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Full Length Research Paper

An Analysis of the Proven Antibacterial and Immunomodulatory Qualities of Six Chosen Ethnomedicinal Plants that are Utilized by Traditional Healers in the KwaZulu-Natal, South Africa, Area as a Remedy for Urinary Tract Infections

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Significant bacterial growth and the presence of microbial pathogens anywhere throughout the urinary tract with associated symptoms are signs of urinary tract infections (UTIs), which are among the most prevalent bacterial illnesses worldwide. Research has shifted to evaluating locally accessible medicinal plants and their corresponding crude extracts, which contain novel bioactive derivatives, due to the concerning global rise in antibiotic-resistant bacteria that is causing antibiotic therapy failures. Based on scientific evidence that these medicinal plants are scientifically tested for efficacy and adverse side-effects through rigorous research, testing, and clinical trials, the World Health Organization (WHO) has declared traditional medicine to be a safe and effective alternative for treating a variety of illnesses and infections. The use of Euclea crispa, Curtisia dentata, Manihot esculenta, Bulbine natalensis, Catha edulis, and Eucomis bicolor as individual preparations with antimicrobial, anti-inflammatory, analgesic, wound healing, and immunomodulatory qualities in the treatment of a variety of ailments, as well as in combination as a traditional remedy for UTIs, is encouraged by South African traditional health practitioners (THPs) in the eThekwini Municipality. Triterpenoids, oleanolic acid, tannins, flavonoids, alkaloids, anthocyanosides, bulbnatalonosides, sterols, homoisoflavonoids, saponins, and cyclooxygenases are all found in these ethnomedicinal species, and the literature reviewed in this article shows how they work against uropathogenic E. coli (UPEC), K. pneumoniae, E. faecalis, P. aeruginosa, S. aureus, C. albicans, and K. pneumoniae. Therefore, these six South African medicinal herbs are good candidates to prevent UTIs caused by microbes.

Keywords: Urinary tract infections (UPEC), Antibiotic resistance, Ethnobotanical species, Traditional medicine, Antimicrobial properties

INTRODUCTION

A significant percentage of people worldwide suffer from urinary tract infections (UTIs). Some similar characteristics are apparent in the published literature, despite the fact that numerous genetic variables may contribute to variations in the aetiology of such diseases in different geographic places around the world (Barber et al., 2016; Beyene and Tsegaye, 2011; Terlizzi et al., 2017). Despite being non-selective and affecting people of both genders, UTIs are particularly common in women, particularly in young adults who have never had one before, pregnant women, women over 65, and patients who are catheterized (Chu and Lowder, 2018; Lewis et al., 2013; Tandogdu et al., 2016).

The precise worldwide incidence of UTIs is still unknown, despite the fact that urology has undertaken and continues to conduct a great deal of study on the subject (O€ ztu€rk and Murt, 2020). The global incidence of this illness was projected to be 150 million UTIs per year in 2016 (McLellan and Hunstad, 2016). However, it is currently estimated to afflict 11% of the world's population, or 800 million individuals annually (Medina and Cas- tillo-Pino, 2019). The precise prevalence of UTIs in South Africa is uncertain due to a lack of data on the disease's occurrence (Lewis et al., 2013). The dearth of such data in South Africa may be due to the inability to get recorded records of patients seeing general practitioners in clinics or hospitals, as well as the absence of information on patients using THPs to treat this infection. Additionally, patients may turn to over-the-counter self-medication or home treatments (Gasson et al., 2018).

Numerous microorganisms have been identified as the cause of UTIs, including Escherichia coli (E. coli), Enterococcus faecalis (E. faecalis), Klebsiella pneumoniae (K. pneumoniae), Proteus mirabilis (P. mirabilis), Candida albicans (C. albicans), Pseudomonas aeruginosa (P. aeruginosa), and Staphylococcus aureus (S. aureus). Uropathogenic Escherichia coli (UPEC) is the most common causative agent linked to this condition. The World Health Organization's (WHO) Global Antimicrobial Surveillance System (GLASS) has identified UPEC and K. pneumoniae as important UTI indicator organisms (Kajihara et al., 2020). In many parts of the world, this has prompted the creation of several guidelines for the treatment of UTIs based on scientifically sound research (Kang et al., 2018). According to Foxman (2010) and Klein and Hultgren (2020), broad-spectrum antibiotics are currently the standard treatment for UTIs in South Africa. In search of novel, effective, and natural treatment options, however, research into evaluating crude extracts and purified derivatives from locally available traditional medicinal plants has been prompted by the rise in antibiotic resistance worldwide (Gurib-Fakim, 2006; Kon and Rai, 2013; Mahomoo-dally and Gurib-Fakim, 2013; Porras et al., 2020).

Although the therapeutic qualities of many species employed in traditional medicine have not yet been confirmed, South African ethnobotanical literature is rather well documented. The potential application of these plant species for a variety of ailments has also been highlighted by a notable rise in research in recent years that screens and validates the use of South African traditional medicines (van Vuuren and Holl, 2017). The antibacterial activity of these plants has drawn the most attention among the medicinal qualities studied; nevertheless, only a small number of those studies have specifically explored antimicrobial activity against urinary tract infections (UTIs) (Cock et al., 2021).

