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Philip Ifesinachi Anochie[1]*, Bakoh Ndingkokhar[2], Juan Bueno[3], Felix Emeka Anyiam[4], Linus Ndidi Ossai-Chidi[5], Edwina Chinwe Onyeneke[1] and Anthony Chidiebere Onyeozirila[1]

[1]TB/HIV/AIDS Research Group, Philip Nelson Institute of Medical Research, Lagos, Nigeria
[2]Chemical Bioactivity Information Centre (CBIC) Cameroon, Department of Chemistry, University of Buea, South West Region, Cameroon
[3]Fundación centro de investigación de bioprospección y biotecnología de la biodiversidad BIOLABB, Colombia
[4]Center for Health and Development, University of Port Harcourt Teaching Hospital, University of Port Harcourt, Nigeria
[5]Department of Haematology, Blood Transfusion and Immunology, University of Port Harcourt Teaching Hospital, University of Port Harcourt, Nigeria

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***Corresponding author:** Philip Ifesinachi Anochie, TB/HIV/AIDS Research Group, Philip Nelson Institute of Medical Research, Lagos, Nigeria, Tel: +2348166582414, +2348140624643, +23473175179; E-mail: philipanochie@yahoo.co.uk; philipanochie@gmail.com

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Review article

African Medicinal Plants that Can Control or Cure Tuberculosis

Abstract

This review contains a compendium of medicinal plants in Africa that can control or cure tuberculosis. A good number of plant secondary metabolites are reported to have antitubercular activity comparable to the existing antitubercular drugs or sometimes even better. Information regarding the chemistry and pharmacology of plants leads to insight into their structure–activity relationship and potency. A well-defined strategy is required to exploit these phytomolecules as antitubercular drugs.

Introduction

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 antituberculosis drugs. Medicinal plants have 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.

In Ethiopia, the acetone fraction obtained from the stem bark of *Combretum molle* (Combretaceae) showed significant inhibitory action against *Mycobacterium tuberculosis* strain. The acetone fraction of the stem bark of *C. molle* caused complete inhibition at concentrations higher than 1 mg/mL. Phytochemical analysis of the bioactive fraction led to the isolation of a major tannin and two oleanane-type pentacyclic triterpene glycosides. The tannin was identified as the ellagitannin, punicalagin, whilst the saponins were characterized as arjunglucoside (also called 4-epi-sericoside) and sericoside. All the pure compounds were further tested against the *M. tuberculosis* ATCC strain. Punicalagin was found to inhibit totally growth of the ATCC and also of a patient strain, which was fully sensitive to the standard antituberculosis drugs, at concentrations higher than 600 g/mL and 1.2 mg/mL, respectively.

Also, in Eastern Cape, South Africa has been assayed antitubercular activity of polyherbal formulations with several medicinal plants active to concentrations between 25-50 µg/mL [1].

In addition, essential oils have been derived from *S. aratocensis, T. diffusa and L. americana*, three aromatic plants of Colombia that are active against tuberculosis.

Emergence of new drug resistant variants

A number of antimicrobial agents already exist for various purposes but the search for new antimicrobial agents should be a continous one since the target microorganisms often evolve into new genetic variants which subsequently become resistant to existing agents [2].

The current first line drugs for TB (isoniazid, rifampicin, pyrazinamide and ethambutol) were discovered decades ago and are becoming less effective due to the emergence of drug resistance and the counteractions of HIV infection. Furthermore, effective use of these drugs require months of combination therapy, leading to issues with compliance and significant side effects. Thus, there is an urgent need to discover new TB drugs.

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Better and safer drug regimens to shorten treatment is vital in attaining the WHO's ambitious targets of 95% reduction in TB deaths and 90% reduction in TB incidence by 2035 [3].

Natural products of plant biodiversity have received considerable attention as potential anti-TB agents since they are a proven template for the development of new molecules against tuberculosis. Many antitubercular compounds that may prove to be useful leads for TB drug discovery have been derived from medicinal plants [4,5].

Natural product drug discovery works on the basis that biological diversity is the key to chemical diversity [6]. One prerequisite for the discovery of novel bioactive compounds is choosing suitable source material which significantly increases the chance of "hitting a target". Plants have long been viewed as a common source of remedies, either in the form of traditional preparations or as pure active principles. This forms a strong basis to utilize local plants that have been traditionally used as medicine and investigate them for their active chemical constituents [7-10].

