identify bacterial strains with 6 out of the 7 most common types of drug resistance in almost 100% of patients, in a fraction of the time necessary for other methods.

Material & Methods

Collection of plants: Leaves of Acalypha indica L. (Euphorbiaceae), Adhatoda vasica Nees. (Acanthaceae), Aloe vera L. (Aloaceae) and bulbs of Allium cepa L. (Alliaceae) and Allium sativum L. (Alliaceae) were collected between spring and summer season during March to May 2004 from Paliwal Park and Khandari campus Agra, UP. All specimens were identi□ed at Department of Botany, School of Life Sciences, Dr B.R. Ambedkar University, Agra.Material & Methods Collection of plants: Leaves of Acalypha indica L. (Euphorbiaceae), Adhatoda vasica Nees. (Acanthaceae), Aloe vera L. (Aloaceae) and bulbs of Allium cepa L. (Alliaceae) and Allium sativum L. (Alliaceae) were collected between spring and summer season during March to May 2004 from Paliwal Park and Khandari campus Agra, UP. All specimens were identi□ed at Department of Botany, School of Life Sciences, Dr B.R. Ambedkar University, Agra.

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Mycobacterial Diseases (ICMR), Agra. Susceptibility profile of the strains against standard anti-tuberculosis drugs was as follows: DKU156 resistant to RIF (rifampicin), INH (isoniazid), EMB (ethambutol), STR (streptomycin); JAL-1236 resistant to RIF, INH, STR, KAN (kenamyein), and OFL (ofloxacin) Assay protocol:

Antimicrobial assays were performed in Lowenste in ensen (L-J) medium and Middlebrook 7H9 broth in (i) Determination of Colony forming units (cfu) on Lowenstein-Jensen (L-J) - The ten-fold dilution of standard 1 mg/ml M. tuberculosis suspension19 were streaked on L-J medium for determining cfu in the presence and absence of plant extracts. An M. tuberculosis suspension of 1 mg/ml is equivalent to MacFarland standard-120. One loopful (6 µl) of this suspension was streaked on the L-J slants using 3 mm external diameter loop. Reagents of L-J media included potassium di hydrogen phosphate anhydrous (Qualigens), magnesium sulphate anhydrous (Qualigens), magesium citrate (Loba Chemie), L-asparagine (Hi-media, Mumbai), glycerol (Fisher Scientific, Mumbai), and malachite green (Hi-Media, Mumbai). The plant extract was incorporated in the medium at concentration of 2 per cent v/v and 4 per cent v/v (2 ml and 4 ml of fresh plant extract was dissolved into 100 ml of culture medium) prior to inspissation. The medium set inoculated with the standard bacterial suspension and incubated at 37°C for 42 days. Reading was taken weekly. For comparison, extract free control slants were used. Susceptibility testing of MDR isolates was also performed against standard drugs like: rifampicin and isoniazid in the same batch of media for comparison of cfu on drug free controls. Each test was done in duplicate.

Percentage inhibition was calculated by mean reduction in number of colonies on extract containing as compared to extract free controls.

(ii) Middlebrook 7H9 broth in BacT/ALERT 3D system - Exposure of mycobacterial suspension (0.2 ml, 1mg/ml) to the millipore (0.22 µm) filtered plant extract (4% v/v) was done for 15 min at room temperature. The resultant mixture was inoculated into Mycobacterial Process (MP) bottles containing Middlebrook 7H9 broth supplemented with reconstitution fluid (Oleic acid, glycerol, & bovine serum albumin) in colorimetric BacT/ALERT 3D system (BioMerieux, France). The bottles were loaded in the instrument's incubation module at 37° C. As per the prescribed method for determining susceptibility to anti- TB drugs, the relative delay of 3.5 days in positivity of drug (plant extract)- containing bottles as compared to that in drug (plant extract)-free control was considered as the criterion for susceptibility to particular drug (plant extract in this case) containing medium21,22. An isolate was considered to be susceptible to (inhibited by) a drug if the drugcontaining bottle was not flagged positive within 3.5 days of the positive signal in drug-free control bottle. This has been correlated with more than 90 per cent inhibition of growth by a drug (anti-microbial agent) as compared to that in the drug free medium

Progress

Research and Development Breakthroughs in technology are required to accelerate the annual decline in the global TB incidence rate to an average of 17% per year. Area of research focus include a vaccine to lower the risk of infection, a vaccine or new drug treatment to reduce the risk in latently infected people, rapid diagnostics for use at the point of care and simpler, shorter drug regimens for treatment. There is slow progress in the development pipelines with few diagnostic technologies emerging in 2017 in spite of recent increase funding for TB research and development. Presently under clinical trials are 20 drugs, several treatment regimens and 12 vaccine candidates.

Conclusion

Despite vast improvements in research and technology and the development of multiple drug regimens to battle this insidious killer, M. tuberculosis continues to be a major health concern worldwide. As TB infection continues to be the most prevalent fatal infectious disease in the world, funding for research and program implementation has trailed global investment in other diseases. Advances in diagnostic tools, active patient supervision, and a global focus in detecting and mapping strains of drug-resistant pathogens are proven strategies for controlling this disease. However, integral .

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