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A Review On Of Invasive Alien Plant Species Useful For Treatment and Manaement of Respiratory Infections in Animals and Human South Africa

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Abstract
Respiratory tract infections can be caused by a wide variety of phathoges(Bacteria,mycobacteria,fungus,viruses) which can infect both animals and human. Airborne transmission via droplets and aerosols enables some of these viruses to spread efficiently among animals-humans, causing outbreaks that are difficult to control. Many outbreaks have been investigated retrospectively to study the possible routes of inter- animal-human virus transmission. Ethno-veterinary and herbal practices have been in use for centuries, resulting in transfer of knowledge to the common people of the society including the farming sector. The main advantages lie in the facts that they are accessible, easy to prepare and administer, with little cost involved. This paper reviewed the Alien medicinal plants in South Africa that possessed antibacterial ,antimycobacterial , antifungal ,antiviral activities and immunodulatory.
Keywords: Antimicrobial,Alien medicinal plants, Bronchitis, Chronic obstructive pulmonary disease,Phathogens, immunodulatory.

I. INTRODUCTION

Breathing is one of the essential function in both animals and human that support our life. Malfunctioning of any of the parts of our respiratory system starting from nose till the lungs leads to disorders that are grouped under respiratory ailments.

Respiratory disease is a medical term that encompasses pathological conditions affecting the airways, including nasal passages, bronchi and lungs. They range from mild and self-limiting, such as the common cold, to acute infections such as bacterial pneumonia, bronchitis and chronic conditions like asthma or chronic obstructive pulmonary disease.

Tuberculosis is a disease caused by bacterial infection, particularly to the lung and could lead to death if not treated properly. Tuberculosis is one of the top ten causes of death in the world. [209]. Pneumonia is a form of acute respiratory infection that affects the lungs. The lungs are made up of small sacs called alveoli, which fill with air when a healthy person breathes. When an individual has pneumonia, the alveoli are filled with pus and fluid, which makes breathing painful and limits oxygen intake. Pneumonia is the single largest infectious cause of death in children worldwide. Pneumonia killed 808 694 children under the age of 5 in 2017, accounting for 15% of all deaths of children under five years old[209] . Respiratory disease causes a huge worldwide health burden.

Microbial infections are great challenge to both animals and human health concern and it is even exacerbated by the growing resistance to the conventional drugs[1,4]. Thus, researchers have resort to find remedy from plants for infectious diseases. Natural products are typically secondary metabolites, pro-duced by plants in response to external stimuli such as nu-tritional changes, infection and competition[6,7]. There-fore, bioactive natural products are chemical substances produced by the host as defensive and protective mecha-nisms against predation by microorganisms, insects and herbivores[8]. A large majority of essential medicines, which exist nowadays in drug stores, are cultural and therapeutic legacies handed down from the past.To treat respiratory disease, people and ethno Veterinaries from many regions around the world (Africa, Asia and Latin America) use traditional medicine which enables them to meet some of their needs in terms of primary health care and Animal health care . [8]. Africans in general South African in particular have been using plants as a source of drugs, power and beautification since ancient times

Transmission

Transmission via each of these three routes is complex and depends on many variables such as environmental factors (e.g. humidity and temperature), crowding of people, but also on host factors such as receptor distribution throughout the respiratory tract. The fact that all these variables affect the different transmission routes of the different respiratory pathogens in a dissimilar way, makes it very difficult to investigate them experimentally [9,10].Respiratory pathoges spread via three different transmission routes: contact (direct or indirect), droplet and aerosol transmission [2,3]. Contact trans-mission refers to direct pathoens transfer from an infected person to a susceptible individual (e.g. via contaminated hands) or indirect pathogens transfer via intermediate objects (fomites). Transmission of pathogens through the air can occur via droplets or aerosols. The commonly accepted cut-off size between the large droplets and small aerosols is 5 mm, although this varies considerably between studies, ranging up to 12 mm [5,9,10]. Droplets generated during coughing, sneezing or talking do not remain suspended in air and travel less than 1 m before settling on the mucosa of close contacts or environmental surfaces. Aerosols have a slow settling velocity, thus they remain suspended in the air longer and can travel further [5,9,10].

Respiratory pathogens and related symptoms

Bacterial and Fungus

Streptococcus pneumoniae

Streptococcus pneumoniae, a Gram-positive bacterium, is the common cause of pneumonia - an acute illness in which the lung's alveolar air spaces become inflamed and filled with white blood cells and fluid. Even though pneumonia can be caused by a viral or parasitic infection, the most severe cases are caused by bacteria [210].

Klebsiella pneumoniae

Klebsiella pneumoniae and other Gram-negative rod shaped bacteria, often cause pneumonia in immunocompromised people. Symptoms of *Klebsiella* pneumonia include chills, fever, mucoid sputum, cough, chest pain and bloody sputum[210].

Cryptococcus neoformans

Cryptococcus neoformans is not part of the normal flora of the respiratory tract in humans or animals and is commonly found in pigeon droppings, but inhalation of cryptococcal particles can cause cryptococcosis[212] Pulmonary cryptococcosis leads to pleural effusions, causing symptoms like coughing and chest pain [211].

Moraxella catarrhalis

Moraxella catarrhalis is part of the natural flora of the nasopharynx, but has recently emerged as a real pathogen causing upper respiratory tract infections in healthy elderly people and children *Moraxella catarrhalis* is also an important cause of infections of the lower respiratory tractspecifically with adults suffering from COPD. Young children often fall victim to otitis media, a painful inflammation of the middle ear commonly caused by *M. catarrhalis* [210].

Staphylococcus aureus

Staphylococcus aureus an opportunistic pathogen, is carried in the noses of about 20% of healthy people, and can also cause otitis media [210]. Lower respiratory tract infections such as pneumonia can also be caused by *S. aureus*.

Mycobacterium tuberculosis

Most cases of Tuberculosis are caused by *Mycobacterium tuberculosis*, and this disease has recently risen in incidence due to the HIV/AIDS epidemic. It is a chronic disease, and symptoms characteristic of this illness include night sweats, a chronic cough, weight loss, fever, and often also blood in the sputum [210].

Viruses

Rhinoviruses

Rhinoviruses (RVs) are the most common cause of the common cold. They chiefly cause upper respiratory tract infections (URTIs) but may also infect the lower respiratory tract. Potential complications of infection include otitis media, sinusitis, chronic bronchitis, and exacerbations of reactive airway disease. Although rhinovirus infections occur year-round, the incidence is highest in the fall and the spring. but little to no infectious rhinovirus could be demonstrated in sneezes and coughs as detected by virus titration [213].

Influenza A virus

There are four types of influenza viruses: A, B, C and D. Human influenza A and B viruses cause seasonal epidemics of disease (known as the flu season) almost every winter in the South Africa. Influenza A viruses are the only influenza viruses known to cause flu pandemics, i.e., global epidemics of flu disease. Influenza D viruses primarily affect cattle and are not known to infect or cause illness in people. Due to the severity of the yearly influenza epidemics and the potential of zoonotic influenza A viruses to cause severe outbreaks, there have been many studies on influenza A virus transmission among humans. [214]

Coronavirus

In humans, alpha (229E and NL63) and beta corona viruses (OC43, HKU1, SARS and MERS) are associated with respiratory disease [215]. Alpha coronaviruses have a high attack rate early in life and spread rapidly during outbreaks. SARS-CoV and MERS-CoV appeared to have an unusual capacity to survive on dry surfaces as compared to HCoV-229E, HCoV-OC43, and HCoV-NL63 [215,216]. The third novel coronavirus to emerge in this century is called SARS-CoV-2. It causes coronavirus disease 2019 (COVID-19), which emerged from China in December 2019 and was declared a global pandemic by the World Health Organization on March 11, 2020. [217]

Adenovirus

Adenoviruses are common viruses that cause a range of illness. They can cause cold-like symptoms, fever, sore throat, bronchitis, pneumonia, diarrhea, and pink eye).People with weakened immune systems or existing respiratory or cardiac disease are more likely than others to get very sick from an adenovirus infection.Adenoviruses can cause respiratory disease (mainly type 1–5, 7, 14 and 21) [218], conjunctivitis or infantile gastroenteritis (type 40 and 41) [219]. They are a common cause of respiratory illness and pneumonia in children [220,221] , whereas infections are generally asymp-tomatic in adults.

Alien Plants used against respiratory disorders in South Africa

In this current review, to throw light into the importance of home remedies against respiratory ailments and, the various medicinal properties possessed by them, we have chosen 19 invasive alien medicinal plants use in SouthAfrica. The aspects covered include Antimicrobial, Immunomodulatory,Isolations and Cytotoxic activity as scientifc evidence supporting there use.

AGAVE SISLANA

Antimicrobial, Immunomodulatory and Cytotoxic activity

Animicrobial activity of *Agave sisalana is* reported by several workers against various gram positive, gram negative bacteria and fungus *Staphylococcus aureus, Salmonella typhi,Escherichia coli,* S*treptococcus pyogenes, Candida albicans, B. cereus, M. luteus, P.aureginosa, S. cholereasuis, C. albicans Shigella dysenteriae, Bacillus atrophaeus,Enterococcus faecalis, Pseudomonas aeruginosa, Candida albicans, Bacillusm stearothermophilus* [172,186,203,204]. *Agave sisalana* was found tremendously potent antimicrobial agent against various species.

