African medicinal plant derived products as therapeutic arsenals against multidrug resistant microorganisms

Assob Jules Clement Nguedia1* and Nsagha Dickson Shey2

1Department of Biomedical Sciences, Faculty of Health Sciences, University of Buea, Cameroon. P. O. Box 63 Buea, Cameroon.
2Department of Public Health and Hygiene, Faculty of Health Sciences, University of Buea, Cameroon. P. O. Box 63 Buea Cameroon.

Received 16 November, 2013; Accepted 5 May, 2014

Infectious diseases due to resistant pathogenic strains are rampant and the burden is worsened by the emergence and spread of microorganisms resistant to cheap and effective first-choice drugs. Medicinal plants could be an alternative solution to this and the aim of the present review is to summarize available evidence and knowledge concerning African medicinal plants used to treat multidrug resistant (MDR) bacteria, fungi and protozoa infectious agents. A literature search using the keywords: Africa, medicinal plants and multi-resistant microorganisms on google scholar, African Index Medicus, PubMed, Medline and EMBASE was conducted. We also scanned reference lists for important citations. Key pharmaceutical journals, workshop and conference proceedings were reviewed. Common medicinal plants found are *Brucia javanica*, *Prunus Africana*, *Mangifera indica*, *Picralima nitida*, *Aloe arborescens*, *Aloe striata*, *Vernonia adonensis*, *Markhamia tomentosa*, *Garcinia lucida*, *Garcinia kola*, *Phyllanthus muellerianus*, *Gladiolus gregasius*, *Sida alba*, *Trichila heudelotti*, *Piptadeniastrium africana* and *Dorstenia picta*. Most researches on the use of medicinal plants to treat multidrug resistant agents were conducted in South Africa, Nigeria, Cameroon, Congo, Kenya, Zimbabwe, Burkina Faso and Uganda. African medicinal plants possess important therapeutic agents that can be used as new phyto-medicines against MDR microorganisms.

Key words: Africa, medicinal plants, therapeutic products and multidrug resistant microorganisms.

INTRODUCTION

The spread of microorganisms which are resistant to cheap and effective first-choice drugs, although a natural phenomenon, is becoming a public health concern. Favorable factors accounting for this include auto-medication, treatment outside of recognized treatment centers and consumption of drugs without medical supervision and during insufficient length of time. Other confounding factors include frequent movements of population, overcrowding which provides opportunities for the rapid spread of microorganisms including multidrug resistance. African medicinal plants could be an alternative solution to this and the aim of the present review is to summarize available evidence and knowledge concerning African medicinal plants used to treat multidrug resistant microorganisms.
resistant strains (Njunda et al., 2012). Multidrug resistance to as many as seven antibiotics has been observed in many epidemiological studies in Africa (Iruka and Sosa, 2008; Njunda et al., 2012). Antibiotics that usually face resistance are ampicillin, amoxicillin, co-trimoxazole, gentamicin, ceftriaxone and augmentin (amoxicillin + clavulanic acid) because of their wide indiscriminate use. Microorganisms that usually cause antibiotherapy failure include those that affect the urogenital tract such as beta-lactamase producers Neisseria gonorrhoeae, Escherichia coli, Pseudomonas aeruginosa, Proteus mirabilis, methicillin resistant Staphylococcus aureus (MRSA) and mycoplasmas (Njunda et al., 2011). Those responsible for pulmonary infections include Mycobacterium tuberculosis, Klebsiella pneumonia and Streptococcus pneumonia. Agents responsible for gastrointestinal infections include Escherichia coli, Entamoeba histolica, Salmonella typhi and Shigella dysenteriae (Njunda et al., 2011).

Various mechanisms to acquire or develop intrinsic resistance to antibiotics which are developed by pathogens include active efflux of drugs, alteration of target sites, enzymatic degradations and propagation of resistance genes (Sibanda and Okoh, 2007). Bacterial resistance to penicillin is expanding to cephalosporins leading to the development of plasmid-mediated extended spectrum β-lactamases (ESBLs) strains. As new antimicrobial compounds are discovered, there is a need to assess their potentials in combination therapies with old antibiotics that have been rendered ineffective by the development of resistant strains (Sibanda and Okoh, 2007).

Management of infectious diseases caused by beta-lactam-resistant bacteria strains in developing countries where efficient antibiotics are not affordable for the majority of the population is becoming urgent and alternative agents can be obtained from medicinal plants. In Africa, medicinal plants are used in the fight against many infectious ailments; they still play a great role as alternative agents can be obtained from medicinal plants. The vast majority of the population is becoming urgent and非洲 is faced with ever increasing infectious diseases, emerging and re-emerging infectious diseases due to multidrug resistant microorganisms and immune deficient diseases such as HIV/AIDS. It is estimated that more than 5,000 active principles have been identified in fruits, vegetables and grains, but a large percentage still remain unknown and need to be studied to increase our understanding of their health benefits (Kuete and Efferth, 2010).

Studies on the antimicrobial properties of medicinal extracts on resistant strains of microorganisms are scanty and only few antimicrobial agents as isolated compounds have been proven to possess inhibitory properties on multidrug resistant microorganisms. However, phytomedicines as antimicrobial agents have been evaluated scientifically in various countries in Africa. They present a low risk of resistance development to their action, because they are complex mixtures, making microbial adaptability very difficult (Daferera et al., 2003). This review summarizes the currently available knowledge on medicinal plants used to treat multidrug resistant infections and the efficacy of plant-derived extracts and compounds across Africa.

