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The potential of South African plants against *Mycobacterium* infections

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ABSTRACT

Ethnopharmacological relevance: In South Africa, tuberculosis (TB) caused by *Mycobacterium tuberculosis* is the most commonly notified disease and the fifth largest cause of mortality, with one in ten cases of TB resistant to treatment in some areas. Many plants are used locally in traditional medicine to treat TB-related symptoms.
Aim of the study: The aim was to summarize currently available knowledge on South African plants used to treat TB symptoms, and antimycobacterial efficacy of plant-derived extracts and compounds.
Materials and methods: The traditional uses of plants for respiratory ailments and TB were collated and tabulated. The antimycobacterial activity tests of extracts and chemical constituents of several of these plants and others using different methods and target organisms were summarized.
Results: Almost 180 plants used for TB-related symptoms in South African traditional medicine were documented. About 30% of these have been tested for antimycobacterial efficacy, mostly against fast-growing, non-pathogenic *Mycobacterium* species.
Conclusions: Many plant species are used in traditional South African medicine to alleviate symptoms of TB, and several interesting leads have originated for further inquiry following *in vitro* antimycobacterial activity evaluation. However, much work remains to be done on the systematic assessment of anti-TB efficacy of local plants against pathogenic *Mycobacterium* species, both *in vitro* and *in vivo*.

1. Introduction

Together with the spread of HIV infection, tuberculosis caused by *Mycobacterium tuberculosis*, as well as other opportunistic *Mycobacterium* infections, is becoming rampant, especially in countries lacking adequate health care systems to provide the required expensive and lengthy treatment (World Health Organisation, 2008; Zager and McNerney, 2008). The emergence of resistant and multiple drug resistant (MDR) strains is a further crisis, fuelled by the discovery of extremely drug resistant (XDR) *Mycobacterium tuberculosis* strains (Jones et al., 2008).

Although the number of tuberculosis (TB)-related deaths appears to have stabilized at around 2 million per annum, the incidence of new infections is rising, largely owing to the HIV epidemic (Gutierrez-Lugo and Bewley, 2008). There are many challenges to eradicating TB, not least of which are the complexities associated with the disease, such as latency and drug resistance (Gutierrez-Lugo and Bewley, 2008). New targets for novel anti-TB drugs need to be identified, especially in the light of the emergence of MDR- and XDR-TB. However, following recent advances in technology, noteworthy progress has been made in the field of TB genomics, proteomics and target identification (Gutierrez-Lugo and Bewley, 2008).

Natural products continue to play a most significant role in the drug discovery and development process (Newman and Cragg, 2007), and plants are recognized as a useful source of highly active antimycobacterial metabolites (Gibbons, 2005; Pauli et al., 2005). South Africa is host to a large percentage of the global floral diversity, and prides itself on longstanding cultural traditions of medicinal plant use. Several works have been published recording the ethnobotanical use of plants in South Africa (for example, Watt and Breyer-Brandwijk, 1962; Hutchings et al., 1996; Van Wyk et al., 1997), and although full documentation of various cultural systems and practices is far from complete, encouraging progress is being made in this area of research. Many South African plants have ethnobotanical uses for the treatment of tuberculosis and related symptoms such as coughing, respiratory ailments and fever. Extracts prepared from some of these plants as well as others selected on a random basis have been screened by South African

Abbreviations: AIDS, acquired immune deficiency syndrome; HIV, human immunodeficiency virus; MBC, minimum bactericidal concentration; MDR, multi-drug resistant; MIC, minimum inhibitory concentration; MOTT, mycobacteria other than tubercle bacilli; PPEM, potentially pathogenic environmental mycobacteria; TB, tuberculosis; XDR, extremely drug resistant; WHO, World Health Organisation.

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researchers for activity against several *Mycobacterium* species using various methods, and these will be described in more detail in this paper. Programmes for *in vitro* screening of plant remedies are important for validating the traditional use of herbal treatments, and for providing leads in the discovery of new active principles. Such screening programmes should be supported by toxicity testing, as well as selectivity and stability studies (Fennell et al., 2004). This research provides value not only in terms of identifying leads for possible future development as anti-TB drugs, but also in promoting the value of the South African floral diversity.

2. Impact of tuberculosis worldwide and in South Africa

Tuberculosis, a chronic contagious disease caused by infection with *Mycobacterium* species, has become an increasingly serious worldwide health concern in recent years. The disease remains one of the most important notifiable infectious human diseases in the developing world. About 2 billion people, or one-third of the world's population, are infected with the causal organisms of TB, although most never develop the active TB disease. Globally, there were an estimated 9.2 million new cases and 1.7 million deaths in 2006 (World Health Organisation, 2008).

TB is largely a disease of poverty, with the highest incidence of the disease (more than 80% of cases) occurring in Asia and Africa (Zager and McNerney, 2008). In sub-Saharan Africa, 9 countries recently reported estimated annual incidences over 600 cases per 100 000 (Corbett et al., 2006), and the persistent increase of TB in this region may largely be attributed to the AIDS (acquired immune deficiency syndrome) pandemic combined with inadequate healthcare systems (Zager and McNerney, 2008). Of the estimated 1.7 million people who died of TB in 2006, 14% were co-infected with HIV (World Health Organisation, 2008).

Considerable progress in fighting the disease in many countries has been made by the STOP–TB Partnership and the WHO (Zager and McNerney, 2008). However, the emergence of *Mycobacterium tuberculosis* strains resistant to current standard anti-TB drugs is a major threat to control programmes. Drug resistance arises following inadequate chemotherapy which selects for mutated strains with increased survival capabilities. Multi-drug resistant tuberculosis (MDR-TB) has been defined in terms of resistance to at least the two major anti-TB drugs, rifampicin and isoniazid, and requires long and expensive chemotherapy using second-line drugs of higher toxicity (Zager and McNerney, 2008). Extensively drug resistant tuberculosis (XDR-TB) has been reported in all regions of the world and involves resistance to at least rifampicin, isoniazid, a second-line injectable drug (capreomycin, kanamycin or amikamycin) and a fluoroquinolone (CDC, 2006). The recent outbreak of XDR-TB in Tugela Ferry, a rural town in the South African province of KwaZulu-Natal (KZN), recorded an unprecedented fatality rate, with a median survival from the time of sputum collection of 16 days for 52 of the 53 infected individuals (Singh et al., 2007).

Insufficient case management of MDR-TB, which allows partially treated and relapsed patients to become sequentially resistant, may play a significant role in the development of XDR-TB (Jones et al., 2008). Effective treatment of XDR-TB is challenging for various reasons, including an extended period of treatment of up to 2 years, lack of accessibility and elevated expense of the drugs, low adherence owing to toxicity of second-line drugs, and the difficulty of co-administration of the medication with antiretroviral therapy in HIV positive patients (Jones et al., 2008). There are also concerns that the prevalence of drug resistant TB as a whole is much higher than reported owing to deficiencies in sophisticated monitoring methods required to detect the presence of resistance.

It is all too likely that the emergence of even more resistant *Mycobacterium* strains will be experienced in the future, exhausting the current arsenal of chemical defenses at our disposal. As a result, new classes of anti-TB agents are urgently needed, and research programmes into alternative therapeutics should be encouraged. Although chemicals that stimulate the immune system for example should not be discounted, it has been suggested that the best available *in vitro* indicator of possible therapeutic activity is the early bactericidal activity of a drug or combination of drugs (Donald et al., 2003).

3. *Mycobacterium tuberculosis*, *Mycobacterium bovis* and other infective species

The genus *Mycobacterium* (order Actinomycetales, family Mycobacteriaceae) consists of about 50 acid-fast, aerobic, non-motile and non-spore-forming bacterial species. Most of these species are environmental saprophytes, existing in various substrates including soil, water, plants, and on mammals and birds. The genus is divided into the fast-growing species (which are usually saprophytic) and the slow-growers (generally pathogenic). The fast-growing species are usually not pathogenic but some species may cause opportunistic infections in animals and humans (Grange and Yates, 1986), for example, *Mycobacterium fortuitum* can be responsible for pyogranulomas in the skin of man and other mammals.

With regard to the pathogenic species, these are obligate parasites and include those members of the genus that make up the *Mycobacterium tuberculosis* complex, namely *Mycobacterium tuberculosis*, *Mycobacterium bovis*, *Mycobacterium africanum*, *Mycobacterium microti* and *Mycobacterium canetti*. These "tubercle bacilli" cause tuberculosis in humans and animals. *Mycobacterium tuberculosis*, *Mycobacterium africanum* and *Mycobacterium canetti* are human pathogens while *Mycobacterium microti* causes disease in rodents. *Mycobacterium bovis* has a wide host range and mainly affects cattle, but may also colonize other species (including humans) if there is contact with infected cattle or their products. *Mycobacterium leprae* causes leprosy in man, and *Mycobacterium lepraemurium* infections in rats and cats result in leprosy, a rare disease in these animals.

The non-tuberculous group of mycobacteria is also referred to as "mycobacteria other than tubercle bacilli" (MOTT), "potentially pathogenic environmental mycobacteria" (PPEM) or atypical mycobacteria (Wayne and Sramek, 1992). Mycobacterioses caused by these species may be encountered following surgery and also as opportunistic infections in immunocompetent and immunosuppressed patients (Daely and Griggith, 2002; Thami et al., 2002). Of concern is the natural resistance of these saprophytic mycobacteria to current antimycobacterial drugs (Wayne and Sramek, 1992; Gillespie et al., 2001). Mycobacteria of the *Mycobacterium avium* complex (comprised of *Mycobacterium avium*, *Mycobacterium intracellulare*, *Mycobacterium paratuberculosis*, *Mycobacterium lepraemurium* and *Mycobacterium avium* subsp. *silvaticum* subsp. nov.) (Thorel et al., 1990) are the most widespread of the mycobacteria in the environment. While some species are saprophytes, others are pathogenic on birds and mammals, and they are a significant source of opportunistic infection in humans with AIDS (Grange et al., 1990).

Mycobacterium bovis, the cause of bovine TB, is an important zoonosis that can spread to humans through ingestion of raw milk or inhalation of infectious droplet nuclei, and reservoirs in wildlife make the disease difficult to eradicate (Thoen et al., 2006). People exposed to livestock carrying bovine TB or infected products, for example, unpasteurised milk or poorly heat-treated meat, may

be at risk of infection (Ayele et al., 2004; Michel et al., 2006). As mentioned earlier with regard to opportunistic infections, this risk increases considerably in HIV-infected individuals (Raviglione et al., 1995). There is cause for concern surrounding the occurrence of *Mycobacterium bovis* disease by reactivation or primary infection in HIV-infected patients, and transmission of the disease from patients with infectious pulmonary *Mycobacterium bovis* to immune-competent individuals (Thoen et al., 2006). Zoonotic incidences of *Mycobacterium bovis* have not been thoroughly investigated, and may be a serious problem in sub-Saharan Africa where a high burden of TB in animals is a major obstacle to *Mycobacterium bovis* control. Insufficient monitoring of the TB status of rural cattle herds results in zoonotic *Mycobacterium bovis* infections posing a significant risk to human health in South Africa. Additionally, many laboratories do not employ the specialized diagnostic methods necessary to distinguish between *Mycobacterium bovis* and *Mycobacterium tuberculosis*, genetically very similar species (Drobniewski et al., 2003; Ayele et al., 2004). The standard test for TB, microscopic examination of sputum smears, does not differentiate between *Mycobacterium bovis* and *Mycobacterium tuberculosis*. Therefore, the actual incidence of *Mycobacterium bovis* in humans is unknown but current speculation suggests that it is a largely underestimated problem. Alarmingly, it is estimated that up to 10% of human TB cases worldwide are likely to be caused by *Mycobacterium bovis* (Cosivi et al., 1998).

4. The investigation of plants as sources of new anti-TB agents

Natural products from plants are proven templates for new drug development (Cragg et al., 1997), and have shown many interesting biological activities. A wide structural diversity of antimycobacterial compounds has been discovered from plants and other organisms including fungi and marine organisms. Several recent reviews have highlighted the underutilized potential of plant species and natural products as sources of antimycobacterial extracts and chemicals (Cantrell et al., 2001; Newton et al., 2002; Okunade et al., 2004; Gibbons, 2005; Pauli et al., 2005). Plant-derived antimycobacterial compounds belong to an exceptionally wide diversity of classes, among them alkaloids, terpenoids, coumarins, peptides and phenolics.

