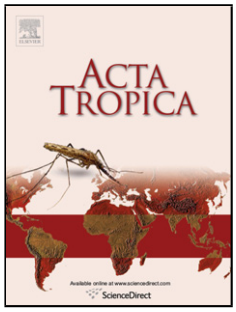

Title: Tuberculosis and Nature's Pharmacy of Putative Anti-tuberculosis Agents

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Tuberculosis and Nature's Pharmacy of Putative Anti-tuberculosis Agents

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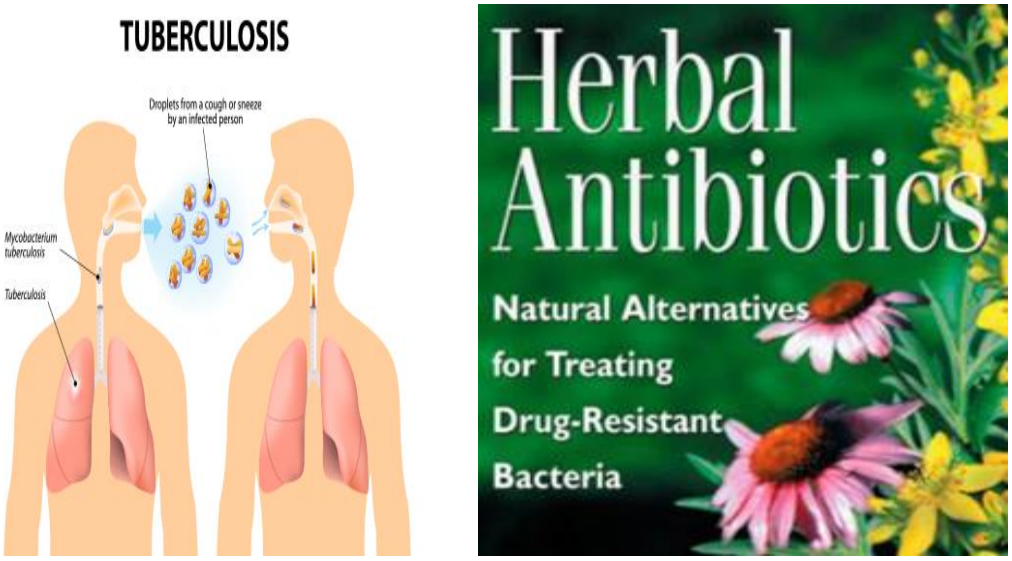
Graphical Abstract



Several antimycobacterial chemical compounds have been isolated plants: ellagitannin punicalagin, allicin, anthraquinone glycosides, iridoids, phenylpropanoids, beta-sitosterol, galanthimine, crinine, friedelin, gallic acid, ellagic acids, anthocyanidin, taraxerol, termilignan B, arjunic acid, glucopyranosides, 1-Epicatechol, leucopelargonidol, hydroxybenzoic acids, benzophenanthridine alkaloids, neolignans, and decarine. These compounds may provide leads to novel and more efficacious drugs to lessen the global burden of TB and drug-resistant *Mycobacterium tuberculosis* strains.

Highlights

Natural products used to treat tuberculosis are reviewed

At least 60 plant species are known to display anti-TB activity in Africa

Anti-TB active compounds include 1-Epicatechol, termilignan B and leucopelargonidol

Others are β-sitosterol, friedelin, gallic acid, ellagic acids, decarine and anthocyanidin

Abstract
Due to the growing problem of drug resistant *Mycobacterium tuberculosis* strains, coupled with the twinning of tuberculosis (TB) to human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS), the burden of TB is now difficult to manage. Therefore, new antimycobacterial agents are being sought from natural sources. This review focuses on natural antimycobacterial agents from endophytes and medicinal plants of Africa, Europe, Asia, South America and Canada. In the countries mentioned in this review, numerous plant species display putative anti-TB activity. Several antimycobacterial chemical compounds have also been isolated, including: ellagitannin punicalagin, allicin, anthraquinone glycosides, iridoids, phenylpropanoids, beta-sitosterol, galanthimine, crinine, friedelin, gallic acid, ellagic acids, anthocyanidin, taraxerol, termilignan B, arjunic acid, glucopyranosides, 1-Epicatechol, leucopelargonidol, hydroxybenzoic acids, benzophenanthridine alkaloids, neolignans, and decarine. These compounds may provide leads to novel and more efficacious drugs to lessen the global burden of TB and drug-resistant *M. tuberculosis* strains. If there is a long-term remedy for TB, it must lie in nature's pharmacy of putative antimycobacterial agents.

Keywords: Tuberculosis; humans; natural products; antimycobacterial activity; active compounds.

1. Introduction

Tuberculosis (TB) is a contagious disease which latently infects over 2 billion people worldwide (Baldwin et al., 2015), almost one-third of the world's population (Xie et al., 2015). TB generally infects the lungs, transmitting from person to person via droplets from the throat and lungs of people with the active disease. However, the disease may affect different parts of the body. It spreads rapidly in overcrowded settings and in conditions of malnutrition and poverty (Green et al., 2010). Thus, it has been suggested that *Mycobacterium tuberculosis*, the most common agent of TB, is responsible for more human deaths than any other single microbial pathogen (Fyhrquist et al., 2014). Abuzeid et al. (2014) also noted that among all infectious diseases, TB remains one of the major causes of death. The World Health Organization (WHO) estimated that TB is spreading at the rate of one person per second.

M. tuberculosis is an intracellular obligate and aerobic bacillus that multiplies within macrophages. While the bacterium triggers the production of free radicals, it avoids killing by the same radicals (Agarwal et al., 2010). Latent TB infection occurs when pathogenic *M. tuberculosis* bacteria exist in dormant form, and patients do not show any symptoms of the disease (Ganihigama et al., 2015). Although patients with the dormant form of *M. tuberculosis* cannot transmit the disease, they have a lifelong risk of TB reactivation more especially during HIV infection (Ganihigama et al., 2015). It is estimated that 50% of the population in Sub-Saharan Africa is infected with latent TB (Frothingham et al., 2005).

Mathematical models projected that between the years 2000 and 2020, nearly one billion people would have been newly infected, 200 million would develop TB, and 35 million would have died from the disease (WHO, 2000). A major public health problem, TB killed more than 1.4 million in 2011 (Dye and Williams, 2010; WHO, 2012). In 2009, an estimated 8.8 to 9.9 million new TB cases were reported throughout the world. In 2005, the global incidence of TB was estimated at 136 cases per 100,000 of the population (Askun et al., 2009).

Approximately half a million people in Africa died of TB in 2004 (Madikizela et al., 2014a). Therefore, WHO declared TB an emergency in Africa, mainly because the average incidence of TB in African countries more than doubled between 1990 and 2005, largely driven by rising HIV infections (Chaisson and Martinson, 2008). With 15,700 new cases of TB infections, the disease was one of the major causes of death in Ethiopia around 1997 (Cambanis et al., 2005). In Tanzania, the number of TB cases steadily increased between 1983 and 2000, mainly due to HIV/AIDS (Egwaga, 2003).

In 2008, WHO estimated that the largest number of new TB cases occurred in South-East Asia, which accounted for 34% of incident cases globally (WHO, 2010a). By the year 2007, Asia had 60% of the global burden of TB (Vermund and Yamamoto, 2007). In the former Soviet Union, TB also reached epidemic proportions (Toungoussova et al, 2006). Around the same time, Africa and the Americas recorded about 1.7 million deaths from TB annually (Askun et al., 2009). Due to the HIV/AIDS epidemic, TB re-emerged as a global emergency, peaking in 2006 to more than 9.9 million cases annually, then falling to an estimated 8.8 million by 2010 (Ralph et al., 2013; WHO, 2012). By 2011, TB was more prevalent in the world than at any other time in human history (Koul et al., 2011).

Currently, one of the most pressing global health challenges involves resistance of *M. tuberculosis* to drugs (Askun et al., 2009). Globally, over 4% of TB patients are infected with

Mycobacterium strains that are resistant to first line drugs (Fomogne-Fodjo et al., 2014). The increasing rate of multi-drug resistant tuberculosis (MDR-TB), extensively drug resistant tuberculosis (XDR-TB), and totally drug resistant tuberculosis (TDR-TB) strains is a major global public health concern because these drug resistant strains are associated with poor disease outcomes and treatment failure (Pablos-Méndez et al., 1998). MDR-TB refers to strains that resist isoniazid and rifampin, while XDR-TB is resistant to isoniazid, rifampin, fluoroquinolone, and the second-line injectable drugs kanamycin, amikacin, and capreomycin (Ganihigama et al., 2015). In 2012, estimates suggested 450,000 people developed MDR-TB and 170,000 people died from the same (Ganihigama et al., 2015). In 2013, the number of MDR-TB cases rose to 480,000. South Africa was among the four countries with the highest number of MDR-TB and XDR-TB in the world (WHO, 2010b).