METHODOLOGY

A literature search using the keywords: Africa, medicinal plants and multi-resistant microorganisms on Google scholar, African Index Medicus, PubMed, Medline and EMBASE was conducted. We also scanned reference lists for important citations. Key pharmaceutical journals, workshop and conference proceedings were reviewed. African researchers of medicinal plants were contacted.

RESULTS

Plant compounds with activity against multi-resistant bacteria pathogens in Africa

Some isolated pure compounds of plant origin have been reported to have resistance modifying activities in vitro. This has prompted the search for such compounds from a variety of medicinal plants. Some of the compounds which have been observed to have direct antimicrobial activity were also able to potentiate the activity of antibiotics when used at low minimum inhibitory concentration (MIC) levels. For instance the antimicrobial property of tea (Camellia sinensis) is due to polyphenols (Kim et al., 2000). Bioassay directed fractionation of its extracts revealed its content in bioactive components such as epicatechin gallate (ECG), epigallocatechin gallate (EGCG), epicatechin (EC) and caffeine (CN). Used in combination in vitro, ECG and CG reduced MIC values for oxacillin from 256 and 512 to 1 and 4 mg/L against methicillin resistant Staphylococcus aureus (MRSA) (Kim et al., 2000). Ethyl gallate is a congener of alkyl gallates, purified from a dried pod of tara (Caesalpinia spinosa) native to South America, intensified beta-lactam susceptibility in MRSA and MSSA strains (Kim et al., 2000).