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 [11]. In this way, natural terpenes have the ability of produce microbial cell wall disruption causing lysis [12]. Amino acid and co-factor biosynthesis; targeting the amino acid synthesis and co-factor pathways in the bacteria causes reduced metabolism and reproductive activity in the organisms [13], 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 antitubercular activity because biofilms provides a niche for establish antimicrobial resistance [14,15].

Selected natural products with Anti-Tb prospects

Antimycobacterial bioactive chemical molecules have been found from many natural product skeletons, mainly from plant biodiversity, but also from other organisms, such as fungi and marine organisms. Because natural products are a proven template for the development of new scaffolds of drugs, they have received considerable attention as potential anti-TB agents. A wide range of phytoconstituents are responsible for anti-tubercular activity includes alkaloids, glycosides, tannins, phenolics, xanthones, quinones, sterols, triterpenoids etc. These phytoconstituents present in plant exert desired pharmacological effect on body and thus act as natural anti-tubercular agents. Constituents from Medicinal plants play a key role in drug discovery programs, both serving as drugs and as templates for the synthesis of new drugs. This review summarizes the correlation between the uses of plants in Traditional African medicine against Tuberculosis (TB) and the biological activities of the derived natural products (both extracts and isolated compounds), with the aim to validate the use of traditional medicine against TB in African countries. The study was done by curating data from journals in natural products and phytomedicine. It was observed that the ethnobotanical uses of the plant species surveyed correlated with the bioactivities of the plant extracts and isolated compounds identified. In addition in drug–extract combination assays has been possible to determinate synergistic activity of combinations of antimycobacterial drugs with medicinal plants, opening the horizon of new impact studies on traditional medicine uses [16].

Socio-economic need of Anti-Tb natural products

Natural products especially plants have played a significant socio-economic role by fulfilling health-care needs and creating business opportunities for the less privileged population of the developing world [17].

Tuberculosis (TB) is the most ancient epidemic disease in the world and a serious opportunistic disease in HIV/AIDS patients. The increase in multidrug resistant *Mycobacterium tuberculosis* (MDR-TB, XDR-TB) demands the search for novel antimycobacterial drugs.

In the past centuries, a majority of the local population in Africa, India, and China have depended on medicinal plants as their main source of treatment of medical disorders and ailments [18]. Therefore, several plant species have been used traditionally to treat various diseases/ailments. Traditional medicine has been defined by the World Health Organization (WHO) as practices, knowledge and belief systems which use minerals, plants and animal based remedies, spiritual therapies and exercises to prevent, treat and maintain well-being [19]. The statement that natural products represent an enormous potential for drugs leads cannot be disputed [20]. This is because natural products often result from an optimized evolutionary process in which chemicals have been under the selective forces of coevolution, organisms producing substances (secondary metabolites) in the presence of their predators for their own defence mechanism and survival.

These natural compounds (secondary metabolites) have been utilized and chemically modified by humans since ancient times to treat and cure their diseases [21]. A quick search of the literature (the main stream natural products journals and PhD theses from university libraries) could give an estimate of >10000 unique compounds which have been previously isolated from natural products (flora, algae and fauna). A lot of these medicinal plants have been widely used in Africa.

Also, is important to validate the ethnopharmacological uses of biodiversity, with the end to promote the proper use of plants and find new sources of medicines. This approach is necessary especially in the countries with tuberculosis high burden [22].

Evaluation of the bioactive natural products

In many countries especially in subSaharan Africa, ethnobotanical and ethnomedical knowledge have been greatly exploited to evaluate the antimycobacterial properties of plants in vitro using crude extracts [23,24]. Some crude extracts

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have shown remarkable antimycobacterial activities against Mycobacterium tuberculosis and other mycobacteria [25].

This review therefore represent a continuation of the survey of the search for anti-tuberculosis agents from African flora. This is backed by correlating the biological activities of the isolated metabolites with the ethnobotanical uses of the plant species.