Methanolic extract of *Canna indica* leaves and flowers showed antibacterial activity against *B subtilis*. Ethyl acetate extracts of flowers and stems/ barks also showed activity against *B subtilis,* while, hexane and distilled water extracts of *Canna indica* leaves, flowers and stems/ barks showed no antibacterial activity [208].The oil showed good antibacterial activity against *Staphylococcus aureus* but mild activity against *Bacillus subtilis* [205]. A novel 10 kDa protein with anti-HIV-1 reverse transcriptase (RT) inhibitory activity was isolated from leaves of *Canna indica*L. [208].Important Flavonoids (+/-)-3,9-dihydroeucomine, dihydrobonducellin and 5,7, dihydroxy-3-(4'-hydroxybenzyl)-4-chromanone was found to show inhibitory effects on human peripheral blood mononuclear cell (PBMC) proliferation activated by PHA and all compounds significantly inhibited the production of interleukin IL-2 and IFN γ in activated (PBMC) [173]. The dichloromethane and ethanol extracts of the leaves of *Canna indica* were evaluated for brine shrimp toxicity. Their LC 50 value were 273.9(167.8-447.0) and>1000 μg/ml respectively [207].

Acalypha indica

Antimicrobial, Immunomodulatory and Cytotoxic activity

Dilution method was employed to determine the effect of petroleum ether extract (40-60 Degree) chloroform and methanolic extract of dried leaves of Acalypha indica Linn (Euphorbiaceae) against fungi (Candida albicans) and bacteria(Escherichia coli, Staphylococcus aureus, Pseudomonas aeruginosa, Salmonella typhosa, Bacillus substilis, Klebsiella pneumoniae). Except the petroleum ether extract, all the extract exhibited a prominent antimicrobial activity. The methanolic extract was further fractionated into acetone soluble and insoluble parts. Both the parts exhibited prominent antimicrobial activity. The acetone insoluble part exhibited MIC of 0.0040 mg/ml against Staphylococcus aureus and both acetone soluble and insolube parts exhibited MIC of 0.05 mg/ml against Salmonella typhosa. [167].Crude ethyl extract, petroleum ether and toluene extract of leaves form *Acalypha indica* were tested for the antibacterial activity against the four bacterial spe cies, *Klebsiella pneumonia, salmonella typhae, Bacillus subtilis* and *pseudomonas putida*. It was found that ethyl acetate extract exhibit the string antimicrobial activity [166].Research treatment related to Tuberculosis is highly recommended for saving more lives, especially with low-cost medication. Since *Acalypha indica* has been used by people in India to treat any disease related to the breathing system[157,162,163,164] ,the attempt to conduct a scientific study using this plant is appreciated. Accordingly,Gupta et al. (2010)[155] conducted an experiment with several tuberculosis bacteria using an aqueous extract of *Acalypha indica*. As a result, the mycobacterium tuberculosis

H37Rv and two multi-drug resistance mycobacterium tuberculosis isolates; DKU-156 and JAL-1236, were inhibited by aqueous extract of *Acalypha indica*. However, the extract had a lower effect on the rapid growth of *Mycobacterium fortuitum* (TMC-1529) [155] Chidambaram et al. (2013) also reported that all tuberculosis bacteria strains H-485, SH-577, SHOF-567 including H37Rv were not affected by the aqueous extract. An oral administration of this plant decoction could contribute minimally in treating this disease.A study was conducted by Ali et al. (1996) [153] to find the inhibition activity of a virus from Malaysian indigenous plant medicines. Among the selected plants, *Acalypha indica* was tested against two types of Herpes simplex virus, Type 1 (HSV-1) and Vesicular stomatitis virus (VSV) on the HeLa cells. They used Minimum Inhibitory Concentration (MIC) to identify the anti-viral inhibition activity. From the results, HSV-1 virus was not affected by the *Acalypha indica* ethanol extract, while VSV virus was inhibited by ethanolic extract with a CD50 value of 0.01 mg/ml. Since VSV is RNA-type virus, they stated the cytotoxic and anti- VSV activities of extract may involve in the mode of action presumably through interaction[153]. Further study is required with more virus species to gather more information related to *Acalypha indica* that can act as an anti-viral agent.Intoxication related to *Acalypha indica* has only occurred in livestock that foraged the weed for food[159]. The symptoms exhibited by the intoxicated livestock were similar to victims of cyanide intoxication[165] The cyanogenic phytochemical inside this plant will be hydrolyzed by the β-glucosidase enzyme before the production of sugars and cyanohydrin. The cyanohydrin will spontaneously decompose to HCN which is very poisonous to humans and livestock[154] Without any specific prescription, uneducated individuals could easily be intoxicated by excessive consumption of the raw plant or drinking its juice. In Malaysia, some elders practice consuming this plant periodically and wait for the poison to be fully excreted from the body. They may not know of the cyanogenic compound but through past experiences, they know this plant has a certain amount of poison that not should be taken regularly. People around the world have been aware that *Acalypha indica* is toxic for a long time (Watt et al., 1962).Indeed, Acalyphin is the cyanogenic phytochemical presented in the *Acalypha indica* species responsible for such accident. There are seven types of cyanogenic phytochemicals, acalyphin, found in this plant. The major cyanogenic phytochemicals can be found at the leaves (roots 0.055%, stem 0.033%, leaves 0.350%, seed; not detectable) [156]. Cyanide is lethal to humans if more than 1 mg/kg is consumed (New Zealand Food Safety Authority, 2016). Therefore, theoretically, if a person weighs 70 kg, they should not eat more than 20g of raw leaves as it contains 70 mg of acalyphin.In the studies conducted by[156,159], the acalyphin compound was detected and successfully isolated by using a fresh sample and methanol as the solvent extractor. Their studies involved no heat during extraction since a cold extraction method was applied. The cyanogenic phytochemical might be degraded if there is heat intervention during the preparation process as occurs on cassava cyanogenic phytochemical, linamarin [161,167].Until now, no single study could figure out how to separate or reduce the cyanogenic effect from *Acalypha indica*. Raw consumption of the whole plant is the riskiest practice because people can be intoxicated. Even so, no records have been found of people dying to excessive consumption of *Acalypha indica*. Apart from that, the traditional practices use water as an extraction medium. Nobody has conducted any study on the number of cyanogenic phytochemicals inside *Acalypha indica* when they perform the therapeutic treatment. Since the plant is used as an aphrodisiac, there is the possibility of the risk of overdosing by uneducated people with obsessive behavior. In Malaysia, some manufacturers have taken advantages of this situation by selling *Acalypha indica* as an instant coffee to the public[158,167] .In the worst case scenarios, they exploit their product by adding a drug like sildenafil to enhance its effect. Consequently, the customers will suffer from an overdose of acalyphin and controlled drug leading to a risk of death. To prevent such an incident, the government has seized some *Acalypha indica* based instant coffees from the market and is strictly prohibiting any unregistered products; however, scholars and governments should work together by educating the public.

Catharanthus roseus

Antimicrobial, Immunomodulatory and Cytotoxic activity

Benzene extract of dried flowers at a concentration of 50% on agar plate was active on *Proteus*, *Pseudomonas*, *Shigella* and *Stphylococcus* species, however, benzene extract of leaves at a concentration of 50% on agar plate was active on *Proteus*, *Pseudomonas*, *Salmonella*, *Shigella* and *Staphylococcus* species. [24] .Ethanol (70%) extract of dried leaves on agar plate was active on *Bacillus megaterium* and *Staphylococcus albus* and inactive on *Bacillus cereus* and *Staphylococcus aureus*. [24] .Total alkaloids of root at a concentration of 500.0 mcg/ml in broth culture were inactive on E.coli, *Salmonella lyphosa* and *Shigella dysenteries.* [18].Water extract of entire plant on agar plate at a concentration of 1:4 was inactive on *Salmonella paratyphi*. [23]. Acetone and water extracts of dried aerial parts at a concentration (50%) on agar plate was inactive on *Neurospora crossa.* [19] Hot water extract of dried leaves in broth culture was active on *Trichophyton mentagrophytes.*16 Hot water extract of dried stem in broth culture was active on *T. mentagrophytes* and weakly active on *T. rubrum.* [21] Leaves and roots on agar plate were active on *Pythium aphanidermatum*. [22].Water extract of callus tissue in cell culture was active on Tobacco Mosaic Virus [26] Alkaloid fraction of dried leaves in cell culture was active on

CA-9KB, ED50 0.0435 mcg/ml.Chloroform extract and culture filtrate of callus tissue in cell culture at dose of 50.0 gm (dry wt of plant) were active on Leuk-L12 [14]culture, water extract.

