Exploring ethnomedicinal approaches in combating infectious tuberculosis: A South African alternative

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ABSTRACT
Tuberculosis (TB) has become a global health crisis, affecting one-third of the global population. It is characterized as a highly infectious disease due to Mycobacterium tuberculosis infection. According to the World Health Organization, TB causes 1.5 million fatalities worldwide per year. Moreover, persistent TB infection in patients with human immunodeficiency virus is responsible for countless deaths and has become a major player in antimicrobial resistance. Despite TB management strategies, multidrug-resistant TB has dramatically increased and anti-TB drugs have become highly toxic and less effective. Studies have validated the scientific importance of traditional African practices in treating infectious diseases. As a result, the global population is gravitating toward a more natural and eco-friendly approach. Hence, there is a growing interest in using medicinal plants as natural alternatives to conventional antimicrobial drugs. No wonder 80% of the global population depends on medicinal plants for primary healthcare. Southern Africa is considered an unexplored “Garden of Eden” for the discovery of novel biocompounds for pharmaceutical applications. Several commercial natural products have southern African origins, which gained international recognition. Furthermore, medicinal plants have been reported to possess several antibacterial, anti-inflammatory, antitumor, antifungal, and antioxidant activities as well as other useful bioactivities. Hence, this review paper highlights some Southern Africa indigenous medicinal plants with anti-TB. We further drive in the traditional uses as well as the phytochemical compounds. The review inspires advanced research on the endless possibilities of the medicinal plant as a promising anti-TB alternative.

INTRODUCTION
Southern Africa is recognized for its rich and remarkable floral diversity, with nearly 22,755 plant species. Besides, approximately 3,000 plant species are used to treat numerous diseases (Neffati et al., 2017; Twilley et al., 2020; Van Wyk and Prinsloo, 2018). Since the beginning of time, humankind has been utilizing plants for their basic requirements, such as clothing, food, shelter, flavors, fertilizers, and fragrances (Jain et al., 2019). Furthermore, traditionally the indigenous people of South Africa have consumed medicinal plants to cure infectious diseases and treat ailments throughout history (Oguntibeju, 2018). Street et al. (2008) have estimated that almost 52% of the South African population, which accounts for nearly 27 million, relies on native medicinal plants for their essential healthcare treatments. In light of the above, African traditional medicine (ATM) has been part and parcel of the legislative framework of South Africa (Gqaleni et al., 2007). This is because traditional medicine and practices have played an integral role in the nation’s history and plant knowledge has been passed down from generation to generation. Furthermore, the use of traditional medicine has exploded because of its easy accessibility, affordability, and considerable tribal knowledge (Semenya et al., 2012). Various scientific reports have supported the claims made by traditional healers about the countless biological properties of plants,
including their antiviral, antibacterial, antioxidant and anti-inflammatory, immunomodulatory, and anticancer activities (Kshirsagar and Rao, 2021; Reddy et al., 2020). Tuyiringire et al. (2020) have shown increasing evidence of medicinal plants as a natural source of anti-tuberculosis (TB) agents. Their study further highlighted that the selected candidates could combat multidrug-resistant (MDR) TB (Tuyiringire et al., 2020).

South Africa is among the eight countries with the highest TB burden worldwide. TB is now the second most infectious disease due to the high number of fatalities worldwide, surpassing the human immunodeficiency virus (HIV). TB is caused by infectious Mycobacterium tuberculosis that usually affects the lungs (Berkowitz et al., 2018). In 2018, approximately 1.5 million individuals died from TB, 10.0 million patients became sick from TB, and nearly 1.7 billion people suffered from M. tuberculosis infection worldwide (Padmapriyadarsini et al., 2021). Moreover, persistent TB infection in patients with HIV is responsible for countless fatalities and has become a major driver of antimicrobial resistance. The current TB treatment has displayed numerous challenges, including expensive drug therapy, its ineffectiveness since the development of drug resistance, and the counteractions of HIV infection.

Moreover, combination therapy causes serious symptoms and high toxicity levels (Anochie et al., 2018). Regarding the current antibiotic therapy, failure is inevitable. Well-documented studies are available on the various biological activities and numerous secondary biocompounds (e.g., polyphenols, flavonoids, and alkaloids) of traditional medicinal plants (Chiocchio et al., 2021; Oguntibeju, 2018; Street et al., 2008). On the other hand, South Africa has an abundant wealth of traditional medicinal plants with tremendous anti-TB properties (Anochie et al., 2018; Madikizela and McGaw, 2017). Hence, untapped alternatives in the drug discovery and development process must be explored to uncover new cost-effective, accessible, more potent, and less toxic natural plant-based drugs. In conclusion, these medicinal plants might be explored for therapeutic prevention, control, management, and treatment of TB.

**METHODOLOGY FRAMEWORK**

In the present review, we searched online databases such as Google Scholar, ScienceDirect, Scopus, and Web of Science to screen and select research papers. Terminologies including biocompounds, TB, medicinal plants, and South Africa alone or in combination were used to search the electronic databases for research papers.

**South African medicinal plants as an alternative to combating infectious TB**

*Artemisia afra Jacq. Ex Willd. (African wormwood)*

*Tradition uses of the African wormwood plant*

*Artemisia afra* Jacq. Ex Willd. is a native aromatic plant distributed in the southern locations of Africa, including South Africa, Zimbabwe, and Namibia; thus, it flourishes in the Gauteng and Limpopo areas of South Africa. The Zulu people named the plant “Mhlonyane,” Xhosa “Umhlonyane,” Sotho “Lanyana,” Afrikaans “Wildelaar,” and Tswana “Lengana,” and English speakers refer to the plant as “African wormwood” (Fig. 1).

![Figure 1. Artemisia afra (African wormwood): (A) Artemisia afra plant, (B) creamy yellow flowers, and (c) monoterpenes α-thujone.](image)

(Liu et al., 2009). Moreover, traditional use of the plant involves the treatment of coughs, fever, headaches, chills, indigestion, loss of appetite, gastric disorders, colic, croup, gout, whooping cough, asthma, diabetes, malaria, bladder, influenza, kidney disorders, heart inflammation, purgative, convulsions, and rheumatism. Various scientific studies have supported the traditional claims that African wormwood showed promising antiviral, anti-inflammatory, and antibacterial activities. In rural areas in the Eastern Cape Province of South Africa, people treat diabetes by infusing the leaves or roots of African wormwood “Umhlonyane” (Kshirsagar and Rao, 2021). Others boil the leaves to cure respiratory infections and inhale the vapor to cure menstrual chill. A tea preparation of African wormwood sweetened with honey is also used for therapeutic purposes. For this, an increasing number of people are becoming more interested in African wormwood due to its infinite possibilities. *Artemisia afra* “African wormwood” is currently one of the most talked-about medicinal plants in South Africa (Du Toit and Van der Kooy, 2019).

*Phytochemical compounds isolated from the African wormwood plant*

Several studies have extracted volatile secondary metabolites from African wormwood. Mbokane and Moyo (2018) reported that numerous biocompounds were detected in *A. afra* extract in high levels, such as polyphenols, phenols, flavonoids, and alkaloids (Mbokane and Moyo, 2018). In 2009, Liu et al. (2009) estimated that 131 biocompounds have been described from the African wormwood. Several monoterpenoids were also highlighted, such as artemisia alcohol, artemisia ketone, artemisyl acetate, camphene, camphor, cis-carveol, caryophylla-2(12),6(13)-dien-5-one, cis-chrysanthanol, chrysanthenone, cis-chrysanthenyl, acetate, 1,8-cineole, cumin alcohol, dihydrocarvyl acetate, limonene, linalool, and linalool acetate. Other diverse chemicals were extracted from the African wormwood plants, such as sesquiterpenes, artemisal, berbenomone, cuminaldehyde, p-cymen-8-ol, and p-cymene. Furthermore, they categorized them under monoterpenes and sesquiterpenes. Another study identified the flavone acacetin and the sesquiterpene lactone lu,4α-dihydroxyguaia-2,10(14),11(13)-trien-12,6α-olide in the *A. afra* extract. The essential oils of African wormwood showed significant levels of α-and β-thujone (Fig. 1C), ketone, alcohol, camphor, and 1,8-cineole (Alhassan, 2017).
Anti-TB properties of the African wormwood plant