Twenty six species of medicinal plants belonging to 19 families were described in previous studies were shown to possess antimicrobial properties on multidrug resistant bacteria species in six different countries across Africa (Table 1). These plants are used in traditional folk medicine against all types of infectious ailments including gastrointestinal, pulmonary, genito-urinary tracts and skin and skin infections. Seeds, stem barks, leaves, bulbs, twigs and roots are the plants’ parts extracted using mostly methanol, water and acetone as major solvents. Although these studies indicated inhibitory activities on
<table>
<thead>
<tr>
<th>Family</th>
<th>Species</th>
<th>Country</th>
<th>Traditional treatment</th>
<th>Plant parts used</th>
<th>Solvent used/screened activity</th>
<th>Bioactive compounds</th>
<th>Microbial strains</th>
<th>Antibiogram resistance profile</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anacardiaceae</td>
<td>Mangifera indica</td>
<td>Zimbabwe</td>
<td>cough and diarrhea</td>
<td>twigs and leaves</td>
<td>Ethanolic extract, efflux inhibitory activity of extract comparable to reserpine</td>
<td>tannins, phenols, alkaloids, glycosides</td>
<td>K. pneumonia; S. aureus; P. aeruginosa; Bacillus cereus</td>
<td></td>
<td>Chitemerere and Mukanganyama 2011</td>
</tr>
<tr>
<td>Apocynaceae</td>
<td>Ficalima nitida (Stapf.) T. &amp; H.Durand</td>
<td>Cameroon</td>
<td>Hypertension, fever, malaria, anti-inflammatory, antimicrobial</td>
<td>Leaves, seeds</td>
<td>Methanolic: 1.25 &lt; MIC ≥ 10 mg/ml</td>
<td>-</td>
<td>E. coli; K. pneumonia; K. oxytoca; S. marcescens; P. aeruginosa; A. baumannii</td>
<td></td>
<td>Gangoué-Piéboji et al., 2009</td>
</tr>
<tr>
<td>Ashodelaceae</td>
<td>Aloe arborescens</td>
<td>South Africa</td>
<td>Treatment of diarrhoea and stomach ailments</td>
<td>Leaves</td>
<td>Acetone. C = 0.078 mg/ml</td>
<td>TLC fingerprint revealed the presence of flavonoids and triterpenoids</td>
<td>S. typhimurium</td>
<td>ESBL positive Amx, Amp, aztreonam, Pip/tazobactam, Cot Oxazole and Tet with reduced susceptibility to CI</td>
<td>Bisi-Johnson et al., 2012</td>
</tr>
<tr>
<td></td>
<td>Aloe striata</td>
<td>South Africa</td>
<td>Treatment of diarrhoea and stomach ailments</td>
<td>Leaves</td>
<td>Acetone. C = 0.078 mg/ml</td>
<td>TLC fingerprint revealed the presence of flavonoids and triterpenoids</td>
<td>S. typhimurium</td>
<td>ESBL positive Amx, Amp, aztreonam, Pip/tazobactam, Cot Oxazole and Tet with reduced susceptibility to CI</td>
<td>Bisi-Johnson et al., 2012</td>
</tr>
<tr>
<td>Asteraceae</td>
<td>V. adoensis</td>
<td>Zimbabwe</td>
<td>boiled decoction active against TB</td>
<td>Leaves</td>
<td>Ethanolic extract, Efflux inhibitory activity of extract with reserpine as reference</td>
<td>-</td>
<td>K. pneumonia, S. aureus, P. aeruginosa, B. cereus</td>
<td></td>
<td>Chitemerere and Mukanganyama 2011</td>
</tr>
<tr>
<td>Bignoniaceae</td>
<td>Markhamia tomentosa (Benth) K. Schum</td>
<td>Nigeria</td>
<td>Anti snake venom/bite, sore eyes, heart pain, scrotal elephantiasis</td>
<td>Leaves</td>
<td>methanolic extract</td>
<td>-</td>
<td>S. aureus; NCTC5671; B. subtilis; NCTC 3610; P. aeruginosa; ATCC 10145</td>
<td>PV CE EM; Aug Tet PV CE EM; Naı̈ PV CE EM</td>
<td>Aladesanmi et al., 2007</td>
</tr>
<tr>
<td>Clusiaceae</td>
<td>Garcinia lucida</td>
<td>Cameroon</td>
<td>Gastric ulcer, fermentation of palm wine, gynecological infections, anti-poison, gastrointestinal infections, snake bites</td>
<td>Seeds, stem bark</td>
<td>Methanolic: 1.25 &lt; MIC ≥ 10 mg/ ml</td>
<td>-</td>
<td>E. coli; K. pneumonia; K. oxytoca; S. marcescens; P. aeruginosa; A. baumannii</td>
<td>AMX, Pip, CE; AMX, Pip, CE, AMX, Pip, CE, ESBL, ESBL, ESBL, AMX, Pip, CE, AMX, Pip, CE</td>
<td>Gangoué-Piéboji et al., 2009</td>
</tr>
<tr>
<td>Plant Name</td>
<td>Country</td>
<td>Uses</td>
<td>parts used</td>
<td>Extract Type</td>
<td>MIC Range</td>
<td>Antibiotics/Clinical Notes</td>
<td>Reference</td>
<td></td>
<td></td>
</tr>
<tr>
<td>----------------------------</td>
<td>-----------</td>
<td>----------------------------------------------------------------------</td>
<td>------------</td>
<td>--------------</td>
<td>-----------</td>
<td>--------------------------------------------------------------------------------------------</td>
<td>--------------------------------</td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Garcinia kola</em></td>
<td>Cameroon</td>
<td>Gastric ulcer, fermentation of palm wine, gynecological infections, anti-poison, gastrointestinal infections, snake bites</td>
<td>Leaves</td>
<td>Methanolic</td>
<td>$1.25 &lt; \text{MIC} \geq 10 \text{ mg/ml}$</td>
<td>-</td>
<td>$E. coli$ 25922, $E. aerogenes$, $E. cloacae$, $K. pneumoniae$, $K. oxytoca$, $S. marcescens$, $P. aeruginosa$, $A. baumannii$ AMX, Pip, CE, AMX, Pip, CE, AMX, Pip, ESBL ESBL, ESBL, AMX, Pip, CE, AMX, Pip, CE</td>
<td>Gangoué-Piéboji et al., 2009</td>
<td></td>
</tr>
<tr>
<td><em>Phyllanthus muellerianus</em></td>
<td>Cameroon</td>
<td>Use for infectious ailments</td>
<td>Stem barks</td>
<td>Methanolic</td>
<td>-</td>
<td>$E. coli$, $K. pneumonia$, $P. aeruginosa$, $P. mirabilis$, $S. flexneri$, $S. typhi$ All resistant against, Amoxicillin Augmentin</td>
<td>Assob et al., 2011</td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Bridelia micantha</em> (Hochst.) Baill.</td>