The most used methods in antitubercular *in vitro* drug discovery have been described as agar dilution, broth dilution, MGIT 960 fluorescence assay, microplate alamar blue assay (MABA), resazaurin microtiter assay (REMA) and tetrazolium microplate assay [26,27, 28]. Also, MBEC™ assay system (MBEC™ Biofilm Technologies Ltd. Calgary, AB, Canada) has been employed for to evaluate antibiofilm activity of new drugs so it can be very useful to complement antimicrobial assays of natural products from medicinal plants [29].

Outcome of evaluated bioactive compounds

Interesting results for classes of compounds which exhibit antituberculosis biological activities correlating with the ethnobotanical uses of the plant species of origin have been widely obtained.

Tabernaemontana elegans (toad tree) is an alkaloid which has been reported to be used traditionally by the Venda and Zulu people of South Africa: a root decoction is applied as a wash to wounds, and drunk for pulmonary diseases and chest pains [30]. It has been previously reported that extracts of this plant has demonstrated antibacterial activity against *S. aureus* and antimycobacterial activity against *M. smegmatis* [31].

Lippia javanica (Verbenaceae) is an aromatic herb that occurs all over Mozambique. Infusions of its leaves is commonly used in Africa as tea against various ailments like influenza, measles, rashes, malaria, stomach problems, fever, colds, cough, headaches [32] and *isolated* triterpene euscaphic acid from this plant [33]. This compound was tested against *Mycobacterium tuberculosis*, it was found to exhibit a minimum inhibitory concentration of 50 µg/mL against sensitive strain of *M. tuberculosis*, H37Rv, reference strain (27294).

The plant species *A. afra* (commonly called African wormwood) is widely distributed in South Africa from the Cederberg Mountains in the Cape, northwards to tropical East Africa [34]. This plant is reported to be used to treat coughs, colds, diabetes, malaria, sore throat, asthma, headache, dental care, gout and intestinal worms in South Africa [35]. In vitro studies of A. afra extracts have revealed that the plant is a potential antidepressant, cardiovascular, spasmolytic effects, antioxidant, and antimycobacterial [36].

The roots of *Euclea natalensis (Ebenaceae)* are used to relief toothache, headache and chest complaints amongst other uses [37]. The compounds shinanolone, 7-methyljuglone and diospyrin isolated from this plant [38] are used to relief toothache, headache and chest complaints amongst other uses. The three naphthoquinones; shinanolone, 7-methyljuglone and diospyrin demonstrated significant activity against drug sensitive and drug-resistant strains of *Mycobacterium tuberculosis* and lends credence to the ethnomedicinal use of the plant [39].

Knowltonia vesicatoria (Ranunculaceae) is a South African plant traditionally used to treat tuberculosis. Extracts of this plant is used in combination with isoniazid (INH) to investigate the possibility of synergy with respect to antimycobacterial activity. The compounds 5-(hydroxymethyl) furan-2(5H)-one and 5-(hydroxymethyl) dihydrofuran-2(3H)-one were isolated from this plant and demonstrated antimycobacterial activity.

The activity validates the traditional use of the plant in the treatment of tuberculosis. Many bioactive compounds was active against drug sensitive *M. tuberculosis* with an MIC of 50.0 mg/mL [40].

Bolusanthus speciosus (Fabaceae) is a common plant that is widely distributed in subtropical South Africa, Botswana, Zimbabwe, Mozambique and Zambia. The dried inner bark of the tree is used traditionally to relieve abdominal pains, emetism and tuberculosis [41]. Two new isoflavanoids 4,7,2'-trihydroxy-4'-methoxyisoflavanol and 5,7,3',4'-tetrahydroxy-5'-(2-epoxy-3-methylbutyl) isoflavanone isolated from the stem bark this plant were tested for antimicrobial activity [42].

Many other bioactive compounds demonstrated moderate activity against gram positive and gram negative bacteria. The results seem to support the traditional use of the plant in treatment of microbial infections.