Chelidonium majus

Antimicrobial, Immunomodulatory and Cytotoxic activity

Chelidonium majus L. belong to the family Papaveraceae. *C. majus* is native in Europe, western and central part of Asia and in northern Africa.*C. majus* is listed among one of the most active antimicrobial plants in a screening study by Kokoska et al. [106] .Crude extracts of and several alkaloids isolated from *C. majus* exhibited antibacterial, antiviral, and antifungal properties [106–119] The glycosaminoglycan present in the latex inhibits intracellular human immunodeficiency virus HIV viral migration and blocks reverse transcriptase [98] . Moreover, individually tested five *C. majus* alkaloids: chelidonine [1], chelerythrine [9], sanguinarine [12], coptisine [31], and berberine [28] were able to inhibit the development of HIV-1. The first two decreased the activity of the virus reverse transcriptase at the concentrations 150–200 μg/ml, while sanguinarine [12], berberine [28], and coptisine [31] were already active at concentrations of 50–150 μg/ml [100].The chloroform extract in the concentration of 35 μg/ml decreased the number of adenoviruses responsible for inducing acute fevelitis of the upper respiratory tract and conjunctiva in humans [100] . The experiments with animals showed that ethanol extract of *C. majus* inhibited encephalomyocarditis virus in 45% of experimental mice, whereas berberine [28] tested in the concentration range between 20 and 125 μg/ml inhibited influenza virus type A and B in chicken embryos with 33–99.97% efficiency (data previously reviewed by [101] . These results were presented only once, and from that time have never been confirmed or repeated.*In vitro studies:* An interesting immunomodulatory potential was exhibited by a protein-bound polysaccharide extracted from *C. majus* (CM-Ala), which showed mitogenic activity on spleen cells, bone marrow cells, and increased the number of granulocyte macrophage-colony forming cells (GM-CFC) [25]. When *C. majus* extract was used in combination with recombinant IFN-gamma, there was a marked combined induction of NO and TNF-alpha production in mouse peritoneal macrophages [120].Repeatedly, studies and case reports occur that suggest hepatic injury/hepatotoxicity. It is especially important because one of the main indications of *C. majus* relates to liver and biliary tract disorders due to its cholagogue and hepatoprotective activities. The incidence of hepatotoxic cases and the possible clinical importance and safety issues have been reviewed recently[104] . Specifically, the results from animal studies are ambiguous and suggest a rather complex mixture of various mechanisms, such as inducing or alleviating oxidative stress or modulation of hepatic enzymes such as MAO and SOD, or slowing down mitochondrial respiration. The mitochondrial toxicity was related to DNA intercalating properties of sanguinarine [12] and chelerythrine [9].In humans, numerous reports have been recorded since the 1990's. The main symptoms included cholestasis and mild to severe liver impairments with quite well documented causality in a majority of cases. In total, over 50 such cases have been reported from Europe, mostly from Germany [97,105].However, no certain constituent has been directly linked to the toxicity of the herb. On the contrary, it has been suggested that drug interactions rather than intrinsic toxicity are responsible for reported cases. Also, individual hypersensitivity or allergy has to be considered. Latex contained in the fresh plant is also possibly more toxic or allergenic than the dried material [92] (EMA report, 2011).In an *in vitro* study on HepG2 cells treated with various solvent extracts [103] , the biotransformation and toxicity-related gene expression was enhanced, but the dichloromethane extract richest in chelidonine [1] and total alkaloids was the weakest inducer and least cytotoxic, whereas ethanolic extracts containing more coptisine [31] and sanguinarine [12] were more cytotoxic. However, the *in vivo* relevance of these results is uncertain. In rats, the high doses (up to 3g/kg body weight;[102] did not elicit any symptoms of hepatic injury and did not alter liver function.Despite proven interaction of sanguinarine [12] and other alkaloids with DNA, no genotoxicity was observed using well established methods such as Ames tests or *in vivo* DNA damage[92] (EMA report, 2011). Nonetheless, uncontrolled internal use of unstandardized preparations should be discouraged and appropriate pharmacovigilance measures should be implemented to prevent unnecessary complications following *C. majus* administration. The comprehensive pharmacotoxicological investigation is also needed and should encompass establishing toxic doses range of various forms and preparations as well as individual constituents.

Datura stramonium

Antimicrobial, Immunomodulatory and Cytotoxic activity

Datura stramonium The antimicrobial activity of the aqueous and ethanolic extract of the stem-bark of *Datura stramonium* was investigation against *Staphylococcus aureus, Salmonella typhi, Shigella spp, Eschericia coli and Klebsiella pneumonia.* Ethanolic extract showed more antibacterial activity than the aqueous extract. It showed antibacterial activity against all the tested bacteria.The aqueous extract showed activity only against *Staphylococcus aureus*[121]. The antimicrobial properties of whole plants (extracted sequentially with different organic solvents) of *Datura stramonium* were studied against *Escherichia coli, Staphylococcus aureus, Pseudomonas aeruginosa* and the fungal strains *Aspergillus flavus, Aspergillus niger, Fusarium culmorum* and

Rhizopus stolonifer. All the solvent extracts showed significant activity against all the tested microorganisms. Methanolic extract was the most active against all microorganisms, whereas all the extracts showed significant activity against *P. aeruginosa.* All the solvent extracts showed low MIC against *A.niger*[122]. The antibacterial and antifungal effects of benzene, chloroform and ethanol extracts of branches and leaves of *Datura stramonium* branches and leaves were studied against *Enterobacter* (clinical strain/PIMS), *Micrococcus luteus* (clinical strain/PIMS), *Pseudomonas aeruginosa* (clinical strain/PIMS), *E.coli* ATCC 25922, *Staphylococcus aureus* (clinical strain/PIMS) and *Klebsiella pneumonia* ATCC 700603. *Datura stramonium* chloroform extract produced maximum zone of inhibition 16±0.7mm against *Enterobacter,* while it produced minimum zone of inhibition (7±0.7mm) against *K. pneumonia.* Benzene extract of the plant exhibited maximum zone of inhibition (15±0.7mm) against *Enterobacter* and *M. luteus,* while it produced minimum zone of inhibition (9±0.3mm) against *S. aureus* and *K. pneumonia,* ethanol extract of *Datura stramonium* gave maximum zone of inhibition against *K. pneumonia* and minimum against *E. coli.* The MBC values revealed that benzene extract (3.12mg/ml) was effective against *P. aeruginosa* while the same concentration of chloroform extract was very active against *S. aureus, P. aeruginosa* and *M. luteus.* All the extracts of *Datura stramonium* possessed significant antifungal activity against *Saccharomyces cerevisiae, Aspergillus fumigatus* and *Aspergillus niger* with maximum antifungal activity against *S. cerevisiae* and zone of inhibition was about 16±0.2mm by ethanol extract, 15±0.3mm by chloroform and 14±1.6mm by benzene extract, while minimum antifungal activity was observed against *A. niger* [123].*Datura stramonium* extracts were investigated for their *in vitro* activity against *Staphylococcus aurers* ATCC25923, Methicillin-resistant *S. aureus, Enterococcus sp., Escherichia colii* ATCC25922, Enteroinvasive *Escherichia coli* and *Pseudomonas aeruginosa. Datura stramonium* leaf extracts exhibited a considerable antibacterial activity even at low concentrations. Methanolic leaf extracts showed the maximum inhibitory effect. The growth inhibition zone against *Escherichia coli* was 9.8mm and against *Staphylococcus aurers* was 6.8mm[124]. The antimicrobial effect of methanol extract from flower, seed and leaf of explant callus was studied against (*Escherichia coli, Pseudomonas aeruginosa, Staphylococcus epidermidis* and *Bacillus subtilis*) and four fungi strains (*Fusarium semithectum, Fusarium colmorum, Ceratocystis ulmi* and *Rhizoctoina solani*). The result showed that the methanol extract from green leaf explant callus possessed inhibitory effects on the growth of *B. subtilis* (22mm) and *S. epidermidis* (23mm). The methanolic extract of the vegetative root and the flower of *Datura stramonium* show an effective antifungal activity against *Rhizoctonia solani* fungus[125]. Aqueous and organic solvent extracts of different parts of the plant were investigated for its anti-*Vibrio cholera* non-O1, and *Vibrio parahaemolyticus* using the disk diffusion method. The results revealed that *Datura stramonium* possessed a broad-spectrum vibriocidal effect [126]. The antifungal effects of acetone extracts of *Datura stramonium* seeds were studied against selected phytopathogenic fungi (*Penicillium janthinellum, Penicillium expansum, Aspergillus niger, Aspergillus parasiticus, Colletotrichum gloeosporioides, Fusarium oxysporum, Trichoderma harzianum, Phytophthora nicotiana, Pythium ultimum* and *Rhizoctonia solani*). Extracts exhibited moderate to good antifungal activity, with minimum inhibitory concentrations ranged from 0.125 mg/ml to 2.50 mg/ml [127]. Aqueous and ethanolic extracts of various parts of *Datura stramonium* were examined for their potential antimicrobial activity against pathogenic bacteria [*Bacillus subtilis*-2699, *Escherichia coli*-2803, *Staphylococcus aureus*-2602, *Proteus vulgaris*-2027, *Salmonella typhi*-2501; and pathogenic fungi such as *Aspergillus flavus*-525, *Aspergillus niger* (local isolate), *Candida albicans*-3100 and *Rhizopus stolonifer* (local isolate)].The results showed that the ethanolic extracts were more potent than the aqueous extracts and leaf extract possessed better antimicrobial activity than stem, and root. Aqueous extract of te leaves showed antibacterial activity against *Bacillus subtilis* and *Escherichia coli* with zone of inhibition of 16 and 10 mm respectively, while ethanolic extracts of the leaves exerted antibacterial activity against *Bacillus subtilis* (31mm), *Escherichia coli* (18mm), *Staphylococcus aureus* (24mm), *Salmonella typhi* (10mm), *Aspergillus flavus* (8mm) and *Candida albicans* (10mm) [128].

ERIGERON CANADENSIS (SYN: *CONYZA CANADENSIS*)

Antimicrobial, Immunomodulatory and Cytotoxic activity

The bacteriostatic and fungistatic activities of the oil of *Erigeron canadensis* were investigated by agar-diffusion method, against *Enterococcus faecalis* (ATCC29212), *Staphylococcus aureus* (ATCC25923) and *Streptococcus pyogenes* (HNCMB80002) as Gram-positive bacteria and *Escherichia coli* (ATCC25922), *Pseudomonas aeruginosa* (ATCC27853) as Gram-negative bacteria. Antifungal activity was evaluated against *Candida albicans* (UK-NEQUAS4661), *Candida glabrata* (ATCC90030), *Candida parapsilosis* (ATCC22019), *Candida tropicalis* (UKNEQUAS4893), *Cryptococcus neoformans* (INF5855) reference fungal strains, and Candida kefyr, *Rhodotorula glutinis, Trichophyton interdigitalis* and *Aspergillus fumigatus* fungal strains isolated from patients. None of the oils showed any activity against the tested bacterial strains, but exhibited moderate-to-strong activity against all fungi with the only exception of *A. fumigatus*. The MIC values varied from 1.25 μg/ml to 20.00 μg/ml for the tested fungal strains. The highest antifungal potency was exhibited by herb and root oils against *Cryptococcus neoformans* with MIC value of 1.25 μg/ml. In addition, substantial efficacy (MIC = 2.50

µg/ml) was detected against other Candida strains (*C. glabrata, C. tropicalis*) and *Rhodotorula glutinis* [11].The methanol extract of aerial parts of *Erigeron canadensis* was extracted with four organic solvents (petroleum ether, chloroform, ethyl acetate and butanol) and investigated for antivirus activity against human cytomegalovirus (HCMV)AD-169 and Cox-B3 viruses by modified shell-vial assay. The results showed that chloroform, ethyl acetate, butanol and methanol extracts possessed antiviral activity, however, butanol extract antiviral activity was 95.75 and 90.10 % for 200 and 100 µg/ml of the extract respectively and methanol extract antiviral activity was 100 and
99.10% for 200 and 100 µg/ml of the extract respectively [12]. Health risks or side effects following the proper administration of designated therapeutic dosages were not recorded [13].

Eucalyptus camaldulensis

Antimicrobial, Immunomodulatory and Cytotoxic activity

Eucalyptus camaldulensis were screened for activity against *Mycobacterium tuberculosis* H37Rv (MtbH37Rv). The extracts inhibited the growth of *Mycobacterium tuberculosis* with MIC of 4-64 µg/ml. Spectroscopic characterization led to the identification of two compounds, hydroxymyristic acid methylester and a substituted pyrenyl ester, a sterol. These two compounds had MIC of 49.45 and 46.99 µg/ml; IC50 >100 and 38.21 µg/ml; selectivity index (SI) >2.02 and 0.81, respectively, and a minimum bactericidal concentration of 62.50 µg/ml[90].Essential oil of the leaves of *Eucalyptus camaldulensis* possessed high antibacterial effects against Gram positive and negative bacteria with inhibition zones ranged from 9.3 to 12.5 Mm. The same effect was observed against yeast (21% inhibition) and fungi (10% inhibition) [91].The antibacterial effect of essential oil of *Eucalyptus camaldulensis* was evaluated against *L. monocytogenes, S. aureus, E. coli, K. pneumoniae, S. cerevisiae, C. albicans, M. ramamnianus and A. ochraceus*. Essential oil of *Eucalyptus camaldulensis* showed activity against *S. aureus* (21mm), *B. subtilis* (24mm) and *E. coli* (10mm). Significant anti fungal activity was also shown by essential oil of *Eucalyptus camaldulensis* against *A. niger* (28mm) and *R. solani* (12mm) [93] The essential oils of *Eucalyptus camaldulensis* were screened for their antifungal activities against common phytopathogenic fungi using the paper disk diffusion method, they showed activity at low doses against the tested fungi[93]The antibacterial activity of the crude leaf extracts of *Eucalyptus camaldulensis* were studied against clinical isolates of *Escherichia coli, Staphylococcus aureus, Salmonella typhi, Proteus mirabilis* and *Klebsiella pneumoniae.* The growth of all the pathogenic bacteria was arrested at 50 mg/ml concentration of extracts. The least activity was possessed by aqueous extract against *E. coli* (7 mm), *K. pneumoniae* (9 mm), *P. mirabilis* (13 mm), *S. typhi* (12 mm) and *S. aureus* (12 mm), while the highest was recorded for the acetone extract, with a diameter of inhibition for *E. coli (*12 mm), *K. pneumonia* (13 mm), *S. typhyi* (14 mm), *P. mirabilis* (15 mm) and *S. aureus* (14 mm) [99].The antibacterial activities of *Eucalyptus camaldulensis*, have shown to be very good. *Eucalyptus camaldulensis* essential oil and polymyxin B combination which reduced bacterial count under detection limit very fast, after 6h of incubation[95] The *in vitro* antimicrobial activities of the crude oil of *Eucalyptus camaldulensis* leave was investigated against *Escherichia coli* and *Staphylococcus aureus*. The diameter of zones of inhibition by the crude oil of leaf extracts of *Eucalyptus camaldulensis* was 10- 31mm and 10-26mm for *Escherichia coli* and *Staphylococcus aureus*. Gram positive, *Staphylococcus aureus* was more resistant than Gram negative, *Escherichia coli*[96] .The antiviral effect of the leaf essential oil of *Eucalyptus camaldulensis* was studied against many viruses. Rotavirus Wa strain, Coxsackievirus B4, and herpes virus type 1 were affected by essential oil with percentage of reduction 50%, 53.3%, and 90% respectively, but no effect was found against adenovirus type 7[198]. The methanolic extracts of *Eucalyptus camaldulensis* was tested against human enteroviruses: Poliovirus type I, Coxsackievirus B and Echovirus 6. The virucidal tests showed that the crude extracts were active against the tested viruses. Poliovirus type 1, coxsackievirus B and echovirus 6 giving a neutralization index of one log and above [94].

Eucalyptus globulus

Antimicrobial, Immunomodulatory and Cytotoxic activity

Dried residue of methalonic extract of *Eucalyptus globulus* leaves show antimicrobial activity against *Staphylococcus aureus, Escherichia coli ,Pseudomonas aeruginosa* and *Candida albicans* with minimum inhibitory concentration of 5.0, 10.0,10.0,1.25 mg/mlrespectively[63] .The antibacterial activity of *Eucalyptus globulus* leaf extract was determined for 56 isolates of *Staphylococcus aureus*, 25 isolates of *Streptococcus pyogenes*, 12 isolates of *Streptococcus pneumoniae* and seven isolates of *Haemophilus influenzae* obtained from 200 clinical specimens of patients with respiratory tract disorders[86].Twelve euglobals from *Eucalyptus globulus* and their twenty-six related compounds were examined for their inhibitory effects on Epstein-Barr virus activation by a short-term in vitro assay. The results showed that most of the euglobals having monoterpene structures, and euglobal-III had strong inhibitory activity. Grandinol, homograndinols showed stronger inhibitory effects[87]. *Eucalyptus* oil showed antiviral activity against herpes simplex virus (herpes simplex virus-1 and -2). IC50 of *Eucalyptus* oil was determined at 0.009% and 0.008% for HSV-1 and HSV-2, respectively[88].Terpineol, a

volatile terpenoid alcohol of low toxicity, is widely used in the perfumery industry. It is an important chemical constituent of the essential oil of many plants with widespread applications in folk medicine and in aromatherapy. Terpineol, a relatively nontoxic, volatile monoterpenoid alcohol, is a major component of the essential oil of *Eucalyptus globulus* (*Eucalyptus*), which is widely used in folk medicine and aromatherapy. The effects of terpineol on the compound action potential (CAP) of rat sciatic nerve were studied Terpineol induced a dose-dependent blockade of the CAP[89].

Eucalyptus microtheca

Antimicrobial, Immunomodulatory and Cytotoxic activity

The aqueous, ethanolic, chloroform and acetone extracts of *Eucalyptus microtheca* showed inhibitory effects against *Staphylococcus aureus* while benzene extract was not effective. The aqueous, ethanolic and acetone extracts also possessed inhibitory effects against *S. typhimurium*. The extracts also showed synergistic inhibitory activity when combined with antibiotics against both *Staph. aureus* but not against *S. typhimurium* [38]. The antibacterial activity of *Eucalyptus microtheca* leaves crude (ethanolic, methanolic and aqueous) extracts were tested against *Pseudomonas aeruginosa* isolates. All crude extracts exhibited an *in vitro* antibacterial activity against all *Pseudomonas aeruginosa* isolates with a zone of inhibition ranged between 17-25mm for methanolic extract, 20-29mm for ethanolic extract at a concentration of 1 mg/ml, while the zone of inhibition for aqueous extract was 12-16mm [44]. The antibacterial activity, MIC, and MBC of alcoholic extracts of *Eucalyptus microtheca* were studied against *Bacillus cereus*, *Staphylococcus aureus*, *Salmonella typhi*, *Escherichia coli*, *Pseudomonas aeruginosa*, *Klebsiella pneumonia*, and *Proteus mirabilis* using standard disk diffusion method. The structural changes following the exposure to these extracts were also investigated in the tested bacteria. Significant antibacterial activity was found against Gram positive and Gram negative bacteria, among them, *Escherichia. Coli* and *Pseudomonas. aeruginosa* showed the most sensitivity and *Staphylococcus aureus* the least. The value of MIC and MBC for both extracts were 8 mg/ml for *E. coli*, 8 and 16 mg/ml for *Bacillus cereus*, respectively. MIC and MBC values of methanolic and ethanolic extracts against *P. aeruginosa* were 8 and 16 mg/ml respectively. Scanning electron microscopy revealed structural changes in the affected bacteria, which suggested that the cell wall was the main target site of active constituents [70]. The antibacterial effect of essential oil of *Eucalyptus microtheca* was evaluated against *L. monocytogenes*, *S. aureus*, *E. coli*, *K. pneumoniae*, *S. cerevisiae*, *C. albicans*, *M. ramamnianus* and *A. ochraceus*. Essential oil of *Eucalyptus microtheca* showed activity against *S. aureus* (16mm), *B. subtilis* (20mm) and *E. coli* (11mm). Significant antifungal activity was shown by essential oil of *Eucalyptus microtheca* against *A. niger* (21mm) and *R. solani* (17mm) [37]. The antifungal activity of the *Eucalyptus microtheca* leaves crude aqueous, ethanolic and methanolic extracts were tested *in vitro* by agar well diffusion method against *Penicillium digitatum* and *Aspergillus niger*. Alcoholic extracts significantly inhibited the mycelial growth of *P. digitatum* and *A. niger* more than aqueous extracts. Methanolic extracts showed higher inhibition activity than ethanolic extracts [85].

Eucalyptus largiflorens

Antimicrobial, Immunomodulatory and Cytotoxic activity

The *in vitro* antimicrobial activity of the essential oil and methanol extracts of *Eucalyptus largiflorens* (*Eucalyptus bicolor*) was studied against *Aspergillus niger* ATCC 16404, *Candida albicans* ATCC 10231, *Pseudomonas aeruginosa* ATCC 27853, *Bacillus subtilis* ATCC 6633, *Staphylococcus aureus* ATCC 29737, *Escherichia coli* ATCC 10536, *Klebsiella pneumoniae* ATCC 10031, *Staphylococcus epidermidis* ATCC 12228, *Shigella dysenteriae* PTCC 1188, *Proteus vulgaris* PTCC 1182 and *Salmonella paratyphi*-A serotype ATCC 5702. The essential oil of *Eucalyptus largiflorens* exhibited moderate to high antimicrobial activity against all the bacteria, yeast and mold tested, except three microorganisms, *Pseudomonas aeruginosa*, *Escherichia coli* and *Shigella dysenteriae*. The evaluation of methanol fraction indicated that polar fraction showed strong activity against 7 out of 11 microorganisms while non-polar fractions did not posses any inhibitory action against the strains evaluated except *Escherichia coli* [15].The antimicrobial properties of essential oil, its major component, 1,8-cineole, and extracts of *Eucalyptus largiflorens* (*Eucalyptus bicolor*) were evaluated *in vitro*. Minimum inhibitory concentration of the extracts was calculated by broth dilution method and the zone of inhibition was studied by agar disk diffusion method. Gentamicin (10 µg/disk) and rifampin (5 µg/disk) were used as reference controls for antibacterial, and nystatin (100 µg/disk) for antifungal tests. The results of MIC study revealed that the essential oil has a stronger activity and broader spectrum than those of methanol extracts. The oil also had greater antimicrobial potential than 1,8-cineole [16].Disk diffusion method was used to determine the antimicrobial activity of aqueous extract and essential oils of *Eucalyptus incrassata* leaves against eight isolates of multidrug- resistant *Staphylococcus aureus*. It was found that aqueous extract and essential oils possessed variable antimicrobial activity (the inhibition zone diameter ranged from 7 to 14 mm respectively). Essential oils showed more antibacterial effect than aqueous extract [20].

Lantana camara

Antimicrobial, Immunomodulatory and Cytotoxic activity

Lantana Camara flower extract posses strong antibacterial activity All few types' yellow, lavender, red and white L*antana camara*, flowers displayed almost similar antibacterial activities [49] The chloroform extract of *Lantana camara* showed activity against all three strains of mycobacterium tuberculosis [56]Recently Ashish Saraf [48], have reported antimicrobial activity of *lantana camara* have reported that the leaves extracts of Lantana camara be active against various gram positive and gram negative bacteria. The extract of flower, leaf, stem and root of *Lantana camara* showed antibacterial activity against *E.coli, p.aeruginosa, s.aureus, and s.saprohiticus* [55]. The polymethoxylated flavone, isolated from the methanol extract of dried leaves of Lantana camara exhibited the antibacterial and antifungal properties [51].In Tanzania the root bark extract of Lantana camara showed an in vitro antimalaria test with Plasmodium falciparum [52]The essential oil containing ß-caryophyllene, geranyl acetate, terpinyl acetate, bornylacetate and limonene remarkably inhibited the growth of many tested against fungi [50]*L. camara* is one among the most toxic plants known so far, possibly within top ten. Reports of *L. camara* toxicity have been reported from Australia, India, New Zealand, South Africa and America. However, the toxicity occurs only on the consumption of high amount of plants material. It is reported that sheep, cattle and goats are susceptible to lantadenes A, B, D and icterogenic acid toxicity, where as horses, rats, neonatal calves and lambs are not susceptible to lantadene A. The prominent clinical sign of poisoning includes photosensitisation and jaundice. Loss of appetite in poisoned animals occurs within 24 hours and decrease in appetite also observed. The most severely poisoned animals die within 2 days of poisoning but usually death occurs after 1 -3 weeks after poisoning. The kidneys are swollen and pale in colour, the gall bladder is grossly distended and the liver is enlarged. The oral toxic dose of lantadene A for sheep is 60 mg/kg is toxic and 1–3 mg/kg by intravenous route. [53,54]

Hypericum perforatum

Antimicrobial, Immunomodulatory and Cytotoxic activity

A methanol extract of Herba Hyperici inhibited the growth in vitro of *Escherichia coli*, *Proteus vulgaris*, *Streptococcus mutans*, *Streptococcus sanguis*, *Staphylococcus oxford* and *Staphylococcus aureus (*MIC 0.31-1.25 mg/ml) [60]. An acetone, hot aqueous or ethyl acetate extract of the herb was active against influenza virus A2 (Mannheim 57), herpes simplex virus 2, poliovirus II and vaccinia virus in vitro [61,62].In vitro activity of hypericin has been demonstrated against Friend murine leukaemia virus, hepatitis B virus, murine cytomegalovirus, human cytomegalovirus (Davis strain), parainfluenza 3 virus, Sindbis virus, vaccinia virus, vesicular stomatitis virus and equine infectious anaemia virus [64-70]. Hypericin and pseudohypericin also inhibited herpes simplex virus types 1 and 2, and HIV-1 in vitro[68,69-76].Hypericin inhibited the activity of HIV reverse transcriptase in vitro (IC_{50} 0.77 mmol/l)[67,73,84], and inhibited herpes simplex virus, Rauscher murine leukaemia and Friend murine leukaemia viruses in mice after intravenous, intraperitoneal or intragastric administration [73-75].Intraperitoneal administration of a 5% aqueous extract of the herb to mice resulted in viricidal activity against tick-borne encephalitis virus [78]. However, incubation of the virus with hypericin prior to infection resulted in viricidal activity against all enveloped viruses tested (IC_{50} 1.56-25 µg/ml), but not against non-enveloped viruses[75].The antiviral activity of hypericin appears to involve a photoactivation process that forms a singlet oxygen and inactivates both viral fusion and syncytia formation [65,68,79].Phototoxicity has been reported in cattle after ingestion of *H. perforatum* during grazing. However, the doses were estimated to be approximately 30-50 times higher than normal therapeutic doses [80]. A single case of acute neuropathy after exposure to sunlight has been reported in one patient taking the herb[82]. Drug-monitoring studies indicate that side-effects of the herb are rare and mild, and include minor gastrointestinal irritations, allergic reactions, tiredness and restlessness. However, these studies did not last longer than 8 weeks [57,58,59]. Clinical studies have suggested that the use of the herb does not affect general performance or the ability to drive [83,84].

Terminalia avicennioides

Antimicrobial, Immunomodulatory and Cytotoxic activity

Terminalia avicennioides (Combretaceae) is a tree commonly found in West Africa. Its root bark, fruit and mistletoes are used traditionally to treat diarrhea, hemoptysis, sore throat, TB, asthma and cough [181].The *in vitro* antibacterial studies using broth dilution method of methanolic extract of *T. avicennioides* showed a significant antimycobacterial activity (MIC 78 µg/mL) against clinical isolates of *M. tuberculosis.*The n-hexane and ethyl acetate fractions obtained from the crude methanol extract of *T. avicennioides* showed inhibitory activity (MIC 200 and 625 µg/mL, respectively) against attenuated strains of *M. bovis BCG*. A further study of *T. avicennioides* fraction obtained demonstrated anti-mycobacterial activity (MIC 4.7 µg/mL)[180].There-fore, bioactive natural products are chemical substances produced by the host as defensive and protective mecha-nisms against predation by microorganisms, insects and herbivores [174]. Compounds like terpenoids give plants their odours and flavour; tannins are responsible for pigment [175.] These natural products isolated from higher plants

have been isolated as major source of novel biologically active phar-macophores or chemically active drugs[176]. Some reviews on antimycobacterial natural products indicate that triter-penes possess potential structural skeletons which could provide useful scaffolds or templates for the development of new antimycobacterial drugs[177-179]. This observation makes this class of compounds interesting for further inves-tigation and special attention on the T. avicennioides. Consequent upon this and in continuation of our search for antimycobacterial activities from T. avicennioides, the fractionate the root bark of T. avicennioides in order to exploit the individual bioactive constituents responsible for the exhibited activities. Previous investigations of the root bark of T. avicennioides exhibited significant inhibitory activity against BCG at 200 µg/ml [169,180,181].The isolated triterpenoids namingly: arjunolic acid (1, TAP40), α-amyrin (2, TAPE51) and 2, 3, 23 -trihydroxylolean-12-ene (3, TAP28) were investigated for antimycobacterial activity against BCG. Only compound 1(1, TAP40) exhibited moderate activity (MIC 156 µg/mL), when compared to the positive control, INH (MIC 78 µg/mL). From the phyto-chemical analysis, the isolated compounds (1-3) are triterpenoidal derivatives. It could be suggested that compound 1 (arjunolic acid) with triterpenoidal moiety might be important for the observed activity and carboxyl group may be responsible. Previous studies have confirmed that some of the species produces compounds that exert some pharmacological activities like asiatic, oleanolic, betulinic acids, and β-amyrin, which have antimicrobial activities. The related compounds such as lupeol, betulin, and ursolic acid have been found to be antimycobacterial activity. The isolated compound (arjunolic acid) investigated for antimycobacterial activity against BCG revealed moderate activity against BCG at156 µg/mL. From the results obtained so far, there appears to be a rationale for the use of T. avicennioides to treat bloody sputum and cough in humans. These results provide promising baseline information for the potential use of the isolated compound in the treat-ment of bacterial infections.Antifungal test of aqueous, ethanolic, methanolic, chloroform and ethyl acetate extracts of *Terminalia avicennioides* showed that the plants exhibit antifungal activity against *A. niger, A. fumigatus, Penicillium species, M. audouinii* and *T. rubrum.* It was revealed in this study, that increase in the antifungal activity of the extracts was enhanced by increase in the concentration of the extracts. This finding agrees with the report of Banso *et al.* (1999) [170] that higher concentration of antimicrobial substance showed appreciation in growth inhibition. The fact that the results of this study showed that root extracts of *Terminalia avicennioides* exhibit antifungal properties justifies their traditional use as medicinal plants. [171].The acute lethal study of ATA on rats shows that no animal died within 24 hours after treatment with the extract and the LD50 was greater than 5000 mg/kg b.w. Again, no death was recorded among all the dose groups throughout the two weeks experimental period. Observation: The LD50 > 500 mg / kg b.w. Furthermore, a dose-dependent weight loss occurred but the weight variations noticed among the extract-treated groups were not found to be significant ($p>0.05$) when compared with the control group,gives the gross pathological features of some internal organs. Liver congested was seen in all rats treated with the extracts. This observation appears to be in harmony with the increased OBR values, though the values were not statistically significant ($p>0.05$). [168]

Tithonia diversifolia

Antimicrobial, Immunomodulatory and Cytotoxic activity

The solvent leaf extracts and fractions of T. diversifolia exhibited different levels of inhibitory activity (from moderate to very good chosen with reference to Eloff [47] and Sánchez and Kouznetsov [48]) against all tested bacterial strains .Ethanol (70%) and acetone extracts of T. diversifolia displayed good activity with MIC of 0.07 mg/ml against E. faecalis. The hexane and chloroform fractions were very active against P. aeruginosa (0.07 mg/ ml).. Antimycobacterial activity The MICs of antimycobacterial activity displayed by Tithonia diversifolia **.** Although most of the extracts and fractions of T. diversifolia displayed weak antimycobacterial activity, the DCM and acetone extracts were moderately active against M. aurum while only the acetone extract was moderately active against M. bovis BCG. Only the 70% EtOH and 50% MeOH extracts showed moderate activity against M. smegmatis.Different levels of antifungal activity were displayed by the solvent extracts and fractions of Tithonia diversifolia at varying concentrations .EtOH (70%), 50% MeOH and acetone extracts only showed good activity against C. neoformans at 48 h with MIC of 0.07 mg/ml in all cases. Candida albicans was only inhibited moderately by the acetone extract, while the hexane fraction was very active against C. neoformans at 48 h and good at 72 h (MIC 0.03 and 0.07 mg/ml) and had moderate activity (0.15 mg/ml) against A. fumigatus at 48 h and 72 h. The chloroform fraction was moderately active only against C. neoformans at 48 h.The results of the cytotoxicity test carried out on different solvent extracts of T. diversifolia against Vero monkey kidney cells using the MTT colorimetric assay are presented. The selectivity indexes for bacterial and fungal strains tested In the study refer to the lethal concentration (LC50) below 0.1 mg/ml to be toxic, and above 0.1 mg/ml to be less toxic or non-toxic depending on the range. Extracts with selectivity index (LC50 / MIC) above 10 are regarded as non-toxic, between 1 and 9 as less toxic and more active, and below 1 as toxic. Results showed that all extracts of T.diversifolia are toxic with LC50 values far lower than 0.1 mg/ml except the hot water extract with LC50 of 0.275 mg/ml. Three (3) solvent extracts of T. diversifolia namely DCM, acetone and hot water were chosen for the genotoxicity assay. This is because, of the six (6) solvent extracts tested, these three showed a wide spectrum

of antimicrobial activity. Results presented showed that none of the plant extracts was genotoxic or mutagenic against the tested strains, although this experiment was carried out without exogenous metabolic activation.

Tithonia rotundifolia

Antimicrobial, Immunomodulatory and Cytotoxic activity

The solvent leaf extracts and fractions of T. rotundifolia exhibited different levels of inhibitory activity (from moderate to very good chosen with reference to Eloff [133] and Sánchez and Kouznetsov [134]) against all tested bacterial strains . Hot water extract of T. rotundifolia showed very good activity against E. coli and S. Typhimurium with MIC of 0.01 mg/ml and good activity (0.07 mg/ml) against E. faecalis, followed by the acetone extract with MIC of 0.03 mg/ml against E. faecalis, 0.07 mg/ ml against K. pneumoniae, S. aureus and S. Typhimurium. The DCM extract showed good activity (0.07 mg/ml) against S. aureus. Activities displayed by the different fractions of T. rotundifolia were moderate except for the butanol fraction which showed no inhibitory effect against all tested strains. Antimycobacterial activity The MICs of antimycobacterial activity displayed by Tithonia rotundifolia**.** Among the extracts and fractions of T. rotundifolia tested, most of the activities ranged from weak to moderate. However, the DCM and acetone extracts showed good activity (0.07 mg/ml) against M. aurum and M. smegmatis and very good activity (0.03 mg/ml) against M. fortuitum. The acetone and ethyl acetate extracts inhibited the growth of M. bovis BCG at MIC 0.07 mg/ml, while the DCM extract had MIC of 0.03 mg/ml. Different levels of antifungal activity were displayed by the solvent extracts and fractions of Tithonia rotundifolia at varying concentrations .EtOH (70%), 50% MeOH and acetone extracts only showed good activity against C. neoformans at 48 h with MIC of 0.07 mg/ml in all cases. Candida albicans was only inhibited moderately by the acetone extract, while the hexane fraction was very active against C. neoformans at 48 h and good at 72 h (MIC 0.03 and 0.07 mg/ml) and had moderate activity (0.15 mg/ml) against A. fumigatus at 48 h and 72 h. The chloroform fraction was moderately active only against C. neoformans at 48 h. The DCM and acetone extracts showed good inhibitory activity against C. neoformans (0.07 mg/ml) and moderate activity (0.15 mg/ml) at 72 h, and was active againstC. albicans (0.07 mg/ml) only at 48 h. Only the acetone extract of T.rotundifolia showed good activity (0.07 mg/ ml) against A. fumigatus, while the DCM extract was moderately active (0.15 mg/ml). The ethyl acetate fraction also showed moderate activity against C. neoformans and C. albicans at 48 h. The results of the cytotoxicity test carried out on different solvent extracts of T. rotundifolia against Vero monkey kidney cells using the MTT colorimetric assay are presented. The selectivity indexes for bacterial and fungal strains tested. In the study refer to the lethal concentration (LC50) below 0.1 mg/ml to be toxic, and above 0.1 mg/ml to be less toxic or non-toxic depending on the range. Extracts with selectivity index (LC50 / MIC) above 10 are regarded as non-toxic, between 1 and 9 as less toxic and more active, and below 1 as toxic. All extracts of T. rotundifolia tested were classified as being less toxic to non-toxic.

Three (3) solvent extracts of T. rotundifolia, namely DCM, acetone and hot water were chosen for the genotoxicity assay. This is because, of the six (6) solvent extracts tested, these three showed a wide spectrum of antimicrobial activity. Results presented showed that none of the plant extracts was genotoxic or mutagenic against the tested strains, although this experiment was carried out without exogenous metabolic activation.