Various assay systems and mycobacterial test organisms have been used to screen plant extracts and constituents of active plants for antimycobacterial activity. Logically, the most favourable test organism for antimycobacterial investigations is *Mycobacterium tuberculosis*, but the practicalities of working with a pathogenic organism make this option difficult in many laboratories. The virulent strain *Mycobacterium tuberculosis* H_{37}Rv is commonly used where possible as it has a drug susceptibility profile fairly representative of most drug susceptible clinical isolates, and is available from the American Type Culture Collection (ATCC 27294). Alternatives to this microorganism include the slow-growing avirulent strain known as *Mycobacterium tuberculosis* H_{37}Ra, and the commonly used vaccine strain, *Mycobacterium bovis* BCG, which are more closely related in terms of genetic composition and drug susceptibility profiles to *Mycobacterium tuberculosis* H_{37}Rv than the fast-growing mycobacteria (Pauli et al., 2005). Many researchers prefer to work with the rapidly growing, avirulent, saprophytic surrogate *Mycobacterium* species. These include *Mycobacterium smegmatis* and *Mycobacterium fortuitum* (Gillespie et al., 2001; Gibbons, 2005), and *Mycobacterium aurum* is also a popular choice (Chung et al., 1995; Eldeen and Van Staden, 2007). Chung et al. (1995) held that their broth microdilution assay using *Mycobacterium aurum* represents a system highly predictive of activity against *Mycobacterium tuberculosis* because of the comparable drug sensitivity profiles of the two organisms. In such cases, the strain of mycobacterium used may have a significant impact on susceptibility to current drugs, so caution should be used in selecting the organism with which to work.

Reports have been published on antimycobacterial activity of plant-derived substances utilizing a number of bioassay systems. These range from agar diffusion and dilution assays to radiorespirometry (using a BACTEC 460 instrument), and from broth macro- and micro-dilution assays to reporter gene assays. Anti-TB activity in macrophages is also a useful assay as *Mycobacterium tuberculosis* grows in both intra- and extracellular environments. Naturally, *in vivo* bioassays using animal models are the ultimate test of antimycobacterial efficacy at a tolerable dose. These screening systems and others have been well discussed in recent review papers (Copp, 2003; Pauli et al., 2005; Gautam et al., 2007). Mechanism-specific bioassays such as inhibition of mycobacterial cell wall synthesis and mycolic acid biosynthesis, and inhibition of certain enzymes are useful in confirming selective antimycobacterial efficacy. The mechanisms of action of current anti-TB drugs have been concisely yet comprehensively reviewed by Janin (2007).

5. Ethnobotanical use of plants against respiratory diseases in South Africa

Medicinal plants are used in many parts of southern Africa to treat TB-related symptoms including chest complaints, respiratory ailments, fever and coughing. Extremely useful reviews of traditional medicinal use of plants in the region are available (for example, Watt and Breyer-Brandwijk, 1962; Bryant, 1966; Hutchings et al., 1996; Van Wyk et al., 1997) although much work remains to be done regarding the documentation of existing ethnobotanical knowledge. South Africa is blessed with possibly the richest temperate flora in the world, possessing an estimated 24 000 species and intraspecific taxa in 368 families—more than 10% of the world's vascular plant flora (Germishuizen and Meyer, 2003). There is consequently much potential for discovery of structurally interesting metabolites with activity against *Mycobacterium* species from these plants. South Africa also enjoys a strong cultural reliance on the use of plants in traditional medicines for healing a range of ailments.

In a review of Indian medicinal plants as a source of antimycobacterial agents, Gautam et al. (2007) reported that, interestingly, many of the plant species surveyed showed a strong positive correlation between antimycobacterial activity results and ethnomedical use for TB and TB-related diseases. This provides support for investigating plants customarily used in other cultures to treat symptoms relating to TB.

A summary of the plants used to treat chest complaints, coughing and tuberculosis in South Africa (and surrounding regions) is presented in Table 1. A large number of plants are used to treat fever in traditional medicine, and all of these plants have not been included, as fever is taken to be a non-specific indication of many infections not restricted to TB. The exception to this is where fever is treated in conjunction with other TB-related symptoms such as coughing. Skin diseases have not been included in the literature review although *Mycobacterium* species such as *Mycobacterium leprae* may be implicated as causal organisms, as numerous plants are used to treat such disorders. In Table 1, MIC values of plant extracts and pure compounds against *Mycobacterium* species are included where these are available. A comprehensive survey of the chemistry of plant species has not been performed as the focus of the paper is to review uses of South African plants against TB and

Table 1
Plants used in South Africa for treating possible TB-related diseases (respiratory or chest complaints and coughing)

Family	Species	Use	Plant part used	Potentially bioactive compounds	Screened for antimycobacterial activity
Acanthaceae	*Justicia flava* (Vahl) Vahl [syn. *Adhatoda flava* (Forssk.) Nees]	Coughs (Hutchings et al., 1996)	Leaves, roots	Lignans, hydrocarbons, β-sitosterol, stigmasterol, campesterol, β-sitosterol-β-D-glucoside, salicylic acid, podophyllotoxin-type justicinol, helioxanthin, (+)-isolariciresinol, docosanoic acid (Hutchings et al., 1996)	–
Adiantaceae	*Adiantum capillus-veneris* L.	Cough suppressant, respiratory problems (Hutchings et al., 1996)	Whole plant, leaves	Gallic, tannic and quinic acids, terpenoids, glycosides (Hutchings et al., 1996)	–
Agavaceae	*Agave* L. sp.	Chest pains, coughing (Pujol, 1990)	Shoots and roots	Steroidal saponins (Hutchings et al., 1996)	–
Aizoaceae	*Carpobrotus* L. spp.	TB, infections (Watt and Breyer-Brandwijk, 1962; Springfield et al., 2003; Springfield and Weitz, 2006)	Leaf juice	Tannins, malic acid and citric acid (Watt and Breyer-Brandwijk, 1962). Flavonoids, hydrolyzable tannins, phytosterols, aromatic acids in *Carpobrotus mellei* (Springfield and Weitz, 2006)	Ethyl acetate extracts of *Carpobrotus mellei* leaves MIC = 15 mg/ml, water extract MIC = 30 mg/ml (*Mycobacterium smegmatis*) (Springfield and Weitz, 2006). *Carpobrotus muirii* and *Carpobrotus quadrifidis* active (*Mycobacterium smegmatis*) in disc diffusion and bioautography (Springfield et al., 2003)
Aizoaceae	*Galenia africana* L.	Chest pains, TB (Mativandlela et al., 2008)	Leaves	5,7,2′-Trihydroxyflavone (Mativandlela et al., 2008)	Ethanol extract of leaves MIC = 0.78 mg/ml (*Mycobacterium smegmatis*), MIC = 1.2 mg/ml (*Mycobacterium tuberculosis*); 5,7,2′-trihydroxyflavone MIC = 0.031 and 0.10 mg/ml (*Mycobacterium smegmatis* and *Mycobacterium tuberculosis*, respectively) (Mativandlela et al., 2008)
Alliaceae	*Agapanthus africanus* (L.) Hoffmg.	Chest troubles, coughs (Watt and Breyer-Brandwijk, 1962)	Roots	Sitosterol, yuccagenin, agapanthagenin, steroid spirostan sapogenins (Hutchings et al., 1996)	–
Alliaceae	*Tulbaghia alliacea* L.	TB symptoms (Bamuamba et al., 2008)	Rhizomes	–	Aqueous extract and acetone:water (4:1) extract inactive in bioautography (*Mycobacterium aurum*) (Bamuamba et al., 2008)
Alliaceae	*Tulbaghia violacea* Harv.	TB (Watt and Breyer-Brandwijk, 1962)	Bulbs and leaves	Sulfur compounds (Van Wyk et al., 1997)	–
Amaryllidaceae	*Boophane disticha* (L.F.) Herb.	Chest pains (Hutchings et al., 1996)	Bulb	Several alkaloids (Watt and Breyer-Brandwijk, 1962; Hutchings et al., 1996)	–
Amaryllidaceae	*Brunsvigia grandiflora* Lindl.	Coughs (Watt and Breyer-Brandwijk, 1962)	Bulb	An alkaloid (Watt and Breyer-Brandwijk, 1962)	–
Amaryllidaceae	*Haemanthus albiflos* Jacq.	Chronic coughs (Hutchings et al., 1996)	Bulb	The alkaloids lycorine and tazettine (Watt and Breyer-Brandwijk, 1962)	–
Amaryllidaceae	*Scadoxus puniceus* (L.) Friis & Nordal	Coughs (Watt and Breyer-Brandwijk, 1962; Hutchings et al., 1996)	Bulbs and roots	Isoquinoline alkaloids, such as lycorine, haemanthamine and haemanthidine (Dictionary of Natural Products, 1996)	–
Anacardiaceae	*Ozoroa paniculosa* (Sond.) R. & A. Fernandes	Acute inflammatory conditions of the chest (Watt and Breyer-Brandwijk, 1962)	Bark	Volatile oil (Watt and Breyer-Brandwijk, 1962)	–
Apiaceae	*Alepidea amatymbica* Eckl. & Zeyh.	Chest complaints, colds (Watt and Breyer-Brandwijk, 1962; Pujol, 1990; De Castro and Van Wyk, 1994; Hutchings and Van Staden, 1994)	Rhizomes and roots	Kaurene-type diterpenoids (Rustaiyan and Sadjada, 1987; Holzapfel et al., 1995)	–
Apiaceae	*Alepidea longifolia* E. Mey	Coughs (Watt and Breyer-Brandwijk, 1962)	Roots	–	–

Table 1 (*Continued*)

Family	Species	Use	Plant part used	Potentially bioactive compounds	Screened for antimycobacterial activity
Apiaceae	*Foeniculum vulgare* Mill.	Chronic coughs (Grieve, 1967)	Syrup made from the juice	Fruits contain flavonoids and furanocoumarins (Dictionary of Natural Products, 1996). Essential oil from fruit contains phenylpropanoids, mainly anethole (Bruneton, 1995)	–
Apiaceae	*Heteromorpha trifoliata* (Wendl.) Eckl. & Zeyh. [syn. *Heteromorpha arborescens* (Thunb.) Cham. & Schlechtd.]	Coughs, fever, shortness of breath (Watt and Breyer-Brandwijk, 1962; Gelfand et al., 1985; Pujol, 1990; Hutchings and Van Staden, 1994; Hutchings et al., 1996)	Roots, and sometimes stem bark and leaves	Falcarindiol and saricin (Villegas et al., 1988), volatile oil contains α-pinene, germacrene D and sabinene as major constituents (Mwangi et al., 1994)	–
Apiaceae	*Lichtensteinia interrupta* (Thunb.) Sond.	Chronic coughs (Hutchings et al., 1996)	Roots	–	–
Apiaceae	*Lichtensteinia kolbeana* H. Bol.	Chest complaints (Hutchings et al., 1996)	Roots	–	–
Apocynaceae	*Rauvolfia caffra* Sond.	Coughs (Hutchings et al., 1996)	Bark	Rauvolfine (Watt and Breyer-Brandwijk, 1962), various alkaloids including reserpine and rescinnamine (Hutchings et al., 1996)	–
Apocynaceae	*Tabernaemontana elegans* Stapf	Chest complaints (Pooley, 1993)	Roots	–	–
Araceae	*Stylochiton natalensis* Schott	Chest diseases (Watt and Breyer-Brandwijk, 1962)	Rhizome	–	–
Asclepiadaceae	*Asclepias fruticosa* L. (and *Asclepias physocarpa* (E. Mey.) Schltr.)	TB (Watt and Breyer-Brandwijk, 1962), headache (Hutchings and Van Staden, 1994) and emetic to strengthen the body (Pujol, 1990)	Leaves, and sometimes roots	Cardiac glycosides including 15β-hydroxygomphoside and 19-deoxy-uscharin from *A. fruticosa* (Dictionary of Natural Products, 1996)	–
Asclepiadaceae	*Ceropegia woodii* Schltr.	Chest complaints (Hutchings et al., 1996)	Stems and leaves	–	–
Asclepiadaceae	*Secamone gerrardii* Harv. Ex Benth.	Chest pains (Hutchings et al., 1996)	Roots, bark	–	–
Asparagaceae	*Protasparagus africanus* (Lam.) Oberm.	TB (Hutchings et al., 1996)	Shoots	–	–
Asphodelaceae	*Kniphofia laxiflora* Kunth	Chest ailments (Hutchings et al., 1996)	Rhizomes	–	–
Asphodelaceae	*Kniphofia rooperi* (Moore) Lem.	Chest ailments (Hutchings et al., 1996)	Rhizomes	–	–
Asteraceae	*Arctotis auriculata* Jacq.	Infectious diseases (Salie et al., 1996)	Unspecified parts	Tannins, flavonoids, alkaloids, cyanogenic glucosides (Salie et al., 1996)	Leaf, stem, root extracts active; petroleum ether leaf extract MIC = 8.5 mg/ml (*Mycobacterium smegmatis*) (Salie et al., 1996)
Asteraceae	*Artemisia afra* Jacq. ex Willd.	Coughs, colds, fever, loss of appetite, chest pains (Watt and Breyer-Brandwijk, 1962; Iwu, 1993; Hutchings and Van Staden, 1994; Scott et al., 2004; Mativandlela et al., 2008)	Leaves, and sometimes roots	Volatile oil, consisting mainly of 1,8-cineole, α-thujone, β-thujone, camphor and borneol (Graven et al., 1992), terpenoids of the eudesmadien and germacratien types, coumarins and acetylenes (Dictionary of Natural Products, 1996)	Ethanol extract of leaves MIC = 1.56 mg/ml (*Mycobacterium smegmatis*), not active (*Mycobacterium tuberculosis*) (Mativandlela et al., 2008); no activity of aqueous infusion (*Mycobacterium smegmatis*) (Scott et al., 2004)
Asteraceae	*Aster bakeranus* Burtt Davy ex C.A. Sm.	Chronic coughs (Hutchings et al., 1996)	Roots	–	–
Asteraceae	*Athrixia phylicoides* DC.	Coughs (Watt and Breyer-Brandwijk, 1962)	Roots and leaves	Diterpenoid (Hutchings et al., 1996)	–
Asteraceae	*Berkheya rhapontica* (DC.) Hutch. & Burtt Davy	Coughs (mixed with parts of *Athrixia phylicoides*) (Watt and Breyer-Brandwijk, 1962)	Roots	Terpenoids (Hutchings et al., 1996)	–
Asteraceae	*Conyza podocephala* DC.	Coughs (Watt and Breyer-Brandwijk, 1962)	Leaves	Terpenoid derivatives (Hutchings et al., 1996)	–
Asteraceae	*Conyza scabrida* DC.	Coughs, chest complaints, fever (Watt and Breyer-Brandwijk, 1962; Hutchings et al., 1996; Scott et al., 2004; Thring et al., 2007)	Leaves	Diterpenoids, hautriwaic acid, clerodane derivatives (Hutchings et al., 1996)	No activity of aqueous infusion (*Mycobacterium smegmatis*) (Scott et al., 2004). Aqueous decoctions and infusions of leaves and stems MIC = 1.25 and 0.625 mg/ml, respectively (*Mycobacterium smegmatis*); methanol extract MIC = 0.313 mg/ml; ethanol and ethyl acetate extracts MIC = 5 mg/ml (Thring et al., 2007)
Asteraceae	*Conyza ulmifolia* (Burm. F.) Kuntze	Coughs (Watt and Breyer-Brandwijk, 1962)	Leaves	Sesquiterpenes and sesquiterpenoids (Hutchings et al., 1996)	–