<td>Cameroon</td>
<td>Cough, antimicrobial, diarrhoea, gastric ulcer, intestinal worms, eye diseases</td>
<td>Stem barks</td>
<td>Methanolic</td>
<td>$1.25 &lt; \text{MIC} \geq 10 \text{ mg/ml}$</td>
<td>-</td>
<td>$E. coli$ 25922, $E. aerogenes$, $E. cloacae$, $K. pneumoniae$, $K. oxytoca$, $S. marcescens$, $P. aeruginosa$, $A. baumannii$ AMX, Pip, CE, AMX, Pip, CE, ESBL ESBL, ESBL, Oxytetracycline (OT), cephalosporinase producer</td>
<td>Gangoué-Piéboji et al., 2009</td>
<td></td>
</tr>
<tr>
<td><em>Dorstenia picta</em></td>
<td>Cameroon</td>
<td>Diarrhoea, infected wounds, anti-inflammatory, antimicrobial, eye diseases, snake bites</td>
<td>leaves</td>
<td>Methanolic</td>
<td>$1.25 &lt; \text{MIC} \geq 10 \text{ mg/ml}$</td>
<td>-</td>
<td>$E. coli$ 25922, $E. aerogenes$, $E. cloacae$, $K. pneumoniae$, $K. oxytoca$, $S. marcescens$, $P. aeruginosa$, $A. baumannii$ AMX, Pip, CE, AMX, Pip, CE, ESBL ESBL, ESBL, Amoxicillin, Pip/tazobactam, COT Oxazole and Tet with reduced susceptibility to CI</td>
<td>Gangoué-Piéboji et al., 2009</td>
<td></td>
</tr>
<tr>
<td><em>Dorstenia Bateri</em></td>
<td>Cameroon</td>
<td>Twigs</td>
<td>CH$_2$C$_2$/MeOH (1:1) or in MeOH, 5&lt;$\text{MIC}$&gt;36 µg/ml</td>
<td>Flavoids:</td>
<td>$N. gonorrhoea$ NGCS$S$ (_L+)</td>
<td></td>
<td></td>
<td>Kute et al., 2010</td>
<td></td>
</tr>
<tr>
<td><em>Psidium guajava</em></td>
<td>South Africa</td>
<td>Use in the treatment of diarrhoea and stomach ailments</td>
<td>Leaves</td>
<td>Acetone:</td>
<td>C=0.312-0.625 mg/ml</td>
<td>TLC fingerprint revealed the presence of flavonoids and Interpenoids.</td>
<td>S. Typhimurium ESBL positive Amoxicillin, Augmentin, Piptazobactam, COT Oxazole and Tet with reduced susceptibility to CI</td>
<td>Bisi-Johnson et al., 2012</td>
<td></td>
</tr>
<tr>
<td><em>Calistemon citrinus Skeels</em></td>
<td>Zimbabwe</td>
<td>Antibacterial, hemorrhoid treatment</td>
<td>Leaves</td>
<td>Ethanolic extract</td>
<td>efflux inhibitory activity of extract comparable to reserpine</td>
<td>-</td>
<td>$K. pneumoniae$, S. aureus, $P. aeruginosa$, Bacillus cereus</td>
<td>Chitemerere and Mukanganya ma 2011</td>
<td></td>
</tr>
<tr>
<td>Family</td>
<td>Genus</td>
<td>Country</td>
<td>Use</td>
<td>Parts</td>
<td>Extraction</td>
<td>Antimicrobial Activity</td>
<td>Reference</td>
<td>Year</td>
<td></td>
</tr>
<tr>
<td>-----------------</td>
<td>---------------------------</td>
<td>---------</td>
<td>------------------------------------</td>
<td>----------------</td>
<td>--------------</td>
<td>----------------------------------------------------------------------------------------</td>
<td>-------------------------------------</td>
<td>------</td>
<td></td>
</tr>
<tr>
<td>Iridaceae</td>
<td><em>Gladiolus gregasius</em></td>
<td>Cameroon</td>
<td>Use for infectious ailments</td>
<td>Bulbs</td>
<td>Methanolic</td>
<td>Sap Tan Gly CG RS; E. coli, K. pneumonia, P. aeruginosa, P. mirabilis, S. flexneri, S. typhi</td>
<td>Assob et al., 2011</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Malvaceae</td>
<td><em>Sida alba</em></td>
<td>Burkina Faso</td>
<td>Use in treating infectious diseases in children, malaria, fever, pain, varicola, antibacterial, anti-inflammatory, analgesic activities and hepatoprotective</td>
<td>Leaf stems</td>
<td>Aqueous/acetone (80%, v/v); Synergistic effect when polyphenol rich fractions are combined to COT</td>
<td>Polyphenols; Shigella dysenteriae, Shigella boydii, Enterococcus faecalis, Proteus mirabilis</td>
<td>Kessoun et al., 2012</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Meliaceae</td>
<td><em>Trichila heudelotti</em></td>
<td>Nigeria</td>
<td>Sores, heart troubles, pila</td>
<td>Leaves</td>
<td>Methanolic extract ID obtained at 250 mg/ml</td>
<td>-</td>
<td>E. coli NCTC 10418, S. aureus, NCTC6571, B. subtilis, NCIB 3610, P. aeruginosa, ATCC 10145</td>
<td>Kuete et al., 2010</td>
<td></td>
</tr>
<tr>
<td>Mimosaceae</td>
<td><em>Piptadeniastreum africana</em></td>
<td>Cameroon</td>
<td>Use for infectious ailments</td>
<td>Leaves</td>
<td>Methanolic</td>
<td>Fla Pol Cou Gly CG RS; E. coli, K. pneumonia, P. aeruginosa, P. mirabilis, S. flexneri, S. typhi</td>
<td>Assob et al., 2011</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nyctaginaceae</td>
<td><em>Boerhavia diffusa</em></td>
<td>Nigeria</td>
<td>Diabetes, anti inflammatory, Abscess, boils</td>
<td>Leaves</td>
<td>methanolic</td>
<td>-</td>
<td>E. coli, K. pneumonia, P. aeruginosa, P. mirabilis, S. flexneri, S. typhi</td>
<td>Kuete et al., 2010</td>
<td></td>
</tr>
<tr>
<td>Campylobacter</td>
<td><em>Campylobacter densiflorum</em></td>
<td>Cameroon</td>
<td>Chest and gastric pains</td>
<td>Leaves, roots</td>
<td>Methanolic: 1.25 &lt;MIC ≥ 10 mg/ ml</td>
<td>-</td>
<td>E. coli 25922, E. aerogenes, E. cloacae, K. pneumoniae, K. oxytoca, S. marcescens, P. aeruginosa, A. baumannii</td>
<td>Gangoué-Piéboji et al., 2009</td>
<td></td>
</tr>
<tr>
<td>Ochnaceae</td>
<td><em>Campylobacter zonkeri</em></td>
<td>Cameroon</td>
<td>Chest and gastric pains</td>
<td>Roots</td>
<td>Methanolic: 1.25 &lt;MIC ≥ 10 mg/ ml</td>
<td>-</td>
<td>E. coli 25922, E. aerogenes, E. cloacae, K. pneumoniae, K. oxytoca, S. marcescens, P. aeruginosa, A. baumannii</td>
<td>Gangoué-Piéboji et al., 2009</td>
<td></td>
</tr>
</tbody>
</table>
Table 1. Contd.