Strong antimicrobial activity against UPEC, E. faecalis, C. albicans, and Streptococcus has been demonstrated by international studies on the use of traditional medicinal plants, such as species of Verbascum thapsus L., C. bolivianum, Salanum tor- vum, and Agropyron repens L., for the treatment of UTIs. These studies were carried out in Turkey, Sweden, India, and Germany (Begam and Senthilkumar, 2014; Dulger et al., 2015; Mohanty et al., 2017). One hundred and fifty-three Southern African plant species that are used to treat UTIs were identified and evaluated against the activity of bacteria that cause UTIs in a recent comprehensive analysis by Cock et al. (2021). Of them, 85 were found to have advantageous inhibitory activity against the major bacteria that cause UTIs, such as Proteus vulgaris, E. coli, E. faecalis, K. pneumoniae, P. mirabilis, P. aeruginosa, and Staphylococcus saprophyticus (Cock et al., 2021). For a sizable section of the community, THPs are seen as vital healthcare resources and play a critical role in South Africa's healthcare system (Campbell-Hall et al., 2010; Zuma et al., 2016). According to the WHO, a THP is a person who is recognized by their community as a skilled healthcare provider who employs a range of techniques, including as plant, animal, and mineral substances, in addition to other customs derived from social, cultural, and religious traditions (Organization, 2013). The South African National Department of Health is currently in charge of overseeing the continuous process of regulating this profession (Street et al., 2018). Four categories of traditional healers are recognized and registered under the South African Traditional Health Practitioners Act (Act No. 22 of 2007): diviners (izangoma, abathandazi); herbalists (izinyanga); traditional birth attendants (ababelethisi); and traditional surgeons with regard to circumcisions (iingcibi). These individuals must complete education and training at any accredited training institution under the supervision of a traditional healer ("Department of Health, Government Gazette, 2015,; Street et al., 2018; Zuma et al., 2016).

A number of factors, such as historical and cultural factors, legal frameworks, and the accessibility of traditional, complementary, and alternative medicine (TCAM) in comparison to modern treatments, influence the prevalence of TCAM in third-world countries (Aware et al., 2022; Organization, 2013). The WHO estimates that over 80% of people in low-income countries use

TCAM (Aware et al., 2022; Organization, 2019). Because of the high expense of obtaining modern healthcare or the restricted resources of conventional healthcare services, TCAM ends up being the patients' first choice (Organization, 2019). According to reports, the proportion of traditional healers and western doctors in Africa is 1:500 and 1:40,000, respectively (Organization, 2019, 2013). This indicates that there are less THPs available than western doctors, yet the public still prefers THPs. In many areas, traditional medicine remains a major healthcare choice despite the paucity of science supporting it (Aware et al., 2022).

This review seeks to explore documented literature on the antimicrobial potential of a select group of South African medicinal plants (Euclea crispa (Thunb.) Gu€rke (uMshekisane), Curtisia dentata (Burm. f.) C.A.Sm. (uMlahleni), Manihot esculenta Crantz (uMdumbulu), Bulbine natalensis Baker (Ibhucu), Catha edulis (Vahl) Endl. (uMhlwazi), and Eucomis bicolor Baker (uMbola)) which are popular among the THPs in the region of KwaZulu-Natal, as alternative medicinal agents in treating commonly occurring UTIs (Euclea crispa (Thunb.) Gu€rke; Manihot esculenta Crantz; Eucomis bicolor Baker; Catha edulis (Vahl) Endl; Bulbine natalensis Baker; Curtisia dentata (Burm.f.) C.A.Sm) Moreover, their phytochemical constituents and bioactive compounds that possess immunomodulatory properties will also be reviewed.

2. Methodology

We used ScienceDirect, PubMed, Open Knowledge Maps, Google Scholar, and Websites in a methodical manner to choose the articles for our review. An open source knowledge mapping program called Open Knowledge Maps uses a combination of similarity metrics and summarizing strategies on article metadata that are connected. Based on the open-source web-based knowledge mapping program Head Start2, which can provide a range of knowledge-based data, including text, metadata, and references, Open Knowledge Maps (Fig. 1) seeks to develop a visual interface of the world's scientific knowledge. The Public Library of Science (PLOS) is the source of the data generated by Open Knowledge Maps, which are also connected to PubMed and the Directory of Open Access Journals (Kraker et al., 2016).

Eucomis bicolor antimicrobial activity, Manihot esculenta antimicrobial activity, Bulbine natalensis antimicrobial activity, Euclea crispa antimicrobial activity, Catha edulis antimicrobial activity, and South African traditional health practitioners treating urinary tract infections were among the search terms developed to extract sources from published literature and websites in order to collect the pertinent articles. Mendeley Reference Manager was used to review and store the bibliographies of the papers that were retrieved. The herbs included for this study were chosen because of their suggested traditional use in KwaZulu-Natal for the treatment of UTIs.

Studies containing simply abstracts, insufficient information, and articles written in languages other than English were disqualified. The following topics were deemed eligible for screening: taxonomy, ethnobotanical and ethnomedicinal use, phytochemical composition, immunomodulatory properties, antimicrobial evaluation of UTI implicated microorganisms, evaluated antimicrobial potential, health benefits of the six plants in question, and the role of traditional health practitioners. Scientific and non-scientific literature published between 1990 and 2023 at the time the manuscript was submitted was taken into consideration because of the rarity and paucity of information pertaining to the topic of this study. Only 136 of the 312 articles that Open Knowledge Maps produced were used for this study after thorough screening.

3. The classification of commonly occurring UTIs

Significant bacterial growth and the presence of microbial pathogens anywhere in the urinary tract, coupled with related symptoms, are indicators of urinary tract infections (UTIs) (Pulipati et al., 2017; Schellack et al., 2018). The ability of the bacteria to successfully latch onto the urothelial cells of the hosts determines the pathogenicity of this infection (Foxman, 2014; Smelov et al., 2016). There are three main categories into which UTIs are classified. According to their location along the urinary system, UTIs fall into one of two categories in the first category: upper UTIs, which affect the kidneys and ureters, or lower UTIs, which invade the bladder and urethra (Barber et al., 2016). Pathogenic bacteria infiltrate healthy uroepithelium in the urethra (urethritis), bladder (cystitis), ureters (ureteritis), and kidneys (pyelonephritis) to cause the second category, which is categorized based on the organ infection site (Hung et al., 2009). Finally, there are two types of UTIs: difficult and uncomplicated. Acute pyelonephritis, which is linked to underlying kidney or urinary tract abnormalities, causes complicated UTIs, which are characterized by an infection of the urinary tract parenchyma. On the other hand, an infection in a urinary tract that is structurally and neurologically normal is what distinguishes uncomplicated UTIs (Pulipati et al., 2017; Schellack et al., 2018; Terlizzi et al., 2017).