Asteraceae	*Dicoma anomala* Sond.	Coughs, respiratory complaints (Hutchings et al., 1996)	Unspecified parts	Germacranolides (Hutchings et al., 1996)	–
Asteraceae	*Dicoma speciosa* DC.	Coughs, chest ailments (Hutchings et al., 1996)	Unspecified parts	–	–
Asteraceae	*Dicoma zeyheri* Sond.	Coughs, chest ailments (Hutchings et al., 1996)	Unspecified parts	–	–
Asteraceae	*Dittrichia graveolens* L.	TB symptoms (Bamuamba et al., 2008)	Whole plant	–	Aqueous extract inactive; acetone:water (4:1) extract active in bioautography (*Mycobacterium aurum*) (Bamuamba et al., 2008)
Asteraceae	*Eriocephalus africanus* L.	Chest complaints, coughs (Salie et al., 1996)	Unspecified parts	Tannins, flavonoids, triterpene steroids (Salie et al., 1996)	Leaf, stem, root extracts inactive (*Mycobacterium smegmatis*) (Salie et al., 1996)
Asteraceae	*Felicia erigeroides* DC.	Infectious diseases (Salie et al., 1996)	Unspecified parts	Tannins, saponins, flavonoids, triterpene steroids (Salie et al., 1996)	Leaf, stem, root extracts inactive (*Mycobacterium smegmatis*) (Salie et al., 1996)
Asteraceae	*Gerbera ambigua* (Cass.) Sch. Bip.	Coughs (Hutchings et al., 1996)	Roots	A tricyclic sesquiterpenoid (Hutchings et al., 1996)	–
Asteraceae	*Gerbera piloselloides* (L.) Cass.	Coughs (Hutchings et al., 1996)	Roots	Chromenes, acetophenones and 3-geranyl-4-hydroxy-5-coumarincarboxaldehyde (Hutchings et al., 1996)	–
Asteraceae	*Helichrysum* spp. (including *Helichrysum nudifolium* (L.) Less., *Helichrysum odoratissimum* (L.) Sweet, *Helichrysum pilosellum* (L.f.) Less., *Helichrysum melanacme* DC., *Helichrysum crispum* (L.) D. Don.)	Coughs, TB (Watt and Breyer-Brandwijk, 1962; Hutchings et al., 1996; Salie et al., 1996; Lall and Meyer, 1999; Scott et al., 2004)	Leaves, whole plant	Flavonoids, sesquiterpenoids, acylated phloroglucinols (Jakupovic et al., 1986; Van Puyvelde et al., 1989; Dictionary of Natural Products, 1996); tannins, saponins, cyanogenic glucosides (Salie et al., 1996); caespitate from *Helichrysum caespititium* (Meyer et al., 2002)	*Helichrysum crispum* active (*Mycobacterium smegmatis*) (Salie et al., 1996). H. *melanacme* acetone extract MIC = 0.1 mg/ml, water extract MIC = 1 mg/ml (*Mycobacterium tuberculosis*) (Lall and Meyer, 1999; Lall et al., 2006), *Helichrysum odoratissimum* acetone extract MIC = 0.5 mg/ml, water extract inactive (*Mycobacterium tuberculosis*) (Lall and Meyer, 1999). *Helichrysum caespitatum* acetone extract MIC = 0.1 mg/ml; caespitate MIC = 0.1 mg/ml (*Mycobacterium tuberculosis*) (Meyer et al., 2002). No activity of aqueous infusion of *Helichrysum petiolare* (*Mycobacterium smegmatis*) (Scott et al., 2004)
Asteraceae	*Leysera gnaphalodes* L.	Respiratory ailments, TB (Scott et al., 2004; Bamuamba et al., 2008)	Whole plant	Oleanolic and ursolic acids (Bamuamba et al., 2008)	No activity of aqueous infusion (*Mycobacterium smegmatis*) (Scott et al., 2004). Aqueous extract inactive; acetone:water (4:1) extract active in bioautography (*Mycobacterium aurum*); oleanolic and ursolic acids active (*Mycobacterium tuberculosis*, *Mycobacterium microti*, *Mycobacterium avium*, *Mycobacterium scrofulaceum*) (Bamuamba et al., 2008)
Asteraceae	*Nidorella anomala* Steetz.	TB symptoms (Lall and Meyer, 1999)	Whole plant	–	Acetone extract MIC = 0.1 mg/ml, water extract MIC = 5 mg/ml (*Mycobacterium tuberculosis*) (Lall and Meyer, 1999)
Asteraceae	*Nidorella auriculata* DC.	TB symptoms (Lall and Meyer, 1999)	Whole plant	–	Acetone extract MIC = 0.5 mg/ml, water extract inactive (*Mycobacterium tuberculosis*) (Lall and Meyer, 1999)
Asteraceae	*Osmitopsis asteriscoides* (L.) Less.	Coughs, chest complaints, fever (Watt and Breyer-Brandwijk, 1962; Scott et al., 2004)	Leaves	Volatile oil contains mainly 1,8-cineole and camphor (Van Wyk et al., 1997), and sesquiterpenoid lactones including osmitopsin have been isolated from the leaves (Bohlmann and Zdero, 1974; Dictionary of Natural Products, 1996)	No activity of aqueous infusion (*Mycobacterium smegmatis*) (Scott et al., 2004)
Asteraceae	*Senecio bupleuroides* DC.	Chest complaints (Hutchings et al., 1996)	Unspecified parts	Alkaloids including isatidine and retrorsine, pterophine, isatinecine, rosmarinecine and isatinic acid (Hutchings et al., 1996)	–
Asteraceae	*Senecio inornatus* DC.	Coughs (Hutchings et al., 1996)	Roots	Cacalol derivatives, furanoeremophilanes and a dihydropeuparin derivative (Hutchings et al., 1996)	–

Table 1 (*Continued*)

Family	Species	Use	Plant part used	Potentially bioactive compounds	Screened for antimycobacterial activity
Asteraceae	*Senecio quinquelobus* (Thunb.) DC.	Coughs (Watt and Breyer-Brandwijk, 1962; Hutchings et al., 1996)	Leaves	Essential oil containing hydrocarbons, sesquiterpenoids and 1,8-cineole (Hutchings et al., 1996)	–
Asteraceae	*Senecio serratuloides* DC. var. *serratuloides*	TB symptoms (Lall and Meyer, 1999)	Aerial parts	–	Acetone extract inactive, water extract MIC = 5 mg/ml (*Mycobacterium tuberculosis*) (Lall and Meyer, 1999)
Asteraceae	*Senecio speciosus* Willd.	Chest complaints (Hutchings et al., 1996)	Leaves, stems	–	–
Asteraceae	*Tarchonanthus camphoratus* L.	Respiratory complaints (Pooley, 1993)	Unspecified parts	Leaves contain volatile oil and tarchonyl alcohol (Watt and Breyer-Brandwijk, 1962) and camphor (Hutchings et al., 1996)	–
Asteraceae	*Ursinia tenuiloba* DC.	Coughs (Hutchings et al., 1996)	Roots	–	–
Asteraceae	*Vernonia adoensis* Sch. Bip. ex Walp.	Chronic coughs, febrile complaints (Hutchings et al., 1996)	Leaves	Glaucolides (Hutchings et al., 1996)	–
Asteraceae	*Vernonia hirsuta* (DC.) Sch. Bip.	Coughs (Hutchings et al., 1996)	Root	Sesquiterpenoid lactones and a guaianolide in roots, germacranolide D, a triterpenoid and lactones in aerial parts (Hutchings et al., 1996)	–
Asteraceae	*Vernonia mespilifolia* Less.	TB, coughs (Hutchings et al., 1996)	Roots	–	–
Balanitaceae	*Balanites maughamii* Sprague	Coughs (Iwu, 1986)	Fruits	*Balanites* species contain steroidal glycosides derived from diosgenin and related sapogenins (Dictionary of Natural Products, 1996)	–
Bignoniaceae	*Tecomaria capensis* (Thunb.) Spach	Chest ailments (Roberts, 1990)	Bark	Sterol (Watt and Breyer-Brandwijk, 1962)	–
Boraginaceae	*Lepidium capense* Thunb.	Coughs (Bryant, 1966)	Tubers	–	–
Boraginaceae	*Lepidium pinnatum* Thunb.	Coughs (Gerstner, 1941)	Unspecified parts	–	–
Boraginaceae	*Lepidium schinzii* Thell.	Coughs (Gerstner, 1941)	Unspecified parts	–	–
Buddlejaceae	*Buddleja saligna* L.	TB symptoms (Bamuamba et al., 2008)	Leaves, stems	Oleanolic acid (Bamuamba et al., 2008)	Aqueous extract inactive; acetone:water (4:1) extract active in bioautography (*Mycobacterium aurum*); oleanolic acid active (*Mycobacterium tuberculosis*, *Mycobacterium microti*, *Mycobacterium avium*, *Mycobacterium scrofulaceum*) (Bamuamba et al., 2008)
Cactaceae	*Rhipsalis baccifera* (J. Mill.) Stearn	Chest complaints (Gerstner, 1938)	Unspecified parts	–	–
Canellaceae	*Warburgia salutaris* (Bertol. f.) Chiov.	Coughs, fever, chest complaints, respiratory ailments (Watt and Breyer-Brandwijk, 1962; Pujol, 1990; Hutchings and Van Staden, 1994; Hutchings et al., 1996)	Bark or root bark	Drimane sesquiterpenoids including warburganal and polygodial (Watt and Breyer-Brandwijk, 1962; Clarkson et al., 2007; Madikane et al., 2007)	Dichloromethane bark extract, sesquiterpene mixture and 11α-hydroxycinnamosmolide active (*Mycobacterium tuberculosis* and *Mycobacterium bovis* BCG) (Clarkson et al., 2007; Madikane et al., 2007)
Capparaceae	*Capparis brassii* DC.	Chronic coughs (Bryant, 1966)	Roots	–	–
Capparaceae	*Capparis tomentosa* Lam.	Coughs, chest pain (Watt and Breyer-Brandwijk, 1962; Pujol, 1990; Iwu, 1993; Hutchings and Van Staden, 1994)	Root	The alkaloids stachydrine (Dictionary of Natural Products, 1996) and 3-hydroxy-4-methoxy-3-methyl-oxindole (Dekker et al., 1987).	–
Celastraceae	*Cassine papillosa* (Hochst.) Kuntze	Chest congestion, TB (Pujol, 1990; Lall and Meyer, 1999)	Bark	–	Acetone extract MIC = 1 mg/ml, water extract inactive (*Mycobacterium tuberculosis*) (Lall and Meyer, 1999)
Celastraceae	*Catha edulis* (Vahl) Forssk. ex Endl.	Coughs, chest ailments (Watt and Breyer-Brandwijk, 1962)	Leaves	Phenethylamines (or khatamines) with cathinone as the major compound responsible for stimulating effect (Crombie et al., 1990)	–
Celastraceae	*Maytenus heterophylla* (Eckl. & Zeyh.) N.K.B. Robson	Coughs (Hutchings et al., 1996)	Roots, thorns	Dulcitol (Watt and Breyer-Brandwijk, 1962), alkaloids, triterpenoids and maytansine (Hutchings et al., 1996)	–