<table>
<thead>
<tr>
<th>Family</th>
<th>Genus</th>
<th>Country</th>
<th>Use</th>
<th>Plant Part</th>
<th>Extraction</th>
<th>MIC Values</th>
<th>Antibiotics &amp; Others</th>
</tr>
</thead>
<tbody>
<tr>
<td>Passifloraceae</td>
<td>Barteria fistulosa</td>
<td>Cameroon</td>
<td>Infected wounds, fever, rheumatism</td>
<td>stem bark</td>
<td>Methanolic</td>
<td>≤ 10 mg/ml</td>
<td>E. coli 25922, E. aerogenes E. cloacae, K. pneumoniae K. oxytoca, S. marcescens P. aeruginosa, A. baumannii</td>
</tr>
<tr>
<td>Phytolacaceae</td>
<td>Hileria latifolia</td>
<td>Cameroon</td>
<td>Use for infectious ailments</td>
<td>leaves</td>
<td>Methanolic</td>
<td>St Tr Cou Gly CG RS</td>
<td>E. coli, K. pneumonia, P. aeruginosa, P. mirabilis, S. flexneri, S. typhi All resistant against Amp Aug</td>
</tr>
</tbody>
</table>

Antibiotics: Nal: Nalidixic acid; Ofl: Ofloxacin; Aug: Augmentin; Amp: Ampicillin; Tet: Tetracycline; Amx: Amoxycillin; Cot: Cotrimoxazole (Trimethoprim/sulpha methoxazole); Nit: Nitrofurantoin; Gen: Gentamycin; CL: Chloramphenicol; Ci: Ciprofloxacin; PV: Penicillin V; CE: Cephalothin; EM: Erythromycin. Pip: piperacillin; ESBL: Extended spectrum beta lactamases; L+: betalactactamase producer; Alk: Alkaloids; Tri: Triterpens; St: Sterols; Ant: Anthraquinons; Fla: Flavonoids; Pol: Polyphenols; Sap: Saponins; Tan: Tannins; Cou: Coumarins; Gly: Glycosides; CG: Cardiac glycosides; RS: Reducing sugars; TLC: Thin Layer Chromatography.

activities on many gram+ and gram- multidrug resistant bacteria strains, only few presented the phytochemical composition of these plants. Alkaloids, flavonoids, phenols and triterpens appear to be the main compounds identified. Microbial strains that dominated in the studies were Escherichia coli, K. pneumonia, S. dysenteriae, E. faecalis, Salmonella typhi, P. aeruginosa, S. aureus meticillin resistant and Bacillus subtilis, Neisseria gonorrhoea betalactamase+. They were found to be resistant to a wide range of antibiotics including amoxicillin, ampicillin, augmentin, cephalotin, ciprofloxacin, ofloxacin, cotrimoxazole, methicillin. Particularly of interest, the study done in Burkina Faso on the aqueous acetone (80%) of Sida alba L., a synergistic effect was observed when polyphenol rich fractions of this plant were combined to cotrimoxazole against Shigella dysenteriae, Enterococcus faecalis and Proteus mirabilis (Konaté et al., 2012). This is an indication that polyphenols could act in combination to cotrimoxazole for potentialization in order to increase its efficacy.

In Cameroon, the studies focused on beta-lactam-resistant bacteria (K. pneumoniae, K. oxytoca, Enterobacter cloacae, Serratia marcescens, Acinetobacter baumannii, S. aureus and Enterococcus sp.) and reference strains of bacteria (E. coli ATCC 35218, Enterobacter aerogenes ATCC 29751, E. aerogenes ATCC 13048, P. aeruginosa ATCC 27853 and Enterococcus hirae ATCC 9790) by using disc-diffusion and agar-dilution assays (Gangoué-Piéboji et al., 2009). The minimal inhibitory con-centration (MIC) values of different plant extracts against the tested bacteria were found to range from ≤ 0.3 to ≥ 10 mg/ml. This study revealed that the most active plant extracts were Dorstenia picta and Bridelia micrantha on beta-lactam-resistant gram-negative bacilli and the extracts from Bridelia micrantha, Mallotus oppositifolius, Garcinia lucida, Garcinia kola, Campylospermum densiflorum (leaves) and Campylospermum zenkeri (root) on beta-lactam-resistant gram-positive cocci (Gangoué-Piéboji et al., 2009). Another innovative approach in searching for new arsenals against multi-resistant bacteria was seen in the study carried out in Zimbabwe by Chitemerere and Mukanganyama (2011), who found that the ethanolic leaves extract of Calistermon citrinus Skeels rich in tannins, phenols, alkaloids and glycosides showed an efflux inhibitory activity against S. aureus, K. pneumonia, P. aeruginosa and B. subtilis comparable to that of reserpine. Reserpine is an alkaloid and is a reference efflux inhibitor with a useful counteracting mechanism against microorganisms’ resistance. Antimicrobial activity of Temnocalyx obovatus (Rubiaceae) root extracts used in folk medicine in Zimbabwe deployed significant activity against bacterial (S. aureus, E. coli, Clostridium perfringens) and fungal (Aspergillus niger and Candida albicans) species with MIC values ranging from 10 to 60 μg/ml (Muna and Fauzia, 2012).

