Millions of people of all age groups die each year worldwide from diseases such as chest and respiratory disorders, bacteraemia, wound suppuration, diarrhoea, dysentery and tuberculosis (TB). Additionally, millions suffer from several long-standing chronic infections such as TB\(^1\). TB is characterized as a chronic bacterial infection caused by \textit{Mycobacterium tuberculosis}, an aerobic acid-fast bacillus. \textit{M. tuberculosis}, the causative agent of human TB, has an exclusive tropism for this host\(^2\) and is the most notable member amongst the five different species of genus \textit{Mycobacterium}, \textit{M. tuberculosis}, \textit{M. canetti}, \textit{M. africanum}, \textit{M. microti} and \textit{M. bovis}. In contrast, \textit{M. bovis}, the etiologic agent of bovine TB, causes only 5-10 % of all human TB cases\(^3,4\) while \textit{M. africanum} is responsible for half of the TB cases in West Africa\(^5\). TB is one of the most devastating bacterial disease with high rates of morbidity and mortality\(^6\) and it continued to be a major health concern all over the world\(^7\) ranking as the second leading cause of death from an infectious disease worldwide, after the human immunodeficiency virus (HIV)\(^8\). TB is the leading killer of HIV-positive people causing one-fourth of all HIV-related deaths. It typically affects the lungs (pulmonary TB) but can affect other sites as well (extra-pulmonary TB). It spreads through the air when people infected with pulmonary TB expel bacteria by coughing\(^9\). Because of the worldwide health problem that TB represents, it is essential to find new drugs that allow better control of TB. In the present review, various aspects of TB were covered along with pharmacological information on 11 medicinal plants and 11 phytochemical constituents showing both immunomodulatory and antimycobacterial activity. These plants might eventually be studied and screened with a well-defined strategy to develop effective new drugs against tuberculosis.

Historical background:

TB is one of the oldest infectious diseases affecting mankind\(^8\). TB is a disease of antiquity, which is thought to have evolved sometime between the seventh and sixth millennia BC\(^9,12\). The earliest references to TB can be found in the ancient Indian scriptures Vedas, where it was referred to as \textit{Yakshma} (wasting disease). Description of a TB-like disease has been documented in ancient Chinese and Arabic literature also\(^8\). Robert Koch announced the discovery of the tubercle bacillus during the monthly evening meeting...
of the Berlin Physiological Society on March 24, 1882. Commemorating the centenary of this event, since 1982, March 24 is being celebrated as ‘World TB day’[8].

**Epidemiology, global burden and Indian scenario:**

The global burden of TB was reported in a report published by World Health Organization (WHO) in 2016[13]. In 2015, about 60% of reported TB cases occurred in 6 countries namely India, Indonesia, China, Nigeria, Pakistan and South Africa. The list of countries with 3 TB high-burden cases, TB, multidrug-resistant TB (MDR-TB), TB/HIV has also been published by WHO in global TB report. An estimated 11% of the incident TB cases were HIV-positive. In addition to the 1.4 million TB deaths among HIV-negative, there were 0.4 million deaths from TB among HIV-positive. In 2015, there were an estimated 10.4 million TB cases worldwide, of which 56% were among men, 34% women and 10% children. There were an estimated 0.48 million new cases of MDR-TB. India, China and the Russian Federation accounted for 45% of the combined total of MDR-TB cases. On average, an estimated 9.5% of patients with MDR-TB had extensively drug-resistant TB.

India is the second-most populous country in the world. It accounts for more than one quarter of the global incident TB cases and deaths annually[14]. Globally, in each year India has the highest number of new TB cases, MDR-TB and deaths related to TB[15]. In 2014, the estimated incidence of TB cases in India was nearly 2.2 million while the estimated TB prevalence figure was 2.5 million. An estimated 5% of the incident TB cases were HIV-positive. In India, 2.2% of new TB cases were estimated to have had MDR-TB[16].