Celastraceae	*Maytenus senegalensis* (Lam.) Excell	Respiratory ailments, TB (Gelfand et al., 1985; Lall and Meyer, 1999)	Aerial parts, roots	–	Aerial parts acetone extract MIC = 1 mg/ml, water extract inactive; root acetone and water extracts inactive (*Mycobacterium tuberculosis*) (Lall and Meyer, 1999)
Celastraceae	*Pterocelastrus echinatus* N.E. Br. (or *P. rostratus* Walp., or *P. tricuspidatus* (Lam.) Sond.	*Pterocelastrus* species used for respiratory ailments (Pujol, 1990)	Bark	–	–
Chenopodiaceae	*Chenopodium ambrosioides* L.	Cough suppressant, TB (Watt and Breyer-Brandwijk, 1962; Lall and Meyer, 1999)	Aerial parts	Saponins (Watt and Breyer-Brandwijk, 1962) flavonoids, quercetin, oxalic, malic and succinic acids, triterpenoid glycosides, chenopodoside A and B, amino acids, ascaridole (Hutchings et al., 1996)	Acetone extract MIC = 0.1 mg/ml, water extract inactive (*Mycobacterium tuberculosis*) (Lall and Meyer, 1999)
Clusiaceae	*Garcinia polyantha* Oliv.	Wounds, various uses (Kuete et al., 2007)	Stem bark	1,3,6,7-tetrahydroxyxanthone, 1,3,5-trihydroxyxanthone, bangangxanthone, 1,3,6,7-tetrahydroxyxanthone, 5-hydroxyflavone (Kuete et al., 2007)	Dichloromethane: methanol (1:1) stem bark extract and some isolated compounds active (*Mycobacterium smegmatis, Mycobacterium tuberculosis*) (Kuete et al., 2007)
Combretaceae	*Combretum imberbe* Wawra	*Combretum* species used for chest coughs, fever, infections (Hutchings et al., 1996)	Leaves	Pentacyclic triterpenes (Katerere et al., 2003), triterpene acids (Rogers and Subramony, 1988) and related glycosides (Rogers, 1988)	Pentacyclic triterpenes MIC = 1.56–25 μg/ml (*Mycobacterium fortuitum*) (Katerere et al., 2003)
Combretaceae	*Combretum kraussii* Hochst.	Fever, inflammation (Hutchings et al., 1996; Neuwinger, 1996)	Bark, roots, leaves	Isomeric flavonoids vitexin and saponaretin, catechins, combretacin and many other compounds in *Combretum* species (Iwu, 1993).	Leaf, bark and root ethanol and ethyl acetate extracts active, MIC = 0.195–1.56 mg/ml (*Mycobacterium aurum*) (Eldeen and Van Staden, 2007)
Combretaceae	*Combretum molle* R. Br. Ex G. Don	Coughs, TB (Hutchings and Johnson, 1986; Lall and Meyer, 1999)	Bark	–	Acetone extract MIC = 1 mg/ml, water extract inactive (*Mycobacterium tuberculosis*) (Lall and Meyer, 1999)
Combretaceae	*Terminalia sericea* Burch. ex DC.	Wounds (Hutchings et al., 1996; Neuwinger, 1996)	Bark, roots	Termilignan B and arjunic acid from roots (Eldeen et al., 2008)	Bark and root ethanol, ethyl acetate and dichloromethane extracts active, MIC = 1.56–3.12 mg/ml (*Mycobacterium aurum*) (Eldeen and Van Staden, 2007); Termilignan B and arjunic acid not active against *Mycobacterium aurum* (Eldeen et al., 2008)
Cucurbitaceae	*Cucumis hirsutus* Sond.	Coughs (Bryant, 1966)	Roots	Cucumin (Watt and Breyer-Brandwijk, 1962)	–
Dioscoreaceae	*Dioscorea sylvatica* (Kunth) Eckl.	Chest complaints (Hutchings et al., 1996)	Roots	Diosgenin (Hutchings et al., 1996)	–
Dipsacaceae	*Cephalaria zeyheriana* Szabo	TB (Watt and Breyer-Brandwijk, 1962)	Roots	–	–
Droseraceae	*Drosera capensis* L.	Fever, TB symptoms (Mativandlela et al., 2008)	Leaves	–	Ethanol extract of leaves MIC = 3.13 mg/ml (*Mycobacterium smegmatis*), not active (*Mycobacterium tuberculosis*) (Mativandlela et al., 2008)
Ebenaceae	*Euclea crispa* (Thunb.) Guerke	Coughs (Gelfand et al., 1985)	Roots	Triterpenoids, naphthoquinones (Hutchings et al., 1996)	–
Ebenaceae	*Euclea natalensis* A. DC.	Respiratory chest problems, coughs, TB (Bryant, 1966; Lall and Meyer, 1999)	Roots	Pentacyclic terpenoids, naphthoquinones, triterpenoids (Van der Vijver, 1975; Hutchings et al., 1996; Lall et al., 2005; Van der Kooy et al., 2006); diospyrin (Lall and Meyer, 2001); octahydroeuclein, 20(29)-lupene-3ß-isoferulate, shinanolone, lupeol, betulin (Weigenand et al., 2004)	Acetone and water extract MIC = 0.1 mg/ml (*Mycobacterium tuberculosis*) (Lall and Meyer, 1999); isolated compounds active against *Mycobacterium tuberculosis* and *Mycobacterium bovis* (Lall and Meyer, 2001; Weigenand et al., 2004; Lall et al., 2005; Bapela et al., 2006; Van der Kooy et al., 2006; McGaw et al., 2008)
Euphorbiaceae	*Andrachne ovalis* (Sond.) Müll. Arg.	Chest complaints (Gerstner, 1941)	Roots	–	–
Euphorbiaceae	*Acalypha peduncularis* E. Mey. Ex Meisn.	Coughs, chest complaints (Bryant, 1966)	Roots	–	–
Euphorbiaceae	*Acalypha punctata* Meisn.	Chest complaints (Watt and Breyer-Brandwijk, 1962)	Roots	–	–
Euphorbiaceae	*Croton gratissimus* Burch.	Coughs (Watt and Breyer-Brandwijk, 1962)	Leaves	Unknown (Van Wyk et al., 1997)	–
Euphorbiaceae	*Croton pseudopulchellus* Pax	TB symptoms (Lall and Meyer, 1999)	Aerial parts	–	Acetone extract MIC = 0.5 mg/ml, water extract inactive (*Mycobacterium tuberculosis*) (Lall and Meyer, 1999)

Table 1 (*Continued*)

Family	Species	Use	Plant part used	Potentially bioactive compounds	Screened for antimycobacterial activity
Euphorbiaceae	*Croton sylvaticus* Hochst.	TB (Hutchings et al., 1996)	Root bark	Crotin (Watt and Breyer-Brandwijk, 1962)	–
Euphorbiaceae	*Phyllanthus meyerianus* Müll. Arg.	Coughs (Gerstner, 1941)	Root bark	–	–
Fabaceae	*Acacia nilotica* (L.) Willd. ex Del. subsp. *kraussiana* (Benth.) Brenan	Respiratory ailments, TB, coughs (Sawhney et al., 1978; Khan et al., 1980; Hutchings et al., 1996)	Roots, leaf, bark	Hydroxyproline, serine, dimethyl-triptamine, ß-amyrin, betulin and many other compounds in *Acacia* species (Ayoub, 1982; Anderson and McDougall, 1987; Hutchings et al., 1996)	Leaf, bark and root ethanol and ethyl acetate extracts active, MIC = 0.195–1.56 mg/ml (*Mycobacterium aurum*) (Eldeen and Van Staden, 2007)
Fabaceae	*Acacia robusta* Burch.	Chest complaints (Hutchings et al., 1996)	Bark	Cyanogenic glycosides and hydrocyanic acid (Watt and Breyer-Brandwijk, 1962)	–
Fabaceae	*Acacia sieberiana* DC. var. *woodii* (Burtt Davy) Keay & Brenan	Fever, infectious diseases (Gelfand et al., 1985; Hutchings et al., 1996)	Bark, roots, leaves and other parts	Hydroxyproline, serine, dimethyl-triptamine, β-amyrin, betulin and many other compounds in *Acacia* species (Ayoub, 1982; Anderson and McDougall, 1987; Hutchings et al., 1996)	Leaf, bark and root ethanol, ethyl acetate and dichloromethane extracts active, MIC = 0.78–6.25 mg/ml (*Mycobacterium aurum*) (Eldeen and Van Staden, 2007)
Fabaceae	*Acacia xanthophloea* Benth	TB symptoms (Lall and Meyer, 1999)	Bark	Hydroxyproline, serine, dimethyl-triptamine, β-amyrin, betulin and many other compounds in *Acacia* species (Ayoub, 1982; Anderson and McDougall, 1987; Hutchings et al., 1996)	Acetone extract MIC = 0.5 mg/ml, water extract inactive (*Mycobacterium tuberculosis*) (Lall and Meyer, 1999)
Fabaceae	*Alysicarpus rugosus* (Willd.) DC.	Chest complaints (Gerstner, 1939)	Unspecified parts	–	–
Fabaceae	*Cyclopia intermedia* E. Mey	Coughs, TB (Kamara et al., 2003)	Leaves and stems	Flavonoids, phenols and their glycosides, glycosylated flavonols, flavanones, isoflavonoids, flavones (Kamara et al., 2003)	–
Fabaceae	*Elephantorrhiza elephantina* (Burch.) Skeels	Chest complaints (Gerstner, 1939)	Roots	Tannin (Watt and Breyer-Brandwijk, 1962)	–
Fabaceae	*Faidherbia albida* (Del.) A. Chev.	Infections (Watt and Breyer-Brandwijk, 1962)	Bark	Tannin (Watt and Breyer-Brandwijk, 1962)	Leaf and bark ethanol and ethyl acetate extracts active, MIC = 3.12–12.5 mg/ml (*Mycobacterium aurum*) (Eldeen and Van Staden, 2007)
Fabaceae	*Glycyrrhiza glabra* L.	Coughs (Grieve, 1967; Gibson, 1978; Bruneton, 1995), TB (Watt and Breyer-Brandwijk, 1962)	Rhizome	Roots contain flavonoids, isoflavonoids, chalcones and saponins (Gibson, 1978; Bruneton, 1995; Dictionary of Natural Products, 1996)	–
Fabaceae	*Indigofera tenuissima* E. Mey.	Chest ailments (Hulme, 1954)	Roots	–	–
Fabaceae	*Lotus discolor* E. Mey.	Chest complaints (Hulme, 1954)	Roots	–	–
Fabaceae	*Tephrosia grandiflora* (Ait.) Pers.	Chest ailments (Hulme, 1954)	Roots	Rotenoid compounds (Allen and Allen, 1981)	–
Fabaceae	*Tephrosia kraussiana* Meisn.	Coughs (Watt and Breyer-Brandwijk, 1962)	Roots	Saponin (Watt and Breyer-Brandwijk, 1962)	–
Fabaceae	*Tephrosia macropoda* (E. Mey.) Harv.	Chest ailments (Hulme, 1954)	Roots	Toxicarol and deguelin (Watt and Breyer-Brandwijk, 1962)	–
Flacourtiaceae	*Gerrardina foliosa* Oliv.	Coughs (Gerstner, 1939)	Root bark	–	–
Geraniaceae	*Pelargonium* spp. (notably *P. reniforme* Curt. and *P. sidoides* DC.	TB, cough (Scott et al., 2004; Seidel and Taylor, 2004; Bladt and Wagner, 2007)	Tuber	Tannins and other phenolic compounds (Van Wyk et al., 1997), umckalin and related coumarins in *P. reniforme* tubers (Wagner and Bladt, 1975), essential oils (Dictionary of Natural Products, 1996), flavonoids and phytosterols (Kolodziej, 2000), fatty acids (Seidel and Taylor, 2004)	Aqueous infusions of four species inactive, *P. grossularioides* mildly active (*Mycobacterium smegmatis*) in disc diffusion assay (Scott et al., 2004); unsaturated fatty acids from *P. reniforme* and *P. sidoides* active (*Mycobacterium aurum, Mycobacterium smegmatis, Mycobacterium fortuitum, Mycobacterium abscessus, Mycobacterium phlei*) (Seidel and Taylor, 2004); extracts of *P. reniforme* active (*Mycobacterium tuberculosis*) (Mativandlela et al., 2006)
Gunneraceae	*Gunnera perpensa* L.	TB symptoms (Lall and Meyer, 1999)	Roots	–	Acetone and water extracts inactive (*Mycobacterium tuberculosis*) (Lall and Meyer, 1999)
Hyacinthaceae	*Eucomis autumnalis* (Mill.) Chitt. subsp. *clavata* (Bak.) Reyneke	Coughs, respiratory ailments (Watt and Breyer-Brandwijk, 1962; Hutchings et al., 1996)	Bulb	Homoisoflavones, benzopyrones and steroidal triterpenoids (Tamm, 1972; Ziegler and Tamm, 1976; Dictionary of Natural Products, 1996)	–
Iridaceae	*Aristea ecklonii* Bak.	Coughs (Hutchings et al., 1996)	Leaves	Plumbagin, neoisoshinanolone, sitosterol (Hutchings et al., 1996)	–
Iridaceae	*Gladiolus dalenii* van Geel	Chest ailments (Hutchings et al., 1996)	Corms	Saponins, phenolics and flavonoids (Hutchings et al., 1996)	–
Lamiaceae	*Ballota africana* (L.) Benth.	Cough, lung infections (Scott et al., 2004)	–	–	No activity of aqueous infusion (*Mycobacterium smegmatis*) (Scott et al., 2004)

