PHARMACEUTICALS

Antimycobacterial activity of indigenous South African plants

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South Africa has a heavy burden of tuberculosis (TB); an incidence of 526 cases per 100 000 of the population makes it one of the highest in the world.[1] Along with other severely affected countries in eastern and southern Africa, there is a significant degree of coinfection with HIV and *Mycobacterium tuberculosis* (MTB). In the World Health Organisation (WHO) African Region, 31% of adults aged 15 - 49 years with TB are also HIV-positive.[2] In South Africa, the cure rate for new smear-positive cases is 54%, and 63% of patients successfully complete their treatment regimen;[3] these figures are well below WHO targets. They should be viewed within the context of rising caseloads and a projected fall in public sector health care investment, after a period of substantial growth from 1993 to 1998.[4,5] Although the incidence of multiple-drug-resistant TB in South Africa is currently low,[6] HIV has been associated with epidemic outbreaks of multidrug-resistant strains.[2] There is an emerging view that the efficacy of TB control programmes, particularly with regard to adherence, could be increased if patients' beliefs about their infection were taken into account.[7] Traditional healers are widely consulted in rural areas of South Africa and have been successfully recruited as short-course DOTS (directly observed therapy short-course) programme supervisors.[8]

There may be other aspects of traditional medicine that could supplement conventional treatments and impact on adherence and cure rates. For example, Honeybush tea, an infusion of leaves and stems of *Cyclopia intermedia*, indigenous to South Africa and rich in flavonoids, has been used for restorative purposes, such as soothing coughs and alleviating bronchial complaints including TB, pneumonia and catarrh.[9] We have been investigating another herbal concoction with a long history of use in South African native medicine. Extracts of the roots of two species of indigenous geraniums, *Pelargonium sidoides* and *P. reniforme*, known locally as *umckaloabo*, were introduced into Europe as a 'vegetable germicide' and are still widely available, particularly in Germany, where they are used as over-the-counter preparations for treatment of various respiratory ailments.[10]

'Stevens' cure'

In 1897 Charles Stevens, a young mechanic from Birmingham, UK, fell ill with pulmonary TB and was sent by his doctor to South Africa to optimise his chances of recovery.[11] A fellow sufferer who claimed to have been cured of consumption directed him to a traditional healer, Mike Kijitse, who administered a preparation of the roots. Stevens persevered with the extracts and 3 months later felt well. Upon returning to England he was pronounced free of TB.[12] He later served in the Boer War and then stayed in South Africa to establish a company to sell *umckaloabo*, which he obtained from Kijitse.[12] Stevens promoted his business by writing to doctors in South Africa and England in praise of the anti-TB properties of *umckaloabo*. Having been fined for unauthorised medical practice, Stevens returned to England in 1907 and set up an establishment in Wimbledon to prepare and sell the remedy. In 1909, the British Medical Association (BMA), in a campaign against 'secret remedies', accused Stevens of quackery and fraud.[13] His income suffered as a result and he brought an action for libel against the BMA, which was heard in London in 1912. The jury could not agree on a verdict and a second trial took place in the summer of 1914. Despite the support of a number of expert witnesses who gave evidence in favour of Stevens, the jury found in favour of the BMA and Stevens was ordered to pay substantial costs.[12]

At the first trial, eight physicians who had used 'Stevens' Consumption Cure' offered clinical evidence in support of Stevens's contention that his extracts were efficacious. The majority were convinced that many of the patients they had treated, totalling around 130, had obtained significant benefit from the remedy. These doctors were ill at ease in finding themselves in conflict with their professional body and did not appear at the second trial. In 1920, a Swiss physician, Dr Adrien Sechehaye, heard of Stevens' Cure and decided to use it. He subsequently published a large body of evidence relating to its efficacy.[14,15] The first patient he treated was a young girl with severe TB who recovered after taking *umckaloabo* powder in a cup of water twice daily for 3 months. Sechehaye was impressed with the fact that fever and pain abated within days

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of commencement of treatment. During convalescence the patient stopped taking the extract and iliac cavity pain returned along with loss of appetite and general lassitude. When treatment was recommenced, she again improved, continued with the medication and this time recovered fully.[11] Periods of improvement therefore coincided exactly with those in which *umckaloabo* was administered. This prompted Sechehaye to administer *umckaloabo* to around 800 patients over the next 9 years, to present many of these cases to the Medical Society of Geneva[14] and to commission laboratory investigations of the antibacterial action of *umckaloabo*.[11]

Sechehaye published detailed case histories of 64 patients who had received extracts over the period 1920 - 1929,[11] paying particular attention to the accuracy of diagnosis, the possibility of spontaneous remission and the length of time patients remained symptom-free. In the large majority of patients he established the presence of TB through radiology, skin reactivity, isolation of MTB and the application of Koch's postulates. In most cases the disease was of a progressive nature, and was persistent. Many patients had a marked tendency to relapse with aggravated symptoms, and showed no tendency to spontaneous recovery. Patients were observed for up to 9 years after cessation of treatment with *umckaloabo*. In evaluating his case studies Sechehaye set aside 14 cases that he considered too recent, 2 who died, 1 whose recovery he ascribed to the Leysin sanatorium and 4 who disappeared. Of the remaining 43, 29 remained healthy. He ascribed some of the treatment failures to 'insufficient continuance of the treatment', 'indiscipline of the patient', unfavourable material and moral conditions', 'concomitant illnesses' and 'refractory cases'. Other less detailed case histories were published by Sechehaye.[14,15] He applied the same exacting criteria, and a large number of apparent cures were evident. During this period Stevens continued to send extracts to subscribers and some of the outcomes were described in a book published in 1931.[16] Conversations with patients, or their relatives, who were treated with *umckaloabo* supplied by Stevens support the view that the extracts were efficacious (TB patients continued to be treated with *umckaloabo* until the late 1950s).[17]

How it worked

Mainstream medical opinion at the time dismissed this work because the term *umckaloabo* had not been recorded in any recognised pharmacopoeia or contemporary book on pharmacy,[12] so the precise botanical nature of the remedy was in doubt for many years. Subsequent analysis indicated that the roots were obtained from species of the order Geraniaceae.[18] Phytochemical studies of *P. sidoides* and *P. reniforme* roots have revealed the presence of a large number of secondary metabolites, including coumarins, flavonoids, phenolic acid derivatives, phytosterols and tannins.[19] Constituents of both species show antibacterial activity against Gram-positive and Gram-negative isolates.[20] In the 1920s Sechehaye commissioned experiments in which MTB was grown on potato slices soaked in extract, with no noticeable effects on either growth or viability.[11] He cogently argued that indirect, macrophage-stimulating effects against the intracellular pathogen were most likely to explain any clinical efficacy. More recently, crude extracts have been tested against MTB by the Tuberculosis Antimicrobial Acquisition and Coordinating Facility, Alabama and showed some activity, with minimum inhibitory concentrations (MICs) typically around 12.5 g/ml.[19] We are systematically searching for compounds in roots with antimycobacterial activity and with the capacity to increase uptake and killing of mycobacteria by macrophages.[21] We found that antimycobacterial activity was restricted to extracts obtained with the apolar solvent *n*-hexane and gas chromatographic and spectroscopic analysis enabled us to identify mono- and diunsaturated fatty acids with antimycobacterial activity. The most potent were oleic acid and linoleic acid with MICs about 2 g/ml.[21]

We are now searching for compounds with the capacity to stimulate the uptake of MTB by macrophages and other phagocytic cells of the immune system. Our goal is to define the full repertoire of bioactive components of *umckaloabo* and to reconstitute and enhance the antimycobacterial activities of the concoction. Stevens experienced vomiting after drinking the extract provided by Kijitse, probably root bark boiled in goat's milk,[11] but the standard formulation he provided to his customers (0.75 g *umckaloabo* powder made from an infusion with hot water, taken twice daily[11]) was usually well tolerated.[11] The removal of inactive, often insoluble,[11] components should increase pharmaceutical acceptability. Such modified, enhanced formulations are likely to be culturally acceptable in sub-Saharan Africa; the plants are indigenous to the region and if proven efficacious there is no reason why formulations could not be prepared locally for local markets and form an effective supplement to conventional anti-TB therapy.

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