Other efflux inhibitory mechanisms were observed by Aiyeogoro et al. (2009) who showed that the activity of presumed plant antimicrobials against gram+ and gram- organisms was significantly
enhanced by synthetic multidrug-resistance (MDR) inhibitors of MDR efflux proteins. Combinations of antibiotics are progressively being used in the treatment of drug resistant infections; this is advantageous because they deploy various mechanisms of action. The production of intrinsic antimicrobial compounds by plants can have a MDR inhibitory property that improves the inhibitory effect of antibiotics (Aiyegoro et al., 2009). The use of Catha edulis extracts for instance at sub-inhibitory levels was reported to reduce the MIC values of tetracycline and penicillin G against resistant oral pathogens, Streptococcus oralis, Streptococcus sanguis and Fusobacterium nucleatum. Polyphenols (epicatechin gallate and catechin gallate) were also found to be able to reverse beta-lactam resis-tance in methicillin resistant S. aureus (MRSA). Whereas diterpenes, triterpenes, alkyl gallates, flavones and pyri-dines showed resistance modulating abilities on various antibiotics against resistant strains of S. aureus (Aiyegoro et al., 2009). The methanolic and ethylacetate extracts of Phyllanthus muellerianus and Piptadeniastum africanus were found to be highly active against gram+ and gram- infectious resistant microorganisms with MIC varying from 2.5 to 0.31 mg/L. The in vivo acute toxicity study carried out on the methanolic extracts of these two plants indicated that they were not toxic (Assob et al., 2011). This is important because selective inhibition is crucial to conclude on the efficacy of antimicrobial compounds.

Other studies from Cameroon on plant extracts showed interesting results due to their exceptional inhibitory power on both bacteria and fungi. Among these are Bersama engleri, Dorstenia angusticornis, Dorstenia barteri, Diospyros canaliculata, Diospyros crassiflora, Newbouldia laevis, and Ficus cordata (Kuete et al., 2010). Compounds like isobavachalcone, kanzanol C and 4-hydroxylochnocarpin isolated from Dorstenia spp., plumbagin, cassiflorone and diospyrone isolated from Diospyros spp., and also new boudiaquinone and lapachol isolated from Newbouldia laevis (16) displayed important inhibitory activity against resistance microorganisms. Thecacoris annobonae Pax & K. Hoffm (Euphorbiaceae) has a significant antimicrobial (MIC < 10 µg/ml) activity against Mycobacterium tuberculosis H37Rv, B. cereus and P. aeruginosa (Kuete et al., 2011). The effect of combinations of the methanolic extract of Helycrisus pendunculatum leaves and selected antibiotics evaluated using the time-kill assay method showed a synergy rate of 59.1% (Extract + Tetracycline; Extract + Amoxycillin), 54.6% (Extract + Penicillin G; Extract + Chloramphenicol), 63.6% (Extract + Ciprofloxacin; Extract + Oxytetracycline), 68.2% (Extract+ Erythromycin) and 27.3% (Extract + Ampicillin) on all isolates at both ½ MIC and MIC values. Overall, synergistic response could attain 60% of all combinations of extract and antibiotics against all tested organisms (Aiyegoro et al., 2009).

In Libya, antituberculosis activity was obtained with dichloromethane extract of Tulbaghia violacea Harv. against M. aurum; Marrubium vulgare L., Pistacia lentiscus L, Quercus cocciifera L, Thymus capitatus (L.) Hoffm. & Link are active against M. tuberculosis (Aiyegoro et al., 2009; Korir et al., 2012).

**Plant compounds with efficacy against multi-resistant fungi pathogens in Africa**

A good number of studies have been done on the efficacy of medicinal plants against fungi. In Nigeria, Sphenoeceutrum jollyanum Pierre (Menispermaceae) used in traditional medicine as chewing sticks and for stomach pains was shown to possess significant antifungal activity against Candida albicans, Candida pseudotropicalis and Trichophyton rubrum. In South Africa (Aladesanmi et al., 2007), extract of the rhizomes Gunnera perpensa was proven effective against Penicillium notatum, Aspergillus flavus and A. niger (LC50 values ranging from 0.07 to 3.81). This is important as these fungi have been implicated in cases of immune-compromised patients that frequently develop opportunistic and superficial mycosis (Nkomo and Kambizi, 2009).

An important antifungal activity was obtained with the acetone bark extract of Erythrina caffra Thunb. The bark of E. caffra is used in South Africa to treat sores, tuberculosis, respiratory infections, wounds, abscesses, arthritis and toothache. Dose dependent inhibitory activity was observed against a wide range of fungi strains (Candida krusei, C. albicans, Candida neoformans, Candida rugosa, P. notatum, A. niger, Aspergillus terreus, Aspergillus flavus, Absidia corymbifera, Candida glabrata, Trichophyton mucoides, Trichophyton tonsurans and Fusarium Sporotrichioides) (Nkomo and Kambizi, 2009) with MIC and minimum fungicidal concentrations (MFC) values ranging between 0.625 and 20 mg/ml and indicating fungicidal activity (Olajuyigbe and Afolayan, 2012). In Cameroon, another study presented the efficacy of Ficus polita (Moraceae) against C. albicans (Kuete et al., 2011). The bark and roots infusions are used in the treatment of infectious diseases, abdominal pains and diarrhea. Phytochemical analysis of the plant indicated the presence of compounds with enough evidence of their antimicrobial microbial activities such as lupeol, betulinic acid, ursolic acid, b-sitosterol, sitosterol-3-O-b-D-glucopyranoside (Kuete et al., 2011).