Lall et al. [43], reported the antiviral and antituberculous activity of *Helichrysum melanacme* by carrying out bioassay guided fractionation of the acetonic extract of this plant. *Helichrysum melanacme (Asteraceae)* is a widely used medicinal plant in Southern Africa to treat cough, fever, headache, colds and chest pain. The plant extracts, and isolated compounds 2,4′,6′-trihydroxy-3′-prenylchalcone and 4′,6′,5″-trihydroxy-6″,6″- dimethyldihydropyrano [2″,3″-2′,3′] chalcone were active against *M. tuberculosis* with MICs of 0.5 and 0.05 mg/ml, respectively [44], *Leonotis leonurus*, commonly called Wild dagga or Lion's ear, is a robust perennial shrub which is widespread throughout eastern South Africa, growing amongst rocks in grassland [45]. The plant has found a wide variety of medicinal applications in treating colds, bronchitis, tuberculosis, coughs, asthma, feverish headaches, and dysentery and chest infections [30]. It was identified as a potential source of novel anti-tuberculosis compounds.

The organic extracts of this plant showed greater than 99% growth inhibition against *Mycobacterium tuberculosis* when tested at 1000 mg/ml with rifampicin as the positive control (2 mg/ml), and was considered to have potent activity against *Mycobacterium tuberculosis* [46], which correlate to it application in traditional use.

Green et al. carried out a study in which some selected medicinal plants were collected and their inhibitory properties against *Mycobacterium tuberculosis* was evaluated [47]. The acetone extracts of *Bridelia micrantha*, *Terminalia sericea*,

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and *Warbugia salutaris* showed a MIC of 25µg/mL against the two tested MTBs trains. The acetone extracts of Berchemia discolor demonstrated the highest antimycobacterial activity with MIC of 12.5µg/mL [48]. Prenylated flavonoid [49], and other secondary metabolites including friedelin, epifriedelin and phenolic derivatives such as gallic acid, ellagic acids, anthocyanidin, taraxerol, taraxerone and caffeic acid have been isolated from these plants species [50]. And generally, flavonoids are known for their antituberculosis properties [51]. *Ziziphus mucronatha*, *Scotia brakepetale*, *Rhus rogersii*, *Securidaca longepedunculata*, *Peltophorum africanum*, *Cassia petersiana*, *Scherocarya birrea*, *Rhoicissus tridentate*, *Grewia villosa*, *Piper capense* and *Carisa edulis* presented lower but interesting activities with MIC between 50 and 100µg/mL [52].

According to Ngemenya et al. [53], some drugs do show potent activity in vivo due to metabolic transformation of their components into highly active intermediates, so can some of these plants with weak activity (Tables 1,2) [39-42,44-52,54-73].

Challenges of developing Anti-Tb drug from plants

The classic pathway towards anti-TB drug discovery from natural products and other infectious diseases must overcome a number of challenges.

The first is to reliably detect efficacious and safe hits and be able to identify already known compounds at the early stages of the drug discovery program.

The second major challenge is the de novo structure elucidation of new molecular entities. Though current advances in spectroscopic techniques, specifically the high resolution neutron magnetic resonance (NMR) technologies have been contributed to the resolution of this challenge. Many approaches have been developed to solve the major hurdle, but it still remains a major challenge in anti-TB drug discovery from natural products [55]. Innovative technology is needed to impact the early phases of anti-TB drug discovery from natural products, innovative technologies need to be leveraged for

Table 1: Compounds that exhibit biological activities correlating with the ethnobotanical uses of the plant species of origin.