Lamiaceae	*Leonotis leonurus* (L.) R. Br.	Coughs, respiratory ailments (Watt and Breyer-Brandwijk, 1962; Hutchings et al., 1996; Scott et al., 2004)	Leaves and stems	Volatile oil and diterpenoids (labdane-type lactones) for example marrubin (Dictionary of Natural Products, 1996)	No activity of aqueous infusion (*Mycobacterium smegmatis*) (Scott et al., 2004)
Lamiaceae	*Mentha longifolia* (L.) L.	Coughs, respiratory ailments, fever (Watt and Breyer-Brandwijk, 1962; Scott et al., 2004)	Leaves	Volatile oil contains many monoterpenoids, including carvone, limonene, menthone and menthol (Bruneton, 1995)	No activity of aqueous infusion (*Mycobacterium smegmatis*) (Scott et al., 2004)
Lamiaceae	*Orthosiphon labiatus* N.E. Br.	–	–	Labdane diterpenoids, (+)-*trans*-ozic acid (Hussein et al., 2007)	Labdane diterpenoid MIC = 157 μM (*Mycobacterium tuberculosis*) (Hussein et al., 2007)
Lamiaceae	*Plectranthus laxiflorus* Benth.	Coughs (Hutchings et al., 1996)	Unspecified parts	–	–
Lamiaceae	*Plectranthus madagascariensis* (Pers.) Benth.	Coughs, chest complaints (Watt and Breyer-Brandwijk, 1962)	Roots, leaves	–	–
Lamiaceae	*Salvia* L. spp.	Infections, TB, fever (Watt and Breyer-Brandwijk, 1962; Scott et al., 2004; Kamatou et al., 2007)	–	Carnosol, rosmadial, carnosic acid from *Salvia africana-lutea* (Hussein et al., 2007). Carnosol, 7-O-methylepirosmanol, oleanolic acid and ursolic acid from *Salvia chamelaeagnea* (Kamatou et al., 2007)	*Salvia radula*, *Salvia verbenaca* and *Salvia dolomitica* extracts MIC = 0.1 mg/ml; other species MIC = 0.5 mg/ml (*Mycobacterium tuberculosis*) (Kamatou et al., 2007). *Salvia africana-lutea* MIC = 2, 1, 8 mg/ml against *Mycobacterium aurum*, *Mycobacterium tuberculosis* and *Mycobacterium smegmatis*, respectively (Seaman, 2005). No activity of aqueous infusion (*Mycobacterium smegmatis*) (Scott et al., 2004). Carnosic acid MIC = 28 μM (*Mycobacterium tuberculosis*) (Hussein et al., 2007)
Lamiaceae	*Tetradenia riparia* (Hochst.) Codd	Respiratory ailments, coughs, TB symptoms (Watt and Breyer-Brandwijk, 1962; Hutchings et al., 1996; Lall and Meyer, 1999; Scott et al., 2004)	Leaves, roots	A diterpene diol, ibozol, and related diterpenoids, large amounts of α-pyrones (Zelnik et al., 1978; Van Puyvelde et al., 1979; Dictionary of Natural Products, 1996)	Root acetone and water extracts inactive (*Mycobacterium tuberculosis*) (Lall and Meyer, 1999); no activity of aqueous infusion (*Mycobacterium smegmatis*) (Scott et al., 2004)
Lamiaceae	*Thymus vulgaris* L.	TB symptoms (Lall and Meyer, 1999)	Aerial parts	–	Acetone extract MIC = 0.5 mg/ml, water extract MIC = 5 mg/ml (*Mycobacterium tuberculosis*) (Lall and Meyer, 1999)
Lauraceae	*Cryptocarya latifolia* Sond.	Chest ailments, TB (Gerstner, 1941; Lall and Meyer, 1999)	Bark	–	Acetone extract MIC = 1 mg/ml, water extract MIC = 5 mg/ml (*Mycobacterium tuberculosis*) (Lall and Meyer, 1999)
Leguminosae	*Albizia adianthifolia* (Schumach.) W. F. Wight.	Fever, headaches (Pujol, 1990; Neuwinger, 1996)	Bark, roots	–	Bark extract inactive; root ethanol extract MIC = 6.25 mg/ml (*Mycobacterium aurum*) (Eldeen and Van Staden, 2007)
Loganiaceae	*Buddleja saligna* Willd.	Coughs (Watt and Breyer-Brandwijk, 1962; Pooley, 1993)	Unspecified parts, leaves	–	–
Loganiaceae	*Buddleja salviifolia* (L.) Lam.	Coughs (Watt and Breyer-Brandwijk, 1962)	Roots	–	–
Meliaceae	*Ekebergia capensis* Sparrm.	Chronic coughs, respiratory chest complaints, TB (Watt and Breyer-Brandwijk, 1962; Bryant, 1966; Mabogo, 1990; Pujol, 1990; Lall and Meyer, 1999)	Roots, leaves, bark	Unknown (Van Wyk et al., 1997)	Acetone extract of bark MIC = 0.1 mg/ml, water extract inactive (*Mycobacterium tuberculosis*) (Lall and Meyer, 1999)
Meliaceae	*Trichilia dregeana* Harv. & Sond.	Fever, pain (Watt and Breyer-Brandwijk, 1962; Iwu, 1993; Hutchings et al., 1996)	Bark, roots, leaves	–	Leaf, bark and root ethanol, ethyl acetate and dichloromethane extracts active, MIC = 0.78–6.25 mg/ml (*Mycobacterium aurum*) (Eldeen and Van Staden, 2007)
Moraceae	*Ficus sur* Forssk.	TB (Watt and Breyer-Brandwijk, 1962; Hutchings et al., 1996)	Bark, roots, fruit, leaves	–	Leaf, bark and root ethanol, ethyl acetate and dichloromethane extracts active, MIC = 0.78–3.12 mg/ml (*Mycobacterium aurum*) (Eldeen and Van Staden, 2007)
Myricaceae	*Myrica serrata* Lam.	Coughs (Gerstner, 1941)	Root bark	–	–
Myrsinaceae	*Rapanea melanophloeos* (L.) Mez	TB symptoms (Lall and Meyer, 1999)	Bark	–	Acetone extract MIC = 5 mg/ml, water extract inactive (*Mycobacterium tuberculosis*) (Lall and Meyer, 1999)
Myrothamnaceae	*Myrothamnus flabelliformus* Welw.	Respiratory ailments (Watt and Breyer-Brandwijk, 1962; Hutchings et al., 1996)	Leaves and twigs	Volatile oil contains camphor with small amounts of α-pinene and 1,8-cineole (Van Wyk et al., 1997)	–

Table 1 (*Continued*)

Family	Species	Use	Plant part used	Potentially bioactive compounds	Screened for antimycobacterial activity
Myrtaceae	*Psidium guajava* L.	Cough (Watt and Breyer-Brandwijk, 1962; Hutchings et al., 1996)	Leaves	Tannins and other phenolic compounds, guiajaverin (a glycoside of quercetin), essential oils and triterpenoids (Dictionary of Natural Products, 1996)	–
Myrtaceae	*Syzygium cordatum* Hochst.	Respiratory ailments, TB (Watt and Breyer-Brandwijk, 1962; Pooley, 1993; Hutchings et al., 1996)	Bark, also leaves and roots	Proanthocyanidins, pentacyclic triterpenoids, steroidal triterpenoids, gallic acid, ellagic acid (Candy et al., 1968)	–
Myrtaceae	*Syzygium gerrardii* (Harv. ex Hook. f.)	TB, coughs, chest pains (Watt and Breyer-Brandwijk, 1962; Mativandlela et al., 2008)	Bark	Tannin (Watt and Breyer-Brandwijk, 1962)	Ethanol extract of leaves MIC = 6.25 mg/ml (*Mycobacterium smegmatis*), not active (*Mycobacterium tuberculosis*) (Mativandlela et al., 2008)
Nymphaeaceae	*Nymphaea nouchali* Burm. f.	Coughs (Roberts, 1990; Hutchings et al., 1996)	Stems, rhizomes, flowers	–	–
Oleaceae	*Olea capensis* L.	Higher upper respiratory tract infections, sore throat, TB symptoms (Bamuamba et al., 2008 and references therein)	Leaves	–	Aqueous extract and acetone:water (4:1) extract inactive in bioautography (*Mycobacterium aurum*) (Bamuamba et al., 2008)
Passifloraceae	*Adenia gummifera* (Harv.) Harms	Chest pains (Hutchings et al., 1996)	Roots, unspecified parts	Leaves and stems are reported to contain the toxalbumin modeccin (Watt and Breyer-Brandwijk, 1962)	–
Phytolaccaceae	*Phytolacca americana* L. (and *Phytolacca heptandra* Retz. and *Phytolacca octandra* L.)	Lung sickness (Gerstner, 1941)	Roots	Triterpenoid saponins, lignans and many other compounds (Hutchings et al., 1996)	–
Poaceae	*Cymbopogon marginatus* (Steud.) Stapf ex Burtt Davy	Chest diseases (Hutchings et al., 1996)	Unspecified	–	–
Polygalaceae	*Polygala fruticosa* Berg.	TB (Watt and Breyer-Brandwijk, 1962)	Whole plant	Coumarins, namely frutinones A, B and C (Di Paolo et al., 1989)	–
Polygalaceae	*Polygala myrtifolia* L.	TB symptoms (Lall and Meyer, 1999)	Aerial parts	–	Acetone extract MIC = 0.1 mg/ml, water extract inactive (*Mycobacterium tuberculosis*) (Lall and Meyer, 1999)
Polygalaceae	*Securidaca longipedunculata* Fresen.	Coughs and chest complaints (Watt and Breyer-Brandwijk, 1962)	Roots	Sapogenins, securinine (a toxic indole alkaloid) and some ergot alkaloids, volatile oil in roots contains methyl salicylate (Dictionary of Natural Products, 1996)	–
Polygonaceae	*Rumex crispus* L.	TB symptoms (Lall and Meyer, 1999)	Aerial parts	–	Acetone and water extracts inactive (*Mycobacterium tuberculosis*) (Lall and Meyer, 1999)
Polygonaceae	*Rumex sagittatus* Thunb.	TB (Jacot Guillarmod, 1971)	Unspecified parts	–	–
Portulacaceae	*Talinum caffrum* (Thunb.) Eckl. & Zeyh.	Chest complaints (Gerstner, 1941; Watt and Breyer-Brandwijk, 1962)	Roots	–	–
Proteaceaae	*Protea repens* L.	Chest disorders (Forbes, 1986)	The nectar is boiled to a syrup	Nectar contains mainly glucose and fructose, about 5% xylose and almost no sucrose (Van Wyk and Nicolson, 1995)	–
Ranunculaceae	*Ranunculus multifidus* Forssk.	Coughs (Bryant, 1966)	Leaves	Ranunculin (Hutchings et al., 1996)	–
Rhamnaceae	*Ziziphus mucronata* Willd.	Coughs, chest ailments, fever (Watt and Breyer-Brandwijk, 1962; Bryant, 1966; Hutchings et al., 1996; Mativandlela et al., 2008)	Bark	Alkaloids (Dictionary of Natural Products, 1996)	Ethanol extract of leaves not active (*Mycobacterium smegmatis* and *Mycobacterium tuberculosis*) (Mativandlela et al., 2008)
Rhodomelaceae	*Polysiphonia virgata* C. Agardh	–	–	Fatty acids (Saravanakumar et al., 2008)	Fatty acid mixture active (*Mycobacterium smegmatis* and *Mycobacterium tuberculosis*) (Saravanakumar et al., 2008)
Rosaceae	*Agrimonia bracteata* E. Mey. ex C.A. Mey.	Coughs (Hutchings et al., 1996)	Unspecified parts	Condensed tannins, polysaccharides, coumarins, flavonoids and many other compounds (Hutchings et al., 1996)	–

