Review

Methicillin-resistant *Staphylococcus aureus* (MRSA) and anti-MRSA activities of extracts of some medicinal plants: A brief review

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Abstract: The increasing emergence of multidrug-resistant infection causing microorganisms has become a significant burden globally. Despite the efforts of pharmaceuticals in producing relatively new antimicrobial drugs, they have resulted in a high rate of mortality, disability and diseases across the world especially in developing countries. Supporting this claim was the report of the Centre for Disease Control and Prevention (CDC) who estimated that over 2 million illnesses and 23,000 deaths per year are attributable to antibiotic resistant pathogens in the United States. They include Methicillin-resistant *Staphylococcus aureus* (MRSA), Vancomycin-intermediate *Staphylococcus aureus* (VISA), Vancomycin-resistant *Staphylococcus aureus* (VRSA), Vancomycin-resistant enterococci (VRE), Extended spectrum beta-lactamases (ESBLs) producing gram-negative bacilli, Multidrug-resistant *Streptococcus pneumoniae* (MDRSP), Carbapenem-resistant Enterobacteriaceae (CRE) and Multidrug-resistant *Acinetobacter baumannii*. For MRSA, resistance is as a result of Methicillin-sensitive *S. aureus* (MSSA) strains that have acquired Staphylococcal Cassette Chromosome mec (SCCmec) which carries mecA gene. The gene encodes the penicillin-binding protein (PBP2a) which confers resistance to all β-lactam antibiotics. Vancomycin was previously the widely preferred drug for the treatment of MRSA infections. It is no longer the case with the emergence of *S. aureus* strains with reduced vancomycin sensitivity limiting the conventional treatment options for MRSA infections to very scanty expensive drugs. Presently, many researchers have reported the antibacterial activity of many plant extracts on MRSA. Hence, these medicinal plants might be promising candidates for treatment of MRSA infections. This work is a brief review on Methicillin-resistant *Staphylococcus aureus* (MRSA) and the anti-MRSA activities of extracts of selected medicinal plants.
Keywords: Methicillin-resistant *Staphylococcus aureus* (MRSA); Vancomycin-intermediate *S. aureus* (VISA); Vancomycin-resistant *S. aureus* (VRSA); Staphylococcal Cassette Chromosome mec (SCCmec); anti-MRSA plants

1. Introduction

Multidrug-resistant bacteria (MDRB) are microorganisms that are resistant to one or more antimicrobial agents. They are usually resistant to all but one or two commercially available antimicrobial agents. This definition includes microbes that have acquired resistance to at least one agent in three or more antimicrobial categories. The MDRB of clinical interest include: Methicillin-resistant *Staphylococcus aureus* (MRSA), *Staphylococcus aureus* with resistance to vancomycin [these are Vancomycin-intermediate *Staphylococcus aureus* (VISA) and Vancomycin-resistant *Staphylococcus aureus* (VRSA)], Vancomycin-resistant enterococci (VRE), Extended spectrum beta-lactamases (ESBLs) producing gram-negative bacilli, Multidrug-resistant *Streptococcus pneumoniae* (MDRSP), Carbapenem-resistant Enterobacteriaceae (CRE) and Multidrug-resistant *Acinetobacter baumannii* [1–3].

Infectious diseases caused by MDRB are an important burden globally. They have for centuries been among the leading causes of death, disability, growing challenges to health security and human progress, especially in developing countries [4].

Although, many new antibacterial drugs have been produced, bacteria exhibiting resistance to them have increased and is becoming a global concern as we are fast running out of therapeutic options [5,6]. The challenges of antimicrobial resistance are faced in both the health care and community settings, necessitating a broad approach with multiple partners across the continuum of care. For example, 18–33% of MRSA colonized patients subsequently developed MRSA infections. Community-acquired methicillin-resistant *Staphylococcus aureus* (CA-MRSA) strains also constitute an increasing proportion of hospital-onset MRSA infections. The Centre for Disease Control and Prevention (CDC) estimated that over 2 million illnesses and 23,000 deaths per year are attributable to antibiotic resistance in the United States [3].

