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A REVIEW ON NATURAL TREATMENT OF TUBERCULOSIS

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ABSTRACT

Tuberculosis is a serious infectious bacterial disease. The disease is highly contagious and mostly transmitted from person to person, usually by bacteria and it is mostly transmitted by inhaling bacteria-carrying air droplets. Tuberculosis most generally attacks the lungs, but it can also infect other organs. It has resulted in progressive increase in number of orphans due to parental deaths which is estimated to be 10 million out of which 6%-15% is maternal mortality, which counts up to 15%-34% if only indirect causes are taken into account. Tuberculosis screening is done using an intelligible clinical technique that checks for the absence of current cough, sputum production, fever, weight loss, and night sweats. The concern of discovering new, imperatively needed anti-TB drugs from natural sources necessitates a multidisciplinary research. The use of allopathic drugs in such a convoluted disease gives rise to more dangerous complexities like cross resistance whereas natural drugs have proven to be better in this scenario. The investigation of new remedies for the successful weakening of the unhealthy condition associated with tuberculosis is the crucial requirement. Anti-tuberculosis agents: Actinobacteria, Artemisia annua, Camellia sinesis.

KEYWORDS: Tuberculosis, MDR-TB, XDR-TB, Natural drug.

1. INTRODUCTION

Tuberculosis is a deadly contagious bacterial disease that is the second biggest killer in the world. Robert Koch; A German microbiologist discovered the causes of tuberculosis in 1882 which is a bacteria of a Mycobacterium genus named as Mycobacterium tuberculosis. Following his discovery, Development of efficacious drug treatment along with vaccines promised the ultimate cure of the disease.[1] Indeed, at one point, Predictions were made by the United Nations regarding the elimination of tuberculosis worldwide by 2025.[2]

Tuberculosis (TB), which has been and still remains a serious disease to the global human population causing millions of deaths worldwide. The recent increase in the number of multi-drug resistant clinical isolates of *Mycobacterium tuberculosis* has created an urgent need for the discovery and development of new anti-tuberculosis drugs. Medicinal plantshave had a great influence on the daily lives of people living in developing countries, particularly in Africa, as the population in these countries cannot generally afford the cost of Western medicines.[3]

TB at first was thought to be a mild disease that could be managed with antibiotics. The first antibiotic was introduced in 1944 and it worked wonders but soon the mono-therapy of streptomycin stopped showing results due to its drug resistance and gave a lesson of defining a new therapy with multiple drug system to prevent the further resistance of the bacteria. Soon the multi drug regimen initiated, accompanied by assorted drugs with anti- tuberculosis activity but then, new type of antibiotic resistance emerged which is Multidrug resistant TB (MDR-TB), caused by the bacteria resistant to at least rifampicin and isoniazid; the first line drug for the treatment of the TB. Extensively drug-resistant (XDR) TB strains are resistant to front-line and second-line drugs for TB.[4] This antibiotic-resistance catastrophe has become the serious issue of discussion amongst the physicians, researchers, governments and the public. Knowledge from the history of antibiotic discovery and the new understanding of cell's biology and antibiotic mechanism have the potential to compose medicines that would be able to control the infection.[5]

Historical Background

TB is one of the most seasoned irresistible illnesses influencing humanity. According to an old Indian sacred text Vedas, the TB was alluded to as Yakshma (which means the wasting illness). The revelation of the tubercle bacillus was declared by the Robert Koch during the monthly evening meeting on 24th of March 1882 which was of the Berlin Physiological Society. Thus because of the same, the day of 24th March is being praised as with the 'World TB day.[6]

Symptoms & Diagnosis

Coughing, loss of weight, torment within the chest, bloodcolored sputum, perspiring/fever, is some noteworthy signs and symptoms of TB. Various appearances may also consolidate shortcoming, visit colds, sleepiness, shortness of breath, lack of hunger, limited wheeze. These reactions can be a direct end result of some top notch contamination additionally. In

this way, evaluation of sputum for the certification of TB pollution is a flat out need.[7] Examination of TB is typically reliant at the display of damaging snappy bacilli from the clinical models, clinical features, and histopathology.[8] TB end relies upon mostly upon microscopy of sputum smear, radiography of chest, and skin tests as tuberculin.[9] The investigation of TB is a couple of snappy strategies difficulty to explicit exceptional tests, lipid examination, polymerase chain reaction difficulty piece duration polymorphism strategies and ribosomal RNA sequencing.[8]