**Infection:**

TB infection is a cascade mechanism, which initiates an intracellular signalling that culminates in a pro-inflammatory response (beneficial to the host) or dampens the innate immune response, which is beneficial to the pathogen[17]. The infection process of TB can be divided into 3 different interrelated stages[18]. The first stage is the aerosol transmission of the droplets containing *M. tuberculosis* from an infected individual to a healthy individual. In the primary infection, *M. tuberculosis* multiplies in the lungs and causes mild inflammation. Although alveolar macrophages are thought to be an effective barrier to contain pathogens, *M. tuberculosis* has evolved various mechanisms to evade and survive within these cells[19]. In the next stage of infection, *M. tuberculosis* bacilli that escape the cytolytic effects of the alveolar macrophages, multiply and result in their destruction. After 6-8 w of infection, antigen presenting dendritic cells travel to lymph nodes where activated T-lymphocytes migrate to the site of infection and proliferate to form an early stage granuloma. This marks the persistent stage of infection (latency), where the growth and spread of bacteria into additional tissue sites are limited[20]. The third and final stage is when latent and controlled *M. tuberculosis* infection is reactivated due to a decline in the host’s immunity and failure to develop and maintain immune signals[21]. Under these circumstances, the granuloma structure disrupts and results in the lung cavitation and pulmonary TB[22,23]. The spread of *M. tuberculosis* bacilli may rapidly result in extra-pulmonary TB[24].

**Factors responsible for the emergence of TB:**

A number of factors make people more susceptible to TB infection. The risk factors for developing disease following infection with *M. tuberculosis* include factors that affect immunity[24]. Some of them are age and sex[25], nutrition[15], drug-induced immunosuppression[26] and poverty[27].

**Symptoms and diagnosis:**

Cough, blood-stained sputum, loss of weight, fever/sweating, pain in the chest are some important symptoms of TB. Other symptoms may include breathlessness, weakness, localized wheeze, frequent colds, tiredness, loss of appetite. These symptoms could be due to some other illness too. Hence, examination of sputum for the confirmation of TB infection is a must[24]. Diagnosis of TB is mainly based on the clinical features, histopathology and demonstration of acid-fast bacilli from the clinical specimens[28]. TB diagnosis depends primarily on sputum smear microscopy, chest radiography and tuberculin skin tests[29]. Several rapid methods based on lipid analysis, specific gene probes, polymerase chain reaction-restriction fragment length polymorphism methods and ribosomal RNA sequencing have also been used for the diagnosis of TB[28].

**AntiTB drugs and their adverse effects:**

The antiTB drugs are classified in five groups as mentioned in Table 1[30-32]. The targets of each member of the first-line drugs have been identified except for pyrazinamide, whose mechanism remains controversial[33]. Directly-observed treatment; the most
cost effective way to stop the spread of TB, is one of the five key elements in the WHO global TB control programme-strategy. The use of antiTB drugs is also associated with significant side-effects such as hepatitis, neuropathy, hypersensitivity syndrome, thrombocytopenia, fever, dyspepsia. Such adverse effects are responsible for termination of therapy during the intensive phase, which makes the situation even more difficult to cure. Bacterial resistance to one or more antiTB drugs has resulted in resistant forms of TB. The emergence of such resistant forms of TB poses formidable challenges to global TB control efforts. Thus, there is an urgent need of novel antiTB drugs, which are safe, able to shorten the course of treatment, effective against drug-resistant strains and latent TB infection.

Role of immunomodulators in TB control:

In view of the limited protection against TB afforded by Bacillus Calmette-Guérin vaccination, attempts are being made to develop some more effective alternative. Immunotherapy for TB enhances the treatment success of resistant forms of TB, shortens the treatment course for chemo-sensitive TB, reduces TB recurrence after chemotherapy by improving immunity and alleviates immune pathological damage. The immunotherapy strategy for TB includes restoring the balance of T helper cells (enhancing Th1 and suppressing Th2 response) by altering the dominant bacteriostatic response to a bactericidal response. The use of immunotherapy for TB lacks efficacy in clinical trials and also associated with severe side effects such as hematopoietic toxicity, liver damage and muscle necrosis, teratogenicity, peripheral neuropathy, hypertension, hyperglycaemia. Therefore, exploring the vast untapped natural resource for TB control as a safer alternative appears a valid option, which can reduce the possibility of generation of drug resistant bacteria, reduce the treatment length, possibility of re-infection and reactivation.

Plants as immunomodulatory and antimycobacterial agents:

In every region, based on the climatic and geographic conditions, special medicinal plants grow and many of them have unique medicinal properties. Due to the adverse effects of modern drugs and therapies, plants have been a common resource of medicaments in the treatment of a wide range of ailments. Therefore, a number of pharmaceutical products derived from plants serve as cheap and safe alternative.

Failure to control or resolve infectious disease such as TB often results from an inappropriate rather than insufficient immune response. In this regard, the immune system can be stimulated by natural products of plant origin. A number of medicinal plants used in traditional medicine and their several active substances have also been reported to modulate the

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**TABLE 1: DIFFERENT GROUPS OF ANTITUBERCULAR DRUGS WITH SUITABLE EXAMPLES**

<table>
<thead>
<tr>
<th>Description</th>
<th>Group</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>First-line</td>
<td>1</td>
<td>Oral drugs (isoniazid, pyrazinamide, ethambutol, rifampicin, rifabutin)</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>Injectable amino-glycosides (kanamycin, amikacin, streptomycin); injectable polypeptides (capreomycin, viomycin)</td>
</tr>
<tr>
<td>Second-line</td>
<td>3</td>
<td>Oral and injectable fluoroquinolones (ciprofloxacin, levofloxacin, moxifloxacin, ofloxacin, gatifloxacin)</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>Oral drugs (para-aminosalicylic acid, cycloserine, terizidone, ethionamide, prothionamide)</td>
</tr>
<tr>
<td>Third-line</td>
<td>5</td>
<td>Drugs with unclear efficacy or undefined role (clofazimine, linezolid, amoxicillin plus clavulanate, imipenem plus cilastatin, TMC 207, nitroimidazoles)</td>
</tr>
</tbody>
</table>

**TABLE 2: DRUG RESISTANT TUBERCULOSIS AND ASSOCIATED EFFECTS**

<table>
<thead>
<tr>
<th>Resistant forms of TB</th>
<th>Resistance to antiTB drugs</th>
<th>Effect (treatment is expensive and toxic for each resistant form of TB)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multidrug-resistant TB</td>
<td>Isoniazid and rifampicin</td>
<td>Worse cure rate (40-80 %)</td>
</tr>
<tr>
<td>Extensively drug-resistant TB</td>
<td>Group 2 and 3 drugs</td>
<td>Cure and survival rates are worse than multidrug-resistant TB</td>
</tr>
<tr>
<td>Beyond extensively drug-resistant TB</td>
<td>Group 1, 2, 3 and 4 drugs</td>
<td>Cure and survival rates could be worse than extensively drug-resistant TB</td>
</tr>
<tr>
<td>Extremely drug-resistant TB</td>
<td>Group 1-5 drugs</td>
<td>Cure and survival rates could be worse than beyond extensively drug-resistant TB</td>
</tr>
<tr>
<td>Totally drug-resistant TB</td>
<td>Group 1-5 drugs</td>
<td>Cure and survival rates could be worse than extremely drug-resistant TB</td>
</tr>
</tbody>
</table>

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[54-51]
immune response\textsuperscript{[62-66]}. It has been discovered that the plant extracts possess antimycobacterial activity. The crude 80% methanol extracts of \textit{Ocimum basilicum} seeds, \textit{Calpurnia aurea} roots, and leaves of \textit{Croton macrostachyus}, \textit{Artemisia abyssinica} and \textit{Eucalyptus camaldulensis} showed promising antimycobacterial activity against \textit{M. tuberculosis}\textsuperscript{[67]}. Ethiopian plants like \textit{Allium ursinum} bulb, \textit{Dodonaea angustifolia} leaves and \textit{Pterolobium stellatum} leaves have been traditionally used to treat TB and related symptoms in Northern part of Ethiopia. Their traditional claim was experimentally validated using 80% ethanol extracts against \textit{M. tuberculosis}\textsuperscript{[68]}. Plants are also a promising source of antimycobacterial compounds, which may have important role in the chemotherapy of TB and other respiratory tract infections. Various major groups of phytochemical constituents like alkaloids, flavonoids, chalcones, coumarins, lignans, phenols, terpenes, chromones, alkanes and alkenes found in plant extracts have been reported to possess antimycobacterial activity. It has been reported that the most effective isolated compounds from plants are plumbagin, maritinone, aloe-edomin, epigallocatechin and umckalin, tiliacorinine, mauritine, globiferin, beilschmin, 7-methyljuglone\textsuperscript{[69,70]}. The traditional knowledge of plants is becoming an important asset in developing newer and better drugs\textsuperscript{[71]}. Recently, the antimycobacterial activity of a plant extracts rich in allicin and ajoene has been reported\textsuperscript{[72]}. A considerable number of plant species, which have been mentioned in Ayurveda for the treatment of TB and related disorders were found more active with minimum inhibitory concentration (MIC) value between 10-100 µg/ml\textsuperscript{[73]}. Literature also reported the antimycobacterial activity of many classes of natural products\textsuperscript{[70,74-77]}

In this review, pharmacological information on 11 medicinal plants and 11 phytochemical constituents was compiled (fig. 1) with reference to the immunomodulatory (\textit{in vitro} in preclinical models/\textit{in vivo} in cell lines) and antimycobacterial (\textit{in vitro} against drug-susceptible strain \textit{M. tuberculosis} H37Rv) activities. These plants were from a wide range of families such as Rutaceae, Acanthaceae, Amaryllidaceae, Apiaceae, Clusiaceae, Lamiaceae,
Leguminosae, Verbenaceae and Solanaceae. The reported pharmacological activity of these plants has been summarized in Table 3 and 4, which is further discussed hereafter.

Administration of the methanol extract of *Aegle marmelos* fruits significantly stimulated the immune system by acting through cellular and humoral immunity in experimental animals at a dose of 100 mg/kg[78]. In another study, hexane and acetone extract of *Aegle marmelos* leaves showed MIC value of 50 µg/ml, whereas methanol extract showed MIC value of 100 µg/ml against H37Rv strain of *M. tuberculosis* by Alamar blue assay and thus indicating their antimycobacterial activity[79]. An immunomodulatory study on the aqueous extract of *A. sativum* bulbs showed significant increase in total leukocytes count at 100 mg/kg in Wistar albino rats[80]. In addition, its aqueous extract also showed promising antimycobacterial activity when evaluated against *M. tuberculosis* H37Rv strain using REMA and was more significant compared to the standard drugs[72]. Puri *et al.* reported that the administration of the ethanol extract of *Andrographis paniculata* whole plant induced significant stimulation of the antibodies and delayed type hypersensitivity response to sheep red blood cells stimulated Balb/c mice. It also stimulated antigen specific as well as non-specific immune response suggesting its immunostimulatory

<p>| <strong>TABLE 3: MEDICINAL PLANTS AND EXTRACTS WITH IMMUNOMODULATORY AND ANTIMYCOBACTERIAL ACTIVITIES</strong> |</p>
<table>
<thead>
<tr>
<th><strong>Plant name (family)</strong></th>
<th><strong>Immunomodulatory activity</strong></th>
<th><strong>Antimycobacterial activity</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Aegle marmelos</em> (L.) Correa (Rutaceae)</td>
<td>Methanol (fruits)</td>
<td>Significant increase in biochemical parameters at 500 mg/kg, p.o., in Wistar albino rats[72]</td>
</tr>
<tr>
<td><em>Allium sativum</em> L. (Amaryllidaceae)</td>
<td>Aqueous (bulbs)</td>
<td>Significant increase in biochemical parameters at 100 mg/kg, p.o. in Wistar albino rats[80]</td>
</tr>
<tr>
<td><em>Andrographis paniculata</em> (Burm.f.) Nees (Acanthaceae)</td>
<td>Ethanol (whole plant)</td>
<td>Significant increase in biochemical parameters at 25 mg/kg, p.o. in Balb/c mice[81]</td>
</tr>
<tr>
<td><em>Calophyllum brasiliense</em> Cambess. (Clusiaceae)</td>
<td>Methanol (roots)</td>
<td>Significant proliferation at 200 µg/ml in splenocytes[83]</td>
</tr>
<tr>
<td><em>Centella asiatica</em> (L.) Urb. (Apiaceae)</td>
<td>Aqueous and ethanol (whole plant)</td>
<td>Significant increase in PBMCs proliferation and IL-2 production at 500 µg/ml[85]</td>
</tr>
<tr>
<td><em>Glycyrrhiza glabra</em> L. (Leguminosae)</td>
<td>Aqueous (roots)</td>
<td>Significant increase in biochemical parameters at 1500 mg/kg, p.o., in Swiss albino mice[86]</td>
</tr>
<tr>
<td><em>Adhatoda vasica</em> L. (Acanthaceae)</td>
<td>Methanol, chloroform and diethyl ether (leaves)</td>
<td>Significant increase in biochemical parameters at 400 mg/kg, p.o. in Wistar albino rats[88]</td>
</tr>
<tr>
<td><em>Ocimum basilicum</em> L. (Lamiaceae)</td>
<td>Aqueous and ethanol (leaves)</td>
<td>Significant increase in biochemical parameters at 400 mg/kg, p.o. in Swiss albino mice[89]</td>
</tr>
<tr>
<td><em>Stachytarpheta cayennensis</em> (Rich.) Vahl (Verbenaceae)</td>
<td>Methanol (leaves)</td>
<td>139.64% phagocytic stimulation at 100 µg/ml in neutrophils[90]</td>
</tr>
<tr>
<td><em>Thymus vulgaris</em> L. (Lamiaceae)</td>
<td>Aqueous and hexane (aerial)</td>
<td>Significant decrease in splenocytes proliferation at 100 µg/ml[92,93]</td>
</tr>
<tr>
<td><em>Withania somnifera</em> (L.) Dunal (Solanaceae)</td>
<td>70 % methanol (roots)</td>
<td>Significant increase in biochemical parameters at 20 mg, i.p., in Balb/c mice[95]</td>
</tr>
</tbody>
</table>
TABLE 4: PHYTOCHEMICAL CONSTITUENTS WITH IMMUNOMODULATORY AND ANTIMYCOBACTERIAL ACTIVITIES

<table>
<thead>
<tr>
<th>Phytochemical constituents</th>
<th>Immunomodulatory activity</th>
<th>Antimycobacterial activity</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Group</strong></td>
<td><strong>Name</strong></td>
<td><strong>Source</strong></td>
</tr>
<tr>
<td>Alkaloid</td>
<td>Piperine</td>
<td>Pure standard</td>
</tr>
<tr>
<td></td>
<td>Quercetin</td>
<td>Preclinical dose</td>
</tr>
<tr>
<td></td>
<td><strong>Flavonoids</strong></td>
<td>Urtica dioica</td>
</tr>
<tr>
<td></td>
<td>Genistein</td>
<td>Pueraria tuberosa</td>
</tr>
<tr>
<td></td>
<td><strong>Quinone</strong></td>
<td>Plumbagin</td>
</tr>
<tr>
<td></td>
<td>Phenolics</td>
<td>Propolis (bee glue)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Gentiana kurroo</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Eucalyptus tereticornis</td>
</tr>
<tr>
<td></td>
<td>Ursolic acid</td>
<td>Pure standard</td>
</tr>
<tr>
<td></td>
<td>Oleanolic acid</td>
<td>Pure standard</td>
</tr>
<tr>
<td></td>
<td>Terpenoids</td>
<td>Pure standard</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pure standard</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pure standard</td>
</tr>
</tbody>
</table>

potential[81]. In an another study, the aqueous extract of *A. paniculata* exhibited 100 % inhibition against *M. tuberculosis* H37Rv strain at 5 mg/ml using Lowenstein-Jensen proportion method suggesting its antimycobacterial potential[82]. Methanol extract of *Calophyllum brasilense* roots has been reported to significantly stimulate proliferation of splenocytes from mice at 200 µg/ml using in vitro cellular proliferation assay[83]. Antimycobacterial activity of the dichloromethane and aqueous extracts prepared from *Calophyllum brasilense* leaves was reported with MIC values of 62.5 and 125 µg/ml against *M. tuberculosis* H37Rv strain, respectively using resazurin microtiter assay[84]. Punturee et al. reported that the aqueous and ethanol extracts of *Centella asiatica* whole plant significantly increased production of IL-2 and TNF-α in human peripheral blood mononuclear cells at 500 µg/ml. In addition, it also showed greater response to both primary and secondary antibodies in BALB/c mice at 100 mg/kg, which indicated a promising effect on non-specific cellular and humoral immune system[85]. The aqueous extract of *Centella asiatica* whole plant showed antiTB activity at 5 mg/ml with 78.5 % inhibition of *M. tuberculosis* H37Rv strain using Lowenstein-Jensen proportion method[82]. Administration of the aqueous root extract of *Glycyrrhiza glabra* exhibited significant increase in the biochemical parameters at 1500 mg/kg in Swiss albino mice, which suggested immunomodulatory potential with respect to cellular immunity, phagocytic response and anaphylactic reaction[86]. In another study on the ethanol extract of *Glycyrrhiza glabra* root, significant antimycobacterial activity was observed against *M. tuberculosis* H37Rv strain at 500 µg/ml using BACTEC 460 radiobiopmetric assay[87]. A study reported by Vinothapooshan and Sundar validated the immunomodulatory properties of methanol, chloroform and diethyl ether extracts of *Adhatoda vasica* leaves in experimental animals. Oral administration of the extracts at 400 mg/kg in Wistar rats significantly increased the neutrophil adhesion to nylon fiber and induced delayed type hypersensitivity reaction to sheep erythrocytes[88]. While in other
study, the aqueous extract of A. vasca leaves showed 70% inhibition of M. tuberculosis H37Rv strain at 4% v/v in Lowenstein-Jensen proportion method\(^{[57]}\). Oral administration of the aqueous and ethanol extract of Ocimum basilicum leaves at 400 mg/kg showed a significant increase in the production of circulating antibody titer, delayed type hypersensitivity reaction in sheep erythrocytes sensitized mice\(^{[89]}\). In another study, 80% methanol extract of O. basilicum seeds exhibited antimycobacterial activity against M. tuberculosis strains with the MIC value 25 μg/ml using resazurin microtitre assay\(^{[88]}\).

Methanol extract of Stachytarpheta cayennensis leaves showed 139.64% phagocytic stimulation at 100 μg/ml in neutrophils suggesting its immunostimulatory action\(^{[90]}\). Carrion et al. reported the antimycobacterial activity of the aqueous extract of S. cayennensis leaves and roots with the MIC value greater than 200 μg/ml using resazurin microtitre assay\(^{[91]}\). A study on the aqueous and hexane extract of Thymus vulgaris aerial parts reported significant decrease in the number of splenocytes at 100 μg/ml indicating potent immunomodulatory activity\(^{[82,93]}\). Whereas, acetone and aqueous extract of T. vulgaris aerial parts inhibited the growth of M. tuberculosis showing the MIC value 0.5-5 mg/ml by the agar plate method\(^{[84]}\). Administration of 70% methanol extract of Withania somnifera roots exhibited significant increase in the total leucocytes count, bone marrow cellularity and also produced an enhancement in the circulating antibody titre, number of plaque forming cells and phagocytic activity of peritoneal macrophages at 20 mg in Balb/c mice\(^{[85]}\). Adaikkappan et al. reported the antimycobacterial activity of the aqueous extract of W. somnifera leaves with MIC value 1 mg/ml and 64.47% inhibition of M. tuberculosis H37Rv (MTB) strain by proportion and absolute concentration method\(^{[86]}\). These reports clearly suggested that these plants are rich source of phytochemical constituents with immunomodulatory and antimycobacterial potential.

Piperine (C\(_{15}\)H\(_{17}\)NO\(_3\)) an alkaloid significantly reduced the toxicity of allethrin in Swiss albino mice at 100 mg/kg by increasing the number of leucocytes\(^{[97]}\). Additionally, it exhibited proliferation of T and B cells and enhanced macrophage activation at 1 μg/ml concentration in the splenocytes of BALB/c mice\(^{[98]}\). In murine model of MTB, combination of piperine and rifampicin (1 mg/kg) exhibited better efficacy and resulted in 1.4 to 0.8 log reduction in the bacterial load\(^{[98]}\). Thus, piperine can be used as an adjunct therapy in the management of TB. Flavonoids, a large group of polyphenolic compounds having a benzopyrone structure are ubiquitously present in plants. Quercetin (C\(_{15}\)H\(_{10}\)O\(_5\)), the major compound of the methanol extract of the aerial parts of Urtica dioica L. enhanced the stimulation of neutrophils at 16 μg dose in an in vitro experiment\(^{[99]}\). On the other hand, quercetin isolated from the aerial parts of Tussilago farfara showed antitubercular activity against MTB H37Rv strain using a high throughput spot culture growth inhibition assay\(^{[100]}\). In another study, Maji et al. reported that the administration of genistein (C\(_{15}\)H\(_{10}\)O\(_3\)) significantly modulated the innate as well as humoral immune responses against SRBCs challenged Swiss albino rats at a dose of 25 mg/kg\(^{[101]}\). Amongst the various coumarins and flavonoids isolated from the ethyl acetate extract of Ficus nervosa roots, genistein showed the antimycobacterial activity against MTB H37Rv\(^{[102]}\). Plumbagin (C\(_{11}\)H\(_{8}\)O\(_3\)), a naphthoquinone found in the roots of Plumbago zeylanica showed significant modulation of T-cell proliferation and cytokine response in DBA/1 mice at 3.3 mg/kg\(^{[103]}\). This study demonstrated the novel therapeutic role of plumbagin in the pathogenesis of rheumatoid arthritis. In addition, plumbagin isolated from the hexane fraction of the stem bark of Diospyros anisandra showed the strongest antimycobacterial activity against the resistant strain\(^{[104]}\).

Caffeic acid (C\(_{8}\)H\(_{6}\)O\(_3\)), a polyphenolic compound from propolis exhibited significant proliferation of leukocytes at a dose of 50 mg/kg in CBA mice and demonstrated a modulatory activity on the macrophages\(^{[105]}\). In another study, trans-caffeic acid isolated from the aerial parts of Tussilago farfara showed antitubercular activity against MTB H37Rv strain using a high throughput spot culture growth inhibition assay\(^{[100]}\). Maurya et al. reported that the administration of two purified triterpenoids; lupeol (C\(_{36}\)H\(_{56}\)O) isolated from Gentiana kurroo roots and ursolic acid (C\(_{30}\)H\(_{48}\)O\(_3\)) isolated from Eucalyptus tereticornis leaves, exhibited significant increase in the antibody titer in rabbit red blood cells immunized Swiss albino mice at doses of 10 and 1 mg/kg, respectively\(^{[106]}\). Also, lupeol isolated from Zanthoxylum capense roots\(^{[107]}\) and ursolic acid from Lantana hispida aerial parts\(^{[108]}\) showed ability to inhibit the growth of M. tuberculosis H37Rv inducing potential antimycobacterial activity. Oleanolic acid (C\(_{30}\)H\(_{48}\)O\(_3\)), another pentacyclic triterpenoid compound
exhibited significant expression of IFN-γ and TNF-α in the lungs of BALB/c mice at 5 mg/kg[109]. On the other hand, oleancolic acid isolated from Lantana hispida aerial parts showed antitubercular activity against MTB H37Rv with a MIC value of 50 µg/ml[108]. Stigmasterol (C₂₉H₄₈O), a plant sterol has been reported to inhibit the inflammatory mediators at 20 µg/ml[110]. In another study, stigmasterol isolated from the hexane fraction of Morinda citrifolia leaves showed antimycobacterial activity with MIC value 32 µg/ml[111]. β-sitosterol (C₂₉H₄₈O), a phytosterol isolated from Cordia rothii leaves has also been evaluated for immunomodulatory activity and was found to increase significantly the number of neutrophils and T-cells at 100 µg/ml[112]. Also, β-sitosterol isolated from the hexane fraction of M. citrifolia leaves showed antimycobacterial activity with an MIC value of 32 µg/ml[111]. A study reported by Ghannadian et al. suggests that betulinic acid (C₃₆H₅₃O₅), a pentacyclic triterpenoid isolated from Euphorbia spinidens aerial parts resulted in the stimulation of lymphocyte proliferation at 50 µg/ml[113]. Moreover, betulinic acid isolated from Valeriana laxiflora aerial parts also showed antitubercular activity against M. tuberculosis with MIC value of 62.5 µg/ml[114]. Thus, the phytochemical constituents like terpenoids, phenolics, flavonoids, quinones possess both immunomodulatory and antimycobacterial potential.

As globally around 2 million people die annually due to TB, this review could be of help to the scientists making attempts to discover novel natural products to develop as new antiTB drugs. There are many active plant extracts from which active compounds are yet to be isolated. It is necessary to make efforts to identify and characterize the active constituents from medicinal plants. In addition, drugs acting synergistically could be developed from plant extracts. Promising leads from plant sources might also act on newer targets and thus, could play a crucial role in the development of new generation of antiTB drugs. For eradicating TB, instead of focusing on a single drug that hits a single target, the approach of systems biology should be followed using multiple compounds that hit multiple targets in different pathways.

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Conflict of interest:

The authors declare that they have no conflict of interest.

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