Vancomycin is widely prescribed for the treatment of infections caused by MRSA; but the emergence of VISA and VRSA has been reported by many authors. Really, teicoplanin, daptomycin, linezolid, etc are expensive drugs which are currently prescribed when faced with MRSA with low sensitivity to vancomycin. However, development of resistance to these drugs has been identified worldwide [7–11].

Usage of plants in fighting against illnesses and diseases has deep roots in man’s history. Researchers are interested in plant extracts as medicines because there are several reports regarding the antimicrobial activity of their crude extracts which might be better substitutes for conventional antibiotics. Recent published reports opined that medicinal plants with anti-MRSA activity can be considered for treatment of MRSA infections [8,12]. This present work is a brief review on MRSA, VISA, VRSA and some medicinal plants with anti-MRSA activities.
2. Emergence and resistance mechanisms of MRSA, VISA and VRSA

2.1. MRSA

*Staphylococcus aureus* is a Gram-positive coccoid bacterium. The cells are arranged in irregular grape-like appearance and they are usually found as normal flora in humans and animals. It is ubiquitous in the human population and 30–40% of adults are asymptomatic carriers. It is also a major pathogen of human and can cause a range of infections from mild skin infections and food poisoning, to life threatening infections [13–17].

Resistance to methicillin by *S. aureus* was initially observed in 1961 shortly after the antibacterial agent was introduced clinically and since then, there has been a global epidemic of Methicillin-resistant *Staphylococcus aureus* (MRSA) in both healthcare and community settings [18–20]. MRSA isolates from the UK and Denmark in the early 1960s constituted the very first epidemic MRSA clone soon after methicillin was introduced and it has since emerged as an important pathogen in human medicine [21–23]. Although, methicillin is no longer prescribed for patients and has been replaced by isoxazolyl penicillins, particularly flucloxacillin in the UK, the acronym MRSA has stayed [24]. It is characterized by antibiotic resistance to penicillins, cephalosporins, carbapenems and has tendency of developing resistance to quinolones, aminoglycosides, and macrolides [10,25,26].

The origination of MRSA was as a result of Staphylococcal Cassette Chromosome *mec* (SCCmec) genes acquired by methicillin-susceptible *S. aureus* (MSSA). The SCCmec harbours the *mecA* gene which encodes the penicillin-binding protein (PBP2a) that confers resistance to all β-lactam antibiotics [10,27–29]. SCCmec also contains the cassette chromosome recombinases (*ccr*) gene complex. The *ccr* genes (composed of *ccrC* or a pair of *ccrA* and *ccrB*) encode recombinases mediating integration and excision of SCCmec into or from the chromosome. The *ccr* genes and surrounding genes form the *ccr* gene complex. In addition to *ccr* and *mec* gene complexes, SCCmec contains a few other genes and various other mobile genetic elements such as: insertion sequences, transposons and plasmids [30,31].

Eleven different types of SCCmec (I-XI) and five allotypes of the *ccr* gene complexes (*ccrAB1*, *ccrAB2*, *ccrAB3*, *ccrAB4* and *ccrC*) have been reported. Generally, SCCmec types I, II, III, VI and VIII are called hospital-acquired MRSA or (HA-MRSA). Types IV, V and VII as community-acquired (CA-MRSA) while types IX, X and XI as livestock-associated MRSA (LA-MRSA) [31,32]. Expression of methicillin resistance in *S. aureus* is commonly under regulatory control by *mecI* or *blaI* gene. The *mecI* and *blaI* repressors are controlled by the *mecRI* and *blaRI* transducers [20].

MRSA remains a major public health concern worldwide and a therapeutic challenge as the antibacterial drugs effective for treatment are scanty and costly. The changing epidemiology of MRSA infections, varying resistance to commonly used antibiotics and involvement in hospital and community infections are influencing the use and clinical outcomes of currently available anti-infective agents [33].

2.2. Resistance of vancomycin by *S. aureus*

Vancomycin is an antibacterial agent that inhibits cell wall production by binding with the D-alanyl-D-alanine C terminus of the bacterial cell wall precursors, and subsequently preventing cross-linking by transpeptidation. Vancomycin acts extracellularly and inhibits late-stage peptidoglycan
biosynthesis which results in the intracellular accumulation of UDP-linked MurNAc-pentapeptide precursors. The vancomycin complex involves a number of hydrogen bonds between the peptide component of vancomycin and the D-Ala-D-Ala residue. Any process that interferes with vancomycin binding to D-Ala-D-Ala residues in the cell wall will decrease the potency of the drug [13,36].