Rosaceae	*Prunus africana* (Hook. f.) Kalkm.	Chest pain, fever (Pujol, 1990; Mativandlela et al., 2008)	Bark	B-sitosterol (Bruneton, 1995), terpenoids and various other compounds (Van Wyk et al., 1997)	Leaf and bark ethyl acetate and dichloromethane extracts active, MIC = 0.78–6.25 mg/ml (*Mycobacterium aurum*) (Eldeen and Van Staden, 2007) Ethanol extract of leaves not active (*Mycobacterium smegmatis* and *Mycobacterium tuberculosis*) (Mativandlela et al., 2008)
Rosaceae	*Rubus pinnatus* Willd.	Respiratory ailments (Watt and Breyer-Brandwijk, 1962; Pujol, 1990)	Roots	Tannin (Watt and Breyer-Brandwijk, 1962)	–
Rubiaceae	*Pentanisia prunelloides* Walp.	TB, chest pain (Watt and Breyer-Brandwijk, 1962; Hutchings et al., 1996)	Fleshy, tuberous root	Unknown (Van Wyk et al., 1997)	–
Rubiaceae	*Rubia cordifolia* L.	Chest complaints (Watt and Breyer-Brandwijk, 1962; Hutchings et al., 1996)	Roots, leaves	Anthraquinones, pentacyclic triterpenes and other compounds (Hutchings et al., 1996)	–
Rubiaceae	*Spermacoce natalensis* Hochst.	Chest complaints (Gerstner, 1938)	Bark	–	–
Rubiaceae	*Vangueria infausta* Burch.	Chest complaints, coughs (Pooley, 1993)	Roots, leaves	Sterols (Watt and Breyer-Brandwijk, 1962)	–
Rutaceae	*Coleonema album* (Thunb.) Bartl. & Wendl.	–	–	Phenolic acids, flavonoids, coumarins, prenylated coumarins and terpenoids (Eldeen and Van Staden, 2008b)	Acetone and ethanol leaf extracts active, MIC = 3.1 mg/ml (*Mycobacterium aurum*) (Eldeen and Van Staden, 2008b)
Rutaceae	*Ruta graveolens* L.	Respiratory ailments (Watt and Breyer-Brandwijk, 1962)	Leaves	Coumarins, furanocoumarins, furanoquinolone alkaloids (Dictionary of Natural Products, 1996)	–
Rutaceae	*Teclea gerrardii* Verdoorn	Coughs (Hutchings et al., 1996)	Bark	–	–
Rutaceae	*Zanthoxylum capense* (Thunb.) Harv.	Chest pains, chronic coughs (Gerstner, 1938; Bryant, 1966)	Roots	Tannins (Watt and Breyer-Brandwijk, 1962)	–
Rutaceae	*Zanthoxylum davyi* (Verdoorn) Waterm.	Severe coughs (Watt and Breyer-Brandwijk, 1962)	Bark	–	–
Salicaceae	*Salix mucronata* Thunb.	Anti-infective, fever (Iwu, 1993)	Bark, roots, leaves	–	Leaf, bark and root ethanol, ethyl acetate and dichloromethane extracts active, MIC = 1.56–.25 mg/ml (*Mycobacterium aurum*) (Eldeen and Van Staden, 2007)
Santalaceae	*Thesium hystrix* A.W. Hill.	Coughs, TB (Watt and Breyer-Brandwijk, 1962)	Roots	Quercetrin (Watt and Breyer-Brandwijk, 1962)	–
Sapindaceae	*Cardiospermum halicacabum* L.	Pulmonary disorders (Watt and Breyer-Brandwijk, 1962)	Unspecified parts	Stigmasterol, quebrachitol, proanthocyanidin, apigenin (Hutchings et al., 1996)	–
Sapindaceae	*Dodonaea angustifolia* L.f.	TB, chest pains, fever (Watt and Breyer-Brandwijk, 1962; Thring et al., 2007; Mativandlela et al., 2008)	Leaves	Dodonic acid (Sachev and Kulshreshtha, 1984a), hautriwaic acid and structurally similar diterpenoids (Dictionary of Natural Products, 1996), β-sitosterol and stigmasterol (Sachev and Kulshreshtha, 1984a) and several flavonoids including santin (Sachev and Kulshreshtha, 1984b)	Ethanol extract of leaves MIC = 3.13 mg/ml (*Mycobacterium smegmatis*), MIC = 5 mg/ml (*Mycobacterium tuberculosis*) (Mativandlela et al., 2008). Aqueous decoctions and infusions of leaves and stems and ethyl acetate extract MIC = 5 mg/ml; ethanol and methanol extracts MIC = 1.25 mg/ml (*Mycobacterium smegmatis*) (Thring et al., 2007)
Solanaceae	*Solanum capense* L.	Coughs (Hutchings et al., 1996)	Roots	–	–
Solanaceae	*Solanum incanum* L.	Chest complaints, coughs (Watt and Breyer-Brandwijk, 1962; Gelfand et al., 1985)	Roots, leaves	Nitrosamines, alkaloids, ursolic acid, sapogenins, β-sitosterol and other compounds (Hutchings et al., 1962)	–
Sterculiaceae	*Dombeya rotundifolia* (Hochst.) Planch.	Chest complaints (Smith, 1966)	Bark	Unknown (Van Wyk et al., 1997)	–
Sterculiaceae	*Hermannia depressa* N.E. Br.	Coughs (Hutchings et al., 1996)	Whole plant	–	–
Thymelaeaceae	*Gnidia anthylloides* (L.f.) Gilg	Coughs (Watt and Breyer-Brandwijk, 1962)	Roots	Volatile oil and hydrocyanic acid (Watt and Breyer-Brandwijk, 1962)	–
Thymelaeaceae	*Gnidia kraussiana* Meisn.	Chest complaints (Hutchings et al., 1996)	Roots	Flavone heteroside from roots, toxic diterpenoid fraction, polysaccharides, daphnane orthoesters (Hutchings et al., 1996)	–
Verbenaceae	*Clerodendrum glabrum* E. Mey.	Coughs (Watt and Breyer-Brandwijk, 1962)	Leaves	–	–
Verbenaceae	*Lantana rugosa* Thunb.	Coughs, chest complaints (Hutchings et al., 1996)	Leaves	Volatile oil and the alkaloid lantanin, pentacyclic triterpenoids (Watt and Breyer-Brandwijk, 1962; Hutchings et al., 1996).	–
Verbenaceae	*Lippia javanica* (Burm. f.) Spreng.	Coughs, chest ailments (Watt and Breyer-Brandwijk, 1962; Hutchings et al., 1996)	Leaves and twigs	Volatile oil and various monoterpenoids (Mwangi et al., 1991)	–
Zingiberaceae	*Siphonochilus aethiopicus* (Schweinf.) B.L. Burtt	Coughs (Watt and Breyer-Brandwijk, 1962; Hutchings et al., 1996)	Roots	Volatile oil with a characteristic sesquiterpenoid, α-terpineol and other monoterpenoids (Van Wyk et al., 1997)	–
Zingiberaceae	*Siphonochilus natalensis* (Schltr. & K. Schum.) J.M. Wood & Franks	Coughs (Watt and Breyer-Brandwijk, 1962; Hutchings et al., 1996)	Roots	–	–

antimycobacterial investigations of these species. The major ethnobotanical inventories of plants used for treating various ailments in southern Africa include those published by Watt and Breyer-Brandwijk (1962), Hutchings et al. (1996), and Van Wyk et al. (1997), and these were valuable sources which assisted in compiling Table 1.

6. Biological activity screening of plant extracts for antimycobacterial effects in South Africa

Published work available on antimycobacterial activity of South African plants largely relies on ethnobotanical leads for selection of plants to investigate. The majority of research has been carried out using fast-growing saprophytic *Mycobacterium* species as test microorganisms. In this section, published work on antimycobacterial activity of South African plants, extended to investigations on other plants performed by researchers in South African groups, will be discussed.

An inter-institutional South African collaboration, the Novel Drug Development Platform (www.sahealthinfo.org/noveldrug/novelpamphlet.htm) aims to develop new medicines derived from plants effective against tuberculosis and other diseases. Although not part of this collaboration, in the Phytomedicine Programme (University of Pretoria) we have had some success using the broth microdilution method (Eloff, 1998) to screen extracts of plants not selected based on ethnobotanical use for antimycobacterial activity using *Mycobacterium smegmatis* as test organism. Out of approximately 330 acetone extracts of plants selected as representatives of most of the families of plants occurring in South Africa, 63 provided minimum inhibitory concentration (MIC) values lower than 0.1 mg/ml against *Mycobacterium smegmatis*. This figure of 19% of plant extracts screened thus far with MIC < 0.1 mg/ml is extremely promising, and work is continuing on these plant species, testing them against other mycobacterial species and isolating the active compounds. More collections of representative species of the families of South African plants are being made on an ongoing basis, extending the variety of plant genera tested for antimycobacterial and other biological activities.

After screening 20 acetone and water extracts of South African plants used to treat pulmonary diseases, Lall and Meyer (1999) reported that 14 of the acetone extracts were active against *Mycobacterium tuberculosis* $H_{37}Rv$. Extracts of six plants were active against a strain of *Mycobacterium tuberculosis* resistant to the drugs isoniazid and rifampicin, possibly indicating a different mechanism of antimycobacterial action by the extracts. The plants were selected on the basis of experience of traditional healers consulted, and using information in published reports (Watt and Breyer-Brandwijk, 1962; Pujol, 1990; Hutchings et al., 1996). MIC values of some plants, including *Euclea natalensis*, *Ekebergia capensis*, *Helichrysum melanacme* and *Polygala myrtifolia* were found to be 0.1 mg/ml using the radiometric method (Lall and Meyer, 1999).

Further work was undertaken on the antimycobacterial effects of the genus *Euclea*. The roots of *Euclea* species are used for various purposes, including treating chest problems, infections, chronic asthma and leprosy in southern African traditional medicine (Watt and Breyer-Brandwijk, 1962; Pujol, 1990; Hutchings et al., 1996). An ethanol extract of *Euclea natalensis* was the source of two new compounds, octahydroeuclein and 20(29)-lupene-3β-isoferulate (Weigenand et al., 2004). The known compounds shinanolone, lupeol and betulin were also isolated, and of all these compounds, only shinanolone was active against *Mycobacterium tuberculosis* with an MIC of 100 μg/ml (Weigenand et al., 2004). Diospyrin was also active against *Mycobacterium tuberculosis* (Lall and Meyer, 2001), and a 2-aminoacetate derivative of dimethylether-diospyrin was shown to have enhanced antimycobacterial effects (Lall et al., 2003).