Plant Species	Phytochemical constituents	Reported pharmacological activity	References
Azadirachta indica A. Juss.	Flavonoids, tannins	Activity against *K. pneumoniae, M. smegmatis* and *M. aurum*	[39]
Chenopodium ambrosioides L.	Phenolics, flavonoids, saponins, ecdysteroids and triterpenoids	Activity against MDR strains of *M. tuberculosis*	[40]
Solanum torvum Sw (fruits and leaves)	Sterols, tannins, saponins, flavonoids, glycosides	Activity against *M. tuberculosis* H37Rv	[41]
Bidens pilosa L	Chalcone glucosides	Activity against drug sensitive *M. tuberculosis*	[42]
Allium sativum	Alkaloids, flavonoids, cardiac glycosides, terpenes, resin	Active against *M. tuberculosis* MDR strains and H37Rv	[44]
Allium cepa (bulb and leaves)	Alkaloids, flavonoids, cardiac glycosides, terpenes, resin	Active against *M. tuberculosis* MDR strains and H37Rv	[45]
Aloe vera var. barbadensis (aqueous and organic extracts)	Tannins, saponins, flavonoids, terpenoids	Active against *M. tuberculosis* MDR strains and H37Rv	[46]
Acalypha indica, (leaves)	Kaempferol, Acalyphamide quinone, sterols, cyanogenic glycoside	Active against *M. avium*	[47]
Allium cepa (bulbs)	allicin, flavonoids; phenolic acids and sterols	Activity against *Mycobacterium tuberculosis*	[49]
Vitex trifolia	Flavonoids-artemetin, luteolin, orientin, casticin; and iridoid glycosides	Activity against *M. smegmatis*	[48]
Zanthoxylum capense (roots)	Benzophenanthridine, decarine, 6- acetonyldyhydronitidine, N-isobutyl-(2E,4E)-2,4-tetradecadienamide	Activity against *M. tuberculosis*	[50]
Trichosanthes dioica (stem and leaves)	Berberine, columbin, chasmanthin, palmarin, inosporon, tinosporic acid and tinosporol	Activity against drug sensitive *M. tuberculosis*	[51]
Ocimum sanctum (leaves and seeds)	Ursolic acid, apigenin, orientin, luteolin	Activity against *M. tuberculosis* H37Rv	[52]
Garcinia nobilis (Stem bark)	Smeathxanthone, 8-hydroxycudraxanthone, morisignin, 4-prenyl-2-(3,7-dimethyl-2,-octadienyl) -1,3,5,8-tetrahydroxyvanthone	Activity against *M. tuberculosis* H37Rv	[54]
Ficus chlamydocarpa (stem bark)	Alpinumisoflavone, genistein, laburnetin and luteolin	Activity against drug resistant *M. tuberculosis*	[55]
Cirtullus colosnthis (deseeded fruits)	Ursolic acid, cucurbitacine E and cucurbitacin I	Activity against *M. tuberculosis* H37Rv	[56]
Morinda citrifolia, (leaves, roots and fruits)	Anthraquinonesalizarin, nordamnacanthol, Ursolic acid; β-Sitosterol, asperuloside and caproic acid	Activity against drug sensitive *M. tuberculosis*	[57]
Terminalia avicennioides (Root bark)	Arjunolic acid, friedelin and friedelin-3β-ol	Activity against drug sensitive *M. tuberculosis*	[58]
Oricia suaveolens (stem bark)	Evoxanthine and 1-hydroxy-2,3-dimethoxy-10- methylacridone	Activity against drug sensitive *M. tuberculosis*	[59]
Andrographis paniculata (Leaves)	Andrographolide	Activity against drug sensitive *M. tuberculosis*	[60]

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Table 2: Biological activity of some derived natural products versus ethnobotanical uses of plant species derived from African flora.