Vancomycin was widely utilized for the treatment of MRSA infections and has led to the emergence of vancomycin-intermediate and vancomycin-resistant S. aureus (VISA and VRSA) [37]. This also triggered off alarms in the medical community as S. aureus causes life-threatening infections in hospitalized and non-hospitalized patients [38]. Vancomycin-intermediate S. aureus (VISA), heterogeneous vancomycin-intermediate S. aureus (hVISA) and vancomycin-resistant S. aureus (VRSA) are the three classes of S. aureus that are resistant to vancomycin which have emerged in different locations of the world [39].

2.3. Vancomycin-intermediate S. aureus (VISA)

Vancomycin-intermediate S. aureus (VISA) was first reported from Japan in 1996 with reduced susceptibility to vancomycin (having a Minimum Inhibitory Concentration (MIC) of 8 mg/L). It has now spread to other hospitals in Asia, France, Brazil, USA, United Kingdom, etc [40]. S. aureus vancomycin breakpoints were redefined by the Clinical and Laboratory Standards Institute (CLSI) in 2006 as follows: resistant at MIC ≥ 16 µg/ml, intermediate at 4–8 µg/ml and susceptible at ≤ 2 µg/ml [34–36].

VISA isolates emerged as a result of mutations (not their acquisition of foreign genetic elements) in MRSA isolates during treatment of patients with vancomycin. The comparison of vancomycin-susceptible and -resistant isolates to the VISA isolates showed that the mutations often occurred in the walkR, vraSR, rpoB (ribosomal) genes and the yvqF/vraSR system. Usually, the relevant mutated genes seemed to be directly or indirectly involved with the biosynthesis/metabolism of the staphylococcal cell wall [41].

Often, there were treatment failures when VISA infections were treated with vancomycin [41]. It was observed that under vancomycin selective pressure usually during treatment, the VISA strains with a vancomycin MIC of 8 µg/ml have emerged and led to therapy failure. However, the nature of this resistance phenotype (VISA) was unstable especially when vancomycin selective pressure is removed as some strains reverted back to vancomycin-susceptible strains with MIC at 2 µg/ml [36].

2.4. Heterogeneous VISA (hVISA)

In 1997, the first case of hVISA was reported in Japan. The cultures of hVISA strains contain both low-frequency subpopulations of bacteria with increased vancomycin MIC value and high frequency of bacteria with low vancomycin MIC values (close to those of susceptible strains) [41]. The MIC for hVISA strains was defined by the presence of subpopulations of VISA at a rate of one organism per 105 to 106 organisms [42,43]. The hVISA strains were detected using vancomycin population analysis profile (PAP) which was proposed as the most accurate method for hVISA detection; however, it is relatively time-consuming and requires the use of a spiral plater. The hVISA strain has generally required formal population analysis using the serial passage of screened isolates of S. aureus on selective agar containing increasing concentrations of vancomycin for its detection [13]. Results are generally not ready until at least 3 to 5 days [36].
VISA and hVISA strains have thickened cell wall with reduced glycopeptide cross-linking as a result of the complex reorganization of cell wall metabolism. It has been proposed that the thickened cell wall may trap and sequester vancomycin and consequently, interferes with its mode of action [13]. This could be due to alteration in peptidoglycan production leading to increased residues of D-alanyl-D-alanine, which bind vancomycin molecules and prevent them from reaching the target sites [18–20].

2.5. Vancomycin-resistant S. aureus (VRSA)

In 2002, the first hospital strain of Vancomycin-resistant S. aureus (VRSA) was reported in the United States [44]. The acquisition of vanA gene from vancomycin-resistant enterococci resulted in the emergence of vancomycin-resistant strains of S. aureus (VRSA) with vancomycin MIC value greater than 16 µg/ml [36,41,45].