4. Common UTI causative pathogens

The Enterobacteriaceae family of bacteria is responsible for most UTIs that are detected, reported, and treated (Dunne et al., 2022). Except for Klebsiella and Shigella, which are non-motile and have peritoneal flagellum surrounding them, respectively, members of this family are facultative anaerobic, which means they can ferment glucose, encourage the reduction of nitrate to nitrite, and are oxidase negative (NICD The National Institute For Communicable Diseases n.d; Rock et al., 2014). Gram-positive and Gram-negative bacteria, as well as some fungal species, are the two main causes of UTIs (Flores-Mireles et al., 2015). UPEC and K. pneumoniae (WHO GLASS indicator organisms) are the most prevalent uro-pathogens and are considered the main cause of both complicated and uncomplicated UTIs (Amawi et al., 2021; Kajihara et al., 2020; Organization, 2016). Proteus species are next in line (Amawi et al., 2021). About 65% and 80% of complicated and uncomplicated UTIs, respectively, are thought to be caused by UPEC (Kang et al., 2018; Medina and Castillo-Pino, 2019).

S. saprophyticus, E. faecalis, Group B Streptococcus (GBS), P. mirabilis, P. vulgaris, P. aeruginosa, S. aureus, and Candida spp. are additional agents that have been linked to uncomplicated UTIs (Flores-Mireles et al., 2015; Foxman, 2014; Kline et al., 2011; Pitart et al., 2015; Ronald, 2002). After UPEC, the following causal agents are most common for complicated UTIs: Enterococcus species, K. pneumoniae, Candida species, S. aureus, P. mirabilis, P. aeruginosa, and GBS. (Flores-Mireles et al., 2015; Levison and Kaye, 2013; Tabibian et al., 2008; Fisher et al., 2011).

Research carried out in South Africa has examined the distribution of the causative agents in patients in public primary healthcare facilities, pregnant women undergoing treatment at antenatal tertiary level facilities, and community-acquired UTIs (CA-UTIs) (Keuler et al., 2022; Kubone et al., 2020; Zwane et al., 2021). At three community health centers in KwaZulu-Natal province's uMgungundlovu District, Kubone et al. (2020) examined the clonality of UPEC linked to CA-UTIs. They found 32 pure bacterial isolates, including E. coli (81.25%), K. pneumoniae (6.25%), Citrobacter Koseri (6.25%), Enterobacter cloacae (3.125%), and Bordetella spp. (3.125%). In four tertiary-level facilities located in the Gauteng area of South Africa, Zwane et al. (2021) examined the aetiology of infections linked to UTIs among women receiving prenatal care. According to their findings, E. coli was responsible for 56% of the infections, followed by E. faecalis (17%), and K. pneumoniae, S. agalactiae, and P. mirabilis (5%). It is crucial to remember that uropathogens vary in the pathogenic processes and virulence factors that enable them to infiltrate and colonize the urinary system; as a result, their prevalence in producing infection will also vary (Govindarajan and Kandaswamy, 2022).

5. Modern treatment methods for UTIs

Although a wide range of antibiotics are typically administered to treat UTIs, there is little research on the evaluation of antibiotic prescription patterns and practices in South African primary healthcare (Gasson et al., 2018). Trimethoprim/Sulfamethoxazole, Fosfomycin, Nitrofurantoin, Cephalexin, and Ceftriaxone are the most often prescribed antibacterial therapies for urinary tract infections (UTIs) (Cock et al., 2021; Kubone et al., 2020). According to Terlizzi et al. (2017) and Zalewska-Piątek and Piątek (2020), imipenem is the most effective antibiotic against all UPEC strains (100%) and is followed by ertapenem (99.98%), amikacin (99.94%), and nitrofur-antoin (99.91%). Ciprofloxacin (Tosun et al., 2016), Cefotaxime, Piperacillin/Tazobactam (Dizbay et al., 2016), azithromycin, and Doxycycline are also effective against UPEC strains (Saha et al., 2015). Ampicillin, first-generation oral cephalosporins, TMP-sulfamethoxazole (Moya-Dionisio et al., 2016), Cefuroxime (Chang et al., 2016), Cotrimoxazole (Saha et al., 2015), Amoxicillin-clavulanate, Nalidixic acid, Cefradine, and Aminopenicillins are among the antibiotics that some isolates are resistant to (Narchi and Al-Hamdani, 2010). Ciprofloxacin is the most often used antibiotic for common UTIs, accounting for 76% of cases, according to a retrospective analysis (Parish and Holliday, 2012). However, the basic antibacterial therapeutic solutions are failing as a result of the growing rise of antibiotic-resistant organisms brought on by the overuse and misuse of clinical antibiotics (Cheesman et al., 2017).

5.1. Antibiotic resistance and alternatives to antibiotic treatment

Oral medicines are less effective as a result of the increased multidrug resistance instances among UTI-causing pathogens caused by the prescription of antibiotics for UTIs without bacterial characterization (Blango and Mulvey, 2010; Erdem et al., 2018; Kubone et al., 2020). According to Gasson et al. (2018), a study carried out in the Cape Town metropolitan municipality of South Africa assessed compliance with the Essential Medicines List for South Africa and Standard Treatment Guidelines for prescribing antibiotics. The most often prescribed antibiotic for UTIs in their study was ciprofloxacin, which also had the lowest adherence rate to recommended practices. The most frequent explanation for prescribing for urological issues that did not follow guidelines was an improper treatment duration (Gasson et al., 2018). According to a another study, 82% of prescriptions for trimethoprim, 73% for nitrofurantoin, and 71% for fluoroquinolones for UTIs were written for longer than the recommended duration (Grigoryan et al., 2015). High doses of levo-floxacin are said to be insufficient to treat UTIs, and in situations where fluoroquinolone resistance is elevated, Ceftolozane/Tazobactam is a more effective alternative treatment (Huntington et al., 2016). In order to tackle UTIs, alternative treatment and prevention techniques are necessary, as evidenced by the rising prevalence of antibiotic resistance among uropathogens (Jansen et al., 2018; Kerrn et al., 2003; Wagenlehner et al., 2005; Zowawi et al., 2015). According to the WHO, there is a discernible global trend toward the adoption of TCAM as the cornerstone of healthcare delivery or as an adjunct to current healthcare systems (Organization, 2019).

