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AFRICAN MEDICINAL PLANTS WITH ANTI-MYCOBACTERIUM TUBERCULOSIS ACTIVITY: A REVIEW

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ABSTRACT

Tuberculosis (TB) is presently a major health pitfall as a result of Multidrug – resistant strains of bacilli. Reported estimate of 10·6 million people became ill with tuberculosis in 2021. Efforts are in progress to eradicate TB using new therapeutic drugs. This review is aimed at highlighting the work on anti-mycobacterium tuberculosis plants in Africa; it involves different plants and their chemical constituents exhibiting anti-mycobacterial properties. Some of the plant species identified and their chemical constituents include *Plectranthus neochilus, Allium sativum Tamarindus indica and Cymbopogon citratus with derived chemicals;* Citronellol, Allicin, Nerol and Geraniol respectively. This review could serve as a guide and stimulate researchers toward utilization of African medicinal plants for drugs development against tuberculosis.

Keywords: Africa, Medicinal, Plant, Antimycobacterium, Tuberculosis.

INTRODUCTION

Tuberculosis has been a major worldwide health threat especially in developing countries (Noro *et al*., 2008). Tuberculosis is transmitted from infected individual to another though droplets from the lungs and throat of individual with active illness, TB generally infect lungs but may affect other body parts. It can be spread rapidly due to malnutrition, poverty and in an overcrowded settings (Green *et al.*, 2010). In 2021, an estimated figure of 10·6 million individuals became ill with tuberculosis and 1·6 million persons died from TB (Bagcchi, 2023). In 2020, Africa and South-East Asia nations contributed 85 percent global death as a results of TB (Obakiro et al., 2022). According to global tuberculosis report of 2014, 9 million new cases of tuberculosis infection was reported in 2013, out of which 1.5 million died. These estimation was found to be greater than number recorded in 2013 global TB report (WHO, 2014). Tuberculosis (TB) is a prevailing global bacterial infection with more impact in developing countries, attributed primarily as a result of increased cases of HIV infection, poor nutrition status, overpopulation and unimpressive TB control measures (Randall *et al*., 2015).

The main pathogenic agent of TB is *Mycobacterium tuberculosis* (Mtb). The establishment of paleopathology and paleoepidemiology in infectious diseases has proven the very prehistoric origin of tuberculosis infection (Arya, 2011). Patients infected with TB necessarily needs long-term antibiotic treatment usually 6-12 months, and failure to conform with the full therapeutic regimen in patient could lead to patient relapse and leading to the development of

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multi- and extensively-drug resistant *M. tuberculosis* (MDR TB and XDR TB) strains (Ganihigama *et al*., 2015). Due to the emergence of MDR and XDR TB strains, there is a pressing need for novel anti-tuberculosis drugs. However, sequel to the recent advances and development in technology, interesting progress have been achieved in the area of tuberculosis genomics, proteomics and identification of target (McGaw *et al*., 2008).

In drug discovery and development process, natural products continue to play a most vital significant role (Newman and Cragg, 2007). Medicinal plants have been in used globally for the treatment of various ailments. About 60% of world's population still depend on medicinal plants as a means of their primary healthcare, anti-mycobacterial natural products may be helpful in recognition of new molecular targets in MDR and XDR strains of mycobacterium leading to new scenes for anti-tubercular drug detection or discovery (Sheeba *et al.*, 2015).

Anti-TB drugs are of two class: first-line drugs or essential that are usually used for the treatment of Tuberculosis patients with susceptible *Mtb* infection and second-line or reserve anti tuberculosis drugs applicable for the treatment MDR-TB (Arya, 2011). The treatment period of tuberculosis is shortened and treatment efficiency increased with the standard treatment regimen using rifampicin, isoniazid, ethambutol and pyrazinamide. However, the common side effect of the anti-tuberculous treatment is drug-induced liver injury (hepatotoxicity) (Lee *et al*., 2016). Hepatic toxicity and possibly fatal drug-induced hepatitis are the most important side effects cause by isoniazid especially in association with rifampicin (Lima and Melo, 2012). Between 5 to 10% of Multi Drug Resistance-TB cases are thought to be as a result of extensively drug XDR-TB i.e. resistance to isoniazid, rifampicin, any fluoroquinolone and one of the second-line agents (kanamycin, capreomycin). In several parts of the world including Africa, Russia, Eastern Europe, India, China and central Asia, MDR-TB and XDR-TB now threaten to weaken TB control (Shean *et al*., 2013). Due an urgent need of new anti-mycobacterial agent, it is of paramount important and particularly relevant at this time to review the literature for information on plants assessed for anti-mycobiacterial activity. This review is aimed at identifying plant species that have antimicrobial activity against *Mycobacterium tuberculosis.*

THE SIGNIFICANCE OF NATURE IN THE DISCOVERY OF TB TREATMENT

Antimicrobial molecules are exemplified by a wide-ranging diversity of chemical compounds. Often they are secondary metabolite compounds and natural products, indicating that they are not requisite for survival under laboratory conditions but still offer some benefits in the environment (DurandRaoult & Dubourg, 2019). Plants are very good source of anti-mycobacterial agents (Gibbons *et al*., 2003; Newton *et al*., 2002). The initial utilization of chemotherapy indicated the role of nature in the fight against disease. Streptomycin (an aminoglycoside) (Figure 1) is the first anti-TB drug discovered in 1943 by Selman Abraham Waksman and his student Albert Schatz at Rutgers University, Streptomycin is isolated from the actinobacterium *Streptomyces griseu* (de Souza, 2009; Kingston, 2004).

Several other Tuberculosis drugs including cycloserine, kanamycin, para-amino salicylic acid, isoniazid and pyrazinamide with different mechanisms of action were discovered and developed in 1950s (Zumla *et al*., 2013). In 1957, Kanamycin, another aminoglycoside antibiotics was isolated from

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Streptomyces kanamyceticus (Nasibullah *et al*., 2015).

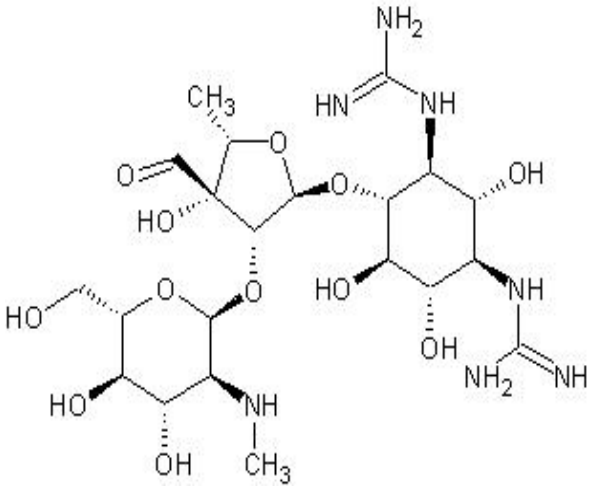

Figure 1: Structure of streptomycin

NATURAL PRODUCTS AS THE SOURCE OF ANTI-TURBERCLUSIS AGENT

The use of herbs and other alternative therapies for the treatment of tuberculosis is on the increase (Lawal *et al.*, 2011). Medicinal plants continue to serve as a foremost source of innovative molecules for the growth of novel therapeutic agents against numerous ailments (Obakiro *et al*., 2022). Wide-ranging data on medicinal plants utilized in the tuberculosis management of TB is vital for the safeguarding of those plant species as some of the species are either endangered or rare to be found. (Obakiro et al., 2020). Natural products derived from plants are proven templates for development of new drugs and have exhibited many fascinating biological activities (McGaw *et al*., 2008) (Table 1).

The popularity of natural products based drugs could be as a result of evolution of secondary metabolites serving as biological active chemicals which conferred selectional advantages the organism producing them (Butler and Buss, 2006). Chemical constituents such as citronellol, geraniol, terpenes, iridoids and nerol have exhibited anti-mycobacterial activities (Chinsembu, 2016; Kumar *et al*., 2013; Wang *et al*., 2012).

Licarin A was reported to act as a potential active anti-TB agent to treat MDR TB, a study revealed that Licarin A was found to be most active compound, with minimum inhibitory concentrations of 3.12 to 12.5 µg/mL against the $H_{37}Rv$ *Mtb* strain, four mono-resistant $H_{37}Rv$ strains as well as twelve clinical MDR isolates (León-Díaz *et al*., 2010).

Roy et al reported (Roy *et al*., 2012) 1′-*S*-1′-Acetoxychavicol acetate obtained from *A. galanga* rhizome was found to exhibit MIC of 0.1 mg/L against *M. tuberculosis* $H_{37}Ra$ (ATCC 25166) strain. Extracts from plants, *Achyrocline alata*, *Bridelia micrantha*, *Dodonea angustifolia*, *Galenia africana*, *Lantana hispida* and *Swinglea glutinosa*, specifically phytochemicals, carvacrol, 1,8-cineole, 5,7,2′-trihydroxyflavone, p-cymene , limonene and thymol, and have been reported to have promising antitubercular activity in vitro (Dubey *et al*., 2013).

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Table 1: A brief description of common anti-tubercular plants

Plants	Location in Africa	Medicinal used
Rose-scented geranium (Pelargonium spp.), a perennial semi shrub, native to South Africa(Ravindra and Kulkarni, 2015)	The plant is cultivated on a commercial quantity in African countries like Algeria, Egypt and Morocco (Ravindra and Kulkarni, 2015)	Citronellol is one the constituents of the plant with anti-bacterial property (Bigos *et al*., 2012; Boukhatem *et al*., 2013)
Ocimum gratissimum (Charles and Simon, 1992)	The plant is widely used in East Africa (Dambolena *et al*., 2010)	Essential oil from the stem, leaves and flower of the plant contain high concentration of geranoil (Charles and Simon, 1992), geranoil had anti *Mycobacteria tuberculosis* property (Cantrell *et al*., 2001)
Warburgia salutaris (Madikane *et al*., 2007)	South Africa (Madikane *et al*., 2007)	11a-hydroxycinnamosmolidecontain of the plant displayed antimycobacterium tuberculosis by inhibiting arylamine N-acetyltransferase activity (Madikane et al., 2007)
Cissampelos pareira (Njeru *et al*., 2015)	*Cissampelos pareira* is distributed in Congo, Tanzania, Kenya, South to North Angola, Zambia, Comoros and Madagasca (Piero *et al*., 2015)	*Cissampelos pareira* was found to exhibit very high antituberculous activity against *Mycobacterium tuberculosis* H37Rv with MIC ranging between 50 to 6.25 µg/ml, it also contained alkaloids, flavonoids, terpenoids, anthraquinones and phenols (Njeru *et al*., 2015)
Albizia coriaria Welw (Asiimwe *et al*., 2013; Chinsembu, 2016)	Found in Uganda (Asiimwe *et al*., 2013; Chinsembu, 2016)	*Albizia coriaria* Welw was reported exhibiting anti-mycobacterial activity(Asiimwe *et al*., 2013; Chinsembu, 2016)
Vernonia amygdalina (Chinsembu, 2016; Tabuti *et al*., 2010)	*V. amygdalina* is found in Uganda (Chinsembu, 2016; Tabuti *et al*., 2010)	*V. amygdalina* had anti-mycobacterial tuberculosis activity (Chinsembu, 2016; Tabuti et al., 2010)
Sterculia setigera (Babalola *et al*, 2012)	East Africa (Babalola *et al*., 2012)	*S. setigera* demostrated promising anti-TB Property (Babalola *et al*., 2012)
Alstonia scholaris (Apocynaceae) (Antony *et al*., 2012)	It is an evergreen tree commonly found in the subtropical regions of Africa (Antony *et al*., 2012)	The *Alstonia scholaris* bark extract showed anti mycobacterial activity against *Mtb* strain H37RV (Antony *et al*., 2012)
Terminalia phanerophlebia (Madikizela et al., 2014)	South Africa (Shai *et al*., 2008)	1,6-di-O-coumaroyl glucopyranoside isolated from indicated inhibitory activity against *Mycobacterium tuberculosis* (Madikizela *et al*., 2014)
The leaves of *Oxyanthus speciosus* (Aro *et al*., 2019*)*	South Africa	Lutein and rotundic acid isolated demonstrated worthy antimycobacterial activity toward four mycobacteria tested with MIC ranging from 0.013 to 0.1 mg/mL (Aro et al., 2019)
Leaf of *Ptaeroxylon obliquum*	South Africa	Obliquumol isolated from exhibited excellent antimycobacterial activities (Ramadwa *et al*., 2019)

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ANTI-MYCOBACTERIAL PLANTS OF AFRICA

Orthodox medicine, especially herbal, has been an integral part of the health of the African communities in Sub-Saharan Africa, with plant serving as the most important single source of natural curative compounds for centuries (Chingwaru *et al*., 2015). In parts Africa diverse plants are locally reported to treat TB (GizachewGiday and Teklehaymanot, 2013; Green *et al.*, 2010; Mariita *et al*., 2010)**.** A study in south Africa, revealed that extracts of *Leyssera gnaphaloides* and *Buddleja saligna* plants had significant anti-mycobacterial activity which is associated primarily due to presence of pentacyclic triterpenoids, oleanolic acid and ursolic acid (Bamuamba *et al*., 2008).

Warburgia salutaris plant extracts and a purified compound (drimane sesquiterpenoid lactone, 11a-hydroxycinnamosmolide) had exhibited anti-mycobacterial activity against Mycobacterium tuberculosis H37Rv, both extract and pure compound inhibited were reported inhibiting the activity of recombinant enzyme arylamine N-acetyltransferase (NAT) that takes part in mycobacterial cell wall lipid synthesis (Madikane *et al*., 2007). The following South African plants were reported as part of the folk remedies of tuberculosis. Wilson *et al*., (2015) reported that extracts of *Sterculia quinqueloba* and *Canthium crissum* have exhibited anti-mycobacterial activity with leaf extracts demonstrated more activity than other parts. All leaf extracts indicated a higher activity than isoniazid for at least 16 times (first line anti-mycobacterial drug).