Several naphthoquinones and triterpenes were isolated from a chloroform extract of *Euclea natalensis* roots and evaluated for activity against *Mycobacterium tuberculosis* (Lall et al., 2005). The chloroform crude extract, diospyrin and 7-methyljuglone displayed MIC values of 8.0, 8.0 and 0.5 μg/ml against drug-sensitive *Mycobacterium tuberculosis*, and 7-methyljuglone activities against a selection of sensitive and resistant *Mycobacterium tuberculosis* strains ranged from 0.32 to 1.25 μg/ml (Lall et al., 2005). Interestingly, 7-methyljuglone presented superior intracellular inhibition of *Mycobacterium tuberculosis* in J774.1 macrophages when compared to the standard anti-TB drugs streptomycin and ethambutol (Lall et al., 2005). Following up on this promising lead, Bapela et al. (2006) studied the activity of 7-methyljuglone in combination with anti-TB drugs. It was concluded that 7-methyljuglone synergistically enhanced the activity of isoniazid and rifampicin against *Mycobacterium tuberculosis* both extracellularly and intracellularly (Bapela et al., 2006).

Another naphthoquinone, neodiospyrin, was isolated for the first time from *Euclea natalensis* roots, together with other known compounds (Van der Kooy et al., 2006). Of the six naphthoquinones isolated, the MIC values of diospyrin (8.0 μg/ml), isodiospyrin (10.0 μg/ml), 7-methyljuglone (0.5 μg/ml) and neodiospyrin (10.0 μg/ml) compared well to those of the anti-TB drugs ethambutol, isoniazid and rifampicin (Van der Kooy et al., 2006). Mamegakinone and shinanolone were the least active of the isolated compounds with MIC values of 100 μg/ml (Van der Kooy et al., 2006). A useful hypothesis on the structure–activity relationships for the naphthoquinones, together with a possible mode of action, is presented (Van der Kooy et al., 2006). It is pointed out that the ketone groups on C1 and C4 are important for antimycobacterial activity, for example. Fig. 1 shows the structure of a representative naphthoquinone, diospyrin, showing the positions of C1 and C4. Another significant discovery is that 7-methyljuglone is structurally rather similar to menaquinone, which is a component of the electron transport system in mycobacteria. This is an attractive drug target because mammals use ubiquinone for this function. It is possible that 7-methyljuglone may interact with enzymes in the mycobacterial electron transport chain, and, owing to differences in redox potential of the substituted compound, the electron flow may be inhibited (Van der Kooy et al., 2006). Alternatively, 7-methyljuglone may bind to the enzymes responsible for forming menaquinone, influencing ATP production (Van der Kooy et al., 2006).

A series of derivatives of the naphthoquinone 7-methyljuglone was prepared and evaluated for antitubercular activity (Mahapatra et al., 2007). The yield of naturally occurring 7-methyljuglone from *Euclea natalensis* is a mere 0.03% (Lall et al., 2005), so ability to synthesize the compound was a prerequisite to enable further development of a potential antimycobacterial product. Mahapatra et al. (2007) investigated the activity of 7-methyljuglone and

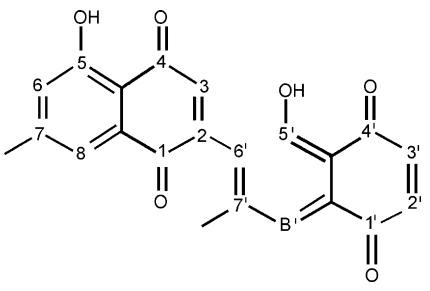

Fig. 1. Diospyrin, a representative naphthoquinone.

several derivatives as subversive substrates for mycothiol disulfide reductase, but found no direct correlation between this activity and antimycobacterial activity against *Mycobacterium tuberculosis*. Reasons put forward for this include the possibility that the compounds could non-specifically react with many biological targets, for example other disulfide reductase enzymes (Mahapatra et al., 2007). Together with anti-TB activity, cytotoxicity of the derived compounds was tested against the Vero cell line, and it was suggested that the quinone motif contributes both to biological activity and cytotoxicity, strengthening the hypothesis that the naphthoquinones may act as non-specific subversive substrates in both bacterial and mammalian cells (Mahapatra et al., 2007). Extended elaboration of the 7-methyljuglone scaffold to optimize specificity was recommended.

In a further related study, several purified constituents of *Euclea natalensis* and *Euclea undulata*, and crude organic extracts of the leaves, were assessed for efficacy against the zoonotic pathogen, *Mycobacterium bovis* ATCC 19210 (McGaw et al., 2008). The *Euclea*-derived extracts and compounds were also screened against *Mycobacterium bovis* BCG (Pasteur strain P1172), and the fast-growing species *Mycobacterium fortuitum* (ATCC 6841) and *Mycobacterium smegmatis* (ATCC 1441) as a comparison. The most active extract against infective *Mycobacterium bovis* was the acetone extract of *Euclea natalensis* (MIC = 26 μg/ml), and the compound with the highest activity was the naphthoquinone 7-methyljuglone, with an MIC of 1.55 μg/ml against pathogenic *Mycobacterium bovis* (McGaw et al., 2008). Interestingly, *Mycobacterium bovis* BCG was not as susceptible to the test compounds as the pathogenic *Mycobacterium bovis*, but highly comparable patterns of activity were observed between all the strains tested. For antimycobacterial activity against pathogenic *Mycobacterium bovis* (and *Mycobacterium tuberculosis*), *Mycobacterium smegmatis* appeared to be the best fast-growing predictor strain, while MIC values obtained using *Mycobacterium fortuitum* correlated well with those of *Mycobacterium bovis* BCG (McGaw et al., 2008).

The antimycobacterial efficacy of *Helichrysum caespititium* acetone and water extracts were investigated using the agar plate method against a drug-sensitive strain of *Mycobacterium tuberculosis* (Meyer et al., 2002). The acetone extract was relatively active, with inhibitory activity at 0.5 mg/ml, and the MIC was determined with the radiometric method to be 0.1 mg/ml. A novel phloroglucinol isolated from *Helichrysum caespititium*, caespitate, was also tested and the MIC was found to be 0.1 mg/ml against drug-sensitive and drug-resistant *Mycobacterium tuberculosis* strains, and it was concluded that this demonstrated the broad spectrum antimycobacterial efficacy of the compound (Meyer et al., 2002).

Another *Helichrysum* species, *Helichrysum melanacme*, was the subject of antitubercular activity investigations performed by Lall et al. (2006). It was reported that two chalcones isolated from the ethanol extract of *Helichrysum melanacme* shoots had MIC values of 0.05 mg/ml against *Mycobacterium tuberculosis* (using the BACTEC method). The ethanol extract presented MIC = 0.5 mg/ml and other compounds from the extract, quercetin and 3-methylquercetin, were inactive (Lall et al., 2006).

The broth microdilution method for antimycobacterial activity was used to screen seventy-eight extracts made from ten trees used in South African traditional medicine for many ailments (Eldeen and Van Staden, 2007). Sequentially prepared dichloromethane, ethyl acetate and ethanol extracts were tested against *Mycobacterium aurum* A+, selected because this species has been reported to be predictive of activity against *Mycobacterium tuberculosis* (Chung et al., 1995). The best activities were shown in ethanol extracts, and MIC values of all the extracts ranged from 0.195 to 6.25 mg/ml (Eldeen and Van Staden, 2007). Eldeen and Van Staden (2008a) also screened extracts of seven Sudanese medicinal plants (not included in Table 1) for antimycobacterial efficacy against *Mycobacterium aurum* A+. Ethanol extracts of *Acacia seyal*, *Combretum hartmannianum*, *Kigelia africana* and *Ziziphus spina-christi* showed MIC values between 0.19 and 1.56 mg/ml (Eldeen and Van Staden, 2008a).

Five plant species used as traditional medicines in the Western Cape Province of South Africa were screened for antimycobacterial effects against *Mycobacterium aurum* A+ using the agar disc diffusion and bioautography methods (Bamuamba et al., 2008). These plants were *Olea capensis*, *Tulbaghia alliacea*, *Dittrichia graveolens*, *Leysera gnaphalodes* and *Buddleja saligna*, and acetone:water (4:1) extracts of the latter two plants were active against *Mycobacterium aurum* A+ in a preliminary screening. Oleanolic acid was isolated from *Buddleja saligna*, and both oleanolic acid and ursolic acids were isolated from *Leysera gnaphalodes*, and these triterpenoids were held to be responsible for the antimycobacterial efficacy of the extracts (Bamuamba et al., 2008). The compounds were active in the disc diffusion and bioautography methods against *Mycobacterium avium*, *Mycobacterium scrofulaceum*, *Mycobacterium microti* and *Mycobacterium tuberculosis* H_{37}Rv, and were shown to be non-cytotoxic against Chinese hamster ovarian (CHO) cells with IC_{50} values greater than 100 μg/ml. These triterpenoids have been identified in many plant species, and possess a wide range of biological activities, with potential to act as lead structures for new antimycobacterial agents (Bamuamba et al., 2008).

A herbal treatment with a long and interesting history of use in South Africa, and more recently in Europe where it was introduced, is *umckaloabo*, comprising the roots of two *Pelargonium* species, *Pelargonium sidoides* and *Pelargonium reniforme* (Taylor, 2003; Bladt and Wagner, 2007). These species contain many secondary metabolites, including flavonoids, coumarins, phenolic acid derivatives, tannins and phytosterols (Kolodziej, 2000). Extracts and constituents of the two species showed antibacterial activity against Gram-negative and Gram-positive bacteria (Kayser and Kolodziej, 1997). Using bioassay-guided fractionation of *n*-hexane extracts of both *Pelargonium reniforme* and *Pelargonium sidoides*, mixtures of straight-chain fatty acids with activity against rapidly growing mycobacteria were identified (Seidel and Taylor, 2004). The test organisms included *Mycobacterium aurum*, *Mycobacterium smegmatis, Mycobacterium fortuitum*, *Mycobacterium abscessus* and *Mycobacterium phlei*. All saturated compounds except 12:0 showed no antimycobacterial activity, but unsaturated compounds were active in relation to their degree of unsaturation, their chain length and the bacterial species tested (Seidel and Taylor, 2004). Linoleic acid was the most potent compound, with MIC of 2 mg/l against *Mycobacterium aurum* (Seidel and Taylor, 2004). Mativandlela et al. (2006) reported mild antitubercular activity of organic solvent extracts of the roots of *Pelargonium reniforme* against *Mycobacterium tuberculosis* using the BACTEC method. It is highly probable that an important component of the antimycobacterial activity exhibited by *umckaloabo* may involve immune stimulating or modulating properties (Kayser et al., 2001; Bladt and Wagner, 2007), and Mativandlela et al. (2006) drew a similar conclusion. This concept requires further investigation, not only with regard to *Pelargonium* species but also for others with reputed anti-TB efficacy.

In a comparative bioactivity study of shoot and root extracts of *Pelargonium sidoides*, Lewu et al. (2008) determined the antibacterial efficacy of these plant parts following large scale exploitation of *Pelargonium sidoides* roots for local and export use. Traditionally the root is used medicinally but this study demonstrated that shoot extracts were equally as effective as those prepared from roots, indicating that sustainable harvesting utilizing the shoots may be substituted for root harvesting (Lewu et al., 2008). Although *Mycobacterium* species were not included in the panel of microorganisms against which the extracts were screened, the conclusion

was drawn that leaves may possibly be substituted for roots in medicinal use for ailments such as tuberculosis and bronchitis (Lewu et al., 2008).

Four species of the Asteraceae, the largest family in the Cape fynbos biome, were investigated for antimicrobial activities by Salie et al. (1996), namely *Arctotis auriculata* Jacq., *Eriocephalus africanus* L., *Felicia erigeroides* DC. and *Helichrysum crispum* (L.) D. Don. These plants were selected on the basis of their traditional use to treat infectious diseases by local peoples. Using the disc diffusion assay, *Arctotis auriculata* and *Helichrysum crispum* showed some activity against *Mycobacterium smegmatis*. The most active extract against the same organism in a broth microdilution assay was the petroleum ether extract of *Arctotis auriculata*, with a relatively high MIC of 8.5 mg/ml and an MBC > 10 mg/ml (Salie et al., 1996).

Hussein et al. (2007) isolated the known (+)-*trans*-ozic acid (1) and two new labdane diterpenoids (2 and 3) from *Orthosiphon labiatus* ethanol extract. From the ethanol extract of *Salvia africana-lutea*, the known abietane diterpenoids carnosol (4), rosmadial (5), and carnosic acid (characterized as its derivative 6) were obtained (Hussein et al., 2007). Compounds 3 and 6 exhibited MICs of 157 and 28 μM, respectively, against *Mycobacterium tuberculosis* (Hussein et al., 2007). Both the plants under study belong to the family Lamiaceae.