Various studies have reported African wormwood as a potent medicinal plant with superior bioactivities (Kshirsagar and Rao, 2021). A recent study determined that the minimum inhibitory concentrations (MICs) of Artemisia annua and A. afra extracts against Mycobacteroides abscessus and M. tuberculosis showed excellent bactericidal activity against M. tuberculosis. The results further showed that African wormwood exhibited potent anti-TB effects. These strains have been reported to be virulent Erdman strains and might be regarded as resistant strains, hence acting as chemotherapeutic agents against infectious M. tuberculosis (Martini et al., 2020). According to Ntutela et al. (2009), the dichloromethane extract of African wormwood inhibited the bacterial replication of Mycolicibacterium aurum. The actions ensured that the drug copying was entirely stopped. This was due to the invasion of the heme molecule that affects the reduced oxygen for the survival of the pathogen (Ntutela et al., 2009). Several studies have established that African wormwood might be a suitable candidate as an anti-TB agent (Gemechu et al., 2013; More et al., 2012). Mativandlela et al. (2008) determined antimycobacterial activity using the MIC of A. afra extracts against Mycobacterium smegmatis and M. tuberculosis. The results showed that A. afra exhibited some anti-TB activity and could be a good candidate for treating TB and TB-related symptoms (Mativandlela et al., 2008).

Three local medicinal plants commonly used for the treatment of TB in the Eastern Cape Province, South Africa, were screened using a twofold microdilution bioassay. The A. afra dichloromethane and ethanol extracts showed good anti-TB activity against M. aurum A+. Further analysis also indicated that A. afra extracts inhibited the growth of Klebsiella pneumoniae, Escherichia coli, Staphylococcus aureus, and Bacillus cereus (Buwa and Afolayan, 2009). Interestingly, a survey study was conducted on 52 Bapedi traditional healers in the districts of Limpopo, South Africa. The results indicated that A. afra was the most widely used medicinal plant in treating and managing TB in the Limpopo province of South Africa (Semenya and Maroyi, 2013). Despite the extensive biological activities of A. afra, several studies have demonstrated that A. afra extracts and their volatile oils possess some toxicological effects (Kane et al., 2019; Mongalo et al., 2020; Mukinda and Syce, 2007; Mungho et al., 2018; Sumonou and Afolayan, 2013).

Ziziphus mucronata Willd. (the buffalo thorn)

Tradition uses of the buffalo thorn plant

Ziziphus mucronata Willd. is a deciduous native sub-Saharan Africa plant, growing from South Africa northwards to Eritrea and Ethiopia. Historians believe that Christ’s crown was made from the Ziziphus spina-christi Wild. plant, which closely resembles Z. mucronata. Ziziphus mucronata is commonly known as buffalo thorn due to its pointed leaves. Moreover, in Latin, “ziziphus” means thorn, and “mucronata” refers to pointed leaves. Various plant parts of Z. mucronata are used traditionally to treat several ailments, such as gastrointestinal conditions, rheumatism, and snake bites. The bark infusions help relieve cough, body pains, respiratory conditions, and chest issues. For the treatment

of gonorrhea, diarrhea, and dysentery, indigenous people use Z. mucronata root drinks (Mekonen et al., 2020; Fig. 2).

Phytochemical compounds isolated from the buffalo thorn plant

Olajuyigbe and Afolayan (2011) reported that in the Z. mucronata extracts, phenolics were the highest, followed by flavonoids and proanthocyanidin contents. A comprehensive study established that Z. mucronata extracts produced various biocompounds, including quinones, terpenoids, alkaloids, flavonoids, phenolics, and quercetin (Auvin et al., 1996; Olajuyigbe and Afolayan, 2011). Mucronine J, a novel cyclopeptide alkaloid biocompound, was isolated from the root bark of Z. mucronata (Rhamnaceae), which was the structure elucidated by mass spectrometry and 1D and 2D NMR (Mukinda and Syce, 2007). Another study concluded that five cyclopeptide alkaloids (sanjoinines A, B, F, G, and G_1) were extraplated from Z. mucronata leaf extract (Foyet et al., 2019). According to KoÅ (2017), 11 phenolics compounds were extracted from an aqueous extract of Z. mucronate, including rutin (quercetin-3-O-rutinoside), isoquercetin (hyperoside), catechin, quercitrin (quercetin-3,7-O-L-dirham pyranoside), and delphinidin-3-glucoside.