6. South African traditional health practices

Traditional medicine (TM), which nevertheless contributes significantly to healthcare systems today, is a primordial source of new therapeutic molecules (Maiyo et al., 2010). According to the WHO (Organisation, 2019), TM is a safe treatment for illnesses caused by both microbial and non-microbial sources. More than a third of people in developing nations do not have access to basic medications in the primary healthcare system; as a result, traditional medicine that is unique to that nation is used pro-actively (Begam and Senthilkumar, 2014; Daferera et al., 2003; Dulger et al., 2015). According to research, over 80% of Africans use extracts from medicinal plants to treat a variety of illnesses and infections, including urinary tract infections (UTIs) (Mahomoodally and Gurib-Fakim, 2013; Mhlongo and Van Wyk, 2019). According to estimates, 72% of Black Africans use African TM, and each user uses it on average 4.8 times annually (Cook, 2009; Mothibe and Sibanda, 2019). To name a few, TM has long made significant contributions to the treatment of a wide range of infectious diseases in the South African community, including bilharzia, malaria, UTIs, reproductive disorders, and wounds (Gebashe et al., 2019; Mhlongo and Van Wyk, 2019; Semenya et al., 2012; Van Wyk and Gericke, 2000). Twelve to fifteen million South Africans are thought to still treat a variety of illnesses using traditional methods and remedies made from up to 700 native plant species (Grierson and Afo-layan, 1999; Meyer and Afolayan, 1995; Van Wyk and Gericke, 2000). Depending on the condition, a sizable section of South Africa's Black African population uses both traditional and conventional medical treatments (Booth and van Vuuren, 2023; Mander et al., 2007). Approximately 20% of all plants worldwide have undergone screening for bioactivity, according to Coopoosamy and Naidoo (2012). Investigating the traits of native plants and their possible application in the control and treatment of UTIs is therefore necessary.

7. South African medicinal plants explored for the management of UTIs

Because medicinal plants have positive effects on treating and managing a wide range of illnesses, historical records describe their use (Sofowora et al., 2013). According to Shaheen et al. (2019), the phytochemical components of the plants in TM function as immunomodulators and nutraceuticals, improve the body's oxidant status by supplying antioxidant compounds that scavenge and neutralize free radicals, stop microbe attachment, and stop the growth and multiplication of microorganisms. Researchers have looked at the potential of medicinal plants' flowers, leaves, bark, fruit, seeds, and even entire components (Table 1) to cure urinary tract infections (UTIs) (Pattanayak et al., 2017; Sha-heen et al., 2019). According to Pattanayak et al. (2017), these plant parts or their extracts are taken orally either as a single preparation or combined with other plants, meals, or beverages like milk or water. Numerous phytochemical constituents, such as alkaloids, anthraquinones, flavonoids, glycosides, phenols, saponins, steroids, sterols, tannins, terpenoids, triterpenoids, phytosterols, hydrocarbons, mono and sesquiterpenes, phlobatannins, and numerous other secondary metabolites of medicinal plants, are responsible for the diverse qualities of medicinal plants. Euclea crispa (uMshekisane), Curtisia dentata (uMlahleni), Manihot esculenta (uMdumbulu), Bulbine natalensis (Ibhucu), Catha edulis (uMhlwazi), and Eucomis bicolor (uMbola) are ethnomedicinal agents with anti-inflammatory, analgesic, wound-healing, and immunomodulatory properties that are useful for the treatment of urinary tract infections (Table 1).

7.1. Euclea crispa (Thunb.) Gu€rke (Ebenaceae)

Euclea crispa (Ebenaceae), also called blue guarri in English and uMshekisane in isiZulu, is a little tree with a single stem that has many smaller branches that form a dense crown. When it is younger, the bark is smooth and grey; as it ages, it becomes rough and dark brown (Fig. 2A). Its tiny, blue to gray leaves come in a variety of forms. The tree produces bell-shaped flowers that range in color from whitish-green to yellow (Fig. 2B). In South Africa, these flowers bloom from October to February.

The fruit with a single seed turns from reddish-brown to black as it ripens (Maroyi, 2018). A noticeable forest component of tropical and subtropical regions of Africa and Asia is the family Ebenaceae. From the Eastern Cape to the coastal areas of KwaZulu-Natal province, this tree is native to South Africa and has a broad range of distribution (Maroyi, 2018).

While Hutchings (1996) reported that naphthoquinones were abundant in the roots of Euclea species and the leaves of other species in the family Ebenaceae, Sibanda et al. (1992) isolated pentacyclic triterpenoids, lupeol, betulin, and oleanolic acid from the root bark of E. crispa.

It is still unknown which of these secondary metabolites have antibacterial qualities despite efforts to separate different chemicals from the plant's bark, roots, and leaves, according to Magama et al. (2003). The antibacterial properties of crude semi-purified extracts from E. crispa leaves were profiled against two human pathogenic fungi and eleven human pathogenic bacteria using an in vitro assay (Magama et al., 2003). Five of the eleven microorganisms that were tested—P. aeruginosa, S. aureus, Moraxella catharralis, Staphylococcus epidermidis, and Bacillus subtilis—exhibited sensitivity to the crude extract (Magama et al., 2003). Additionally, the agar diffusion method was used to assess the antifungal properties of crude, n-hexane, diethyl ether, chloroform, and ethyl acetate leaf extracts of E. crispa against the human pathogenic fungus, C. albicans, and Cryptococcus neoformans. The growth of both human pathogenic fungi was suppressed by all extracts, with the exception of the n-hexane fraction (Mag- ama et al., 2003). The crude extract produced the biggest zones of inhibition, and larger inhibition zones suggested that Candida albicans was marginally more susceptible to inhibition than Candida neoformans (Magama et al., 2003).