Tecoma stans

Antimicrobial, Immunomodulatory and Cytotoxic activity

The methanol extracts of the leaves and stem bark of *Tecoma stans* was studied for their antimicrobial activity using a wide range of gram-positive and gram-negative bacteria and fungi. Methanol extracts of *Tecoma stans* leaves was found to be effective against only *Candida albicans*. It was detected that the extracts of stem bark generally showed better antimicrobial activity than those of the leaves and some organisms were selectively more sensitive to the extracts than others. [129]

The antimicrobial activity of callus (*in vitro*) was compared to leaves (*in vivo*) of *Tecoma stans.* Methanol and chloroform were selected as extractant because of literature survey proving them to be the best extractant, moreover the meager callus amount was the other constraint. *Tecoma stans* methanolic extracts of callus showed inhibition zones diameters of 20 mm for *B. subtilis*, 22 mm for *E. coli*, 19 mm for *S. aureus*, 16 mm for *P. aeruginosa*, 18 mm for *S. mutans*. Chloroform extracts of callus showed inhibition zones diameters of 15 mm for *B. subtilis*, 14 mm for *E. coli*, 19 mm for *S. aureus*, 14 mm for *P. aeruginosa* and 12 mm for *S. mutans* .Methanolic extracts of callus showed better inhibition zones than chloroform. Hence methanol was used as solvent for extraction of bioactive metabolite for antimicrobial assay for callus. *Tecoma stans* callus was less effective against used pathogenic cultures when compared to intact plant leaves. It was clear that callus has less anti microbial potential than leaves of intact plant when compared. Muthu and his associates in 2012 evaluated the antimicrobial activity of various extracts from heartwood of *Tecoma stans*[130].The strong antimicrobial activities were observed in the methanolic and chloroform extracts of *T. stans* than that of other solvents. Mohammed in 2013 with his coworkers reported antibacterial efficacy of different extracts of leaves and branches of *Tecoma stans*[131]. Salem with his associates in 2013 reported the different extracts of the leaves and branches of *T. stans*

have antibacterial potential against the growth of some human bacterial strains [132]. The plant resulted in effective and significant zones of inhibitions against slected bacterial pathogens. Our findings provide scientific proof tosupport medicinal aspects of *T. stans* and a promising potential for development of antimicrobial and antioxidant agents from *T. stans* which is otherwise considered to be a noxious weed. Cytotoxicity is toxic to cells. The cytotoxicity of *Tecomastans* in human hepatoblastoma was determined by incubating the cells up to 72-hours and changingwithconcentrations of herbal extracts. Toxic effects of *Tecomastans* were originated to be attentiveness and time-dependent in the presence and absence of fetal bovine serum. [129]

SCHINUS TEREBINTHIFOLIUS

Antimicrobial, Immunomodulatory and Cytotoxic activity

S. terebinthifolius leaf essential oil has shown antibacterial activity against *Bacillus subtilis*, *Escherichia coli*, *Pseudomonas aeruginosa*, *Shigella dysenteriae*, *Staphylococcus albus*, *Staphylococcus aureus* and *Staphylococcus intermedius* as well as antifungal activity against *Aspergillus niger*, *Aspergillus parasiticus* and *Candida albicans* [141,151].Extracts from *S. terebinthifolius* leaves in ethanol and dichloromethane containing secondary metabolites such as phenols, flavones, flavonoids, xanthones, leucoanthocyanidins,

flavanones and free steroids were active against *E. coli*, *Ps. aeruginosa*, *Staph. aureus* and *C. albicans*[140,141]. An aqueous extract from the leaves of *S. terebinthifolius* showed the highest activity against *Staph. aureus*, and it could inhibit the growth of *B. subtilis*[] (Martinez et al. 1996). In other laboratory tests, the essential oil, as well as leaf and bark extracts of *S. terebinthifolius*, has demonstrated potent antimicrobial properties[] (Ghanney and Rhouma, 2015). On the antibacterial effect of pepper involved terpene compounds, but also other substances[] (Johan et al., 2010), including high molecular compounds[] (Gomes et al., 2013). Brazilian pepper tree has displayed good-to-very strong in vitro antibacterial activity against numerous bacterial strains and antifungal actions against numerous fungi, as well as *Candida* [139,145].The aqueous extracts of *S. terebinthifolius* showed antifungal activity against *Candida albicans* with MIC of 120 ng/ml [150].Hexane, ethanol, and ethyl acetate extracts presented antimicrobial activity against *Staphylococcus aureus.* Aqueous extract showed potential as growth inhibitor for *Candida albicans.*Ethanol extract presented antioxidant activity [135].Dichloromethane extract was a strong growth inhibitor of *Pseudomonas aeruginosa, Staphylococcus aureus, Aspergillus niger, Aspergillus parasiticus,* and showed low activity against *Escherichia coli* [136].Crude extract presented antifungal activity against *Paracoccidioides brasiliensis* (responsible for grave infection in respiratory tract), and also, against *Cryptococcus neoformans* and *Sporothrix schenkii* [137]. Furthermore, was reported antiinflammatory activity [138].

The crude essential oil from leaves showed cytotoxic effects in several cell lines, mainly on leukemia and human cervical carcinoma. Fractions composed mainly of α- and β-pinenes as well as those composed of individually pinenes showed effective activities against all tested cell lines[149,150] The turucallane triterpenoids ((Z)-masticadienoic and (E)-masticadienoic acids and (Z)-schinol), isolated from leaves of *S. terebinthifolius*, as well as some semi-synthetic derivatives were cytotoxic and demonstrated antiparasitic (antileishmanial and antitrypanosomal) activity[147] .Crude hydroethanolic extract from the stem bark of *S. terebinthifolius*, as well as its fractions and isolated compounds, showed anti-HSV-1 (Herpes simplex virus type 1) activity and exhibited potential for future development treatment against orofacial infections associated with HSV-1 [152].

Solanum torvum

Antimicrobial, Immunomodulatory and Cytotoxic activity

Methanolic extracts of sun-dried fruit of *S. torvum* were found to have effective antimicrobial activity against human and animal clinical isolates. Biochemical analyses of methanolic extracts indicate the presence of alkaloids, flavonoids, saponins, tannins, and glycosides. Chah *et al.,* in 2000[182] used methanolic extracts against bacteria (*Actinomyce spyogenes*, *Bacillus subtilis*, *Escherichia coli*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa, Salmonella typhimurium*d, *Staphylococcus aureus, Streptococcus pyogenes*) fungi (*Aspergillusniger*, *Candida*

albicans) isolated from the clinical samples of humans and animalsto evaluate antimicrobial activity by the disc diffusion method. The study concluded that methanolic extracts have significant growth-inhibiting activity against bacteria commonly associated with pyogenic infections .The minimum concentration that inhibits bacterial and fungal activity was 0.3125mg/ml and 1.25mg/ml respectively. [183] However, growth of *Bacillus cereus, Bacillus subtilis, Candida albicans, Escherichia coli*, *Pseudomonas aeruginosa and Staphylococcus aureus* was monitored in the presence of methanolic leaf extracts of *S. torvum* by[202] Wiart *et al.,* in 2004 ; *S. torvum* leaf extracts showed the highest activity against *B. cereus*. Methanolic extracts from fruit and leaves have been described as potentially good sources of antimicrobial agents (David *et al.,* 1998). [195]Herpes simplex virus (HSV) is responsible for human infections in the orofacial region (HSV-1) and in the genital region (HSV-2) (Travis, 2002). Type 1 (HSV-1) of Herpes simplex virus was tested against methanolic fruit extracts of *S. torvum*. HSV-1 was maintained in the Vero cell line (kidney fibroblast of an [199-201] Nguelefack, *et al.,* (2008 & 2009)

