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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