After screening several South African *Salvia* species for antimicrobial activity, Kamatou et al. (2007) found that the best activity was displayed by *Salvia radula*, *Salvia verbenaca* and *Salvia dolomitica*. These extracts of the aerial parts (prepared using methanol:chloroform in the ratio 1:1) showed MIC = 0.1 mg/ml against *Mycobacterium tuberculosis* H_{37}Ra using the BACTEC method. The MIC value of extracts from several other *Salvia* species was 0.5 mg/ml (Kamatou et al., 2007). *Salvia africana-lutea* showed promising activity against *Mycobacterium aurum* and *Mycobacterium tuberculosis* with MIC values of 2 and 1 mg/ml, respectively, and a lesser degree of activity against *Mycobacterium smegmatis* (MIC = 8 mg/ml) (Seaman, 2005).

Cyclopia intermedia (Fabaceae) fermented leaves and stems are used to prepare the popular beverage known as Honeybush tea, and the plant is also used to make a soothing herbal infusion to relieve coughs and bronchial ailments including tuberculosis, pneumonia and catarrh (Kamara et al., 2003). The presence of metabolites with beneficial pharmacological properties, including flavonoids, glycosylated flavonols, flavanones, isoflavonoids and flavones was held to contribute to the health-promoting benefits of the plant (Kamara et al., 2003).

The dichloromethane:methanol (1:1) extract prepared from the stem bark of *Garcinia polyantha* (Clusiaceae) and several compounds isolated from the plant material were shown to be active against *Mycobacterium smegmatis* (MC^2 155) and *Mycobacterium tuberculosis* (H_{37}Rv) using the microdilution and radiometric BACTEC methods, respectively (Kuete et al., 2007). One of the purified compounds, 1,3,6,7-tetrahydroxyxanthone resulted in MIC = 4.88 μg/ml against both *Mycobacterium smegmatis* and *Mycobacterium tuberculosis*, while the crude extract MIC was 78.12 μg/ml against both organisms (Kuete et al., 2007). Another compound isolated, namely 1,3,5-trihydroxyxanthone showed MIC = 39.06 μg/ml against *Mycobacterium smegmatis* and *Mycobacterium tuberculosis*, but two other isolated compounds, bangangxanthone and 1,3,6,7-tetrahydroxyxanthone, were active only against *Mycobacterium smegmatis* with MIC = 78.12 in both cases. The last compound, 5-hydroxyflavone, was inactive against both *Mycobacterium* species (Kuete et al., 2007). The similar levels of activity, or lack of activity, against the two organisms in the cases of these isolated compounds and the crude extract of *Garcinia polyantha* is interesting.

Saravanakumar et al. (2008) investigated the red marine alga, *Polysiphonia virgata* (Rhodomelaceae), for antimycobacterial activity against *Mycobacterium smegmatis* and *Mycobacterium tuberculosis*, isolating a mixture of long-chain fatty acids as the main active components. Commercial standards of these fatty acids were obtained for subsequent analysis. Oleic acid was the most active against *Mycobacterium smegmatis*, with a minimum inhibitory quantity (MIQ) obtained using direct bioautography of 0.8 μg, while linoleic and lauric acids had MIQ values of 1.56 and 3.13 μg, respectively (Saravanakumar et al., 2008). Against *Mycobacterium tuberculosis* H_{37}Rv in the BACTEC method, oleic acid was 100% inhibitory at a concentration of 25 μg/ml, and lauric, myristic and linoleic acids showed 98–100% inhibition at 50 μg/ml (Saravanakumar et al., 2008). Palmitic and stearic acids were not significantly inhibitory. At a concentration of 50 μg/ml against MDR *Mycobacterium tuberculosis*, linoleic acid was moderately inhibitory while lauric acid and myristic acid showed 75% and 88% inhibition, respectively (Saravanakumar et al., 2008).

Ethanol extracts of seven ethnobotanically chosen medicinal plants were tested against *Mycobacterium smegmatis* and *Mycobacterium tuberculosis* (Mativandlela et al., 2008). The extracts were also tested for cytotoxicity against the Vero monkey kidney cell line to determine selectivity. A flavone was isolated from *Galenia africana*, namely 5,7,2′-trihydroxyflavone (Mativandlela et al., 2008). The MIC of this flavone against *Mycobacterium smegmatis* was 0.031 mg/ml and against *Mycobacterium tuberculosis*, 0.10 mg/ml (Mativandlela et al., 2008). The positive results obtained in the preliminary screening for many of the extracts tested was held to lend scientific credibility to the traditional claims of the use of the plants for relieving TB-related symptoms such as cough, chest pains and fever.

Using the bioautography method, Thring et al. (2007) showed the antimycobacterial activity against *Mycobacterium smegmatis* of ethanol, ethyl acetate and methanol extracts of *Conyza scabrida* (Asteraceae) and *Dodonaea viscosa* var. *angustifolia* (Sapindaceae). These plants are used for medicinal purposes, including chest complaints and fever, in the Western Cape Province of South Africa (Thring et al., 2007).

Clarkson et al. (2007) used sophisticated HPLC-SPE-NMR techniques to elucidate seven new and four known drimane- and coloratane-type sesquiterpenes in an antimycobacterial fraction of *Warburgia salutaris* (Canellaceae). Using a spot culture method, Madikane et al. (2007) investigated the same plant species and discovered that a dichloromethane extract of the bark possessed antimycobacterial activity against *Mycobacterium tuberculosis* H_{37}Rv and *Mycobacterium bovis* BCG in the absence of cytotoxicity against mammalian macrophages. The extract and a novel drimane sesquiterpenoid lactone (11α-hydroxycinnamosmolide) isolated from the species inhibited pure recombinant arylamine *N*-acetyltransferase (NAT), an enzyme involved in mycobacterial cell wall synthesis (Madikane et al., 2007).

In the broth microdilution method with *Mycobacterium smegmatis* as test organism, Springfield and Weitz (2006) reported an MIC value of 15 mg/ml for the ethyl acetate extract of *Carpobrotus mellei* (Aizoaceae). Bioautography revealed the presence of three active compounds (Springfield and Weitz, 2006). *Carpobrotus muirii* and *Carpobrotus quadrifidus* were also active against *Mycobacterium smegmatis* in the disc diffusion and bioautography assays (Springfield et al., 2003).

As part of a pharmacognostical study of 26 South African plant species reputed to be used in traditional medicine, Scott et al. (2004) reported on uses of the plants and screened aqueous infusions of the plant material for activity against a number of microorganisms, including *Mycobacterium smegmatis*. The disc diffusion method was used by applying aliquots of 50 μg/ml solutions

onto sterile discs before placing these onto inoculated agar plates, and it was shown that only *Pelargonium grossularioides* was mildly active against *Mycobacterium smegmatis*, with the other infusions showing no activity (Scott et al., 2004).

Eldeen et al. (2008) isolated a new compound, termilignan B, as well as the known arjunic acid from *Terminalia sericea* (Combretaceae), and reported that these compounds displayed insignificant activity against *Mycobacterium aurum* A+. Leaves of another member of the Combretaceae, *Combretum imberbe*, yielded a free aglycone, 1α,3,β-hydroxyimberbic acid, which was highly active against *Mycobacterium fortuitum* with MIC = 1.56 μg/ml, while a second compound, 1α,3,β-hydroxyimberbic acid-23-*O*-α-L-3,4-diacetylrhamnopyranoside had MIC = 12.5 μg/ml (Katerere et al., 2003). Two other compounds from the same species, 1α,3,β-hydroxyimberbic acid-23-α-[L-3, 4-diacetyl-rhamnopyranosyl]-29-*O*-α-rhamnopyranoside and 1α,3,β-hydroxyimberbic acid-23-*O*-α-[L-4-acetyl-rhamnopyranosyl]-29-*O*-α-rhamnopyranoside showed MIC = 25 μg/ml against *Mycobacterium fortuitum* (Katerere et al., 2003).

A South African fynbos species, *Coleonema album* (Rutaceae) was reported to possess promising activity against *Mycobacterium smegmatis* in the bioautography assay (Esterhuizen et al., 2006). Subsequent determination of efficacy against a drug-sensitive strain of *Mycobacterium tuberculosis* revealed that an acetone extract inhibited more than 99% of the bacterial population (MIC_{99}) at 1 mg/ml. Coumarin aglycones were believed to be responsible for the antimicrobial efficacy of the plant extracts (Esterhuizen et al., 2006). *Coleonema album* acetone and ethanol leaf extracts showed moderate activity against *Mycobacterium aurum* in a broth microdilution assay, with both extracts providing an MIC value of 3.1 mg/ml (Eldeen and Van Staden, 2008b).

It was proposed by Taylor (2003) that the removal of inactive, commonly insoluble, components of plant extracts should increase pharmaceutical acceptability, and such modified, enhanced preparations may be culturally acceptable in southern Africa. Furthermore, the plants are indigenous and often readily available, so if proven to be effective there is good rationale for preparing such formulations locally for local markets, thus producing an effective supplement to conventional anti-TB therapy (Taylor, 2003). By appropriately combining components of indigenous medicinal plants that have either a direct or an indirect influence on mycobacterial survival, it may be possible to provide relatively inexpensive therapeutic formulations for treatment of mycobacterial infections, particularly in regions where cost considerations are of paramount importance (Seidel and Taylor, 2004).

7. Future prospects for antimycobacterial investigations of South African plants

Presently used drug regimes to combat TB infections comprise a combination of drugs administered over a period of several months, and patients frequently do not complete the treatment once symptoms begin to lessen. New antimycobacterial therapies that act faster may enhance patient compliance. In addition, lead structures with novel or more effective mechanisms of action are required urgently to overcome the problems of drug resistance. With the great diversity of plants in South Africa, screening of extracts of these plants for antimycobacterial efficacy has much to offer in the search for novel active metabolites that may be effective against *Mycobacterium tuberculosis* and other opportunistically infectious *Mycobacterium* species. Plants screened in studies to date have largely been selected for evaluation on the basis of ethnobotanical use in efforts to validate the traditional use of these plants as well as to obtain valuable active leads. Only a very small percentage of plants used for TB-related symptoms have been screened for activity thus far, and more work needs to be concentrated in this area. Promising results in the area of antimycobacterial screening in the Phytomedicine Programme (University of Pretoria) prove that random selection of plants also has much to offer in revealing active extracts worthy of further investigation.

There is an urgent requirement to standardize methods and cut-off points for describing antimycobacterial activity, as some authors report activity of extracts at 3 or 10 mg/ml while others, including ourselves, believe only MIC values less than 0.1 mg/ml are worthy of labeling active. Other recommendations are to include a parallel screen of mammalian cytotoxicity tests to preclude non-specific cytotoxicity from being interpreted as antimycobacterial efficacy following *in vitro* screens. This has been done in some studies to provide useful selectivity data. *In vivo* and mechanism of action studies are required on active metabolites or extracts, and where resources are available this should be a priority. Microarray studies may provide a useful indication of gene expression changes to assist in revealing the mode of action of promising compounds.

8. Conclusions

Tuberculosis is a major threat to the health of millions of inhabitants of developing as well as developed countries. Not only *Mycobacterium tuberculosis*, but also other species of *Mycobacterium* are emerging as health concerns, and new antimycobacterial drugs are desperately needed to counteract growing resistance towards currently available drugs.

A large number of plants are used in South African ethnomedicine to treat tuberculosis and related symptoms such as chronic coughs and respiratory complaints. Of the close to 180 species that have been documented as being employed for such purposes, around 30% of these have been screened for antimycobacterial activity, as reported in the available scientific literature (Table 1). Most of these investigations consist of *in vitro* tests with saprophytic, non-pathogenic *Mycobacterium* species, and screening methods vary. It is clear that studies with promising lead extracts or isolated compounds utilizing pathogenic strains and *in vivo* systems need to be carried out to verify their antimycobacterial activity.

Certain plant families appear to hold promise for development as anti-TB agents, for example several members of the Asteraceae have been screened for antimycobacterial efficacy with encouraging results. Ethnobotanical leads may yield good results, but it should be kept in mind that other methods of selection of plant material for screening may also be productive. The approach of screening selected representative species from each plant family has also resulted in good leads, and further investigation of bioactive chemical structures in related species may reveal the presence of chemicals of better activity than those in the initial test plant.

The methods of antimycobacterial screening, panel of microorganisms tested, and the way in which results are reported need to be standardized to enable comparisons to be made between different research groups. There is no doubt that natural products, with their range of interesting chemical structures and powerful antimycobacterial effects are certain to remain important participants in the development of new generations of antimycobacterial drugs. With its rich heritage of plant biodiversity coupled with the high local incidence of TB, South Africa is sure to be a key participant in the search for new antimycobacterial agents, whether as purified compounds or developed extracts, of plant origin.

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