The purification and identification of antibacterial components from E. crispa leaves extracted with ethyl acetate were the focus of Pretorius et al. (2003). Essential oils, bitter principles, saponins, alkaloids, phenolic chemicals, and terpenoid derivatives were all present in these leaves. According to Pretorius et al. (2003), five flavonoids—catechin, epicatechin, gallocatechin, hyperoside, and quercitrin—were further characterized and demonstrated antibacterial activity against Haemophilus influenza, Streptococcus pneumoniae, and M. catarrhalis. Using an agar diffusion method and dimethyl dodecyl ammonium chloride (DDAC) as a positive control, Pretorius et al. (2003) also assessed the antibacterial properties of crude leaf extract of E. crispa against Agrobacterium tumefaciens, Clavibacter michiganense, Erwinia carotovora, Pseudomonas solanacearum, and Xanthomonas campestris.

When compared favorably to inhibition zones produced using the conventional bactericide DDAC, E. crispa prevented the development of all five plant harmful test bacteria (Pretorius et al., 2003).

The phytochemical screening of E. crispa leaf extracts was reported by Alayande et al. (2017). The results showed the presence of tannins, flavonoids, steroids, saponins, reducing sugars, and cardiac glycosides, all of which have been linked to antibacterial effects. Among the phytochemicals examined, there was no indication of alkaloids. Additionally, E. crispa leaf extracts showed strong antibacterial activity against S. aureus, Listeria sp., and E. faecalis—a combination of bacteria linked to bacteremia from a very advanced UTI that frequently leads to infective endocarditis (Alayande et al., 2017; Corey, 2009).

Flavonoids are well known for their anti-inflammatory and antioxidant properties (Ibewuike et al., 1997; Gardner et al., 1998; Meyer et al., 1998; Watanabe, 1998). However, some flavonoids have also been shown to exhibit antibacterial properties (Markham 1989, Van der Watt and Pretorius 2001). As phenolic chemicals, flavonoids interact with proteins, enzymes, and biological processes in cells; however, this characteristic renders them rather poisonous (Markham, 1989; Pretorius et al., 2003; Veitch and Grayer, 2011).

7.2. Curtisia dentata (Burm.f.) C.A.Sm. (Carnaceae)

Assegai (English) and uMlahleni (isiZulu) are the local names for Curtisia dentata (Carnaceae), a medium-to-tall evergreen tree that can reach a height of 20 meters. Its bark is square and brown with cracks. This tree has round, smooth, glossy leaves with coarsely serrated margins and pointy points. The blooms (Fig. 3) have round-oval, meaty, bitter berries and measure around 10 mm in diameter (Oyedemi et al., 2012b; Wintola and Afolayan, 2017).

Curtisia is the only species of the genus found in Africa, and it belongs to the family Cornaceae, which consists of 15 genera (Shai et al., 2008). The tree is found in KwaZulu-Natal, Mpu-malanga, Limpopo, the Eastern Cape, the Western Cape (Knysna region), and the Cape Peninsula in South Africa ("Curtisia dentata | PlantZAfrica," n. d.).

Excellent antibacterial activity was demonstrated by C. dentata in a study that screened seven active South African plant species against Candida albicans (Shai et al., 2008). Compared to bark extracts, C. dentata leaf extracts were at least five times as potent and included a greater quantity of antifungal chemicals (Shai et al., 2008). Triterpenoids like b-amyrin, a-amyrin, b-sitosterol, and vitamin E, as well as four pentacyclic triterpene compounds (lupeol, betulinic acid, ursolic acid, and hydroxyursolic acid), were found to have antifungal and antibacterial properties (against Staphylococcus aureus, E. coli, E. faecalis, and P. aeruginosa) (Dikhoba et al., 2019; Shai et al., 2008). According to cytotoxicity experiments conducted on Vero cells, betulinic acid was more hazardous than lupeol, which may account for some of its antifungal and antibacterial properties (Shai et al., 2008). The potential antifungal action of triterpenes against crop-infecting and human fungal strains is well documented (Dikhoba et al., 2019; Hu et al., 2018; Kongue et al., 2013; Liu et al., 2020).

The stem bark of C. dentata is used in traditional medicine in Southern Africa to treat oesophageal cancer, hypertension, diarrhea, fever, asthma, constipation, stomach problems, and as an aphrodisiac ("Curtisia dentata | PlantZAfrica," n.d.; Doughari et al., 2012). Bark infusions were also used to treat acne, according to Grierson and Afolayan (1999). C. dentata has been used in recent research to treat sexually transmitted diseases, cancer, stomach disorders, and tuberculosis (Fadipe et al., 2017; Soyingbe et al., 2018). Given that the plant is used to treat diarrhea, research into its antibacterial properties against bacteria that cause diarrhea, like E. coli, is necessary (Soyingbe et al., 2018).

Nerolidol, 2-Hepatol,3-methyl-, O-Xylene, and M-Xylene, which are among the main constituents of the C. dentata bark, are among the compounds that have been isolated from the stem bark of the plant and may be harmful to human health. They cause irritations to the skin, eyes, and respiratory system (Dan et al., 2017; Ishala et al., 2017; Wang et al., 2017, van Wyk, 2020). Pentane, a substance that affects the peripheral nervous system and can cause euphoria, dizziness, depression, loss of consciousness, and a coma at high concentrations, was also found in high percentages (van Wyk, 2020). When excessive amounts of butane, 2-methyl, which are also present in large amounts in the stem bark of C. dentata, are inhaled, it results in dyspnea, irregular pulse, and unconsciousness. This chemical may cause nausea, vomiting, and stomach pain after consumption (van Wyk, 2020).

7.3. Eucomis bicolor Baker (Hyacinthaceae)

The summer-growing bulbous plant Eucomis bicolor (Hyacinthaceae), sometimes called uMbola (isiZulu) or the forest pineapple blossom (English), with a two-colored crown of leafy bracts (Fig. 4). E. bicolor leaves frequently exhibit purplish-red wavy borders and purplish-red dots at the base. Its blooms, which bloom from January to March, are densely packed together, have a terrible odor, and face downward with either white or green-colored mauve petals. The capsule-shaped, three-angled fruits mature to round in between the seeds after being formed in March ("Eucomis bicolor | PlantZAfrica," n.d.).