CHEMISTRY OF ANTI-MYCOBACTERIAL PLANTS

Plant extracts containing alkaloids, alkanes, alkenes, alkynes, chalcones, coumarines, flavonoids, lignans, phenols, polyketides steroids, terpenes, simple aromatics, and peptides have been used in the treatment of different human ailments around globally, including tuberculosis. (García et al., 2012; Santhosh and Suriyanarayanan, 2014). A diverse class of aromatic plants are among those with antimicrobial activity The pharmacological activities of aromatic plant are partially due to the presence of essential oils (Sieniawska *et al*., 2015). An enormous number of plants and their isolates have been comprehensively screened against *Mtb*. A quite number of plant extracts and pure compounds derived from plants species demonstrated significant inhibitory property against Mycobacterium (Table 2) (Negi *et al*., 2010).

The figure 2 below indicates the structures of some bioactive molecules derived from medicinal plants that exhibited anti-mycobacterial activities.

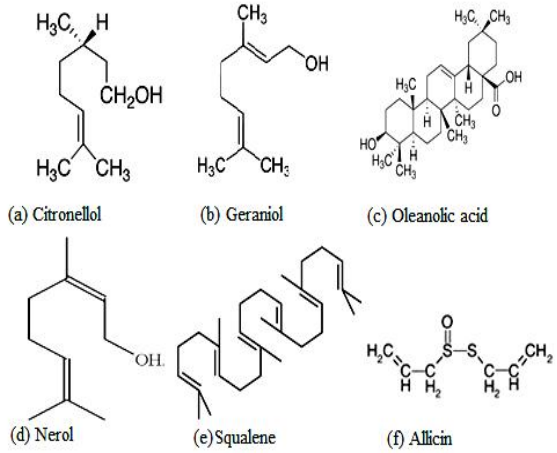

Figure 2: Chemical structures of anti-tuberculosis plant-derived compounds

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Table 2: Metabolite compounds that exhibit anti-mycobacterial activities correlating with the ethno botanical uses of the plant species of origin

Chemical	Reported ant-tuberculosis activity	Source plant
Citronellol	Citronellol was found to exhibit anti mycobacterial activity (Chinsembu, 2016; Kumar *et al*., 2013; Wang *et al*., 2012).	*Plectranthus neochilus* (Lambrechts and Lall, 2020)
Geraniol	Geraniol was found to exhibit antitubercular activity of against *Mycobacterium tuberculosis in vitro* with MIC values between 64 and 128 µg/ml (Cantrell *et al*., 2001)	*Cymbopogon citratus* (Hacke *et al*., 2022)
Oleanolic acid	Oleanic acid was found to produce an effective growth inhibition of *M.tuberculosis* at 100ug/ml concentration(Jiménez *et al*., 2005)	*S. chamelaeagnea* (Kamatou *et al*., 2007)
Nerol	Nerol shown anti mycobacterial property against *Mycobacterium tuberculosis* (Cantrell *et al*., 2001)	*Tamarindus indica* (Escalona-Arranz *et al*., 2010)
Squalene	Squalene isolated from *Chamaedora tepejilote* (Palmae) shown antimycobacterial activity against *Mycobacteriumtuberculosis* (Jiménez et al., 2005)	*Lawsonia inermis* (Abdelrahman et al., 2020)
Allicin	Allicin isolated from aqueous extract of *Allium sativum* exhibited anti- mycobacrium tuberculosis property (Delaha & Garagusi, 1985; GautamSaklani & Jachak, 2007)	*Allium sativum (Bhatwalkar et al., 2021)*
Licarin A	Licarin A isolated from *Aristolochia taliscana* exhibited anti-Mtb property (León-Díaz *et al*., 2013)	*Aristolochia taliscana* (León-Díaz *et al*., 2013)
Punicalagin	Punicalagin was originally isolated from the fruit peel of *Punica granatum*, the growth of *M. tuberculosis* typus humanus ATCC 27294 was totally inhibited at concentrations higher than 600 g/mL. it was tested active on a patient strain of Mtb (Asres *et al*., 2001)	*Combretum hartmannianum* (Salih *et al*., 2021)

CONCLUSION

Plants are utilized in African nations for the treatment of TB. The data obtained indicated that extracts of African plant species have been indicated to have significant anti-mycobacterial activities. Also, various classes of compounds have been isolated. These findings can serve as a guide toward search for novel natural products for new anti-tuberculosis drug. More authentication studies are necessary so as to support the discovery of anti-TB drugs and to offer proof for regularization of herbal medicine use. Consequently, cohesive method of identification of plants with anti-mycobacterial potentials followed by identification of bioactive components will haste up the research and development of plant derived anti-mycobacterial agents. It will be challenging to resolve the challenges associated with TB infection without improved funding for anti-tuberculosis drug discovery as well as establishment of a stronger drug development pipeline via well international coordinated approach.

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