TB is the most significant AIDS-associated opportunistic infection (Frothingham et al., 2005). There is synergy between HIV/AIDS and TB (Raviglione, 2003). The twinning of TB to HIV/AIDS, commonly referred to as the HIV/TB co-epidemic or dual epidemic, is a serious global health challenge. Sub-Saharan Africa accounts for 80% of global HIV-related TB cases (Fyhrquist et al., 2014). Due to the widespread existence of multiple drug resistant strains of *M. tuberculosis* and the increase in the prevalence of HIV/AIDS, TB has become one of the deadliest global health emergencies (Holton et al., 2007).

The number of drugs currently in use against *M. tuberculosis* is very limited as most of them were introduced more than 40 years ago. Since the release of rifampicin in 1976, only rifabutin and rifapentine have been approved for TB treatment. Unfortunately, these drugs have not yet achieved extended distribution for clinical application (León-Díaz et al., 2013). In 2012, a new anti-TB drug TMC207 (or R207910) was approved by the United States of America's Food and Drug Administration (FDA). TMC207 is the first anti-TB drug in four decades with a new mechanism of action, specifically inhibiting ATP synthase (Ganihigama et al., 2015). However, this drug is not available for TB treatment in most settings.

Ibekwe et al. (2014) bemoaned that though there are many efforts to discover new drugs to treat TB, these efforts are not a major focus for pharmaceutical companies. The reasons for the lack tangible investments by pharmaceutical industry are mainly economic, because countries in dire need of new anti-TB drugs are primarily poor, meaning people cannot afford expensive drugs developed by heavily capitalized industries. Since the discovery of the tubercle bacillus *M. tuberculosis* by Robert Koch in 1882, the genome of *M. tuberculosis* was by 1998 completely sequenced, opening the doors to amazing possibilities for target-specific drug development (Chandra et al., 2011). However, post-genomics progress toward novel anti-TB drugs is slow, mainly hampered by the lack of interest from pharmaceutical and biotechnology companies (Holton et al., 2007).

To reduce TB cases in developing countries especially in rural communities where health care systems are generally weak or inadequate, new models of public-private partnerships have been suggested (Asuquo et al., 2015). Bunalema et al. (2014) also suggest the importance of developing a new battery of drugs to curb resistant TB strains. The emergence of multidrug-resistant strains of *M. tuberculosis* highlights the need for continuous development and search for novel antimycobacterial agents from plants (Abuzeid et al., 2014). Plants and other natural products are an important source of new drugs (Abuzeid et al., 2014) and in the last 20 years, nearly 50% of drugs approved by the FDA in the United States of America have been derivatives of natural products (Uc-Cachón et al., 2014).

Green et al. (2010) assert that chemical compounds isolated from plants play an important role in the discovery of drugs against infectious diseases. Cragg and Newman (2013) also aver that nearly 75% of all the approved anti-infective drugs are derived from medicinal plants. The evidence for anti-infective chemical agents from natural products is unequivocal (Farnsworth et al., 1985), as is the successful inhibition of *M. tuberculosis* by extracts from ethnobotanically-selected plants (Boligon et al., 2014). Therefore, natural remedies, especially those derived from ethnomedicinal plants, are still being used worldwide in the management of TB. Natural products play an essential role in the management of TB (Alvin et al., 2014). In certain cases, data on the efficacy of ethnobotanicals against *M. tuberculosis* are available (Mohamad et al., 2011). Herbal constituents like iridoids, terpenes, citronellol, nerol and geraniol have shown antimycobacterial activities (Kumar et al., 2013; Wang et al., 2012). Thus, selecting plants based on ethnobotanical knowledge may enhance the probability of finding species with anti-TB action.

Due to the high burden of TB, compounded by drug resistant *M. tuberculosis* genotypes, there is a global imperative to discover and develop new anti-TB agents (Zumla et al., 2013; Goldman et al., 2007). Indeed, the emergence of multi-drug resistant strains of *M. tuberculosis* makes the discovery of new chemical scaffolds a very urgent biomedical priority (Koul et al., 2011). Corollary, there are several efforts to screen and isolate novel anti-TB principles from natural products (Santhosh and Suriyanarayanan, 2014). This review is a current effort aimed at providing clarity to the species of medicinal plants used as folk medicines for TB, and where possible, to elucidate their antimycobacterial properties and active chemical compounds. These data suggest an opportunity for inventing new anti-TB drugs from plants and other natural products.

2. Common natural products

There are common natural products whose chemical ingredients have antimycobaterial activities: *Hypericum perforatum* L. (a relative of St. John's wort), *Camellia sinensis* (L.) Kuntze (green tea), *Curcuma longa* L., *Salvadora persica* L. (miswak), *Plumeria bicolor* Seem. (champa), *Cannabis sativa* L. (marijuana), *Ocimum basilicum* L. (sweet basil), several *Vernonia* species, and honey/propolis.

Hyperenone A, present in the extracts of the aerial parts of *Hypericum acmosepalum* N.Robson, a very close relative of *H. perforatum*, inhibits the growth of *M. tuberculosis* H37Rv and *Mycobacterium bovis* BCG at 75 mg/l and 100 mg/l, respectively (Osman et al., 2012). Many *Hypericum* species contain phloroglucinols, anthraquinones, xanthones and filicilic acid derivatives; the last group of compounds has potent antimycobacterial activity (Nogueira et al., 2013). Some of these principle chemicals are undergoing clinical trials.

Catechins mostly present in green tea may also alleviate TB symptoms. Patients who receive catechins show increased levels of superoxide dismutase (SOD), an enzyme that inhibits the production of hydrogen peroxide through the dismutation reaction. Catechins have strong anti-superoxide formation effect, by scavenging superoxide anion (Agarwal et al., 2010). These findings suggest that crude green tea catechin extracts may play a definite role as adjuvant therapy in pulmonary TB patients.

Curcumin [1,7-bis(4-hydroxy-3-methoxy phenyl)-1,6- heptadiene-3,5-dione] is a phenolic compound. It was originally extracted from the plant *C. longa*, the primary component of the ubiquitous dietary spice turmeric. For centuries, various Asian societies have used curcumin

as a traditional medicine to treat numerous disorders. Studies now show that curcumin exhibits antimycobacterial activity (Baldwin et al., 2015). Curcumin has antioxidant, anti-cancer and anti-inflammatory properties but is non-cytotoxic to normal human cells. These properties make curcumin a very attractive chemical ingredient to alleviate TB, though it is relatively unstable and beset by poor bioavailability. The anti-TB action of curcumin is due to its ability to induce the cell death of macrophages (Li et al., 2014).

S. persica, commonly used as a chewing stick to improve oral health, inhibits the growth of *M. bovis* (Fallah et al., 2014). Whether *S. persica* extracts are effective against *M. tuberculosis* is not exactly clear. Another excellent antimycobacterial agent is plumericin, a phyto-ingredient of *P. bicolor*, commonly known as champa in India (Kumar et al., 2013). *P. bicolor* is also grown in Indonesia, the Philippines and South Africa. Against four MDR strains of *M. tuberculosis*, plumericin performed better than the standard drugs rifampicin and isoniazid, MIC values of 1.3 to 2 µg/ml.

C. sativa leaves are used by the Zulu people in South Africa to lighten the burden of TB. Leaves of *C. sativa*, also known as Mopatse in the local Pedi language of South Africa, are macerated in warm water overnight. One cup of the decoction is taken orally three times a day as a remedy for TB (Semenya et al., 2012). *O. basilicum* is a perennial plant native to Asia, Africa and South America but widely cultivated in other parts of the world (Jayaweera, 1981). The oil of *O. basilicum* is known to have antibacterial and antifungal properties (Siddiqui et al., 2012). Extracts of *O. basilicum* leaves not only display broncho-dilatory action but also inhibit the proliferation of *Mycobaterium smegmatis* (Boskabady et al., 2005). Siddiqui et al. (2012) found that nine *O. basilicum* compounds inhibit the growth of *M. tuberculosis*. A new compound named bacilicin inhibits the growth of *M. tuberculosis* H37Rv by at least 49%, MIC 6.25 µg/ml.

According to Toyang and Verpoorte (2013), *Vernonia adoensis* Sch.Bip. ex Walp. is used by traditional healers in India and many African countries as a natural remedy for TB. Other *Vernonia* species used to manage TB are *Vernonia amygdalina* Delile, *Vernonia cinerea* (L.) Less., *Vernonia kotschyana* Sch.Bip. ex Walp., and *Vernonia saligna* DC. In Thailand, honey and propolis are regular natural products that work against coughs as well as drug resistant *Staphylococcus aureus* and *M. tuberculosis* (Chanchao, 2013).

3. Endophytes: A new frontier for antimycobacterial agents

There is increasing optimism that novel anti-TB chemical agents may be sourced from endophytes, microorganisms that form a symbiotic relationship with their host plants and function as biological defence agents against foreign phytopathogens (Alvin et al., 2014). Endophytes secrete chemical metabolites that thwart antagonists or lyse pathogen-infected cells. Endophytes can also be beneficial to their host by producing a range of natural products that could be harnessed in medicine, agriculture and pharmaceutical industry. Some of the defensive secondary metabolites secreted by endophytes may have beneficial anti-TB properties.

The possibility of manufacturing novel anti-TB drugs derived from endophytic secretions are not misplaced because antibiotics and anti-cancer drugs (taxol from the endophytic fungi *Taxomyces andreanae*) are already being co-produced from endophytes and plants (Strobel, 2003). From a production standpoint, it is much easier to scale up the fermentation process of endophytic microorganisms thus allowing large-scale production of biologically active

compounds to meet large industrial demands for anti-TB drug production. Endophytes, therefore, not only present an exciting opportunity to discover a plethora of antimycobacterial compounds but also offer a renewable source of natural products as anti-TB agents.

Vermelhotin, a natural tetramic acid isolated from endophytic fungi, is highly active against clinical strains of MDR-TB, MIC of 1.5-12.5 µg/ml (Ganihigama et al., 2015). In addition, there were 28 novel antimycobacterial compounds isolated from endophytic organisms between 2008 and 2012 (Alvin et al., 2014). Of these, 11 were polyketides or polyketide-derived, and 10 were small peptides; all of them showed activity against TB. Nocardithiocin, a peptide produced by the endophyte *Nocardia pseudobrasiliensis* has a MIC value of 0.025 µg/ml against *M. tuberculosis* H37Rv (Mukai et al., 2009). Extracts of 92 isolates of endophytic fungi inhibited the growth of *M. tuberculosis* H37Ra at MIC values of 0.0625–200 µg/ml (Alvin et al., 2014).

The chemical 3-nitropropionic acid is a potent antimycobacterial agent isolated from endophytic fungi (Chomcheon et al., 2005). The symbiotic nature of plant-endophyte relationships means that bioactive compounds secreted by endophytes are less likely to be cytotoxic to eukaryotic cells (Alvin et al., 2014). This is significantly important to the pharmaceutical community because drugs developed from such compounds may not adversely affect human cells. The potential of antimycobacterial drug discovery from endophytes associated with traditional medicinal plants is immense (Alvin et al., 2014).

4. African plants

TB in Uganda is frequently treated using *Albizia coriaria* Welw. (Asiimwe et al., 2013) and *V. amygdalina* (Tabuti et al., 2010). Table 1 shows plants used in the management of TB in Uganda (Bunalema et al., 2014). Other plants used by Ugandan traditional healers are: *Zanthoxylum leprieurii* Guill. & Perr., *Piptadeniastrum africanum* (Hook.f.) Brenan, *Mangifera indica* L., and *Rubia cordifolia* Hochst. ex A.Rich. (Bunalema et al., 2014; Mugisha et al., 2014). Some of the plants contain active compounds with known anti-TB action. For example, ellagitannin punicalagin isolated from *Combretum molle* R.Br. ex G.Don, allicin from *Allium sativum* L. and anthraquinone glycosides (also known as aloin) from *Aloe vera* (L.) Burm.f. are active against various strains of *M. tuberculosis*. *C. molle* contains punicalgin with a MIC value of 600 µg/ml against *M. tuberculosis* strain ATCC 27294 and a drug-resistant clinical isolate (Ibekwe et al., 2014). A hydroxycycloartenol glycoside by the name of mollic acid is also present in the leaves of *C. molle*.

Kigelia africana (Lam.) Benth. fruit extracts were for the first time shown to have activity against *Mycobacterium aurum* (Fomogne-Fodjo et al., 2014). The fruits of *K. africana* contain several chemical ingredients: iridoids (jiofuran, jioglutide, ajugol and verminoside), phenylpropanoid and phenylethanoid derivatives, a flavonoid glycoside, β-sitosterol and three fatty acids- palmitic acid being the main one. Fomogne-Fodjo et al. (2014) cited studies where iridoids, sterols and flavonoids inhibit *M. tuberculosis*.

Studies in South Africa elucidated the anti-TB activity of local plants: Lall and Meyer (1999); Seidel and Taylor (2004); Mativandlela et al. (2006); Eldeen and Van Staden (2007); McGaw et al. (2008); and Green et al. (2010). In KwaZulu-Natal, a survey report by York et al. (2011) revealed the following nine plants were part of the folk remedies for TB: *Acanthospermum glabratum* (DC.) Wild, *Clematis brachiata* Ker Gawl., *Cyperus articulates* L., *Euphorbia tirucalli* Forssk., *Helichrysum kraussii* Sch.Bip., *Parinari capensis* Harv., *Plectranthus neochilus* Schltr., *Senecio deltoideus* Less. and *Terminalia sericea* Burch. ex

DC. The study also showed that other putative anti-TB plants were: *C. molle*, *Ekebergia capensis* Sparrm., *Lippia javanica* Spreng., *Psidium guajava* L., *Scadoxus puniceus* (L.) Friis & Nordal, *Senecio serratuloides* DC., *Syzygium cordatum* Hochst., and *Tetradenia riparia* (Hochst.) Codd.

McGaw et al. (2008) reviewed the potential of South African plants against TB. They stated that about 180 species were employed for alleviating TB and related symptoms. Of those, around 30% were screened for antimycobacterial activity. Some of the screened plants are listed in Table 2. An ethanol extract of the South African plant *Euclea natalensis* A.DC. contains a compound called shinanolone, active against *M. tuberculosis* at MIC of 100 µg/ml. Several naphthoquinones and triterpenes isolated from a chloroform extract of *E. natalensis* also showed good antimycobacterial activity. The Zulu people in Umtentweni area of KwaZulu-Natal Province use *Boophone disticha* Herb. bulb decoctions, endowed with three alkaloids (galanthamine, lycorine, and crinine) to treat TB (Nair and Van Staden, 2014).

Four South African plants have lower MIC values against *M. tuberculosis*: *Berchemia discolor* Hemsl., 12.5 µg/ml on H37Ra and 10.5 µg/ml on a clinical isolate; *Bridelia micrantha* Baill. (25 µg/ml on H37Ra), *Warburgia salutaris* (G.Bertol.) Chiov. (25 µg/ml on H37Ra), and *T. sericea* (25 µg/ml) on both H37Ra and clinical isolate (Green et al., 2010). Laboratory assays confirmed that acetone extracts of *B. discolor*, *B. micrantha*, *T. sericea* and *W. salutaris* may be important sources of chemical compounds against multidrug-resistant *M. tuberculosis*. York et al. (2012) found *T. sericea* bark had weak activity against *M. smegmatis* (0.67 mg/ml).

B. micrantha contains compounds including friedelin, epi-friedelin and phenolic derivatives such as gallic acid, ellagic acids, anthocyanidin, taraxerol, taraxerone, caffeic acid, and flavonoids thought to have anti-TB functions (Green et al., 2010). Compounds isolated from *T. sericea* include termilignan B and arjunic acid. Organic root and bark extracts of *T. sericea* were active against *M. aurum* with MIC = 1.56 to 3.12 mg/ml (Eldeen and van Staden, 2007). South African plants *Abrus precatorius* L., *Ficus sur* Forssk., *Pentanisia prunelloides* Schinz, and *Terminalia phanerophlebia* Engl. & Diels with MIC values of less than 1.00 mg/ml had good anti-TB activity (Madikizela et al., 2014b). One novel compound, identified as 1,6-di-O-coumaroyl glucopyranoside, isolated from *T. phanerophlebia* for the first time, inhibited *M. tuberculosis* at a noteworthy MIC value of 63 µg/ml (Madikizela et al., 2014b). This compound can serve as a lead principle for anti-TB drug discovery.

Ntutela et al. (2009) demonstrated that *Artemisia afra* Jacq. contains *in vitro* antimycobacterial chemical agents that modulate pulmonary inflammation in early TB infection. An organic fraction of *A. afra* reduces replication of *M. aurum* and *M. tuberculosis* in a dose-dependent manner with IC_{50} values of 1.9 µg/ml and 2.0 µg/ml, respectively. There are also plants used as natural medicines for TB by the Bapedi traditional healers of South Africa (Semenya et al., 2012): *Eriobotrya japonica* (Thunb.) Lindl., has anti-inflammation activity; *Eucalyptus camaldulensis* Dehnh., anti-proliferative properties; and *Ficus carica* L. contains phenolic compounds, phytosterols and fatty acids. Green et al. (2010) also found that *Carica papaya* L. leaves had antimycobacterial activity *in vitro*. In other parts of South Africa, TB is managed by using the following natural medicines (Rood, 2013): infusion of *Pharnaceum lineare* Bert. ex Rohrb., bark decoction of *Rauvolfia caffra* Sond., and *Asclepias fruticosa* L., a poisonous plant commonly called milkweed, melkbos, gansiebos or kapokbossie, whose powder of dry leaves is used as a snuff for TB treatment.

According to Rood (2013), other anti-TB remedies are *Helichrysum pedunculatum* Hilliard & B.L.Burtt leaves, brewed like tea and drunk, *Symphytum officinale* L. (comfrey, rich in vitamin B12 and calcium) extract is drunk, *Acacia nilotica* Delile root extract, *Ceratonia siliqua* L. (carob) leaf extract is an expectorant or cough remedy, root extract of *Glycyrrhiza glabra* L. (liquorice root), *Sutherlandia microphylla* Burch. ex DC. (kalkoenbos) leaf powder mixed with syrup is taken to alleviate symptoms, and *Pelargonium ramosissimum* Willd. weak tincture made from a leaf extract is drunk; weak because strong tincture upsets the stomach. Rood (2013) also noted other plant remedies for TB: drinking the sap from leaves of *Agave americana* L. (century plant), root extract of *Bulbine asphodeloides* (L.) Spreng. (copaiva), mixture of honey and olive oil and juice squeezed from *Carpobrotus edulis* N.E.Br., extract of bark and roots of *F. sur* (broom cluster-fig), leaf extract from *Nylandtia spinosa* (L.) Dumort. (tortoise berry), large doses of the root extract of *Thesium hystrix* A.W.Hill, and extracts from the leaf tips of *Dodonaea angustifolia* Thunb. (sand olive).

Tanzanian species of *Terminalia* showed antimycobacterial activities when tested on the model organism *M. smegmatis* ATCC 14468. Fyhrquist et al. (2014) reported for the first time the antimycobacterial efficacies of the root and stem bark extracts of *Terminalia sambesiaca* Engl. & Diels, the fruit extracts of *Terminalia stenostachya* Engl. & Diels and the leaf extracts of *Terminalia spinosa* Northr. *Terminalia* species are known to contain several active chemical compounds including ellagitannins, ellagic acid derivates, gallotannins and condensed tannins that inhibit mycobacteria. Some tannins from *Terminalia* species are known to be very toxic, for example terminalin A, present in *Terminalia oblongata* F.Muell.

Plants from Central Africa had good antimycobacterial action, MIC values below 130 µg/ml: *Xylopia aethiopica* A.Rich., *Desmodium velutinum* DC. (stems), *Desmodium salicifolium* DC. (leaves), *Crinum purpurascens* Herb., *Cyathula prostrata* Blume, and *Albizia ferruginea* Benth. (Fomogne-Fodjo et al., 2014). Interestingly, these species were selected based on the indigenous knowledge of these plants for the treatment of respiratory and TB-related symptoms by the Bakola pygmies living along the Ngoyang area in Cameroon. In Gabon, where 53% of patients with HIV/AIDS had TB, three plants were used to treat TB (Tchouya et al., 2015): *Musanga cecropioides* R.Br.apud Tedlie, *Scyphocephalium ochocoa* Warb., and *Costus afer* Ker Gawl.

Using a luminometry-based method to screen Sudanese plants for antimycobacterial activity, Abuzeid et al. (2014) found that *Khaya senegalensis* A.Juss. (bark and leaves) and *Rosmarinus officinalis* L. (leaves) were potent at concentrations as low as 6.25 µg/ml. Tekwu et al. (2012), studying 15 Cameroonian plant extracts with variable activity against *M. tuberculosis* strains, determined that *Echinops giganteus* hort. ex DC. exhibited the most significant antimycobacterial activity with a MIC value of 32 µg/ml and 16 µg/ml against strains H37Ra and H37Rv, respectively. *E. giganteus* has known antibacterial activity (Kuete, 2010).

Ibekwe et al. (2014) studied the antimycobacterial activity of many Nigerian plants. Their results show that *Abrus precatorius* L., which contains an isoflavanoid quinone (abruquinone), has a MIC value of 12.5 µg/mL against *M. tuberculosis* strain H37Rv. *Anogeissus leiocarpa* Guill. & Perr., the most commonly used plant among the Nigerian herbalists, contains polyphenols and triterpenoids; it has a MIC value 266 µg/mL against *M. bovis*. Anthraquinone and polyphenolic flavonoids (1-epicatechol and leucopelargonidol) contribute to the antimycobaterial activity of *Cassia sieberiana* DC. *Erythrina senegalensis*

A.Rich. contains isoflavonoids (pasellidin and erythobissin) with MIC values of 8-25 µg/ml against *M. tuberculosis*. *Pterocarpus osun* Craib has glycosides, saponins, steroids and tannins which confer antimycobacterial activity. *Securidaca longepedunculata* Fresen. methanol and hexane extracts yielded hydroxybenzoic acids and xanthones, with MICs of 312 µg/ml and 1250 µg/ml, respectively, against *M. tuberculosis*.

Traditional healers and other local knowledge holders in Mozambique harvest *Zanthoxylum capense* Harv. to treat TB. Laboratory assays demonstrated promising antimycobacterial potential of *Z. capense* extracts on a range of mycobacterial strains. Luo et al. (2013) isolated benzophenanthridine-type alkaloids and neolignans from this plant. Decarine, a benzophenanthridine alkaloid, showed good activity against *M. tuberculosis* H37Rv (MIC of 1.6 µg/ml) and low macrophage cytotoxicity (IC_{50} > 60 µg/ml), indicating considerable selective activity (Luo et al., 2013).

Earlier, Luo et al. (2011) found that n-hexane extracts of *Maerua edulis* (Gilg & Gilg-Ben.) DeWolf and *S. longepedunculata*, an ethyl acetate extract of *Tabernaemontana elegans* Stapf, and a dichloromethane extract of *Z. capense* had considerable activity against *M. bovis* BCG and *M. tuberculosis* H37Ra, MIC values of 15.6–62.5 µg/ml. The ethyl acetate extract of *T. elegans*, though potently cytotoxic, displayed strong activity against *M. tuberculosi*s H37Rv, MIC 15.6 µg/ml.

The twinning of HIV/AIDS to TB requires the use of plants that work against both infections. Maroyi (2015) described plants with both anti-HIV and anti-TB activities. Notably, the dual action plants are: *Crinum macowanii* Baker, and *Tulbaghia violacea* Harv., have proven anti-HIV activity and are used to treat TB in South Africa; *Cascabela thevetia* (L.) Lippold inhibits HIV-1, and treats TB in Uganda; *Warburgia ugandensis* Sprague, a known inhibitor of HIV-1 reverse transcriptase and protease, is also a natural remedy for TB in Uganda and Tanzania; and *Carica papaya* L., which has proven anti-HIV activity, is a remedy for TB in Tanzania.

Other anti-HIV and anti-TB plants are (Maroyi, 2015): *Maytenus senegalensis* (Lam.) Exell which inhibits HIV replication, is harvested for use in TB treatment in Uganda and Tanzania; *Garcinia buchananii* Baker and *Garcinia livingstonei* T.Anderson, both block HIV-1 protease, are also natural remedies for TB in Namibia and Tanzania (Chinsembu and Hedimbi, 2012); *C. molle*, a known inhibitor of HIV-1 reverse transcriptase, is harnessed as an anti-TB herbal in Uganda; *E. tirucalli*, has anti-HIV activity, is a natural remedy for TB in Uganda; *Ricinus communis* L., a plant with known anti-HIV reverse transcriptase action, is a treatment for TB in South Africa and Tanzania.

There are other dual action anti-HIV/TB plants: *Peltophorum africanum* Sond., which inhibits HIV-1 reverse transcriptase is a treatment for TB in South Africa; *Hypoxis hemerocallidea* Fisch., C.A.Mey. & Avé-Lall., blocks HIV-1 reverse transcriptase, is also a remedy for TB in South Africa; *Plectranthus amboinicus* (Lour.) Spreng., blocks HIV-1 reverse transcriptase, is a treatment for TB in Uganda; and *Morella salicifolia* (A.Rich.) Verdc. & Polhill, blocks HIV-1 transcriptase and protease, also alleviates TB in Tanzania.

Psidium guajava L. has known anti-HIV activity, and alleviates TB in Namibia (Chinsembu and Hedimbi, 2010), Uganda and Tanzania. *Flueggea virosa* (Roxb. ex Willd.) Voigt, a known inhibitor of HIV replication, alleviates TB in Uganda. *S. longipedunculata* inhibits

HIV replication, and is an anti-TB plant in Ethiopia. *Zingiber officinale* Roscoe, with known anti-HIV activity, is also an anti-TB remedy in Uganda (Maroyi, 2015).

Caution should be taken as some of the plants used to treat TB are cytotoxic to human cells. Southern African plants applied as natural remedies for TB yet are known to be toxic include *Asclepias fruticose* L., *Gnidia kraussiana* Meisn., *Melianthus comosus* Vahl, and *Tulbaghia violacea* Harv. (Ndhlala et al., 2013). Symptoms of toxicity may include fever, paralysis, respiratory problems, weak heartbeat, irritation of the nose and throat, coughing, sneezing, headache, nausea, salivation, foaming vomit, gastrointestinal disturbance, purging, exhaustion, cardiac arrest, and dizziness.

5. European flora

In Turkey, Askun et al. (2009) determined that *Thymbra spicata* Pall. ex M.Bieb., traded under the Turkish name of Karakekik (black kekik), exhibits a high level of activity against *M. tuberculosis* (MIC = 196 μg/ml). Carvacrol, rosmarinic acid, hesperidin and naringenin are the major phenolic compounds in *T. spicata.* Though carvacrol and rosmarinic acid have antibacterial activity, the latter may be responsible for known antimycobacterial efficacy (Askun et al., 2009).

Fifteen *Hypericum* L. species growing in mainland Portugal, Azores and Madeira were tested for antimycobacterial activity. *Hypericum elodes* L. and *Hypericum hircinum* L. subsp. *majus* (Aiton) N.Robson extracts were the most active against MDR-TB strains with MIC of 25–100 μg/mL (Nogueira et al., 2013). Both *Hypericum* species exhibited significant efficacy against MDR-TB clinical isolates. Hypericin and pseudo-hypericin (both are anthraquinones) and hyperforin were effective against all the drug-resistant *Mycobacterium* strains and some of the clinical isolates with MIC values of 25-50 μg/mL (Nogueira et al., 2013). However, only hyperforin showed activity against the strain *M. tuberculosis* H37Rv, MIC of 25 μg/mL (Nogueira et al., 2013). Nogueira and co-workers have a patent on *Hypericum* chemical substances useful for the treatment of persistent tuberculosis.

In the United Kingdom (UK), *Arctium lappa* L. (burdock) is a biennial herbaceous plant traditionally used for its diuretic, carminative, anti-inflammatory, antiseptic and detoxifying properties. Another biennial herbaceous plant in the UK, *Tussilago farfara* L. (coughwort), is used to treat sore throat and lung ailments such as bronchitis, asthma and chronic cough including TB (Allen and Hatfield, 2004). Zhao et al. (2014) found that the n-hexane extracts of both plants, the ethyl acetate extract of *T. farfara* and the dichloromethane phase derived from the methanol extract of *A. lappa* displayed anti-tubercular activity (MIC = 62.5 μg/ml). Best antimycobacterial actions were exhibited by p-coumaric acid (MIC = 31.3 μg/ml) and 4-hydroxybenzoic acid (MIC = 62.5 μg/ml) isolated from both *A. lappa* and *T. farfara*.

6. Anti-TB natural products in Asia

Indonesia is home to one of the largest tropical rainforests of the world. The country has one of the world's largest floral biodiversity, with 40,000 different plant species of which about 16,500 are endemic. Two of the world's 25 biodiversity hotspots are found in Indonesia's Sundaland and Wallacea regions. Approximately 10% of the plant species are believed to possess some medicinal characteristics, thus are utilized as traditional herbal medicines, popularly known as Jamu (Schumacher, 1999). Alvin et al. (2014) listed the following Indonesian Jamu plants used to treat TB symptoms: *Andrographis paniculata* Nees, *Brucea*

javanica (L.) Merr., *Caesalpinia sappan* L., *Centella asiatica* (L.) Urb., *Hibiscus tiliaceus* L., *Lantana camara* L., *Morinda citrifolia* L., *Nasturtium indicum* DC., *Pluchea indica* Less., *Rhoeo spathacea* (Sw.) Stearn, *R. communis*, and *Vitex trifolia* L.

In Taiwan, work by Chen et al. (2011) revealed that cinnamic acid, a natural occurring phenolic plant compound, decreased the viability of MDR-TB bacilli in a dose-dependent way. Their results showed the anti-tuberculosis activity of cis-cinnamic acid was approximately 120-fold that of trans-cinnamic acid. Against TB, cis-cinnamic acid exhibited higher synergistic effect with isoniazid and rifampicin than trans-cinnamic acid. The plants *Albizia lebbeck* (L.) Benth., *Artemisia absinthium* L., *Ephedra gerardiana* Wall., *Ephedra intermedia* Schrenk & C.A.Mey., *Fragaria indica* Andrews, *Inula obtusifolia* A.Kern., and *Punica granatum* L. are employed in the treatment of TB in the communities of Gallies Abbottabad, northern Pakistan (Kayani et al., 2014).

Ayurveda, the ancient practice of medicine developed in India, considers TB as the king of diseases (*Raja-yakshma in Sanskrit*). Despite this fear and respect for TB, many Indian plants are used to manage the disease. Ethyl p-methoxycinnamate isolated from the essential oil of *Kaempferia galanga* L. rhizomes is an anti-TB compound (Lakshmanan et al., 2011). Ethyl p-methoxycinnamate inhibits both drug susceptible and MDR clinical isolates of *M. tuberculosis* (MIC = 0.242–0.485 mM). The roots of *Vetiveria zizanioides* Stapf, popularly known as Khas Khas, Khas or Khus grass in India, inhibit *M. tuberculosis* H37Rv and H37Ra strains. Ethanolic extract of roots produced potent antimycobacterial activity, MIC = 500 µg/ml (Saikia et al., 2012). The hexane fraction also continuously reduced the growth index of *M. tuberculosis*, MIC = 50 µg/ml (Saikia et al., 2012).

Citrullus colocynthis (L.) Schrad. (family Cucurbitaceae) is an Indian folk herbal remedy for TB. Fractions of *C. colocynthis* inhibited 16 clinical isolates of *M. tuberculosis* including 7 drug-susceptible strains, 8 MDRs and one XDR (Mehta et al., 2013). Mehta and co-workers elucidated that ursolic acid and cucurbitacin E2-0-β-D-glucopyranoside were the main active biomarkers against *M. tuberculosis* H37Rv with MIC values of 50 and 25 µg/ml, respectively. Tawde et al. (2012) established that other Indian plants such as *Acacia catechu* (L.f.) Willd., *Ailanthus excelsa* Roxb., *A. paniculata*, *Aegle marmelos* (L.) Corrêa and *Datura metel* L. had *in vitro* antimycobacterial efficacy.

Sharma et al. (2014) in their report indicate that plants such as *Viscum album* L. (European mistletoe), *Tinospora cordifolia* Miers (Guduchi and Giloy), and *Withania somnifera* (L.) Dunal (Indian ginseng) potentiate immune function during TB infection. Piperine, a trans-trans isomer of 1-piperoyl-piperidine isolated from black pepper, *Piper longum* Blume, shuts down microbial virulence proteins. Sharma et al. (2014) cite studies where piperine inhibits the NorA efflux pump of *Staphylococcus aureus*. Murine splenocytes exposed to piperine exhibited proliferation of T and B cells, increased Th-1 cytokines and enhanced macrophage activation. All these properties of piperine may help diminish TB infection. Piperine is also synergistic to the action of antibiotics. Compared to rifampicin alone, a combination of piperine and rifampicin (1 mg/kg) has better efficacy and leads to marked reductions of mycobacteria in the lungs.

Premna odorata Blanco, also known as Alagaw in Filipino, is a small tree abundant in low-altitude thickets and secondary forests in Albay Province, the Philippines (Lirio et al., 2014). A water decoction of the leaves is used to treat patients with TB. The ethnomedicinal plant *P. odorata* possesses antimycobacterial compounds thus supporting the traditional use of this

plant in the treatment of TB. Purification of a dichloromethane fraction active against *M. tuberculosis* H37Rv strain led to the isolation of 1-heneicosyl formate, whose MIC value against H37Rv was 8 µg/ml (Lirio et al., 2014). Macabeo et al. (2011), while studying the plant *Voacanga globosa* Merr. in the Phillipines, discovered the presence of globospiramine, a new spirobisindole alkaloid with an aspidosperma-aspidosperma skeleton. Globospiramine displayed potent activity against *M. tuberculosis* H37Rv in microplate Alamar blue assay (MIC = 4 µg/ml) and low-oxygen recovery assay (MIC = 5.2 µg/ml).

Using a colorimetric microplate-based assay, 36 Malaysian plant species exhibited antimycobacterial activity with MIC values ranging from 1600–400 µg/ml (Mohamad et al., 2011). Notable activity was recorded for the leaf extract of *Angiopteris evecta* (G.Forst.) Hoffm. which exhibited the highest activity, MIC of 400 µg/ml. Five other extracts, namely, *Costus speciosus* (J.Koenig) Sm. (stem and flower), *Piper sarmentosum* Roxb. (whole plant), *Pluchea indica* (L.) Less. (leaf), *P. indica* (flower), and *Tabernaemontana coronaria* (Jacq.) Willd. (leaf) exhibited antimycobacterial activity, each with MIC of 800µg/ml.

In Thailand, Sureram et al. (2012) showed that *Tiliacora triandra* (Colebr.) Diels, an appetizing plant added as an ingredient in local Thai cuisines, contains three bisbenzylisoquinoline alkaloids: tiliacorinine, 2'-nortiliacorinine, and tiliacorine. Tested against 59 clinical isolates of *M. tuberculosis*, the three natural compounds were all active, MIC = 0.7 to 6.2 µg/ml. The three bisbenzylisoquinoline alkaloids were also active against most MDR-TB isolates, MIC = 3.1 µg/ml. Since tiliacorinine, 2'-nortiliacorinine, and tiliacorine had better activity profiles towards MDR-TB strains than some of the current first-line drugs, these chemical compounds may have the potential to become natural scaffolds for novel anti-MDR-TB drugs.

7. Anti-TB plants in South America

Brazil, with 82,755 TB cases in 2012, is the leading South American hub for anti-TB natural products. The plants *Struthanthus concinnus* Mart. and *Struthanthus marginatus* Blume are sold in open-air markets and used to manage TB infections in Brazil, which records about 72,000 new TB cases and 4,700 TB-related deaths every year (Leitão et al., 2013). Bioassay-guided fractionation of hexane extracts from both species led to the isolation and identification of steroids and terpenoids. In anti-tubercular assays, the MIC of the extracts and isolated compounds ranged from 25 to 200 µg/ml. Fractions and sub-fractions of *Tabernaemontana catharinensis* A.DC., a Brazilian plant with high levels of steroids, alkaloids and phenolic compounds were effective against *M. smegmatis* (MIC = 19.53–156.25 µg/ml).

Moreira et al. (2013) observed that Brazil is also home to plants called the everlasting flowers, also known as *sempre-vivas* in Portuguese, since they maintain their appearance and colour after drying. Many of these plants are exported to Europe, Japan and North America as ornamental flowers, giving the people of Minas Gerais State in Brazil a source of income. Moreira et al. (2013) studied the antimycobacterial activity of two of the *sempre-vivas* plants, namely *Paepalanthus latipes* Silveira and *Paepalanthus bromelioides* Silveira.

Two methoxylated flavonoids, flavonoid 7-methylquercetagetin and 7-methylquercetagetin-4′-*O*-β-D-glucopyranoside, isolated from *P. latipes* and naphthopyranone fractions from *P. bromeliodes* had no noteworthy antimycobacterial activity, MIC value of 500-2000 µg/ml for all compounds tested against *M. tuberculosis* H37Rv and *M. avium* ATCC 15769. However,

the compounds induced innate immunity through the production of high levels of hydrogen peroxide which aids in macrophage killing of mycobacteria (Moreira et al., 2013). It was concluded that despite poor activity *in vitro*, the compounds are quite potent *in vivo* (inside the macrophage).

Brazil is home to five genera and approximately 500 species of Piperaceae whose benzoic acid derivatives frequently exhibit antimicrobial, molluscicidal, antifungal and leishmanicidal activities (Regiane et al., 2015). A new benzoic acid derivative called 4-methoxy-3-[(E)-3-methyl- 1,3-butadien-1-yl]-5-(3-methyl-2-buten-1-yl)-benzoic acid was isolated from *Piper diospyrifolium* Kunth. This new compound has moderate activity against *M. tuberculosis* H37Rv, MIC value of 125 mg/ml (Regiane et al., 2015). *Piper regnellii* var. *pallescens* (C.DC.) Yunck., popularly known as Caapeba or Pariparoba in Brazil, contains the antimycobacterial compound neolignans eupomatenoid-5, MIC 1.9 µg/ml on *M. tuberculosis* H37Rv and a good selectivity index of 20.0 (Scodro et al., 2013). Therefore, neolignans eupomatenoid-5 is a good candidate for the future development of anti-TB drugs.

Celastrus vulcanicola Donn.Sm., in the plant family Celastraceae, is a subtropical woody vine distributed in the Caribbean and South American countries of Peru and El Salvador. One of its chemical constituents is a dihydro-β-agarofuran sesquiterpene called 1α-Acetoxy-6β,9β-dibenzoyloxy-dihydro-β-agarofuran which exhibits activity against H37Rv and MDR strains, MIC = 6.2 µg/ml (Torres-Romero et al., 2011). The antimycobacterial ability of this sesquiterpene is similar to or even better than isoniazid or rifampin, two of the best first-line drugs commonly used in the treatment of TB (Torres-Romero et al., 2011).

In vitro assays demonstrated that (-)-Licarin A isolated from the Mexican plant *Aristolochia taliscana* Hook. & Arn. had antimycobacterial activity against mono- and MDR *M. tuberculosis* (León-Díaz et al., 2013). Besides sesquiterpenes, naphthoquinones display antimycobacterial effects too. The genus *Diospyros* L. is one of the most important sources of 1,4 naphthoquinones which confer potent anti-TB activity (Uc-Cachón et al., 2014). Isolated from *Diospyros anisandra* S.F.Blake growing in Mexico, the three naphthoquinones plumbagin, maritinone, and 3,3'-biplumbagin are some of the most active against *M. tuberculosis* (Uc-Cachón et al., 2014). Against the pan-resistant *M. tuberculosis* strain, the bioactivity of maritinone and 3,3'-biplumbagin was 32 times more potent than the TB drug rifampicin. Both compounds were non-toxic to PBMC and Vero cells. These findings make maritinone and 3,3'-biplumbagin uniquely suitable for the development of a new type of anti-TB drug which can overcome resistance to first- and second-line anti-TB medications.

8. Canadian First Nations' anti-TB plants

Juniperus communis Thunb., or the common juniper, is the eighth most extensively used medicinal plant by the indigenous peoples of North America. Carpenter et al. (2012) explained that the First Nations of the Canadian Maritimes use infusions of juniper primarily as a tonic and for the treatment of TB. Isocupressic acid, communic acid and deoxypodophyllotoxin isolated from aerial parts of juniper were active against *M. tuberculosis*.

In another study, Gordien et al. (2009) attributed the antimycobacterial activity of *J. communis* to a sesquiterpene identified as longifolene and two diterpenes characterized as totarol and trans-communic acid. Totarol showed the best activity against *M. tuberculosis*. Totarol was also most active against the isoniazid-, streptomycin-, and moxifloxacin-resistant

variants of TB. Longifolene and totarol were most active against the rifampicin-resistant strains of TB. Gordien et al. (2009) conclude that the presence of antimycobacterial terpenoids in the *J. communis* plant justifies the ethnomedicinal use of this species as a traditional remedy for TB.

Li et al. (2012) noted that extracts from *Aralia nudicaulis* L. rhizomes taken as tea significantly inhibit mycobacterial activity. Two C17 polyacetylenes called falcarinol and panaxydol were the most important ingredients responsible for the antimycobacterial activity of *A. nudicaulis* rhizomes, thus corroborating the ethnopharmacological applications of this plant by the indigenous people of Canada. Correspondingly, falcarinol and panaxydol demosntrated MIC values of 25.6 μM and 36.0 μM, and IC_{50} values of 15.3 μM and 23.5 μM against *M. tuberculosis* H37Ra, despite having low solubilities.

The First Nations of Canada and Native American communities also use infusions of *Heracleum maximum* W.Bartram (or cow parsnip) roots for the treatment of TB (O'Neill et al., 2013). Polyacetylene (3R,8S)-falcarindiol and the furanocoumarin 6-Isopentenyloxyisobergapten exhibited MICs of 24 μM and 167 μM and IC_{50}s of 6 μM and 27 μM against *M. tuberculosis* H37Ra, respectively. Again, this work lends much credence to the ethnopharmacological application of *H. maximum* as a treatment for TB as the plant is prepared as a tea after soaking the roots in hot water.

9. A closer look at natural products as anti-TB agents

In recent decades, TB has re-emerged as a major disease of global significance mainly due to HIV/AIDS. However, it is the increasing caseloads of drug resistant TB that brings into sharp focus the urgent need for novel and new anti-TB drugs to counter the growing plague. Disappointingly, research and development of new anti-TB drugs has not kept pace with the growing global incidence and prevalence of TB. There have been no new anti-TB drugs over the past 40 years. Therefore, the global community should take a wider view and urgent approach toward new treatments for TB. Such a strategy should include a call to operationalize the use of anti-TB natural products as some of them are active against drug resistant strains of *M. tuberculosis*.

Again, with respect to TB, the study of medicinal plants is aimed at ushering in a new generation of innovative anti-TB drugs. This is important for several reasons. Globally, TB cases and mortality are increasing. TB pathogenesis has become complicated because the disease is twinned to HIV infection. There are also challenges surrounding case management under the Directly Observed Treatment Short-course programmes (DOTS) because the six months duration of treatment is too long (De Cock and Chaisson, 1999). DOTS, though helpful in securing treatment for many patients, is still fraught with problems such as poor administration, lack of laboratory facilities for diagnosis, lack of surveillance and monitoring systems, and inadequate drug supplies. TB/HIV dual epidemics are stubborn to DOTS treatment, and the probability of mortality for co-infected persons is high. Some drugs are becoming ineffective partly because of the proliferation of drug resistant strains of *M. tuberculosis*.

Poverty, deplorable living conditions, inadequate nutrition, lack of funding for TB prevention programmes, and poor organization of public treatment programmes negatively impact on TB cure rates. Adherence to treatment is also hampered by the lack of strict supervision by health staff, shortages of drugs, drug toxicity and side effects, and strong beliefs in the use of

traditional medicines or self-medication through natural products. Innovations in post-genomics and systems biology (Chandra et al., 2011) have not yet yielded the new and innovative treatments against TB. In addition, capitalist greed, not the lack of breakthrough scientific ideas, is in reality the far more fundamental obstacle to the development of new and novel drugs against TB.

Understandably, research and development of innovative medicines is very expensive and financially less appealing. In addition, US$ 2 billion per year is needed to fill the resource gap for implementing existing TB interventions. In 2003, the estimated average cost of bringing a new drug to the market was US$ 802 million (DiMasi et al., 2003). However, big pharmaceutical companies fear to invest millions of dollars in the development of new anti-TB drugs because TB is mostly a disease for poor countries. TB drugs, like those for malaria, are classified as 'less profitable drugs'. Pharmaceutical companies are therefore wary they may not reap enough profits to account for their huge investments. In the wake of all these shortcomings, natural products especially medicinal plants still present a unique ray of hope to rejig the situation, especially to lower the cost of research and development. Indeed, pharmacognosy and ethnobotanical studies may unravel plant leads from which novel anti-TB chemical ingredients may be isolated. Novel drugs for TB may also be developed from secondary chemical secretions of endophytic fungi that live symbiotically with plants. Corollary, other earlier scholarly efforts described natural products with the potential to manage TB: Salomon and Schmidt, 2012; York et al., 2011; Varma et al., 2011; Buwa and Afolayan, 2009; Copp and Pearce, 2007; Pauli et al., 2005; and Newton et al., 2000.

In the African countries described in this review, at least 60 listed plant species are known to display anti-TB activity. In South Africa, where more rigorous bioprospecting and antimicrobial studies have been done, at least 20 plants have been shown to inhibit *M. tuberculosis*. Further studies are required to isolate and characterize the main antimycobacterial active compounds from these plants. Already, the following antimycobacterial chemical compounds have been isolated from selected African plants: ellagitannin punicalagin, allicin, anthraquinone glycosides, iridoids, phenylpropanoids, beta-sitosterol, galanthimine, lycorine, crinine, friedelin, epi-friedelin, gallic acid, ellagic acids, anthocyanidin, taraxerol, taraxerone, caffeic acid, termilignan B, arjunic acid, glucopyranosides, terminalin A, 1-epicatechol, leucopelargonidol, hydroxybenzoic acids, xanthones, benzophenanthridine alkaloids, neolignans, and decarine.

Characterization of active compounds from almost half of the plants that are used to manage TB in African countries has not yet been done. More resources and research efforts should be directed not only at bioprospecting but also at antimycobacterial testing and characterization of active chemical compounds from African flora. Given the high burden of TB in African countries, governments and private initiatives should invest more in the search and development of new anti-TB drugs, especially those that are effective against resistant strains. The main African hope for the development of a new anti-TB drug may lie in South Africa, the only African country with a coordinated research effort in bioprospecting, antimicrobial testing, and isolation of active chemical ingredients through various state-of-the-art techniques like high-performance liquid chromatography, thin-layer chromatography and mass spectroscopy.

European plants from three countries (Turkey, Portugal, and United Kingdom) have been evaluated for antimycobacterial action. *T. spicata*, *Hyperricum* species, *A. lappa*, and *T. farfara* inhibit mycobacteria *in vitro*. Several active ingredients: carvacrol, rosmarinic acid, hesperidin, naringenin, hypericin, hyperforin, p-coumaric acid and 4-hydroxybenzoic acid

were potent against mycobacteria. In Asia, some of the countries that have conducted research on natural products for TB include Indonesia, Taiwan, India, Pakistan, the Philippines, Malaysia and Thailand. At least 30 plant species are used to manage TB in these seven countries. Anti-TB active compounds include cinnamic acid, ethyl p-methoxycinnamate, piperine, 1-Heneicosyl formate, globospiramine, ursolic acid, cucurbitacin, and bisbenzylisoquinoline alkaloids. Although TB is very widespread in Asia, research on anti-TB natural products has not matched the high prevalence levels of the disease. Lamentably, very few active chemical compounds have been characterized, not least from the huge reserves of putative medicinal plants that lie in the forests of Indonesia.

In this review, about 13 plants in the South and North American countries of Brazil, Peru, El Salvador, Mexico and Canada are applied as remedies for TB. Some of the active chemical compounds from these plants include benzoic acid derivatives, neolignans eupomatenoid-5, sesquiterpenes, licarin A, and naphthoquinones. Anti-TB plants used by the indigenous people of Canada have yielded interesting antimycobacterial chemical agents, namely, isocupressic acid, communic acid, deoxypodophyllotoxin, longifolene, totarol, falcarinol, panaxydol, and furanocoumarin.

10. Conclusion and way ahead

This review provides an incisive indication of plant species and other natural products that contain chemical substances that stymie TB. Antimycobacterial activities of putative anti-TB plants and other natural products used in different parts of the world, and some of the active chemical ingredients of these natural products have been presented. However, while many of these natural products possess anti-TB properties, their extracts and active compounds should be evaluated for human cytotoxicity and in addition, they should be tested in rigorous animal and human trials.

By converting natural products into new and more potent drugs for TB, and getting these novel drugs to the patients at the right time, it may be possible to end the global TB epidemic. If the WHO strategy to end the global TB epidemic (with targets to reduce TB deaths by 95% and to cut new cases by 90% between 2015 and 2035) is to be achieved, there is need to incorporate the use of anti-TB natural products; they are cheaper and represent low-hanging fruits in the global fight against TB. Use of anti-TB natural products will ensure that poor families are not burdened with catastrophic expenses due to TB. Biomedical scientists ought to understand that the pathway to a robust fight against global TB should start in nature’s neglected pharmacies of putative antimycobacterial agents.

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Tables

Table 1: Plants for managing tuberculosis in Uganda

Scientific name of plant	Plant family	Local name of plant	Plant parts used
Combretum molle	Combretaceae	Ndagi	Stem bark
Phaseolus vulgaris	Fabaceae	Bijanjaro	Husks
Mangifera indica†	Anacardiaceae	Muyembe	Stem bark
Rubia cordifolia	Rubiaceae	Kasalabakesi	Leaves, whole plant
Dracaena steudneri	Asparagaceae	Kajjolyenjovu	Stem bark
Canarium schweinfurthii	Burseraceae	Muwafu	Stem bark, seeds
Callistemon citrinus	Myrtaceae	Mwambala butonya	Stem bark, leaves
Erythrina abyssinica	Fabaceae	Eggirikiti	Stem bark
Hibiscus fuscus	Malvaceae	Lusaala	Leaves
Garcinia buchananii	Clusiaceae	Musaali	Stem bark
Blighia unijugata	Sapindaceae	Enkuza nyana	Stem bark
Vernonia amygdalina	Asteraceae	Mululuza	Leaves
Moringa oleifera†	Moraceae	Moringa	Fruits, seeds
Maytenus senegalensis†	Celastraceae	Naligwalimu, Muwaiswa	Leaves, fruits
Aloe vera	Xanthorrhoeaceae	Kigaji	Leaves
Allium sativum	Amaryllidaceae	Katungulu chumu	Fruits
Eucalyptus spp. †	Myrtaceae	Kalitunsi, Ekalitus	Stem bark
Warburgia salutaris	Canellaceae	Mwiha, Abaki	Stem bark
Ocimum suave	Lamiaceae	Muhumuzanganda	Leaves
Zanthoxylum chalybeum†	Rutaceae	Ntale ya dungu, Eusugu	Roots
Momordica foetida	Cucurbitaceae	Luiwula/Mwishwa	Leaves
Persea americana	Lauraceae	Ovacado	Leaves
Azadirachta indica†	Meliaceae	Neem	Seeds
Allium sativum†	Alliaceae	Garlic	Leaves
Bidens pilosa†	Asteraceae	Nyabarashana	Flowers
Acacia hockii	Mimosaceae	Kashiono	Stem bark
Carica papaya†	Caricaceae	Amapapali	Leaves
Helichrysum odoratissimum†	Asteraceae	Lweza	leaves
Achyranthes aspera†	Amaranthaceae	Muhurura	Flowers

Adapted from Bunalema et al. (2014) and Tabuti et al. (2010); †denotes plants that have proven activity against *Mycobacteria tuberculosis* and other Mycobacteria species.

Table 2: Antimycobacterial activity of selected South African plants

Scientific name of plant	Bioactive compounds	Antimycobacterial activity
Arctotis auriculata	Tannins, flavonoids, alkaloids, and cyanogenic glucosides	Petroleum ether leaf extract, MIC of 8.5 mg/ml against *M. smegmatis*
Artemisia afra	Volatile oil, terpenoids, coumarins and acetylenes	Ethanol leaf extract, MIC = 1.56 mg/ml against *M. smegmatis*
Helichrysum spp.	Flavonoids, sesquiterpenoids, acylated phloroglucinols, tannins, saponins, cyanogenic glucosides, caespitate from *Helichrysum caespititium*	*Helichrysum melanacme* acetone extract, MIC = 0.1 mg/ml and water extract, MIC = 1 mg/ml against *M. tuberculosis*; *Helichrysum odoratissimum* acetone extract, MIC = 0.5 mg/ml; *Helichrysum caespitatum* acetone extract, MIC = 0.1 mg/ml; caespitate, MIC = 0.1 mg/ml against *M. tuberculosis*
Warburgia salutaris	Drimane sesquiterpenoids including warburganal and polygodial	Dichloromethane bark extract, sesquiterpene mixture and 11α-hydroxycinnamosmolide were active against *M. tuberculosis* and *M. bovis* BCG
Combretum imberbe	Pentacyclic triterpenes, triterpene acids and related glycosides	Pentacyclic triterpenes, MIC = 1.56–25 µg/ml against *Mycobacterium fortuitum*
Terminalia sericea	Roots contain termilignan B and arjunic acid	Bark and root ethanol, ethyl acetate and dichloromethane extracts active, MIC = 1.56–3.12 mg/ml against *M. aurum*; Termilignan B and arjunic acid not active against *M. aurum*
Acacia nilotica	Hydroxyproline, serine, dimethyl-triptamine, β-amyrin, and betulin	Leaf, bark and root ethanol and ethyl acetate extracts active, MIC = 0.195–1.56 mg/ml against *M. aurum*
Acacia sieberiana	Hydroxyproline, serine, dimethyl-triptamine, β-amyrin, and betulin	Leaf, bark and root ethanol, ethyl acetate and dichloromethane extracts active, MIC = 0.78–6.25 mg/ml against *M. aurum*
Faidherbia albida	Tannins	Leaf and bark ethanol and ethyl acetate extracts active, MIC = 3.12–12.5 mg/ml against *M. aurum*
Pelargonium reniforme *Pelargonium sidoides*	Tannins, phenolic compounds, umckalin and related coumarins in *P. reniforme* tubers; essential oils, flavonoids and phytosterols, fatty acids	Unsaturated fatty acids active against *M. aurum, M. smegmatis, Mycobacterium fortuitum, Mycobacterium abscessus, and Mycobacterium phlei*
Orthosiphon labiatus	Labdane diterpenoids	Labdane diterpenoid, MIC = 157 µM against *Mycobacterium tuberculosis*
Salvia radula *Salvia verbenaca* *Salvia dolomitica*	Carnosol, rosmadial, carnosic acid, 7-O-methylepirosmanol, oleanolic acid and ursolic acid	Extracts of *Salvia radula, Salvia verbenaca* and *Salvia dolomitica*, MIC = 0.1 mg/ml against *M. tuberculosis*
Syzygium gerrardii	Tannins	Ethanol extract of leaves, MIC = 6.25 mg/ml against *M. smegmatis*; not active against *M. tuberculosis*
Polysiphonia virgata	Fatty acids	Fatty acid mixture active against *M. smegmatis* and *M. tuberculosis*
Prunus africana	β-sitosterol and terpenoids	Leaf and bark ethyl acetate and dichloromethane extracts active, MIC = 0.78–6.25 mg/ml against *M. aurum*; ethanol extract of leaves not active against *M. smegmatis* and *M. tuberculosis*
Coleonema album	Phenolic acids, flavonoids, coumarins, prenylated coumarins and terpenoids	Acetone and ethanol leaf extracts active, MIC = 3.1 mg/ml on *M. aurum*
Salix mucronata	-	Leaf, bark and root ethanol, ethyl acetate and dichloromethane extracts active, MIC = 1.56–.25 mg/ml on *M. aurum*

Dodonaea angustifolia	Dodonic acid, hautriwaic acid and structurally similar diterpenoids, β-sitosterol and stigmasterol, and several flavonoids including santin	Ethanol extract of leaves, MIC = 3.13 mg/ml against *M. smegmatis*, MIC = 5 mg/ml against *M. tuberculosis*; aqueous decoctions and infusions of leaves and stems and ethyl acetate extract, MIC = 5 mg/ml on *M. smegmatis*; ethanol and methanol extracts, MIC = 1.25 mg/ml against *M. smegmatis*

Adapted from McGaw et al. (2008).