Only two members of this family's genus are located in south tropical Africa; all other members are found in South Africa (Sihra, 2012). All nine of South Africa's provinces are home to the E. bicolor species ("Eucomis bicolor | PlantZAfrica," n.d.).

It has been demonstrated that acetone and water extracts of bulbs from specific Eucomis species, including E. bicolor, suppress bacteria linked to common UTIs, including C. albicans, Bacillus subtilis, E. coli, and S. aureus (Akhalwaya et al., 2018; Mizielin´ska et al., 2017b).

Homoisoflavanoids, spirocyclic nortriterpenoids, benzopyranones, saponin glycoside, and chromanone are the main phytochemical components of Eucomis plants. These chemicals have a variety of biological actions (Du Toit et al., 2007). When profiled using gas chromatography—mass spectrometry, E. bicolor produced nine triter-penoid glycoside derivatives, four homoisoflavonoids, six spirocyclic nortriterpenoids, a pentanortriterpenoid, a tetranortriterpenoid, and a lanostane derivative (Sihra, 2012).

The Eucomis plants are widely recognized for their therapeutic anti-inflammatory qualities and are typically used to treat newborn colic ("Eucomis bicolor | PlantZAfrica," n.d.). Numerous eucomis species are used to treat rheumatism, respiratory conditions, and venereal infections ("Eucomis bicolor | PlantZAfrica," n.d.; Hutchings, 1996).

Additionally, its anti-inflammatory, antibacterial, antihistaminic, and antimicrobial qualities have been extensively assessed in both in vitro and in vivo bioassays (Akhalwaya et al., 2018; Amschler et al., 1996). Eucomis species are linked to pain relief, anti-inflammatory properties, and the removal of bacterial and fungal infections (Mizielin´ska et al., 2017b).

In KwaZulu-Natal and the Eastern Cape districts of South Africa, the bulbs of E. bicolor (Fig. 5) are frequently used as a purgative and for the treatment of colic (Hutchings, 1996). The Zulu, Tswana, Sotho, and Xhosa people of South Africa frequently make decoctions, infusions, and enemas from this plant material (the bulb) in milk or water ("Eucomis bicolor | PlantZAfrica," n.d.). Bulbous infusions are also used by the Zulu tribe to improve sexual performance, relieve biliousness, and purify blood (Mander et al., 2007, 1995).

According to Taylor et al. (2002), prostaglandins are essential for both the inflammatory response and pain perception. Through in vitro tests that look for prostaglandin production inhibitory action, researchers have evaluated the potential of plant extracts to lessen pain and inflammation. Assessing the degree of inhibition of the cyclooxygenase enzyme, which is involved in prostaglandin synthesis, is the goal of these works. There are two isoforms of cyclooxygenase, COX-1 and COX-2, which are essential for prostanoid production (Zidar et al., 2009). The anti-inflammatory effectiveness of the ethanolic and aqueous bulb extracts of the Eucomis species for COX-1 inhibition was assessed by Taylor et al. (2002). While the water extracts showed intermediate activity (40–70%), the ethanolic extracts showed significant activity (70–100%). Bulb extracts demonstrated selective COX-2 inhibitory effect, according to additional research on the COX-2 inhibitory activity (Taylor et al., 2002). Pharmacologically valuable, a selective COX-2 inhibitor is indicated by a low COX-2/COX-1 ratio. The COX-2/COX-1 ratio in this instance was 0.8, suggesting that the bulb extract had preferential COX-2 inhibitory action (Taylor et al., 2002).

The E. bicolor bulb was suspected of causing human poisoning in the 1960s (Watt and Breyer-Brandwijk, 1962). Mander et al. (1995) and Hutchings et al. (1996) further supported these suspicions, reporting that the bulbs of E. bicolor also contained a dangerous hemolytic poison and that symptoms of poisoning included abdominal pain, diarrhea, and renal failure. Evidence of higher toxicity among the crude extracts and isolated chemicals of Eucomis species was presented in a review conducted by Koobarnaly et al. (2006). There is little information available about the safety of Eucomis species, according to more recent study, and it is crucial that these plants be evaluated for toxicity and mutagenicity (Taylor and van Staden, 2001; Masondo et al., 2014).

7.4. Catha edulis (Vahl) Endl. (Celestraceae)

Bushman's tea (English) and uMhlwazi (isiZulu) are the local names for Catha edulis (Celestraceae), a lovely little deducious shrubtree with bright green leaves that can grow up to 10 m tall (Fig. 6). The tree produces tiny, cream-white to greenish blooms in the spring (Catha edulis, n.d.). Typically, the stem has a thin crown and is straight and slender. The light gray bark, which turns darker as it grows, is frequently cracked and rough, and it has pinkish juvenile stems. This tree has opposing, hanging leaves that are leathery to the touch, bright green on top, and paler underneath. The leaf stalks are short and pinkish in color, and the leaf margins are strongly serrated (Catha edulis n.d.; Van Wyk & Van Wyk, 1997).

Ethiopia, South Africa (KwaZulu-Natal, Eastern Cape, Mpumalanga, and Limpopo), and the Arabian Peninsula are among the tropical African countries where C. edulis is extensively found (Catha edulis n.d). Because cathinone is its active ingredient, C. edulis is classified as a drug in South Africa and is listed under the Drug Act. According to Balogun and Ashafa (2019), cathinone is an alkaloid that resembles amphetamine and ephedrine. Because its primary active ingredient, cathinone, is converted to cathine and norepinephrine after three to four days, C. edulis does not deliver the expected psychostimulatory effects (Patel, 2019). Alkaloids, glycosides, tannins, flavonoids, terpenoids, amino acids, vitamins, and minerals are among the numerous other substances found in C. edulis (Krizevski et al., 2007). The main active alkaloid, cathinone, is found in a juvenile distribution; it can account for almost 70% of the alkaloid content in young flowers, leaves, and twigs (Patel, 2019).

According to Duncan et al. (1999), the plant also possesses analgesic, anti-inflammatory, and antibacterial qualities. It is claimed that C. edulis has antifungal, cytotoxic, and anti-inflammatory qualities in addition to producing anorexia, hyperactivity, analgesia, and heat (Balogun and Ashafa, 2019). In addition to being used as a remedy for respiratory disorders, exhaustion, and insomnia, the plant is also used to stimulate the heart and prevent coughing, asthma, and other chest conditions (Van Wyk, 2011; Van Wyk & Van Wyk, 1997).

Alkaloids, terpenoids, flavonoids, sterols, glycosides, tannins, amino acids, vitamins, and minerals are among the chemical components of C. edulis. Using the disc diffusion method, crude extracts of C. edulis demonstrated strong antibacterial activity against all bacterial strains, including Gram-positive (Staphylococcus aureus and Streptococcus pyogen) and Gram-negative (Klebsiella pneumonia and Escherichia coli) strains (Andualem et al., 2020).

Compared to other psychoactive chemicals, the WHO considers C. edulis to be a substance with a low potential for misuse (Asfaw, 2023). Mild emotional instability, cognitive impairment, chronic gastritis, constipation, anorexia and weight loss, cirrhosis, urinary retention, impotence, tachycardia, arrhythmia, hypertension, vasoconstriction, and myocardial infarction are just a few of the negative consequences that can arise from consuming C. edulis (Getahun et al., 2010; Ongeri et al., 2019; Al-Duais and Al-Authan, 2021, Asfaw, 2023).

7.5. Bulbine natalensis Baker (Asphodelaceae)

Commonly referred to as the broad-leaved bulbine in English and iBhucu in isiZulu, B. natalensis (Asphodelaceae) is a succulent plant with smooth leaves that resembles aloe. It bears colorful, towering spikes of fluffy yellow flowers and is made up of rosettes of thick, broad, succulent light green leaves (Fig. 7). Intermittently throughout the year, these flowers are produced (Van Wyk et al., 1997; Yakubu et al., 2012).

Bulbine plants can be found in South Africa's KwaZulu-Natal, Western Cape, and Eastern Cape provinces (Van Wyk et al., 1997). Tannins, anthraquinones, cardiac glycosides, saponins, and alkaloids were found in the B. natalensis tuber, but no phenolics, flavonoids, steroids, phloba-tannins, or triterpenes were found (Yakubu and Afolayan, 2010).

Many people use leaf sap to treat burns, wounds, rashes, itches, ringworms, and cracked lips. The root and stem infusion is taken orally to treat rheumatism, diabetes, diarrhea, vomiting, convulsions, and venereal illnesses (Pujol, 1990; Yakubu and Afolayan, 2010). According to Coopoosamy and Naidoo (2012), the species of bulbines are used to cure ringworms, burns, blisters, cold sores, cracked lips, cracked fingers, nails, and heels, bites from insects, fever blisters, mouth ulcers, sunburns, and blisters. Additionally, B. natelensis species are used to treat UTIs, wound infections, diabetes, hypertension, fever, obesity, and sexually transmitted infections (Mocktar, n.d.).

According to Mosa et al. (2011), the extracts of B. natalensis have a high concentration of sterols and sterolins, as well as total phenolic and flavonoid contents. Additional chemicals, including Bulbnatalonoside A, B, C, D, and B, were also identified. E.

In their 2012 study, Yakubu and Quadri examined the antibacterial potential of several B. natelensis tuber extracts at doses of 0.1, 0.5, 1.0, 5.0, and 10 mg/ml. Thus, when tested with 75% of the bacterial strains inhibited, the ethanolic extracts demonstrated significant inhibition against all of the Gram-negative bacteria implicated in UTIs (E. coli, K. pneumoniae, P. aeruginosa, S. marcescens, P. vulgaris, E. cloacae, Acinetobacter calcaoceuticus, and Shigella flex-neri); similarly, the n-butanol fraction repressed nearly 87.5% of the bacteria at MIC values ranging from 3 to 10 mg/ml.

In addition to its remarkable antioxidant action, B. natalensis has been shown to have strong tumor-specific cytotoxicity against human squamous carcinoma cells through its rhizomes (Teffo et al., 2021).

According to Mosa et al. (2011), this plant has anti-platelet properties that increase the risk of bleeding and bruises by preventing blood clotting. In rats, B. natalensis consumption changed liver enzymes and caused negative histological alterations in the liver and renal tubules, which may be a sign of the plant's toxicity, according to a study by Afolayan and Yakubu (2009). Additional research examining the relationship and effects of herb-drug interactions between B. natalensis and common drugs that are CYP3A4 and CYP2C9 protein substrates showed a possible risk and came to the conclusion that these could lead to unexpected side effects or treatment failures (Husain et al., 2021).

7.6. Manihot esculenta Crantz (Euphorbiaceae)

A woody shrub native to South America, M. esculenta (Euphorbiaceae) is widely grown as an annual crop in tropical and subtropical climates for its edible starchy and tuberous root. In isiZulu, it is also referred to as cassava and uMdumbulu. With leaves that are deeply divided into three to seven lobes (Fig. 8), the cassava shrub can reach a height of three meters (Kuete, 2014; Maghuly et al., 2015; Ogunniyi, 2009). At the base of the stem, M. esculenta roots grow in clusters of four to eight. These roots can grow up to 20–40 cm in length and 3–10 cm in diameter. The interior portion of the root is white and typically tougher than that of a potato, while the outer layer is covered in a thin reddish-brown fibrous bark (Fig. 9) that can be scraped off by peeling and scraping (Bahekar and Kale, 2013; Maroyi, 2012).

About 502 million people depend on it as a staple meal in the poor world and as the third-largest source of carbohydrates in tropical regions (Kuete, 2014; Maghuly et al., 2015; Ogunniyi, 2009). Although they are a poor source of protein, the roots of the cassava plant are recognized for being a rich source of carbohydrates (Montagnac et al., 2009). Although cassava comes in a variety of species, it is typically divided into two categories: sweet and bitter (Bahekar and Kale, 2013).