Cryptolepis sanguinolenta Lindl. Schltr. (Periplocaceae) is a shrub that grows in the rainforest and the deciduous belt forest, found in the west coast of Africa. In vitro study showed inhibitory activity against bacteria species (specifically, enteric pathogens, most notably E. coli and vibrio) as well as against Candida spp. (Iwu et al., 1999). Aframomum melegueta (Zingiberaceae) is a perennial herb used as an aphrodisiac and against measles and leprosy, taken for excessive lactation and post partum
hemorrhage, purgative, galactogogue and anthemimetic and hemostatic agent contains gingerol, shagaol, paradol in its essential oil; its antifungal antishistosomal activities have also been demonstrated (Iwu et al., 1999; Kuete et al., 2011). Xylopic acid, one of the constituents of Xylopia aethiopica, Ethiopian Pepper (Abbibacceae) is active against C. albicans (Kuete et al., 2011; Korir et al., 2012). Some extracts from Cameroonian medicinal plants including those from Bersama engleriana, Dorstenia angusticornis, Dorstenia barteri, Diospyros canaliculata, Diospyros crassiflora, Newbouldia laevis and Ficus cordata exhibited a wide range of inhibitory activity on both bacteria and fungi (Kuete et al., 2011). In Kenya, hexane extracts of Senna didymobotrya used in folk medicine showed notably inhibitory activities on Microsporum gypseum, Trichophyton mentagrophyte and Microsporum gypseum (Omoregie and Sisodia, 2012).

Plants with anti-malarial and other anti-protozoa multi-resistant efficacy

Malaria is a serious health concern in Sub-Saharan Africa where it kills a child below five years every thirty seconds and more than 90% of deaths occur due to this pathology (Nsagha et al., 2011). Anti-malarial multidrug resistance is a major public health problem in the world especially in Africa where the health systems are weak resulting in many prescriptions by unqualified health personnel (Nsagha et al., 2012) and home-based treatment (Htut, 2009) which affects its control. Over the years, anti-malaria drug resistance has become one of the most important problems impeding malaria control efforts (Sendagire et al., 2005). This led to the discovery of other antimalarial agents from medicinal plants such as quinine from cinchona bark and artemisinin from Artemisia annua (Saxena et al., 2003). One of such plants with anti-malarial and anti-protozoa potentials on the African continent is Brueca sumatrana Roxb., a shrub belonging to the family Simaroubaceae (Ehata et al., 2012). An important inhibitory activity was obtained in vitro with the seeds’ crude extracts of B. sumatrana against Trypanosoma cruzi, T. brucei brucei, Leishmania infantum and chloroquine and pyrimethamine-resistant K1 strain of P. falciparum in the Democratic Republic of Congo (Ehata et al., 2012).

Plants from Western Cameroon were screened in vitro for their antiplasmodial activity and cytotoxicity. Dacryodes edulis exhibited the highest antiplasmodial activity, followed by Vernonia amygdalina, Coula edulis and Eucalyptus globulus. Dacryodes edulis is a multi-purpose plant in African folk medicine, as its various parts are used as a remedy for parasitic skin diseases, jigger, mouthwash, tonsillitis, sickle cell and malaria (Zofou et al., 2011). Its phytochemistry revealed the presence of phenolic compounds which have previously been shown as having antiplasmodial activity (Zofou et al., 2011). An alkaloid, akuamine (Figure 1) from the seeds of Picralima nitida possesses activity against Plasmodium (Titanji et al., 2008). V. amygdalina and Eucalyptus globulus extracts exhibited high activity (1 < IC50 ≤ 10 μg/ml) on both chloroquine sensitive and multiresistant strains of P. falciparum (10 < IC50 ≤ 25 μg/ml) (Titanji et al., 2008).

Antiprotozoal activities of Albizia zygia (Fabaceae) stem bark and methanolic seeds’ extract of Harungana madagascarensis was obtained against P. falciparum K1 chloroquine-resistant strain, Leishmania donovani, Trypanosoma cruzi, Trypanosoma brucei rhodesiense, protozoa responsible for malaria, visceral leishmaniasis, Chagas disease and African trypanosomiasis by Lenta et al. (2007). In Congo, it was found that the extracts from