Drug Resistance in Tuberculosis

Resistance can be defined as the ability of an organism and its offspring to multiply and remain viable under specific conditions that would inhibit or destroy other members of the strain.[10] When bacteria are least threatened by the antibacterial drug, this condition is defined as bacterial resistance. For the assessment of TB control planning and TB epidemiological trends, identification of drug resistance in M. tuberculosis is very important.[11] If M. tuberculosis shows in vitro resistance to both first line drugs i.e. rifampicin and isoniazid, this condition is defined as Multidrug-resistant tuberculosis (MDR-TB).[12] Extensively drug-resistant tuberculosis (XDR-TB) is defined as resistance to rifampicin and isoniazid, plus resistance to any one fluoroquinolone and to one of three second-line injectable drugs (e.g., kanamycin, capreomycin, or amikacin).[11,13,14] The global health security has been greatly affected by the emergence of XDR-TB and it has derailed the efforts which were made to reduce the incidence of TB.[15] This increase in XDR-TB cases is because of improper TB treatment[16], HIV co infection, poverty and poor observance of anti-TB treatment.[17,18] Globally, despite the poor reporting of TB incidences, an estimate of 480,000 new cases of MDR-TB was reported in 2013. Over 50% of these cases were reported from India, Russian Federation and China.[19] It is noted that nearly 10% of people having MDR-TB are also affected by XDR-TB over 100 countries.[15]

On the other hand, herbal medicines have naturally occurring chemical compounds which can be derived from the whole plant or from its particular part. Herbal medicines have more advantages as they have fewer side effects, cheaper and effective in curing multiple diseases. Because of above mentioned advantages, the demand to use herbal medicines for the treatment of tuberculosis is increasing. A number of medicinal plants are being suggested for the treatment of tuberculosis after anti-mycobacterial activity across the globe.[20-25]

New tuberculosis drug targets

Some selective targets essential to the survival of the microorganism considered in the development of any anti-TB drug include the cell wall which provides protection to the Mycobacteria and is impermeable to a number of drugs, while also conferring inherent resistance.[26] In this way, natural terpenes have the ability of produce microbial cell wall disruption causing lysis.[27] Amino acid and co-factor biosynthesis; targeting the amino acid synthesis and cofactor pathways in the bacteria causes reduced metabolism and reproductive activity in the organisms[28] and DNA metabolism; ribonucleotide reductases are essential to the Mycobacterium and reproduction activities. Equally antibiofilm activity using *Mycobacterium smegmatis*155 mc^2 is a important model for anti-tubercular activity because biofilms provides aniche for establish antimicrobial resistance.[29,30]

Current Drug Therapy

Current Drug therapy uses a combination of drugs that boost the ability of the body to respond better to the treatment and helps in reducing the length of treatment. Rifampicin and isoniazid are amongst the first line drugs used today, Rifampicin is of utmost importance in the regimen as it compresses the duration of treatment and assures desired results. Nine months regimen is undertaken by using rifampicin and isoniazid, along with streptomycin and ethambutol. According to one of the studies done by UK's Medical Research Council, inclusion of pyrazinamide for the first two months of regimen can reduce the treatment length to six months and still be able to maintain cure rate of 95% or even higher.[31]

In order to eliminate TB, the outstanding strategy is to first prevent the infection from spreading which can be done by prioritizing the treatment of those patients who are sputum smear positive that is those individuals which can spread the disease. These individuals can be tested and treated through DOTS which stands for Directly Observed Treatment Short course which is highly effective and economical strategy for TB control recommended worldwide. DOTS constitute of five elements that include continuous political and financial obligation, quality ensured diagnostic procedures, consistent supply of superior quality anti-TB drugs, regulated recording and reporting, standardized short-course (SCC) anti-TB treatment given under direct and supportive observation (DOT).[32]

2. METHODOLOGY

This review included all related published scientific articles as illustrated in this research was conducted by searching the electronic databases NCBI, Google Scholar, Scopus and Science

Direct for relevant studies from the year 2000 to 2020. Relevant studies were reviewed through numerous steps. In the first step, target published articles were identified by using general related terms, such as ‘medicinal plants’

The second step involved screening the resulting articles by using highly specific keywords, including ‘anti-Mycobacterium tuberculosis,’ ‘in vitro’ and ‘in vivo.’ The last step of the review focused on selected studies involving native medicinal plants and their related contributions.

3. MEDICINAL PLANTS SCREENED FOR ANTI-TB ACTIVITY

1. *Piper nigrum L.*

Botanical Name: *Piper nigrum L.*

Part Used for Extract Formation: Seeds Chemical Used for Extract.

Formation: Ethanol, acetone and distilled water.

Chemical constituent:- Piperine.

Anti-Tubercular Activity (MIC Value)

MIC against *M. tuberculosis* H37Rv is 50µg/mL for combination of ethanol and acetone extract and 100µg/mL for acetone extract[33] contribution

2. Allium sativum, Acalypha indica, Adhatoda vasica

Botanical Name: *Allium sativum, Acalypha indica, Adhatoda vasica.*

Part Used for Extract Formation: Allium sativum (bulb), Acalypha indica (leaves), Adhatoda vasica (leaves).

Chemical Used for Extract Formation: Ethyl acetate, petroleum ether and chloroform.

Chemical constituent: - Either fixed oil, fats or derivatives of aryl or phenol amine.

Anti-Tubercular Activity (MIC Value)

MIC of *Allium sativum, Acalypha indica* and *Adhatoda vasica* is 1.25, 5 and 10 mg/mL respectively against HRv37 strain of *M. tuberculosis.*[34]

3. Mallotus philippensis (L) Muell Arg.

Botanical Name: *Mallotus philippensis (L) Muell Arg.*

Part Used for Extract Formation: Leaves.

Chemical Used for Extract Formation: Crude extracts formation using 95% ethanol than fractionation using methanol, chloroform, hexane and ethyl acetate.

Chemical constituent: - *B-sitosterol* and Ursolic acid.

Anti-Tubercular Activity (MIC Value)

MIC of ethyl acetate fraction is 0.125 mg/mL against *M. tuberculosis* H37Ra and 0.25 mg/mL against *M. tuberculosis* H37Rv.[35]

4. Actiniopteris radiate (L)

Botanical Name: *Actiniopteris radiate Linn.*

Part Used for Extract Formation: Whole plant.

Chemical Used for Extract Formation: - Chloroform, n-Hexane & ethanol.

Chemical constituent: Identification is needed.

Anti-Tubercular Activity (MIC Value)

MIC of extracts of chloroform, n-Hexane and ethanolic is 3.125, 12.5 and 25 µg/mL respectively against H37RV strain of *M. tuberculosis.*[36]

5. *Allium sativum*

Botanical Name: *Allium sativum.*

Part Used for Extract Formation: Cloves.

Chemical Used for Extract Formation: 70% ethanol.

Chemical constituent: - Identification is needed.

Anti-Tubercular Activity (MIC Value)

MIC of ethanolic extract of garlic against 5 non-MDR and 15 MDR-TB isolates of *M. tuberculosis* is ranged from 1 to 3 mg/mL.[37]

6. *Humulus lupulus*

Botanical Name: *Humulus lupulus.*

Part Used for Extract Formation: Whole plant.

Chemical Used for Extract Formation: Alcohol.

Chemical constituent:-Not identified.

Anti-Tubercular Activity (MIC Value)

MIC against resistant and sensitive strains of *M. tuberculosis* is 8 and 4 mg/mL respectively.[38]

7. *Chamaedorea tepejilote & Lantana hispida*

Botanical Name: *Chamaedorea tepejilote & Lantana hispida.*

Part Used For Extract Formation: Ariel.

Chemical Used for Extract Formation: Hexane.

Chemical constituent: - Oleanolic acid and ursolic acid.

Anti-Tubercular Activity (MIC Value)

MIC of both compounds ranged from 12.5µg/mL to 50µg/mL for M. tuberculosis H37Rv and four mono-resistant strains of *M. tuberculosis* H37Rv measured by Microplate Alamar Blue Assay (MABA).[39]

8. *Ranunculi Ternati Radix*

Botanical Name: *Ranunculi Ternati Radix.*

Part Used for Extract Formation: Whole plant (Leaves stem and roots).

Chemical Used for Extract Formation: Water and 70% ethanol extracts and water and 70% ethanol eluted part of Ethanol extract from macro porous resin (WEPMR and EEPMR).

Chemical constituent:-Identification needed.

Anti-Tubercular Activity (MIC Value)

70% ethanol eluted part of Ethanol extract from macro porous resin (EEPMR) showed great anti-tubercular activity with MIC 1.0 mg/mL on MDR2314-2 and XDR1220 strain of *M. tuberculosis.*[40]

9. *Withania somnifera (L)*

Botanical Name: *Withania somnifera (L).*

Part Used for Extract Formation: Roots and leaves.

Chemical Used for Extract Formation: water.

Chemical constituent: - Need identification.

Anti-Tubercular Activity (MIC Value)

The highest anti-mycobacterial activity was found 64.47% of 1.0 mg/mL and least inhibition activity was 17.88% of 0.01 mg/mL dose against *M. tuberculosis* H37Rv.[41]

10. *Alstonia scholaris*

Botanical Name: *Alstonia scholaris.*

Part Used for Extract Formation: Leaves, fruit, flower and bark.

Chemical Used for Extract Formation: Water, Butanol and ethyl acetate.

Chemical constituent: - Not identified.

Anti-Tubercular Activity (MIC Value)

Butanol extracts of bark and flower showed good anti-TB activity with MIC at 100 and 500 µg/mL respectively against *M. tuberculosis* H37Rv[42] H37R

11. Kaempferia galanga

Botanical Name: *Kaempferia galanga.*

Part Used For Extract Formation: Rhizome

Chemical Used for Extract Formation: Ethanol

Chemical constituent: - Ethyl p-methoxycinnamate

Anti-Tubercular Activity (MIC Value)

MIC of Ethyl p-methoxycinnamate (EPMC) is 0.242–0.485 mM against *M. tuberculosis* H37Rv, H37Ra, multidrug resistant (MDR) and drug susceptible clinical isolates measured by resazurin microtitre assay (REMA).[43]

12. *Andrographis paniculata*

Botanical Name: *Andrographis paniculata.*

Part Used For Extract Formation: Whole plant.

Chemical Used for Extract Formation: Methanol and hexane (5:1).

Chemical constituent: - Andrographolide.

Anti-Tubercular Activity (MIC Value)

MIC of methanolic extract of *A. paniculata* was 250µg/mL against H37Rv, MDR and drug sensitive clinical isolates of *M. tuberculosis.*[44]

13. Plumeria bicolor

Botanical Name: *Plumeria bicolor.*

Part Used For Extract Formation: Bark.

Chemical Used for Extract Formation: Chloroform.

Chemical constituent: - Plumericin & isoplumericin.

Anti-Tubercular Activity (MIC Value)

Plumericin showed better anti-TB activity than isoplumericin with MIC values of 1.3 ± 0.15, 1.5 ± 0.13, 2.0 ± 0.07, 2.1 ± 0.12 and 2.0 ± 0.14 µg/mL and MBC values of 2.5 ± 0.18, 2.9 ± 0.20, 3.8 ± 0.27, 3.6 ± 0.22 and 3.7 ± 0.32 µg/mL, respectively against all four sensitive as well as MDR clinical isolates of M. tuberculosis.[45]

4. CONCLUSION

The review proposes that there is an increase in demand of phyto-pharmaceuticals all over the globe, firstly because of the adverse health effects of the allopathic medicines and secondly the unique ability of many plants to counter the deadly tuberculosis pathogen. Many plants showed very low MIC value against MDR clinical isolates of M. tuberculosis. Solid steps

surely must be chosen to translate this knowledge into preventive or curative measures for anti-TB therapies.

The critical requirement for advancement of new medications to decrease the worldwide weight of TB has significantly animated the investigation of conventional information as wellspring of novel and successful phototherapeutic operators. Herbal sources appear to be the most ideal way out with significant level of hostile to microbial movement against huge scope of microorganisms and are given ample concoction arrangement. Around the world, many plant species have been and keep on being utilized in different conventional mending frameworks, just as marine life forms and parasites, in this way speaking to an about boundless wellspring of dynamic fixings. Along these lines, disclosure and advancement of new unadulterated items include segregation, refinement and recognizable proof of target mixes from complex rough concentrates is some of the time a significant disadvantage in normal items research. The current investigation has uncovered the significance of plant concentrates to control destructive strains of M. tuberculosis which are being a danger to human wellbeing and for the improvement of exchange, protected and powerful meds. Among the reasons customary information is viewed as solid for the misuse of home remedies cures is a new factor of networks through a long duration of time for experimentation with home remedies drugs are probably going to have held those that are successful and bearably sheltered while disposing of arrangements with low viability or intense toxic.

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