According to Latif and Muller (2015), because M. esculenta leaves are rich in fiber, vitamins, B1, B2, C, crude protein, essential amino acids, and carotenoids, they should receive the same level of attention as the tubers as a source of protein and nutrients for human nutrition. Additionally, pharmacological substances with anti-inflammatory, anti-oxidative, and renal protective qualities have been discovered to be present in M. esculenta (Marie-Magdeleine et al., 2010; Simao et al., 2013).

Alkaloids, flavonoids, tannins, reducing sugars, and anthocyanosides are all present in raw cassava tubers; however, cardiac glycosides, anthraquinone, phlobatinnins, and saponins are absent (Bahekar and Kale, 2013). Many people are skeptical about using M. esculenta for medicinal purposes because of its cyanogenic glycosides, which are known to be toxic. However, it is said to be the most underutilized medicinal herb in the world (Bahe-kar and Kale, 2013; Burns et al., 2012; Maroyi, 2012; Van Wyk, 2011).

Natural antioxidants found in M. esculenta have also been suggested as a treatment for age-related human conditions as cancer, heart disease, arthritis, immune system deterioration, cognitive dysfunction, and cataracts (Yi et al., 2011).

Adam et al. (2014) used the agar well diffusion method to evaluate the antimicrobial activity of dried ground powdered bulb and peel of M. esculenta against four strains of Gram-negative bacteria (E. coli, P. aeruginosa, K. pneumonae, and S. typhimurium), one strain of Gram-positive bacteria (S. aureus), and one strain of yeast (C. albicans) in a study carried out in Sudan. The methanolic bulb extract demonstrated antibacterial efficacy against all test pathogenic bacteria at all concentrations (100, 50, 25, and 10%), with concentration-dependent inhibition zone lengths that varied. Even at 50% and 100% sensitivity to the methanolic peel extract, K. pneumonae was shown to be the most susceptible bacteria.

Cyanogenic glycosides are found in the roots of M. esculenta (Vetter, 2000). When these cyanogenic glycosides are hydrolyzed by interstitial bacteria, hydrogen cyanide is produced, which causes toxicity in humans (Salem et al., 2021). Many chronic illnesses brought on by acute cyanide poisoning have been linked to hydrogen cyanide (Mohidin et al., 2023). In rats, M. esculenta has been observed to cause growth retardation, microcephaly, limb abnormalities, and congenital malformations (Vetter, 2000). In many tropical nations, M. esculenta is a staple food. Kwashiorkor is seen to be common in these locations, and eating of M. esculenta has been strongly linked to Kwashiorkor (Salem et al., 2021). Because it functions as a glycoside, linamarin, one of the strong chemicals found in the M. esculenta plant, causes swelling and cellular edema in the epithelial cells of the renal proximal convoluted tubules (Kamalu, 1995; Vetter, 2000). An compound found in M. esculenta has the ability to exacerbate iodine deficiency conditions like goitre (Delange et al., 1994; Mohidin et al., 2023).Cyanide mimics the consequences of iodine deprivation when it is transformed into thiocyanate.

Because M. esculenta slows down the rhythm of human growth and development and affects thyroid hormone activity, it has also been linked to biological fitness (Banerjee et al., 1997).

8.Conclusion

Antimicrobial resistance poses a serious risk to public health's long-term stability and could have a major detrimental effect. It must be prioritized both domestically and globally since it presents a serious threat to global security. Numerous studies are presently being conducted worldwide to identify alternatives to the usage of antibiotic treatments as a result of this concerning rise in antimicrobial resistance. In South Africa, an estimated 700,000 tons of plant materials valued at between 1.2 and 2.5 billion South African Rands are used each year to produce herbal treatments (Mander and Le Breton, 2006; Street and Prinsloo, 2013). THPs frequently employ these herbal remedies, which are rapidly gaining popularity as complementary and alternative therapy (Cock et al., 2021; Organization, 2013). Few research have specifically addressed UTIs, despite a significant increase in recent years in the number of studies evaluating and validating the use of traditional South African remedies for their antibacterial and therapeutic qualities (Cock et al., 2021). Therefore, the potential for treating UTIs was examined in this review of plants that are part of a medicinal mixture used by THPs in the KwaZulu-Natal province of South Africa. Particular attention was paid to the plants' antibacterial, anti-inflammatory, antioxidant, immunomodulatory, and renal protective qualities against bacterial strains linked to UTIs. According to the reviewed literature, ethnomedicinal plants such as Euclea crispa, Curtisia dentata, Manihot esculenta, Bulbine natalensis, Catha edulis, and Eucomis bicolor are known to contain tannins, flavonoids, saponins, cardiac glycosides, and alkaloids. These compounds are also linked to antimicrobial properties and are implicated in preventing bacterial growth. Furthermore, it has been reported that E. crispa leaf extracts have a high level of bacterial inhibition against S. aureus and P. aeruginosa. It is known that four pentacyclic triterpene compounds that were separated from C. dentata have antibacterial properties against P. aeruginosa and E. coli. Bulb extracts of E. bicolor have been demonstrated to inhibit S. aureus and E. coli, while highly assessed Eucomis species are thought to have anti-inflammatory qualities. When evaluated using the disc diffusion method against K. pneumonia and E. coli, crude extracts of C. edulis and M. esculenta shown strong antibacterial action against the major UTI indicator organisms in the WHO's GLASS (Andualem et al., 2020; Y Adam et al., 2014). It has also been observed that different doses of the B. natelensis tuber extracts exhibit considerable inhibition against all of the Gram-negative bacteria linked to urinary tract infections (UTIs) (Yakubu and Quadri, 2012). The recommendation and use of E. crispa, C. dentata, M. esculenta, B. natalensis, C. edulis, and E. bicolor by THPs in treating UTIs can therefore be justified because this literature shows that these bacteria have bioactive derivatives that have antimicrobial activities against Gram-negative and Gram-positive bacterial species linked to UTIs.

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