Anti-TB properties of the buffalo thorn plant

An in-depth study was conducted on the ATM system for treating TB using medicinal plants. The study highlighted various herbal plants producing secondary biocompounds as potential anti-TB agents and Z. mucronata plant was listed (Anochie et al., 2018). Indigenous people of the South African tribes used medicinal plants to combat TB (Dzoyem et al., 2016; Green et al., 2010; Sharif-Rad et al., 2020). Moreover, Sigidi et al. (2016) reported that Z. mucronata extracts exhibited some anti-TB activity at concentrations >500 μg/ml against the M. tuberculosis H37 strain. Another research study demonstrated that Z. mucronata extracts produced cyclopeptide alkaloids, which were well-known to exhibit significant anti-TB effects against M. tuberculosis (Lomchoey, 2014). The Mycobacterium species have structural cell wall functions to withstand the habitat and anti-TB agents and survive adverse environmental conditions for countless years. This has led to the ever-increasing MDR and extensively drug-resistant genes, which make the treatment of TB challenging (Mongalo et al., 2020).

Knowltonia vesicatoria (brandblaar)

Tradition uses of the brandblaar plant

Knowltonia vesicatoria is a slow-growing perennial fynbos indigenous South African plant that is widely distributed
in the Cape Peninsula stretching to Grahamstown. Furthermore, *K. vesicatoria* is referred to as “brandblaar” by the Afrikaans people of South Africa. It has been popular in South Africa since European colonization due to its wide range of beneficial uses. The native tribes used *K. vesicatoria* leaves to soothe aching backs and joints. Moreover, it was used to treat colds, arthritis, rheumatism, flu, and, sometimes, toothache (van Wyk and Gericke, 2000; Fig. 3).

**Phytochemical compounds isolated from brandblaar plant**

A study was conducted on a crude ethanol extract of *K. vesicatoria* as a promising candidate and a new natural alternative to antimycobacterial drugs. This study was the first to use NMR and silica column chromatography to extract stigmasta-5,23-dien-3-ol and 5-(hydroxymethyl)furan-2-(5H)-one from *K. vesicatoria* using. Other biocompounds extracted included isomer mixture [5-(hydroxymethyl)furan-2-(5H)-one, 5-(hydroxymethyl)dihydrofuran-2(3H)-one] and 5-(hydroxymethyl)furan-2(5H)-one. Moreover, stigmasta-5,23-dien-3-ol displayed the most potency against drug-sensitive *M. tuberculosis* with inhibition of 50.00 μg/ml MIC (Labuschagné et al., 2012). An in-depth study on the phytochemicals and bioactivity of southern African flora established that *K. vesicatoria* produced flavonoids, quinones, and other beneficial biocompounds (Babiaka et al., 2015). Despite the evidence, there is limited research on the phytochemical compounds produced by *K. vesicatoria*.

**Anti-TB properties of brandblaar plant**

In line with the above, another study revealed that *K. vesicatoria* (aerial parts) extracts demonstrated the best bioactive activities against *M. tuberculosis* with inhibition of MIC of 39.06 μg/ml. In contrast, the extracts showed weak bioactivity against nonpathogenic *M. smegmatis*. Moreover, Labuschagné et al. (2012) showed that *K. vesicatoria* extract possessed strong anti-TB properties against drug-resistant *M. tuberculosis* isolates and exhibited a MIC value of 50.00 μg/ml. The combination effect of *K. vesicatoria* extract with other compounds reduces the MIC value (Labuschagné et al., 2012). Regardless of the limited data, various researchers have advocated for using *K. vesicatoria* as a substitute for commercialized anti-TB agents (Anochie et al., 2018; Babiaka et al., 2015; Martolia et al., 2020; Nielsen et al., 2012). Despite the limited studies, several studies supported the anti-TB effects of *K. vesicatoria* based on in vitro laboratory-based reports (Krige et al., 2009; Kuete et al., 2021; Labuschagné et al., 2008; Nielsen et al., 2012; Rawat et al., 2021).

**Lippia javanica (the fever tea)**

**Traditional uses of the fever tea plant**

*Lippia javanica* is an erect woody perennial shrub or herb of 4.5 m tall, with a brownish stem and strong aromatic leaves that emit a lemon-like fragrance when crushed (Maroyi, 2017; van Wyk and Gericke, 2000). It belongs to the verbena (Verbenaceae) family and can be naturally found throughout South Africa (except in Western Cape), extending from Eastern Cape to other tropical African countries (Kipkore et al., 2014; Shikanga et al., 2010). It is referred to as fever tea or lemon bush (English); “lemoenbossie,” “beukesbossie,” or “koorsbossie” (Afrikaans); “umutswane” or “mutswane” (Swati); “inzinziniba” (Xhosa); “umsuzane” or “umswazi” (Zulu); “musukudu” or “bokhukhwane” (Tswana). Generally, *L. javanica* is traditionally consumed as an herbal tea for either recreational or medicinal purposes. When applied for ethnomedicinal purposes, it is consumed in limited amounts for a few days (Krige et al., 2009). *L. javanica* is medically used to treat cough, cold, bronchitis, asthma, chest pains, and other diseases (Chigora et al., 2007; Davids et al., 2014; Njoroge and Bussmann, 2006; Semenya et al., 2013; Fig. 4).

**Phytochemical compounds isolated from the fever tea plant**

*Lippia javanica* is rich in biocompounds and essential oils, such as pipertone, tagetone, ipsdienone, p-cymene, isopene, myrcene, linalool, carvone, sabinene, ocimene, limonene, carophyllene, and myrcene (Shikanga et al., 2010). It has been revealed that pipertone extracted from *L. javanica* could inhibit the growth of *E. coli* and *Bacillus subtilis* at a dilution rate of 1% (Manenzhe et al., 2004). It can also inhibit the growth of *Acinetobacter calcoaceticus, Salmonella typhi, S. aureus,* and *Micrococcus kristinae* with MIC range of 12–50 μg/ml, using kanamycin and dimethyl sulphoxide as control (Samie et al., 2009). The same was observed in the leaf extract (acetone, methanol, and hexane extract) of *L. javanica* against 15 bacterial species with a MIC range of 1.5 to >12 mg/ml (Nyahangare et al., 2012). Biocompounds such as lippialactone derived from ethyl acetate extract of the aerial parts of *L. javanica*, according to Ludere et al. (2013), prevent the growth of *E. coli* and *S. aureus* at 10 mg/ml. Apigenin, a phenolic compound, which is a well-known antibacterial agent, is also extracted from *L. javanica* and has an antibacterial effect on *Vibrio cholera*, *Enterococcus faecalis, S. typhi*, *Proteus mirabilis*, and *Pseudomonas aeruginosa* (Cushnie and Lamb, 2005; Martini et al., 2004; Shikanga et al., 2010). Isoverbascoside and verbascoside were extracted from the leaf of *L. javanica* and can exhibit antifungal activities against mycelia at above 0.6 mg/ml-1 (Lima et al., 2003).

**Anti-TB properties of the fever tea plant**

Mujovo et al. (2008) reported that among all the compounds isolated from *L. javanica*, only eucaphic acid, which is a triterpenoid carboxylic acid, showed antimycobacterial activity when tested against a drug-sensitive strain of *M. tuberculosis* with a MIC of 50 μg/ml. Acetone leaf extract of *L. javanica* showed antimycobacterial activity against *M. smegmatis* with the lowest MIC value of 0.47 mg/ml (Masoko and Nxumalo, 2013). These compounds with antimycobacterial

![Figure 3. (A) Knowltonia vesicatoria plant; (B) Blisterleaf; and (C) chemical compound stigmasta-5,23-dien-3-ol.](image-url)
activities extracted from *L. javanica* have passed through preliminary evaluations and have turned out to be very effective. Thus, they can be used to produce new and more effective drugs for the treatment of TB (Maroyi, 2017; Masoko and Nxumalo, 2013; Mujovo et al., 2008). *Lippia javanica* is regarded as one of the most commonly used medicinal plants by Bapedi traditional healers to cure TB infection in the Limpopo province of South Africa (Semenya and Maroyi, 2013).

**Euclea natalensis** A. DC. *(Natal guarri)*

Traditional uses of the Natal guarri plant

*Euclea natalensis* is a shrub with a dense spreading crown, straight trunk, and branchlets covered in fine rusty hair. It is indigenous in the southeastern part of Africa. It is called “Natal ebony,” “Natal guarri,” and “large-leaved guarri” in English; “Natalghwarrie,” “berggwarrie,” and “swartbasboom” in Afrikaans; “umTshekisani” and “umKhasa” in Xhosa; “iDungamuzi,” “iChitamuzi,” “umZimane,” “umTshikisane,” “inKunzane,” “inKunzi-emnyama,” “umHlalanyamazane,” and “umAnyathi” in Zulu; “umHlangula” in Tsonga. Moreover, its parts are used for different purposes in different communities. The wood, roots, and twigs from *E. natalensis* are used as building materials and for the production of dark red dye and toothbrushes, respectively (Oosthuizen et al., 2020). The roots and twigs of *E. natalensis* are generally used to treat chest ailments, toothache, bronchitis, asthma, snake bite, diarrhea, malaria, stomach problems, diabetes, venereal diseases, and wounds (Lall et al., 2005; Maroyi, 2017; Fig. 5).

Phytochemical compounds isolated from the Natal guarri plant

Several compounds from the class of naphthoquinone and pentacyclic terpenoids were isolated from *E. natalensis* by different researchers (van der Kooy, 2004). Octahydroeuclein, 20(29)-lupene-3β-isofurulate, shinanolone, lupeol, and betulin were isolated from the ethanol extract of *E. natalensis* root bark, and they all exhibited inhibitory characteristics against Gram-positive bacteria species (Lall et al., 2006). According to Lall et al. (2001), 50% inhibition in the replication of herpes simplex virus cells was achieved with 0.1 and 0.2 mg/ml of acetone and water extract from the root bark of *E. natalensis*. Other compounds isolated from the root bark of *E. natalensis* include isodiospyrin, mamegakione, natalenone, 8'-hydroxydiospyrin, euclanone, galpinone, methylaphthazarin, neodiospyrin, diospyrin, 7-methyljuglone, β-sitosterol, 5-hydroxy-4-methoxy-2-

anti-TB properties of the Natal guarri plant

Most of the compounds isolated from *E. natalensis* exhibited inhibitory activities against *Mycobacterium* species. Using a radiometric respiratory BACTEC assay, Lall and Meyer (2001) observed a MIC value of 100 μg/ml while evaluating the antimycobacterial activities of both drug-sensitive and drug-resistant strains of *M. tuberculosis*. Evaluating the antimycobacterial activities of crude extract, diospyrin, and 7-methyljuglone, isolated from the root of *E. natalensis*, against *M. tuberculosis* produced MIC values of 8.0, 8.0, and 0.5 μm/ml, respectively (Lall and Meyer, 2005). Furthermore, 7-methyljuglone and diospyrin are the most bioactive and antimycobacterial compounds isolated from *E. natalensis* based on all evaluations and previous studies (Mahapatra et al., 2007; Maroyi, 2017; Lall; 2001; van der Kooy, 2004; van der Kooy, 2007).

A previous study by Bapela et al. (2008) revealed that naphthoquinone, 7-methyljuglone was the lead bioactive compound in *E. natalensis* extracts. The data showed that *E. natalensis* extracts were potent against *M. tuberculosis* and *M. smegmatis*. In another study, naphthoquinone, 7-methyljuglone was also isolated from the acetone extract of *E. natalensis* and showed a good inhibitory effect against *Mycobacterium bovis* (MIC = 26 μg/ml), compared to *M. smegmatis* and *Mycobacterium fortuitum*. Even though the strains were nonpathogenic, they were used as prototypes to identify the potency of plant-based extracts (McGaw et al., 2008). Furthermore, *E. natalensis* has been shown to be a potent antimycobacterial candidate in the literature; however, more research is warranted as the studies in this area are limited.

**Bridelia micrantha** (Hochst.) Baill. *(coastal golden-leaf)*

Traditional uses of the coastal golden-leaf plant

*Bridelia micrantha* (Hochst.) Baill. is a small- to medium-sized tree with a spreading crown, from the family of Phyllanthaceae (formally Euphorbiaceae). It is commonly known as “mitzerie” or “bruin stinkhout” (Afrikaans), “motsere” (Sotho), “ndzerhe” (Tswana), and coastal golden-leaf (English). It is widely distributed throughout tropical Africa to the Eastern Cape, South Africa. The fruits are widely eaten and can be used for jam and juice, while the root, bark, leaf sap, and leaves are used for medicinal purposes in African communities.

*Figure 4.* (A) *Lippia javanica* plant with white flower and (B) chemical compound pipertenone.

*Figure 5.* (A) *Euclea natalensis* plant and (B) chemical compound octahydroeuclein.

Metaldehyde (Lall et al., 2005; Lal et al., 2016; Maroyi, 2017; van der Kooy, 2004).
countries such as South Africa, Cameroon, Malawi, and Nigeria (Ingram and Shure, 2010; Maroyi, 2017; Meke et al., 2017). The wood from B. micrantha is used for construction, furniture, tool handles, and kitchen utensils in tropical Africa, especially Ethiopia and Kenya (Bosch, 2012; Chekole et al., 2015). B. micrantha is used to treat burns, wounds, stomach ache, dysentery, constipation, malaria, tapeworms, sexually transmitted infections, diarrhea, conjunctivitis, and painful eyes (Maroyi, 2017; Fig. 6).

**Phytochemical constituents isolated from the coastal golden-leaf plant**

*Bridelia micrantha* is rich in phytochemicals such as alkaloids, flavonoids, essential oil, phenolic compounds, sterols, tannins, terpenoids, and oxalate. Compounds isolated from fruit, leaves, and stem of *B. micrantha* include the following: caffeic acid, cycloartenol acetate, ergosterol, stigmast-8(14)-en-3-ol, 5β, 6β-epoxy-7-bromocholoratan-3-one, acacic acid lactone, quercetin, quercetin-3-O-glucoside, delphinidin, ellagic acid, gallic acid, friedelin, taraxerol, taraxerone, trans-triacontyl-4-hydroxy-3- methoxyxinnamate, betulinic acid, catechin, and oleonolic acid (Akinyeye and Olatunya, 2014; Chekole et al., 2015; Munayi, 2016; Shelembe et al., 2016). Adefuye et al. (2011) revealed that ethyl acetate extract of the stem bark of *B. micrantha* was more active in inhibiting the growth of *S. aureus* with a MIC<sub>50</sub> value of 0.078 mg/ml than other extracts.

**Anti-TB properties of the coastal golden-leaf plant**

Using tetrazolium microplate assay, Green et al. (2010) observed that acetone leaf extract of *B. micrantha* was more active against *M. tuberculosis* with a MIC value of 25 μg/ml than other extracts (methanol, hexane, and ethanol). Moreover, Green et al. (2011) used a resazurin microplate assay to evaluate the antimycobacterial activity of n-hexane fraction, a subfraction of ethyl acetate fraction of the acetone stem extract of *B. micrantha* against *M. tuberculosis*. They observed 20% and 35% inhibition in the growth of *M. tuberculosis* H37Ra and *M. tuberculosis* that is resistant to all first-line drugs at 10 μg/ml. The primary ethyl acetate fraction inhibited the growth of *M. tuberculosis* resistant to streptomycin, rifampicin, isoniazid, and ethambutol at 50 μg/ml. The evaluations from researchers (Akinyeye and Olatunya, 2014; Green et al., 2010; van der Kooy, 2007) can serve as scientific validations for producing more effective and efficient drugs for the treatment of TB. Numerous biocompounds with abundant biological activities have been isolated from *B. micrantha*, including alkaloids, flavonoids, essential oils, phenolic compounds, sterols, terpenoids, and tannins, saponins (Akinyeye and Olatunya, 2011; Anywar et al., 2021; Maluleke, 2019; Ngane, 2019; Okeleye et al., 2011).

**Immune adjuvant effect of medicinal plants against infectious TB**

Biological therapy, often known as immunotherapy, is a type of treatment that uses the body’s natural immune system to protect against infection, cancer, and other disorders and mitigate the effects of other treatments. Biological response modifiers (BRMs), which include vaccinations, monoclonal antibodies, cytokines, and adjuvants, are used in biotherapy. BRMs can be utilized individually or in combination (Kuroki et al., 2012). Immunomodulatory activities have been discovered in medicinal plants typically used as herbal medications. Both nonspecific and specific immunity may be stimulated by these substances. These plants may promote both humoral and cell-mediated immunity, or simply one of them, while reducing the immune system’s cell-mediated component (Rao et al., 1994).

Immunomodulatory therapy may be a viable alternative to traditional chemotherapy for a variety of diseases, particularly when the host’s defense mechanisms must be activated in the face of impaired immune responsiveness or when selective immunosuppression is required in situations such as inflammatory diseases, autoimmunity, and organ/bone marrow transplantation (John et al., 2022). Numerous polysaccharides derived from TCM plants have recently been discovered to be biocompatible, biodegradable, and immunomodulatory, indicating that they could be used as vaccine adjuvant options (Khademi et al., 2018; Wan et al., 2022). Due to the lack of innate immune stimulation, conventional vaccinations have been proven to be insufficiently immunogenic. As a result, adjuvants for new-generation vaccines must ensure that the vaccine closely resembles illness in order to elicit a strong immune response. While adjuvants are powerful immunostimulators, most of them are not approved for use in the clinic due to unfavorable side effects. As a result, a substantial study focused on identifying the active components of adjuvants and then modifying them to reduce adverse effects (Song and Hu, 2009).