also supported the findings of Mohan *et al.,* (2009) [197,198]. They orally administered aqueous extracts of *S. torvum* fruit (AEST) to investigate effectively of AEST in hypertensive conditions. Rats were given AEST (200 mg/kg/day, *p.o.*) solely or concomitantly with l- NAME (40 mg/kg/day, *p.o.*) for 30 consecutive days. It was found that AEST induced neither mortality nor visible signs of toxicity. When given solely or in co-administration with. However l- NAME put the rats in hypertensive conditions. Whereas AEST increased the sensitivity to noradrenalin. In normotensive and significantly reduced it in hypertensive animals. AEST significantly increased urinary volume and sodium excretion in l-NAME treated animals while reducing the sodium excretion in normotensive to reduce hypertensive conditions.The methanol extract of S. torvum fruit was previously shown to have in vitro antimicrobial activity against A. pyogenes, B. subtilis, P. aeruginosa, S. aureus, S. pyogenes, A. niger and C. albicans [182] In the present study methanol extract of S. torvum unripe fruit was fractionated on a silica gel column by eluting with solvents of increasing polarity and the fractions were monitored by TLC. Similar fractions were combined. The active principle was identified as methyl caffeate. The structure was elucidated using spectroscopic methods.Methyl caffeate exhibited activity against bacteria using disc diffusion method. The MIC values of methyl caffeate against bacteria and fungi are good that worth noting. Methyl caffeate showed only moderate effect when compared to control drugs of fluconazole for fungi and streptomycin for bacteria. P. aeruginosa has emerged as one of the most problematic Gram-negative pathogen, with an alarmingly high antibiotic resistance rate [187,188] Even with the most effective antibiotics against this pathogen, namely carbapenems (imipenem and meropenem), the resistance rate was found to be 15–20.4 % amongst 152 P. aeruginosa strains[188] . Our study showed that methyl caffeate was active against P. aeruginosa. This activity might be due to its ability to complex with cell wall[189] to inhibit microbial growth[190]. Methyl caffeate is a phenolic compound and antimicrobial capacity of phenolic compounds is well known [191].The MIC values of methyl caffeate against M. tuberculosis using micro-broth dilution assays. Methyl caffeate exhibited potent anti-TB activity against both the tested isolates (8 lg/ml). The MIC values showed good activity against both M. tuberculosis (H37Rv) and M. tuberculosis (RifR) at 8 lg/ml. The methods described here could be useful in determining the mycobactericidal activity of natural products because these assays require smaller volumes and can be performed faster than other methods described by Rastogi et al. [192] and Friis-Moller et al. [193] .Thesium chinense Turcz. has been used as a Korean traditional medicine to treat tuberculosis and methyl caffeate was isolated from it[194]. The in vitro antibacterial and antimycobacterial activities may support the use of S. torvum species in traditional medicine to treat microbial infections. The bioactivity guided fractionation of the methanol extract of the unripe fruit led to the isolation of methyl caffeate as the major active principle. The experiment suggests that S. torvum, an important medicinal herb in medicine, may be a potent candidate for clinical trial for tuberculosis even in coutries where is an invasive weed.Among the chemical constituents of *S. torvum*, steroidal lactone saponins and spirostanol glycosides are important for cytotoxicity. Lu et al. (2009) [196] isolated new steroidal lactone saponins and spirostanol glycosides from ethanolic extracts of aerial parts. All the four compounds (Solanolactoside A, Solanolactoside B, Trovoside M and Trovoside N) were evaluated for cytotoxic effects *in vitro* against a panel of human cancer cell lines: MGC-803 (Human gastric cancer cell line), HepG2 (Human hepatocellular liver carcinoma cell line), A549 (human lung adenocarcinoma cell line) and MCF-7 (Human breast adenocarcinoma cell line). Cis-diamminedichloroplatinum (CDDP, Sigma) was used as a positive control. The dose concentration was maintained at 5mg/ml. The effects of two compounds (Solanolactosdie A, Solanolactoside B) were not significant; however, the other two compounds Torvoside M and Torvoside N had significant cytotoxicity. *S. torvum* was found to be a very potent immunomodulatory and erythropoietic. Aqueous extract of the fruits of *S. torvum* enhanced delayed type hypersensitivity (DTH) response, increased haemagglutination antibody titer and white blood cells (WBC) count. After Phenylhydrazine induced anemia, the number of RBCs and the hemoglobin concentration decreased in animals but the group which was cotreated with *S. torvum* (37.5-150 mg/kg) the number of RBCs and hemoglobin concentration was increased significantly. The WBCs provide the major defense against pyogenic (pus-forming) bacteria and are the first on the scene to fight infection. This suggests that the innate immunity was enhanced by *S. torvum*. This effect may probably be due to its high vitamin B complex and vitamin C content since vitamins are known to boost the body's immune system [184,185].

Xanthium strumarium L.

Antimicrobial, Immunomodulatory and Cytotoxic activity

The plant extract exhibited antimicrobial activity against *Proteus vulgaris, Staphylococcus aureus, Bacillus subtilis, Candida albicans* and *Candida pseudotropicalis*. The activity is due to presence of xanthol.[31]The xanthinin contained in plant acts as a plant growth regulator and has antibacterial activity. Seed yields semi-dry edible oil (30–35%) which resembles sunflower oil and is used in bladder infection, herpes, and erysipelas.[32,33]Two xanthanolide sesquiterpene lactones, 8-epi-xanthatin and 8-epi-xanthatin-5β-epoxide,[29]isolated from the leaves demonstrated significant inhibition on the proliferation of cultured human tumour cells, i.e. A549 (non-small cell lung), SK-OV-3 (ovary), SK-MEL-2 (melanoma), XF498 (CNS) and HCT-15 (colon) *in vitro*. They were also found to inhibit the farnesylation process of human lamin-B by

farnesyltransferase, in a dose-dependent manner *in vitro*[30,34,35].Gautam *et al*. tested the plant extract for *in vitro* antimycobacterium activity and found that the ethylacetate extract and MeOH-petroleum ether extract possess significant *in vitro* antimycobacterium activities against *Mycobacterium tuberculosis* and *Mycobacterium smegmatis*. Ethyl acetate extract exhibited 4 mm zones of inhibition at 20 mg/ml in agar-well diffusion assay using streptomycin sulphate (1 mg/ml) as positive control showing 20 mm zones of inhibition.[36] The petroleum ether and methanol extracts exhibited 70 and 12% inhibition, respectively, at 1 mg/ml in radiorespirometry assay using BACTEC system with rifampin (2 µg/ml) and clarithromycin (32 µg/ml) as positive controls.[58] The plant has potent antifungal activity against pathogenic as well as non-pathogenic fungi due to the presence of terpenes, d-limonene and d-carveol.[40] The antifungal
compound from plant was identified as 4-oxo-1(5),2,11,(13)-xanthatriene-12, 8-olide, known as "deacetyl xanthumin." Fresh sap from *X. strumarium* at 50-fold dilution was highly effective in controlling the disease incidence in pot and field trials. Crude extracts of the plant inhibited mycelial growth and zoospore germination of *Phytophthora drechsleri*, the causal agent of Atractylis rot, *in vitro* at a concentration
of 12.5 and 15.6 µg/ml, respectively.[39] The leaf extract of plant may be used as a potent fungitoxicant against the mycelial growth of *Fusarium moniliforme*. [40] Amerjothy *et al*. studied the hexane, ethylacetate and alcoholic extracts of the leaves for their antimicrobial (antifungal, antibacterial) activities by disc diffusion assay. The antifungal activity was compared with that of fluconazole and nystatin as standards. Hexane extract showed marked inhibition against *C. albicans, Aspergillus niger, P. aeruginosa* and *S. aureus* at a concentration of 200 µg/disc. Ethylacetate extract showed an inhibition against *A. niger, S. aureus* and *E. coli* at a concentration of 200 µg/disc. Alcoholic extract showed an inhibition only against *S. aureus* at a concentration of 200 µg/disc. [41] The plant possesses significant potency against
C. neoformans and *Candida* species with low toxicity to brine shrimps. The 4,5-dihydroxyl groups in the quinic acid moiety were necessary for the activity and introduction of a free amino group increased the inhibitory activity against *Aspergillus fumigatus*.[64] In 2009, it was reported that the WEX (0.01, 0.1 and 1.0 g/kg, i.g., for 10 days) possessed antiviral activity against duck hepatitis B virus, and it can delay pathological changes [28]In addition, five compounds were isolated from the fruits of *X. strumarium*, and their antiviral abilities were also evaluated. The results indicated that norxanthantolide F, 2-desoxy-6-epi-parthemollin, xanthatin, threo-guaiacylglycerol-8′-vanillic acid ether and caffeic acid ethyl ester exhibited notable activity against influenza A virus with IC_{50} values of 6.4, 8.6, 8.4, 8.4 and 3.7 µM, respectively by a cytopathic effect (CPE) inhibition method [27].*X. strumarium* is poisonous to mammals. It is reported to have medium to strong allergenic effects. The toxic principle is a sulphated glycoside, carboxyatractyloside**,** found in the seeds and during the two-leaf seedling stage. [43]The plant is a potential cause of sudden death in pigs extensively reared in Zimbabwe, which is revealed by an investigation in which six healthy porkers of the Mukota breed were fed *ad libitum* either crushed burs (fruits) or the two-leaf seedling stage of *X. strumarium* at 2% of body weight. Major clinical signs were depression, vomiting, abdominal pain, weakness, recumbency, paddling convulsions terminating in death from 6 to 96 hours after ingestion. Microscopically, acute hepatic congestion and haemorrhage, centrilobular hepatocyte necrosis, with occasional binucleation together with discoid lysis of skeletal and cardiac muscle fibres were remarkable changes[27].Another toxicological study on male rats revealed that metabolism of CAT may have a role in its cytotoxic and lethal effects. Clinical signs of toxicosis, duration of illness, lethality, gross lesions and hepatic and renal histopathological lesions were recorded. The CAT toxicosis has independent lethal and cytotoxic components, which could be partly due to an active metabolite formed by *de novo* synthesised P450–P448-independent haemoprotein, while CAT detoxification may occur partly through haemoproteinindependent, (phenyl butazone) PBZ-inducible enzyme,and partly through a P448-dependent (BNF-inducible) enzyme; and CAT detoxification apparently is not P450- or GSH-dependent.[45,46] Atractyloside poisoning is an infrequent, but often fatal, form of herbal poisoning, which occurs worldwide, especially in Africa and the Mediterranean regions. The primary mechanism of atractyloside poisoning is known to be inhibition of the mitochondrial ADP transporter. Atractyloside in large amounts gives rise to massive necrosis, but *in vitro* studies have shown that at lower doses the cells progress to apoptosis.[47] Symptoms of poisoning appear in several hours.

II. CONCLUSION AND FUTURE PROSPECTS

This current information on traditional as well as experimental analysis of the above herbs shows them to be promising in treating respiratory ailments. Further studies need to be taken up in order to find a formulation with an optimized combination of these plants and explore their mechanism of action,combination between them,synergy with antibiotic thus aiming towards reduction as well as gradual eradication of respiratory ailments from our country and to bring down the impact of the pendemic.

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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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