Plant species	Family	Isolated metabolite	Ethnobotanical use	Measured activity	Reference
Tabernaemontan elegans	*Apocynaceae*	Voacangine and dregamine	Applied as a wash to wounds, and drunk for pulmonary diseases and chest pains	Antimicrobial activity	[61]
Artemisia afra	*Asteraceae*	α-Myrin and betulinic acid	used to treat coughs, colds, diabetes, malaria, sore throat, asthma, headache, dental care, gout and intestinal worms	Antimicrobial activity	[43]
Euclea natalensis	*Ebenaceae*	Shinanolone, 7- methyljuglone and diospyrin	Used to relief toothache, headache and chest complaints.	Antimycobacterial activity	[62]
Lippia javanica	*Verbenaceae*	Euscaphic acid, (E)-2(3) Tagetenone epoxide, myrcenone, piperitenone or 3-methyl-6-(1 methylethylidene)-cyclohex-2-en-1-one	Infusion is commonly used in Africa as a tea against various ailments like influenza, measles, rashes, malaria, stomach problems, fever, colds, cough, headaches	Antimycobacterial and antimicrobial activity	[63,64]
Knowltonia vesicatoria	*Ranunculaceae*	5-(hydroxymethyl) furan-2(5H)-one and 5-(hydroxymethyl) dihydrofuran-2(3H)-one	Used traditionally to treat tuberculosis	Antimycobacterial	[65]
Bolusanthus speciosus	*Fabaceae*	4,7,2′-trihydroxy-4′-methoxyisoflavanol and 5,7,3′,4′-tetrahydroxy-5′-(2-epoxy-3-methylbutyl) isoflavanone	Dried inner bark of the tree is used traditionally to relieve abdominal pains, emetism and tuberculosis	Antimicrobial activity	[66]
Helichrysum melanacme	*Asteraceae*	2,4′,6′-trihydroxy-3′-prenylchalcone and 4′,6′,5″-trihydroxy-6″,6″-dimethyldihydropyrano [2″,3″-2′,3′] chalcone	Used to treat cough, fever, headache, colds and chest pain		[67]
Leonotis leonurus	*Lamiaceae*	9,13-Epoxy-6-hydroxy-16,15-labdanolide and 9,13:15,16-diepoxy-6,16- labdanediol	Treating colds, bronchitis, tuberculosis, coughs, asthma, feverish headaches, dysentery and chest infections	Antimycobacteria	[53,68]
Bridelia micrantha	*Euphorbiaceae*	friedelin, epifriedelin, gallic acid, ellagic acids, anthocyanidin, taraxerol, taraxerone and caffeic acid.	For treatment of stomach aches, tapeworms, diarrhoea, headaches, sore joints, sore eyes, venereal diseases, and fevers		[69,70]
Piper capense	*Piperaceae*		Used for cough, bronchial problems, leprosy and infertility		[71]
Ziziphus mucronata	*Rhamnaceae*		Bark, leaves and roots are used to treat boils, sores, glandular swellings, diarrhoea, dysentery, expectorant, emetic for coughs, chest problems, boils, sores, glandular swellings	Antimycobacteria	[72]
Berchemia discolor	*Rhamnaceae*	(3 S)-discoloranone	Infertility and Menorrhagia	Antimycobacteria	[66]
Peltophorum africanum	*Fabaceae*	Catechin (flavonoid), bergenin, betulinic acid	Used to treat tuberculosis, stomach complains and intestinal parasites	Antimycobacteria	[73]

rapid navigation of natural product hits through the detection, validation, isolation, and hit-to-lead and lead optimization phases [56].

Considering that none of the several screened non-microbial natural products with activity against MTB has progressed towards the clinical trial stage in anti-TB drug development, this could possibly be caused by:

i. Low yields of purified compounds;

ii. Structural complexity exhibited by natural products, such as the occurrence of multiple stereoisomers, e.g., triterpenes which contain ten or more chiral centers;

iii. Low activity exhibited by the isolated compounds with MICP 1 lg/ml;

iv. The presence of pan inhibitors (non-specific compounds or paninhibitors);

v. Difficulties in isolating novel bactericidal compounds acting on new targets that can potentially reduce the duration of therapy; and

vi. Difficulties in identification of anti-TB compounds with exceptional safety profiles without the drug-drug-interaction problem presently confronting concurrent TB and HIV therapy.

Crude natural product extracts are complex mixtures of perhaps hundreds of different compounds working together in synergy when the extract is administered as a whole. Discovery of natural product hits and their progression towards development includes extraction of the crude extract from the source, concentration, lyophilization (in cases where polar solvents have been used), fractionation and purification to yield a single bioactive compound.

Finally is very important take in account that in antimicrobial

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drug discovery from natural sources the endpoint criteria for activity should be below 100 µg/mL for crude extracts and 25µM or 10 µg/mL for pure compounds with the end of select new promisory antimycobacterial treatments [57,58].

Conclusion

It will be difficult to resolve the aforementioned challenges without increased funding for anti-TB drug discovery and construction of a more robust drug development pipeline through well-coordinated international efforts. Plants are sole treatment of leprosy and tuberculosis in some African countries. Though anti-mycobacterial MIC of plant materials is higher but they have resistance modifying properties. Therefore, plant derived drugs can help in fighting the drug resistance. Unfortunately, there is no plant derived molecule either in market or under trial for treatment of mycobacterial infections. Majority of studies focused on identification of crude plant extracts with anti-mycobacterial properties and has not been extended to identification of bioactive plant metabolites.

Therefore, an integrated approach of identification of plants with anti-mycobacterial activity followed by identification of bioactive molecule will speed up the research and development of plant derived drug molecules for mycobacterial infections.

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