In a 2020 study, Roy et al. (2020) discussed the possible use of phytochemical-derived efflux pump inhibitors and immunotherapy to combat TB and provided a brief look at the molecular mechanism and structure of drug-efflux pumps seen in MTB. A recent article on monoclonal antibodies against antigens of *Mycobacterium* TB has produced mixed results. It showed that phagocytic cells enhanced antibody-mediated phagocytosis of mycobacteria by phagocytic cells using sera from patients vaccinated with bacillus Calmette-Guérin. Furthermore, cytokines and inhibitors as immunomodulators were examined in a clinical trial involving 50 patients with MDR-TB, where adjunct supplementation with recombinant human IL-2 for 7 months resulted in increased sputum smear conversion and improved immune status (Gupta et al., 2016).

Immunoxel (Dzherelo) is a water–alcohol extract of medicinal plants used in Ukraine as a TB and HIV immunotherapy adjuvant. Patients exhibited faster defervescence, weight increase, higher hemoglobin content, and less inflammation, as shown by the lower leukocyte counts and erythrocyte sedimentation rate.
Only 19% of the individuals in the placebo group converted. These data suggest that solid Immunoxel delivered through the mucosa is equal to the original liquid Immunoxel given twice daily for 2–4 months (Efremenko et al., 2012). In a recent study, patients were divided into two groups: the first (n = 137) received a sublingual honey lozenge formulated with the botanical immunomodulator Immunoxel once daily; the second (n = 132) was given placebo lozenges in addition to conventional ATT. Immunoxel’s sputum clearing was effective in all types of TB. Immunoxel reduced TB-related inflammation, as shown by the decreased defervescence and normalization of high leukocyte counts and erythrocyte sedimentation rate. There were no adverse side effects observed at any period. Immunoxel is a commercially accessible immunotherapeutic intervention that is cost-efficient, safe, and successful in treating TB (Batbold et al., 2017).

In the in vitro and aerosol mouse models of MTB infection, researchers looked at the immunomodulatory effects of G1-4A, a polysaccharide extracted from the Indian medicinal plant Tinospora cordifolia. The findings showed that modulating host immune responses with G1-4A could increase the therapeutic efficacy of existing anti-tubercular medicines and could be a promising technique for developing new TB treatments (Gupta et al., 2016). Isoniazid as a potential host-directed therapy when used with luteolin, a plant-derived hepatoprotective immunomodulator, enhances anti-TB immunity, decreases the period of TB treatment, and avoids disease relapse. Luteolin also promotes central memory T-cell responses, which improves long-term anti-TB immunity. We also discovered that luteolin boosts the activity of natural killer and natural killer T-cells, both of which have antitubercular properties (Singh et al., 2021).

CONCLUSION

Indigenous people of South Africa have relied on medicinal plants for their anti-TB healing properties. In the current review, it can be further deduced that plant-based biocompounds exhibit excellent therapeutic properties and are thus suitable candidates for treating TB, especially multiresistant M. tuberculosis strains. These findings should encourage researchers to pursue such TB management treatments in order to discover novel, cost-effective, efficacious, and sustainable drugs that can inhibit the growth and proliferation of M. tuberculosis and reduce the mortality rate of TB, even in patients with HIV in South Africa and beyond. They also shed light on the importance of South African medicinal plants and the need for more in-depth studies, including clinical studies in TB management.

AUTHOR CONTRIBUTIONS

All authors (MCM, COO, DOM, CAN) have collected the research data and wrote, edited, reviewed, and agreed on the final draft of the manuscript.

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REFERENCES


Krije J, Dreyer LL and Mucina L. Floristic links between the west Coast and south Coast (South Africa)-is the Breede river valley a migration route? S Afr J Bot, 2009; 75(2):408.


the African and Indian subcontinent. Evid Based Complement Alternat Med, 2017; 34:6746071


Masoko P, Nxumalo KM. Validation of antimycobacterial plants used by traditional healers in three districts of the Limpopo Province (South Africa)” Evid Based Complement Alternat Med, 2013; 2013:586247.


Munayi RR. Phytochemical investigation of *Bridelia micrantha* and *Tabernaemontana ventricosa* for cytotoxic principles against drug sensitive leukemia cell lines. Master’s Thesis, University of Nairobi, Nairobi, Kenya.


Van Der Kooy F. Characterisation, synthesis and antymycobacterial activity of naphthoquinones isolated from *Euclea natalensis*. MSc Dissertation, University of Pretoria, Pretoria, South Africa.


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