![Figure 1. Akuamine.](source: Titanji et al. (2008).)
Enanatia chlorantha stem bark, Napoleona vogelii stem bark and Quassia africana root bark are active with IC50 values ranging between 1.87 and 5.5 µg/ml, against Trypanosoma cruzi, Leishmania infantum and P. falciparum K1 (Musum), 7α- obacunyl acetate and a cycloartane derivative which are isolated compounds from the dichloromethane - methanol (1:1) extract of the stem bark of Entandrophragma angolense (Meliaceae) with good activity, IC50 of 2 and 5.4 µg/ml, respectively test against chloroquine resistant strain W2 of P. falciparum malaria parasite in Cameroon (Bickii et al., 2007; Sha’a, et al., 2011). In Benin, two sesquiterpenic lactones isolated (1(15-acetoxy-8β,20α,20β,20α)-acetoxy-15-hydroxy-8β,20α,20β,20α-(2-methylbutyrolyoxy)-14-oxo-4,5-cis-acanthospermolide) from the aerial parts of Acanthospermum hispidum D.C showed in vitro antiplasmodial activity against the chloroquine-sensitive strain (3D7) (IC50 of 2.9 ± 0.5 and 2.23 ± 0.09 µM, respectively), Trypanosoma brucei brucei (IC50 of 2.45 ± 0.49 and 6.36 ± 1.42 µM, respectively) and Leishmania mexicana mexicana (IC50 of 0.94 ± 0.05 and 2.54 ± 0.19 µM, respectively) (Ganfon et al., 2012).

In Nigeria, the ethanolic extract of Jatropha tanjorensis leaves showed moderate sensitivity against P. falciparum. Alkaloids, saponins, anthraquinones, tannins and flavonoids are probably responsible for this activity (Ouattara et al., 2006; Omoregie and Sisodia, 2012). Ethanol extract of V. amygdalina induced an important inhibitory activity against P. falciparum with an IC50 of 11.2 μg/ml (Ouattara et al., 2006; Sha’a et al., 2011). Whereas in Burkina Faso, methanolic extracts of Swartzia madagascariensis and Combretum glutinosum as well as alkaloidal extracts of Tinospora bakis were proven to be active against P. falciparum chloroquine-resistant strain W2 in vitro (5 µg/ml < IC50 < 50 µg/ml) (Ouattara et al., 2006; Dzomba and Muchanyereyi, 2012).

DISCUSSION

In Africa, attitudes towards traditional, herbal medicines vary strongly because of the confusion between herbal medicine and witchcraft (Wright et al., 1988). The use of medicinal plants is often associated with superstition and therefore rejected by some people. However, there are many Africans who prefer traditional methods of treatment (Wright et al., 1993). The Chinese plant, Artemisia annua is cultivated in East African countries to supply pharmaceutical manufacturers in Europe (Wright et al., 1993). The bark of Prunus africana is used in making treatments for prostate cancer (Wright et al., 1993). Brueca sumatrina have been proven to possess antiprotozoal activity against Trypanosoma cruzi, T. brucei brucei, Leishmania infantum and chloroquine and pyrimethamine-resistant K1 strain of P. falciparum. These are in consonance with findings from the Asian species that were investigated for their various biological activities such as antimalarial, antiprotozoal against amoeba (Camacho et al., 2003; Sawangjaroen and Sawangjaroen, 2005), Toxoplasma gondii and Giardia intestinal (Camacho et al., 2003), Trypanosoma brucei brucei and Leishmania donovani (Sawangjaroen and Sawangjaroen, 2005), Blastocystis hominis (Bawm et al., 2008), Trypanosoma evansi (Subeki et al., 2007) and Babesia gibsoni (Elkateeb et al., 2008; Okokon and Nwafor, 2009). Other studies on medicinal plants have been reported from Cameroon (Lenta et al., 2007; Djussi et al., 2013), Nigeria (Runyro et al., 2006; Balagon et al., 2010), South Africa (Wright et al., 1993), Tanzania (Owuor and Kisangau, 2006), Uganda (Sendagire et al., 2005), Kenya (Mehjabeen et al., 2011) and Congo (Wright et al., 1988).

CONCLUSION AND FUTURE PROSPECTS

Several in vitro and in vivo antimicrobial activities have been carried out on traditional medicinal plants and found to be good sources of numerous therapeutic agents, however only few studies on the efficacy of medicinal plants and their derived compounds have been done so far on resistant strains of microorganisms. Many complementary and alternative medicines are being given more consideration because a large number of antimicrobial agents derived from traditional medicinal plants are available for treating various infectious diseases. In most of the studies, interesting antimicrobial properties of extracts against MDR strains were obtained, suggesting their potency, but only few studies have actually addressed the issue of selective toxicity.

Emphasis should be oriented towards the discovery of antibiotic resistance modifying compounds from plants sources which offer greater chances of reversing the resistance pattern of many antimicrobials which otherwise will be abandoned. Combined therapies of plants extracts and their derived products have to be assessed in vivo as well as to determine their clinical relevance. This will surely lead to the production of phytomedicines or medicinal plant-derived therapeutic agents. In order to attain this goal, research institutions in Africa should move further and put in place strong protocols geared towards the evaluation and comparison of the cost-effectiveness and safety-tolerance levels of the medicinal plants and their derived products against multidrug resistant microbial agents. African states should reinforce these efforts by putting in place a common policy that fosters the integration of traditional and modern medicines.

Competing interests

The authors declare that they have no competing interest
ACKNOWLEDGEMENT

The authors acknowledge with thanks the financial support from the Cameroonian Ministry of Higher Education through the Research Modernization scheme and the International Foundation for Science, for the research grant offered to the lead author.

REFERENCES


Balagon MF, Cellona RV, Abalos RM, Gelber RH, Saunderson PR, Grant offered to the lead author.


Btw, we must avoid summarizing the entire reference list here. Instead, we can focus on key references that are relevant to the discussion. For example:


