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A Review of Plants Used in South African Traditional Medicine for the Management and Treatment of Bovine Tuberculosis

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Abstract

Bovine Tuberculosis remains one of the most globally serious infectious agents for both animals and human morbidity and mortality, but with significant differences in prevalence across the globe. In developed countries, the incidence is now low and declining, but control and eradication remain a distant view. The prevalence of bovine TB caused by *Mycobacterium bovis (M. bovis)*, varies significantly across regions, although unlike for *M. tuberculosis*, data are sparse. The reduction in incidence and prevalence and control of both human and bovine TB is difficult and costly, yet some countries have managed to do this with some success. We draw from our experience to ascertain whether we may learn useful lessons from control efforts for both diseases in order to suggest effective control measures for bovine TB. Medicinal plants have multiple therapeutic effects. The assessment of biological activity of plants against Mycobacterium and its use for recovery provides an effective treatment approach. Ethnoveterinary used medicinal plants are the rich source of phytochemicals and secondary metabolites.These compounds can restore normal function, enzymatic activity and structure of hepatic cells against anti-TB drug induced hepatotoxicity. The present review covers comprehensive details on different antimycobacterial plants studied during past few years so that potential a can be studied for Bovine Tuberculosis .

Keywords: tuberculosis, *Mycobacterium bovis*, bovine TB, infectious diseases, zoonotic TB,

INTRODUCTION

Tuberculosis in animals occurs worldwide and is primarily known from cases in cattle and other bovids for which the disease is generally referred to as bovine tuberculosis.Mycobacterium bovis (M. bovis), the causative agent of bovine tuberculosis (BTB), has perhaps the broadest host range of the pathogenic mycobacteria [1] . Although the most commonly affected species are members of the Bovidae, even humans can be affected.

Mycobacterium bovis (M. bovis), the bovine tubercle bacilli, is the cause of bovine tuberculosis. It has a wide range of host animal species, which includes cattle, goats, bisons, antelopes, humans and non-human primates, and can cause disease in susceptible hosts [5].Considerably more attention is devoted to control of Mycobacterium tuberculosis in humans, than M. bovis in its multiple hosts.[2] Bovine tuberculosis is a chronic, debilitating disease, characterized by the formation of typical granulomatous lesions, yet slowly progressive both in the individual as well as on population level. *Mycobacterium bovis,*is an acid-fast organism belonging to the group *of M. tuberculosis* complex bacteria, along with Mycobacterium tuberculosis, Mycobacterium bovis, Mycobacterium africanum, Mycobacterium caprae,Mycobacterium microti, Mycobacterium pinnipedii,Mycobacterium canettii and the *oryx bacillus*.[3] The *M. tuberculosis* complex is generally considered a family of "ecotypes" of very closely related Mycobacteria, with each ecotype being adapted to cause tuberculosis disease in a specific host species or group, even though inter-species transmission can occur. In developing countries, especially in rural settings, where dwelling areas may be shared between humans and animals, humans may become infected. This may occur through the inhalation of cough sprays released by chronic coughing animals [9, 12], or/and by drinking raw milk from infected animals. [4, 8, 10]

Medicinal plants offer great hope to fulfil these needs and have been used for the treatment of various diseases for many centuries. These have been used extensively in the form of crude material or the pure and semi pure compounds isolated from plants. Recently, several reports and review articles appeared in the literature about medicinal plants and natural products with antimycobacterial activity[6,7].The purpose of this paper is to review the available information on medicinal plants use for bovine TB based on scientific evidence in order to identify knowledge resource for drug development , and to assess the burden of animal infections with M. bovis in addition to their public health importance.

Economics of Bovine TB

The negative economic impact of bovine TB is felt by farmers as well as national parks. Cattle are often brought into game reserves during droughts to access waterholes, and buffalo sometimes break through fences and browse with cattle in surrounding areas. [2] Running continuous cattle and wildlife testing programmes is enormously expensive, and the required slaughter of infected cattle can be devastating to local farmers. [2-3] Many game reserves and parks supplement their income with the sale of wildlife locally and abroad. [3-4] If bovine TB is discovered within their borders, the sale and movement of animals is restricted. [3**]** This can cause huge revenue losses, and severely limit the funds available to continue conservation efforts. Bovine TB is particularly concerning in areas where there are communities with high rates of HIV. An immune system weakened by HIV can increase the risk of developing TB infection by up to 31 times.[2-4]

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Methodology of the review

The literature search was performed from June 2018 to January 2020 using electronic search engines such as Google,Google scholar, publishing sites such as Elsevier, Web of Science, science Direct, Science Hub, Scopus ,BioMed Central (BMC) and PubMed. The databases and literature sources were chosen based on the topic covered (i.e. ethnopharmacology, pharmacology, phytopharmacology,
phytochemistry and therapeutic value). The following keyword were used to search literature sources: Bovine Tuberculosis. Other literature sources included papers published in international journals, reports from international, regional and national organizations, conference papers, books, theses, websites and other grey literature.

Treatment TB

The drugs that have been used to fight TB include isoniazid, rifampicin, pyrazina-mide, ethambutol,streptomycin, p-aminosalicylic acid,ethionamide,cycloserine
,rifabutin,aminoglycosides, ciprofloxacin, and ofloxacin, amithiozone, capreomy-cin, kanamycin, and thioacetazone. However, the important first-line anti-TB drugs are streptomycin, isoniazid, rifampicin, ethambutol, and pyrazinamide.[47] The present recommended treatment regimen is highly effective and rates of severe adverse reactions are low. However, unpleasant side-effects and a relatively long course of treatment are the drawbacks that increase the rate of non compliance to treatment regimen.[54] Such non adherence with the course of treatment leads to treatment failure and the development of drug resistance. The second-line drugs used for multidrug-resistant TB are more expensive, less effective, and more toxic than the four-drug standard regimen. This has led to increased pressure on current chemotherapy regimes and necessitated the need to look into new therapeutic and prophylactic measures.[49] Efforts are being made all over the world to explore the potential of natural products as antimycobacterial drugs.
A suitable drug would need to be cost effective, have low side-effects, and have
favorable pharmacokinetic properties. Considering the seriousness of the diseases,
the cost and side-effects of the available drugs, several attempts have been made to
discover antimycobacterial drugs from natural products. .[48] There is an increasing interest in natural products, including plant extracts, as potential therapeutic agents as evidenced by the extensive reviews on this topic [48–50].

Medicinal plants useful in Bovine Tuberculosis

Acacia robusta (Known as Acacia Karoo)

Introduction

Family: Fabaceae

Common names: sweet thorn (English); soetdoring (Afrikaans); mookana (North Sotho); mooka (Tswana); umuNga (Zulu) (Xhosa) mvumbangwenya (Tsonga), muvumba-ngwena (Ven.); umngamanzi (Zul.) [65]

Botanical description

The trees tend to branch quite high up, with nearly vertically spreading, upswept branches.A. karroo varies from a multi-stemmed shrub to a tree of up to 15 m in height [65]. The stem of A. karroo is dark brown to almost black characterized by rough and somewhat flaky, revealing reddish underbark [72]. A. karroo has pairs of large white spines which occur on the twigs and branches. The leaves are finely textured and dark green The leaves comprise about five pairs of leaflets, each divided into ten or more pairs of smaller leaflets of about 5 mm long [65,72]. The branches bear minute golden-yellow, ball-shaped flowers and the fruit is a long, narrow, spirally twisted pod [65]. The flowers appear in early summer in a mass of yellow pompons. The seed pods are flat and crescent shaped, sometimes with constrictions between the seeds. They are green when young becoming brown and dry. The pods split open allowing the seeds to fall to the ground [72].

Distribution description

It is distributed from tropical Africa southwards to Namibia, Mozambique, Swaziland and South Africa: KwaZulu-Natal, Limpopo, Mpumalanga, Northern Cape and North West Provinces. Subsp. *robusta* and *clavigera* occur from Ethiopia and Somalia, south to Namibia and northern and eastern South Africa. [65]

Medicinal Uses

It has been introduced elsewhere, e.g. in South Asia Ground and mixed with water to evict snakes[57] . It is also used for respiratory diseases [65]. It is crushed and boiled, and the steam inhaled to treat chest complaints, or the preparation applied to skin ailments [60] . The sweet thorn gets its common name from the gum which is exuded from wounds in the bark[65,72].

The roots of A. karroo are used as remedy for colic in infants in South Africa [76,100] while bark, gum and leaf infusions are used as remedy for diarrhoea and dysentery in South Africa [76,98]. A. karroo is also widely used as herbal medicine for sexually transmitted infections (STIs) in South Africa [100,72]. The bark, gum and leaves are used as emollient and astringent for colds, conjunctivitis and haemorrhage [60]. Gum of A. karroo is used with Capsicum spp. fruit and vinegar in a plaster dressing for acute osteomyelitis [60]. The gum from A. karroo has been used medicinally as emollient and as pharmaceutical aids such as emulsifiers, stabilisers of suspensions and additives for solid formulations. In South Africa, the gum of A. karroo has been applied to mouth ulcers and is diluted with water and used as a mouthwash against oral thrush and sprue [65,72]. Thorns are used to relieve heart pains [31]. A. karroo is used in ethnoveterinary medicine for diarrhoea, coughs and opthalmia in cattle and dogs [76,32]. Root infusions of A. karroo are used in ethnoveterinary

medicine as an antidote to poisoning as a result of cattle and goats eating Moraea spp. [33]. A. karroo is used to treat cattle which have tulp poisoning, that is poisoning caused by consuming parts of Homeria spp., a bulbous plant species known to be poisonous to stock [65,72].The leaves, flowers, pods and its parasitic mistletoes are excellent fodder for livestock and game in southern Africa [72]. Seeds of A. karroo have been used as a substitute for coffee [76].

Antimycobacterial

Madureira et al [61] evaluated antimycobacterial activities of hexane, dichloromethane, ethyl acetate and methanol extracts of aerial parts of A. karroo against Mycobacterium smegmatis using the broth microdilution method. The minimal inhibition concentration (MIC) of the tested bacterium ranged from 31.0 to >250.0 mg/mL, with the best activity with MIC value of 31.0 mg/mL displayed by n-hexane extract. [61]. Similarly, Nielsen et al [63] evaluated antimycobacterial activities of the stem methanol extract of A. karroo against M. smegmatis and Mycobacterium tuberculosis using the radiometric respiratory techniques with dimethylsulfoxide (DMSO) as control. Both M. smegmatis and M. tuberculosis demonstrated weak activity with minimal inhibition concentration (MIC) values of 1250 and 2500 mg/mL, respectively.

HIV reverse transcriptase/Antiviral activities

Mulaudzi et al [100] evaluated anti-HIVactivities of aqueous and methanol bark extracts of A. karroo using a non-radioactive HIV-1 RT colorimetric ELISA kit. The aqueous and methanol extracts of A. karroo bark showed good HIV-1 reverse transcriptase (RT) inhibition percentage (70%) at 1 mg/mL based on COX-assay, with all tested extracts exhibiting dose dependent IC50 values of (0.03 ± 0.00) and (0.10 ± 0.01) mg/mL, respectively [100].

Mamba et al [59]evaluated anti-HIV activities of ethanol extracts of A. karroo against recombinant HIV-1 enzyme using non-radioactive HIVRT colorimetric assay with doxorubicin as positive control. A. karroo demonstrated moderate inhibition of HIV-1 reverse transcriptase activity with 66.8% inhibition compared to 96.5% inhibitory activity demonstrated by doxorubicin, the positive control.

Cytotoxicity and toxicity

Adedapo et al [64] noted changes in the body weights of the mice but no significant changes were observed in the levels of some electrolytes (sodium, potassium and chloride). Lung with multiple abscess, kidney and liver with mild congestion were also observed histopathologically [64]. Cock and van Vuuren [58] evaluated toxicity of aqueous and methanol leaf extracts of A. karroo using a modified Artemia franciscana nauplii lethality assay. A. karroo leaf water and methanolic ectracts
induced mortalities in the Artemia nauplii below 20% following 24 h and 48 h of exposure, indicating that the extracts are of low toxicity.

Nyila et al [62] evaluated the cytotoxicity of ethyl acetate and chloroform extracts of A. karroo using the XTT method using the cell proliferation kit II (Boehringer-Mannheim) with zearalenone as positive control. Epicatechin 2 was the least toxic compound with IC50 value of >200.0 mg/mL, while b-sitosterol 1 and epigallocatechin 3 were found to be 63.82 and 28.91 mg/mL, respectively [62]. These preliminary cytotoxicity and toxicity evaluations carried out so far [58,62,,64] study concluded that caution must be exercised in the use of the plant for medicinal purposes.

Gunnera perpensa

Introduction

Family: Gunneraceae

Common names: river pumpkin, wild rhubarb (Eng.); rivierpampoen, wilde ramenas (Afr.); qobo (Sotho); uqobho (Swati); rambola-vhadzimu, shambola-vhadzimu (Venda); iphuzi lomlambo, ighobo (Xhosa); ugobhe, ugobho (Zulu)

Botanical description

Gunnera perpensa is a perennial, robust, erect herb up to 1 m. tall that always grows near water. The roots are up to 300 mm thick, creeping in black, muddy soil. The inside tissues are yellow-brown. All the leaves arise from a central tuft near the top of the apex, just above the soil level. [72] They are large, dark bluish green, kidney-shaped and covered with hairs on both surfaces, especially along the veins in young leaves. The margin of the leaves is irregularly toothed. The veins are very noticeable on the lower surface of the leaf, radiating from the point where the petiole joins the leaf, referred to as palmate radiation. The petioles vary in length from 150 to 750 mm. The flowers are numerous, small and not very noticeable, tiny pinkish reddish brown, borne on a long slender spike, which is taller than the leaves. On each spike there will be female flowers at the base, male flowers at the top and bisexual flowers in the middle, flowering between September and February [68,70]

Distribution description

Gunnera occurs naturally in central and southern Africa, Madagascar, New Zealand, Tasmania, Indonesia, the Philippines, Hawaii, Mexico, Central and South America.*G. perpensa* is widespread in tropical Africa from Sudan, Ethiopia, Zaire, Rwanda, Uganda, Kenya, Tanzania, Zimbabwe and Mozambiqu , extending along the central and eastern areas of southern Africa down to the Western Cape , including Swaziland and Lesotho . It has not been recorded in the Northern Cape Province, Namibia and Botswana[66,68,72] .It is an obligate wetland plant that grows in shallow water around the edge of pools in marshy areas or along streams. It cannot tolerate frost and even when growing in warm protective areas it will die back for the coldest months of the year.

Medicinal Uses

In South Africa, a decoction of the roots of *Gunnera perpensa* is used to expel the placenta after birth or to relieve menstrual pains[71,72,73] . According to Fox & Norwood Young (1982) [69] the Sothos, Fingos, Xhosas and Zulus eat the petioles and flower stalks raw. The petioles have a bitter taste unless the fibrous vascular bundles and the outer covering are removed. Root decoctions are used in traditional gynaecological practice as well as traditional veterinary practice to initiate labour, assist delivery or to expel the placenta. [72,73] Decoctions are also taken orally to relieve dysuria, rheumatic pains and dyspepsia, as a stomachic, or for colds. Externally a decoction is used as a wound dressing. Infusions may be taken internally or applied externally to treat psoriasis. [73]

Antimycobacterial

The MIC of the aqueous extracts provided us with the following: *G. perpensa* (0.250 mg/ml) and for *M. smegmatis*; *G. perpensa* (0.250 mg/ml) and for *M. tuberculosis* H37Rv (ATCC 25177 and *G. perpensa* (0.500 mg/ml) for MDR-TB. The mean MIC results of the aqueous crude extracts of each of the active plants showed lower antimycobacterial activities against *M. smegmatis* and *M. tuberculosis* H37Rv (ATCC 25177) in comparison to the positive controls rifampicin and isoniazid Positive controls Rifampicin and Isoniazid were inactive when used for MDR-TB and XDR-TB. [71]

HIV reverse transcriptase/Antiviral activities

Crude extracts from different parts of Gunnera perpensa show similar amount of inhibition:aqueous extracts (97%±0.110%SD) ,Methano / chloroform extracts (94%±2.374%SD), rhizome extracts (96%±0.475%SD) ,stem extracts (94%±3.723%SD),leaf extracts(96%±1.097%SD),Crude extracts were found to be significantly($P \leq 0.027$) non-toxic to CEM.NKR.ccR5 cells and PBMCs at 5 µg/ml.In acutely infected CEM.NKR.ccR5 cells,acutely infected PBMCs ,and chronically infected PBMCs Gunner perpensa extracts did not significantly($P > 0.05$) increase cell viability or reduced HIV core protein content,over 4 days.Gunnera perpensa was identified as containing a potecial active principle that significantly inhibits recombinant HIV reverse trancriptase [43]

Cytotoxicity and toxicity

The bioassay against brine shrimp larvae (nauplii) has been employed to test for the presence of toxic substances, and also as a means of facilitating the isolation of biologically active substances[74] .This assay can be used to evaluate plants for pharmacological activity, taking into account the principle that pharmacology is merely toxicology at a lower dose [84] . All of the *Gunnera* extracts studied were toxic at a concentration of 10 mg ml–1 At 1 and 0.1 mg ml–1, the hexane and dichloromethane extracts had no effect on the nauplii. This indicates that highly non-polar compounds from *G. perpensa* rhizomes are not toxic to brine shrimp nauplii. The acetone extract appeared to be the most toxic, as at a concentration of 1 mg ml–1,no nauplii survived. In

relation to results obtained for other plant extracts, the *G. perpensa* extracts are not regarded as being highly toxic. For instance,Wanyoike, Chhabra, Lang'at-Thoruwa & Omar(2004) [75] reported toxic effects against brine shrimp larvae by a selection of Kenyan medicinal plant extracts at concentrations of less than 0.03 mg ml–1.

Tetradenia riparia

Introduction

Family: LAMIACEAE

Common Name: Misty Plume Bush, Ginger Bush (English); Gemmerbos, Watersalie (Afrikaans); iBoza, iBozane (Zulu)

Botanical description

Tetradenia riparia is a tall, aromatic shrub up to 3 m in height but sometime 5m. It is slightly succulent and has an irregular branch pattern. [65,72] The stems are brown and smooth, except for the younger portions which are covered with glandular hairs and have a ruby tinge. The glandular hairs also cover both surfaces of the leaves and make them slightly sticky to the touch. The leaves spiked and bright green and are slightly heart shaped with the margin irregularly and bluntly toothed. [60,77] Male and female flowers are borne on separate plants in spikes which differ in size and shape. The male flower spikes in profusion create more of the "mist" effect than the female flowers which tend to be more compact. [77] The flowers usually appear when the plants are bare and are carried in the top section of the branches. Flowering occurs from June until August which coincides with the frosts in Highveld gardens. [76] The flowers may be spoiled by this so it is a good idea to plant the ginger bush in a warm spot such as against a north-facing wall or on a succulent rockery. [65,76,77]

Distribution description

The natural distribution ranges from KwaZulu-Natal, Northern Province, Mpumalanga in South Africa to Swaziland, Namibia, Angola and northwards through tropical East Africa into Ethiopia. [60,77]

Medicinal Uses

(Hutchings) in 1996 [60] stated that the plant extracts are used to treat respiratory ailments such as coughs, colds, sore throat and mouth ulcers and Watt and Breyer-Brandwijk (1962) [76] reported that the leaves are used to treat stomach ache, diarrhoea, influenza, fever and malaria.Inhaling the scent of the crushed leaves apparently also relieves headaches. [77]

Antimycobacterial

The MIC of the aqueous extracts provided us with *T. riparia* (0.125 mg/ml) for *M. smegmatis and T. riparia* (0.250 mg/ml) for *M. tuberculosis* H37Rv (ATCC 25177) *T. riparia* (0.250 mg/ml) for MDR-TB.The mean MIC results of the aqueous crude extracts of each of the active plants showed lower antimycobacterial activities against *M. smegmatis* and *M. tuberculosis* H37Rv (ATCC 25177) in comparison to the positive controls rifampicin and isoniazid .Positive controls Rifampicin and Isoniazid were inactive when used for MDR-TB and XDR-TB. [71]

HIV reverse transcriptase/Antiviral activities

No antiviral activity against Coxsackie virus, poliovirus (unspecified), measles virus and Semliki-Forest virus was demonstrated in these studies [75]. Some of the observed antibacterial activity of *T. riparia* has been attributed to the presence of diterpenes [82,83].Research has shown that *Tetradenia riparia* has antibacterial and anti-fungal effects and some anti-malarial activity [66]

The plant extract can also be used to treat immunologically compromised patients including AIDS and malignant disease victims [79,81] . The plant's ability to inhibit the growth of *E. coli* is a scientific justification that the plant can be used to treat against enteric infections caused by the bacteria. The plants extract can also be used to treat against gastro-intestinal diseases, ear infections, urinary tract infections and wounds infections caused by *Proteus vulgaris* [79,80] .

Cytotoxicity and toxicity

Results revealed that aqueous extract of *T. riparia* were not toxic to brine shrimp larvae at all concentrations tested (50 µg/ml, 100 µg/ml and 1000 µg/ml).Following the promising antimycobacterial activity, the cytotoxic effect of the plants extracts *T. riparia* against mouse BALB/C monocyte-macrophage (J774.2) and human peripheral blood mononuclear cells (PBMCs). In vitro cytotoxicity test to measure the damage caused by the antimycobacterial plant extracts on normal living cells. To determine whether the plant extracts could be used for therapeutic purposes without excessive damage to host cells.The aqueous extracts of *T. riparia* showed an increase in cell viability for the J774.2 cell line .As the concentration increased so too did cell viability. It can be noted that the active plant extracts stimulated the growth of the cells and was not toxic to the J774.2 cell line at the highest concentrations tested. [71]

***Carpobrotus edulis* (L.) L.Bolus**

Introduction

Family: Aizoaceae

Common names: sour fig, Cape fig, Hottentots fig (Eng.); ghaukum, ghoenavy, Hottentotsvy, Kaapsevy, perdevy, rankvy, suurvy, vyerank, (Afr.); ikhambi-lamabulawo, umgongozi (Zulu) . [88,90]

Description

A robust, flat-growing, trailing perennial, rooting at nodes and forming dense mats. The succulent horizontal stems curve upwards at the growing point. The leaves are succulent, crowded along the stem, 60-130 x 10-12 mm, sharply 3-angled and triangular in cross-section, yellowish to grass-green, and reddish when older. [77,85]

Flowers are solitary, 100-150 mm in diameter, yellow, fading to pale pink, produced mainly during late winter-spring (August-October). They open in the morning in bright sunlight, and close at night. [85,86] Look into the centre of the flower and you'll see many stamens surrounding a beautiful starfish-like stigma. This species is easily
distinguished from the others as it is the only one with yellow flowers. [87]

Distribution description

Carpobrotus edulis grows on coastal and inland slopes from Namaqualand in the Northern Cape through the Western Cape to the Eastern Cape. It is often seen as a pioneer in disturbed sites. [77,88]

Medicinal Uses

The leaf juice is astringent and mildly antiseptic. It is mixed with water and swallowed to treat diarrhoea, dysentery and stomach cramps, and is used as a gargle to relieve laryngitis, sore throat and mouth infections. [77,89,] Chewing a leaf tip and swallowing the juice is enough to ease a sore throat. Leaf juice or a crushed leaf is a famous soothing cure for blue-bottle stings-being a coastal plant it is luckily often on hand in times of such emergencies. [89] The leaf juice is used as a soothing lotion for burns, bruises, scrapes, cuts, grazes and sunburn, ringworm, eczema, dermatitis, sunburn, herpes, nappy rash, thrush, cold sores, cracked lips, chafing, skin conditions and allergies. [77,89] An old and apparently very powerful remedy for constipation is to eat fruits and then drink brackish water. Syrup made from the fruit is said to have laxative properties. A mixture of leaf juice, honey and olive oil in water is an old remedy for TB. [77,86,87]The leaf juice also relieves the itch from mosquito, tick and spider bites both for people and their animal companions. [87]The Khoikhoi took an infusion of the fruits during pregnancy to ensure a strong, healthy baby and an easy birth and smeared leaf sap over the head of a new-born child to make it nimble and strong. In the Eastern Cape it is also used to treat diabetes, and diptheria. [86]

Antimycobacterial

Carpobrotus edulis aqueous leaf extract demonstrated noteworthy antibacterial activity against *Mycobacterium aurum*. The ethanolic extract showed significant activity against *staphylococcus aureus, Bacillus cereus, S* and *Mycobacerium aurum* [7]

HIV reverse transcriptase/Antiviral activities

Hexane extracts were also effective against all the five fungal isolates while acetone extracts were only effective against *C. krusei* at 0.04mg/ml. The results are consistent with those of Wilfred *et al.* [95] when the effects of the acetone extracts of *arctotis arctotoides* on the growth of some opportunistic fungi associated with HIV/AIDS were evaluated.

Cytotoxicity and toxicity

A selected number of *Carpobrotus* species with medicinal properties were tested for cytotoxicity using the brine shrimp lethality test. The aqueous extract of *Carpobrotus mellei* and tthe methanol extract of *Carpobrotus quadrifidus* showed the highest activity than *Carpobrotus edulis* and other species tested [92]. Akhalwaya *et al.* [93] investigate the cytotoxicity of indigenous South African medicinal plants used to treat oral infections. *Carpobrotus edulis* is one of the medicinal plants tested and was considered non- toxic with percentage mortality rate of 47.43% at 24 hour and 48.06% at 48 hours. Cock and Van Vuuren [94] also found out that aqueous and methanol extracts of *C. edulis* are either non-toxic, or of low toxicity in the brine shrimp lethality bioassay.

Dugesia sicula Lepori, 1948, a freshwater planarian was used to investigate the effect of aqueous-acetone *C. edulis* extracts on regeneration. Morphological changes were evident on microscopic analysis of *Dugesia sicula Lepori* in ordinary medium containing phenolic extracts at non-toxic concentrations. The study suggests that *C. edulis* polyphenols can have harmful effects on the development of stem cells [93]. *Carpobrotus edulis* polyphenols can therefore have ecotoxicological impact on the planarians' physiology in the environment.

***Sutherlandia frutescens* (*Lessertia frutescens*)**

Introduction.

Family: Fabaceae

Common names: sutherlandia, cancer bush, balloon pea (Eng.); umnwele(Xhosa & Zulu); kankerbos, blaasbossie, blaas-ertjie, eendjies, gansiekeurtjie, klappers, hoenderbelletjie (Afr.)

Botanical description

Sutherlandia frutescens (L.) R.Br. belongs to the family Fabaceae known as the legume, pea, or bean family. It is commonly known as the cancer bush because of the reported use by Khoi-San and Cape Dutch people against

internal cancers since 1895 [109, 122 , 123]. It is a small shrub of 0.3 - 1.5m in height[104] The leaves are deep green and divided into numerous small leaflets. They may be slightly to densely hairy often giving the plant a silvery appearance They have a very bitter taste. [105,106] The flowers are orange-red, up to 35 mm long, and are carried in short racemes in the leaf axils at the tips of the branches in spring to mid-summer (September - December). [72,106,108] The seedpods are membranous and bladder like with a papery texture and contain a large number of flattened black seeds [108] The large red owers, around 3 cm long, are followed shortly by bladderlike fruits [118] . It can be used in dry flower arrangements as it dries well, maintaining its colour and form[119] .

Distribution description

With the genus being restricted to southern Africa [101], this so the-wooded shrub with reedy stems is found in Botswana, Namibia, and South Africa [118].The *Sutherlandia frutescens* is mainly found throughout the South West and Southern Cape (the dry parts of Southern Africa) [101] (Namaqualand (Garies to Kamiesberg) and throughout the Karoo[65] It is also found in KwaZulu-Natal and Mpumalanga. It shows remarkable variation within its distribution.(89,99,101)

Medicinal Uses

The original inhabitants of the Cape, the Khoi San and Nama people, used it mainly as a decoction for the washing of wounds and took it internally to bring down fevers. [89,106] It is also known to have been used in the treatment of eye troubles, the eyes being bathed with a decoction of the plant. It continues to be used to this day as a remedy for the above-mentioned ailments. [106].*Sutherlandia frutescens* has been used in the traditional medicine systems of different cultural groups for a wide diversity of ailments, including stomach ailments, backache, diabetes, stress, fever, and wounds [109,118] . It is used for internal cancers, but despite numerous claims and anecdotes, there is no scientific evidence to corm this [72]. The dried leaves and other preparations are used as a general tonic[118] *Sutherlandia* along with *H. hemerocallidea* are the two main African medicinal plants used for treatment of HIV/AIDS and are endorsed by the South African Ministry of Health for HIV management [120].It is also used to treat colds, 'flu, asthma, TB, bronchitis, rheumatism, rheumatoid arthritis and osteo-arthritis, liver problems, haemorrhoids, piles, bladder, uterus & 'women's' complaints, diarrhoea & dysentery, stomach ailments, heartburn, peptic ulcers, backache, diabetes, varicose veins and inflammation. [72] It is also used in the treatment of mental and emotional stress, including irritability, anxiety and depression and is used as a gentle tranquillizer. [112] It is said to be a useful bitter tonic and that a little taken before meals will aid digestion and improve the appetite. It is considered to be a good general medicine. [108-111]

Antimycobacterial

The DCM:MeOH 1:1 extract had the lowest MIC value against *M. smegmatis* The water extract showed the highest MIC value after 24 h of incubation.The crude extract was assayed against *M. smegmatis* to determine its

MIC values. The DCM:MeOH 1:1 extracts had the greatest activity with MIC values ranging from as low as 0.28 mg/mL to 1.04 mg/mL and water extracts had the least. The same observation was made by[114] Katerere and Eloff (2005) where the hexane, DCM and ethylacetate extracts produced better antimicrobial activities (MIC values of 2.50 mg/mL, 1.25 mg/mL and 0.31 mg/mL, respectively) against *Staphylococcus aureus* which is a Gram positive microorganism that cannot be compared to Mycobacterium spp.; their water, ethanol and acetone extracts had MIC values as high as 10 mg/mL.

HIV reverse transcriptase/Antiviral activities

Mills, Foster *et al.* (2005) [116]have reported that the herbal remedy has been recommended for HIV management, which was shown to cause an improvement in CD4 counts together with a decrease of viral loads in AIDS patients. It is hoped that this treatment regime will delay the progression of HIV into AIDS. They further reported that *Sutherlandia* contained inhibitory compounds active against HIV target enzymes. Canavanine, which was found to be present in the extracts, has also been reported to have antiviral activity against influenza and retroviruses. *Sutherlandia* extracts have also been reported to have effects on cytochrome P450 3A4 metabolism, together with activation of the pregnane X-receptor, which are involved in anti-retroviral metabolism. Mills, Foster *et al.* (2005), [116] have further indicated that factors which need to be taken into consideration with HIV patients are risk of treatment failure, induced viral resistance or subsequent drug toxicity. They also considered that uncontrolled human consumption of *Sutherlandia* extracts could affect anti-retroviral drug metabolism, leading to bi-directional drug interactions and loss of therapeutic efficacy. *Sutherlandia* has also recently been shown to interact with the permeability glycoprotein (P-gp) receptor, to allow for increased absorption of anti-retroviral drugs (such as Amprenavir) into the cell system, which could lead to drug intoxication, but had no significant interaction with the drug itself [115].

Cytotoxicity and toxicity

The long history of traditional use, with no reports of any serious side effects, suggests that *Sutherlandia* can be considered as being generally safe [109,125] .The South African Ministry of Health has concluded that this product is safe based on primate safety studies [120] Recent preclinical studies indicate that concomitant administration of *Sutherlandia* with prescription drugs (CYP3A4 substrates) could
possibly lead to therapeutic failure and clinically relevant drug-herb interactions [124,125].

Extract (aqueous extract of the fresh leaves) was chosen because it showed an increase in cancer cell viability at 25 µg/ml and a decrease in cancer cell viability at 100 µg/ml for all three cell lines and at 25 µg/ml it shows an increase in TNF and IL8 .To determine the effects of this extract on macrophage immune cells would provide evidence as to whether *S. frutescens* is cytotoxic to the immune cells at the same concentrations. [126] Extract illustrated an increase in cancer cell viability at 25 µg/ml and a decrease at 100 µg/ml but the effect on macrophage cell viability increased at both concentrations (V = 208.03 and 197.28 **%** at 25 and 100 µg/ml respectively). [126] From these observations it can be stated that *S. frutescens* was not cytotoxic to the macrophage cells, favoured their survival and growth and displayed selectivity for immune cells. These results are supported by Ngcobo (2008) [113] who also found that aqueous extracts were not cytotoxic to normal T cells. Nbcobo (2008) [113] also showed that the ethanol extract induced proliferation in the T cells after 24

hours but had the opposite effect after 48 hours, while the aqueous extract significantly increased the T cell viability only after 48 hours of exposure. The results concluded that higher concentrations could be toxic to the normal T cells while lower concentrations of *S. frutescens* could stimulate the immune cells. To conclude, the above observations give reason to suggest that if *S. frutescens* was to be administered to cancer patients, at the correct dosages and time intervals, it could possibly have an additive effect on the immune cells of the body and increase their numbers so that there would be more cells to help fight off the invading microorganis.

***Lippia javanica* (Burm.f.) Spreng**

Introduction

Family: Verbenaceae

Common names: fever tea, lemon bush (English); koorsbossie, beukesbossie, lemoenbossie (Afrikaans); mutswane, umsutane (Swati); inzinziniba (Xhosa); umsuzwane, umswazi (Zulu); musukudu, bokhukhwane (Tswana)

Description

Lippia javanica (Burm.f.) Spreng is an erect woody shrub stands erect and is multi-stemmed of 1 up to 2 m high, with strong aromatic leaves, which gives off a lemon-like fragrance when crushed. [72,76,89] The stems have a square appearance when looked at in cross-section. The leaves are hairy with noticeable veins and when crushed gives off a strong lemon-like smell. [72,99,] It is said to be one of the most aromatic of South Africa's indigenous shrubs. The small cream flowers can be found on the shrub from summer to autumn in some areas and in others are produced all year. [69] These flowers are arranged in dense, rounded flower heads. The fruit are rather inconspicuous, small and dry. [72,89]

Distribution and habitat

These plants are widespread throughout large parts of South Africa, with the exception of the Western Cape. *Lippia javanica* grows from the Eastern Cape northwards extending into tropical Africa including Botswana, Swaziland, Mozambique, Malawi, Tanzania, Zambia, Tanzania, and Kenya.It grows in open veld, in the bush, as well as on forest margins. [69,72,99,]

Medicinal Uses

Its infusion is commonly used in Africa as a tea against various ailments such as influenza, measles, rashes, malaria, stomach problems, fever, colds, cough, headaches. [69,72] This plant is well known medicinally to many African people and to many avid herbalists and herb gardeners. [72,89] Different parts (the leaves, twigs and occasionally the roots) of the plant are used for different reasons. The Xhosa people are known to drink it in a weak infusion as a tea substitute and in a stronger infusion for the treatment of coughs, colds and bronchial

problems in general. [65,72,89] They use the leaves and stem and drink it with milk or water. In addition the Xhosa people also use *Lippia javanica* for the disinfection of meat that has been infected with anthrax. [65,89]

This herb is also said to be affective against fever, especially in cases of malaria, influenza, measles, and as a prophylactic against lung infections. The smoke from the herb has proven to be affective, if inhaled, against asthma, chronic coughs and pleurisy. [72] The leaves and stems are burned. Skin disorders, such as heat rash and other rashes, as well as scratches, stings and bites can also be treated. Here the tea is usually cooled and then applied like a lotion. [72] Even lice and scabies can be treated with it. Apart from its medicinal uses *Lippia javanica* is also used ritually in a cleansing ceremony when someone has been in contact with a corpse and apparently for protection against dogs, crocodiles and lightning. [65,72,76,89] The Masai make a red ointment from it, which is used to decorate their bodies. [83]

Antimycobacterial

To evaluate antimycobacterium activity ten plants species were tested against H37Rv, a drug-sensitive strain of *Mycobacterium tuberculosis* at concentrations ranging from 0.5 to 5.0 mg/ml using BACTEC radiometric method. [91] The plant species tested *Lippia javanica* were observed to be active against the H37Rv. (ATCC 27294) strain of TB at a concentration of 0.5 mg/ml which was the lowest concentration used in this study. [91]

HIV-1 reverse transcriptase/Antiviral activities

In study, [91] compounds isolated from *Lippia javanica* were investigated for their ability to inhibit HIV-1 Reverse transcriptase activity *in vitro* using a non-radioactive assay. [91] Two compounds "1-(3,3-dimethyoxiranyl)- 3-methyl-penta-2, 4-dien-1-one" and **"**Pipertinone" from *L. javanica* demonstrated inhibitory activity against the enzyme by 90 %, at 100 µg/ml. One compound "5, 7-dimethoxy-6-methylflavone"
Evaluation of these compounds against HIV RT showed that compounds 28 and 30 inhibited the enzyme by 91, 53 and 52% at 100 mg/mL. [91] , Mojovo[91] and co-workers35 isolated eight compounds from *L. javanica* ethanolic extract. The eight compounds were: 4-ethyl-nonacosane (27), three monoterpenes, (E)-2(3)-tagetenone epoxide (28), myrcenone (29), piperitenone (30) and four flavanones, apigenin (31), cirsimaritin (32), 6-methoxyluteolin 4'- methyl ether (33) and 6-methoxyluteolin 3',4',7-trimethyl ether (34) [91].The results indicated that compound 28 could be of interest as a template in drug discovery research due to the to the higher activity as compared to the other compounds. The MIC of compound (32) was found to be 200 mg/mL against the H37Rv strain[91].

Cytotoxicity and toxicity

The crude extracts *L. javanica* isolated compounds were evaluated *in vitro* for their inhibitory ability against the growth of Vero cell line. These cell line was inhibited by all the compounds at the highest concentration tested (200 µg/ml), except the compound piperitenone. [91] The results obtained from the calculation made from spectrophotometer readings, indicated that the crude extracts *L. javanica* and piperitenone compound

have little or no toxicity on Vero cells by exhibiting IC50 values of greater than 100 µg/ml. [91]The compounds 5,7-dimethoxy-6-methylflavone and Jacarandic acid or Euscaphic acid showed very high toxicity by exhibiting IC50 values ranging from 2.735 µg/ml to 19.21 µg/ml. [91]

Conclusion and future perspectives

The review proposes that there is an increase in demand of phyto-pharmaceuticals all over the globe, firstly because of the adverse health effects of the allopathic medicines and secondly the unique ability of many plants to counter the deadly pathogen. Zoonotic *M. bovis* infections cause a threat to individual health, mainly in developing countries. This is exacerbated by inadequate monitoring of the TB prominence of rural cattle herds, coupled with the high incidence of HIV and AIDS. Many plant-based remedies are used in traditional medicine to treat TB-related symptoms.[127] Bovine tuberculosis (BTB) is one of the oldest and deadliest bacterial diseases. It is still affecting and posing major health, social and economic burden at the global level. However, most affected people are mainly in low and middle income countries. TB exists in both active and latent, with one-third of the world population being latently infected. Anti-TB drugs with specific mechanisms of action were discovered. Despite this, the length, the cost, the emergence of *Mycobacterium tuberculosis* resistant strains and post-treatment relapse pose serious threats the disease elimination and there is an urgent need of approaches to develop new and more effective news drugs. Target structure-based high throughput screening for anti-TB drugs leads has been used before. The lack of complete knowledge of *M.tb* biology and the complex *M.tb* pathogenesis have led to the failure. The metabolomics approach is likely to provide new insights into the discovery through understanding their mechanism of action and eventual development of anti TB drugs especially from medicinal plants. To render this feasible, the mechanisms action of the plant-derived antimycobacterial agents should be clearly understood. Metabolomics protocol has to be established in such way as to identify the metabolites affected by antimycobacterial drug leads from the plant extract screened that will guide elucidation of their targets and the mechanisms of their actions.

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CONFLICT OF INTEREST

The author declares that he has no conflict of interest..

AUTHORS' CONTRIBUTIONS

The author declares that this work was done by the author named in this article.

Ethics approval and consent to participate

Not applicable.

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1.1 Plants derived compound for Bovine TB

Plant	Compound	Organism	MIC	References
Cetraria islandica	protolichesterinic acid	*M. aurum*	125µg/ml	[42]
Cladonia arbuscula	ursnic acid	*M. aurum*	32µg/ml	[42]
Evodia rutaecarpa	evocarpine	*M. fortuitum* *M. smegmatis* *M. phlei*	2µg/ml 2µg/ml 2µg/ml	[40]
Galenia africana	Trihydroxyflavone	*M.smegmatis*	0.031µg/ml	[56]
Parmelia saxatilis	salazinic acid	*M. aurum*	125µg/ml	[42]
Pelargonium sidoides	palmitic	*M. aurum* *M.smegmatis* *M.fortutium* *M. abscessus* *M. phlei*	2µg/ml	[20]
Sanguinaria canadensis	Chelerythrine sanguinarine	*M. aurum* *M.smegmatis* *M. bovis BCG* *M. aurum* *M.smegmatis*	7.3µg/ml 29µg/ml 14.3µg/ml 9.61µg/ml 41.2µg/ml	[46]

		M. bovis BCG	24.5µg/ml	
Stereocaulon alpinum	atranorin lobaric acid	*M. aurum*	125µg/ml	[42]
E. natalensis	7-methyljuglone	*M.smegmatis* *M. bovis BCG* *M. bovis ATCC* *M. fortuitum* *M. tuberculosis*	1.57µg/ml 11.78µg/ml 1.55 µg/ml 22.14 µg/ml 0.50µg/ml	[127]
Ducrosia anethifolia	furocoumarin	*M. fortuitum* *M. aurum* *M. phlei* *M.smegmatis*	64 -128 µg/ml	[45]
Mitracarpus scaber	azaanthraquinone	*M.intracellulare*	6.25 µg/ml	[34]
Cleistopholis patens	cleistopholine	*M.intracellulare*	12.5 µg/ml	[35],
Strobi-lanthes cusia	Tryptanthrin	*M. tuberculosis*, *M. avium* complex, *M. smegmatis*	1 µg/ml 4 µg/ml 6 µg/ml	[36, 37].
Cryptolapis sanguinolenta	Cryptol-epine (**11**) neocryptolepine (**12**) dimer biscryptolepine(**13**)	*M. fortuitum*	25 µg/ml, 31 µg/ml, 6.25 µg/ml	[38]
Amyris elemifera	texalin (**14**),	*M. avium* *M. kansasii*	25 µg/ml	[39].
Peucedanum ostruthium	furanocou-marin	*M. abscessus M. aurum* *M. fortuitum* *M. phlei* *M. smegmatis*	3.4 -107.4 µg/ml	[44].
Pelargonium reniforme	linoleic acids	*M. aurum* *M. smegmatis* *M.fortutium* *M. abscessus*	2 µg/ml 2 µg/ml 2 µg/ml 2 µg/ml	[20].

		M. phlei	2 µg/ml	
Psoralea corylifolia	Chelerythrine Bakuchiol	*M. avium* *M.smegmatis* *M. aurum* *M. bovis* BCG	29.0 µg/ml 75.56µg/ml 15.8 µg/ml 21.4 µg/ml	[46].
Aframomum melegueta	6-paradol (**16**) and 6-shogaol (**17**)	*M. chelonei* *M.intracellulare* *M. smegmatis* *M. xenopi*	10–15 µg/ml	[47]
Commiphora mukul	benzophenanthridine	*M. avium*	62.5 µg/ml	[46]
Ferula communis	ferulenol (**20**), Licochalcone A	*M. fortuitum* *M. phlei* *M. aurum* *M.smegmatis* *M.intracellulare* *M. xenopi* *M. chelonei* *M. smegmatis* *M. bovis* *M. bovis* BCG	2µg/ml 2µg/ml 2µg/ml 0.5µg/ml 1.25 µg/ml 10–20 µg/ml 5–10 µg/ml	[41] [51] [52,53]