3. Prevalence of MRSA and S. aureus with reduced sensitivity to vancomycin

MRSA has spread worldwide, and its prevalence has increased in both health-care and community environments. The proportion of MRSA varied among countries such as for instance: 0.4% in Sweden [24]; 25% in western part to 50% in southern India [10]; 33%–43% in Nigeria [46]; 37–56% in Greece, Portugal and Romania in 2014 [47]. High prevalence of MRSA with rates greater than 50% has also been reported in hospitals worldwide including in Asia, Malta, North and South America [29,48]. Variation in the prevalence rates of MRSA was due to different epidemiological factors such as geographical and health system capability in running infection control program [49].

Akanbi and Mbe [50] reported a prevalence range of 0% to 6% VRSA in southern parts of Nigeria among clinical isolates and also 57.7% in Zaria, northern Nigeria. Goud, et al., [51] reported a vancomycin resistance in 1.4% of S. aureus isolates in southern India. Other countries such as: Australia, Korea, Hong Kong, Scotland, Israel, Thailand, South Africa, etc have also reported S. aureus with vancomycin sensitivity reduction with prevalence ranges from 0–74% [20,36,52].

4. Therapeutic measures

Currently, there are seven common antibiotics used against MRSA, which are: vancomycin, daptomycin, linezolid, Sulfamethoxazole and trimethoprim (TMP-SMZ), quinupristin-dalfopristin, clindamycin and tigecycline. These antibiotics are gradually losing their efficiency as MRSA strains are developing resistance against them [8,20,53]. Presently, the therapeutic alternatives available for treatment of infections caused by MRSA and S. aureus with reduced vancomycin susceptibility are limited. Therefore, there is a global urgency for the development of novel drugs that will be effective in the treatment of S. aureus exhibiting multidrug resistance so as to combat the scourge caused by the microorganism in the globe [52].

4.1. Prospects of medicinal plants as therapeutic option for MRSA

Natural products including medicinal plants have contributed immensely to human health, well-being and development of novel drugs. They are useful natural blueprints for the development of new drugs (especially in western countries) or/and phytomedicines purified to be used for the
treatment of disease (commonly in developing countries and Europe) [54]. Medicinal plants can be valuable therapeutic resources. In numerous developing countries, including Nigeria, 80% of patients use home-made phytomedicines to treat infectious diseases. Despite the availability of modern medicine in some communities, the use of medicinal plants has remained high due to their efficacy, popularity and low cost. They also represent sources of potentially important new pharmaceutical substances since all the plants parts are utilized in traditional treatment and can therefore, act as lead compounds (Table 1).

The applications of phytomedicines for human well being and as blueprints for developing novel useful drugs have drastically increased worldwide in recent years [77].

The emergence of multidrug-resistant infectious agents associated with over- and inappropriate use of antibiotics has necessitated the World Health Organization (WHO) to acknowledge and pronounce the urgent need to develop novel antimicrobials and/or new approaches to tackle the menace caused by them in the globe; these have subsequently led to the resuscitation of the interest in medicinal plants [78]. The most common bacteria that have been used in susceptibility tests with numerous medicinal plants include: \textit{Staphylococcus aureus}, methicillin-resistant \textit{Staphylococcus aureus} (MRSA), vancomycin-resistant \textit{Enterococcus} (VRE), \textit{Pseudomonas aeruginosa Helicobacter pylori}, etc [54]. Presently, numerous studies have reported the antibacterial activity of many plant extracts against MRSA. In this study, only fifty-one (51) plants with anti-MRSA activities from thirty-five (35) families were mentioned (Table 1). The minimum inhibitory concentrations (MIC) values of the plants on the tested MRSA strains were between 1.25 µg/ml to 6.30 mg/ml. Twenty-nine of the plants had MIC values < 1.0 mg/ml while the remaining twenty-two MIC values were > 1.0 mg/ml but < 8.0 mg/ml. Extracts exhibiting activities with MIC values below 8 mg/ml are widely accepted to possess some antimicrobial activity while those with values below 1 mg/ml are considered noteworthy [77,79]. However, most of the plants in this review were not tested on \textit{S. aureus} strains with reduced vancomycin susceptibility.

The solvents used for the medicinal plants extraction in this review were ethanol and methanol (Table 1). This is probably because alcoholic extracts have higher antimicrobial activity than aqueous extracts. It has been reported that ethanolic extracts have higher antimicrobial activity than aqueous extracts because of the presence of higher amounts of polyphenols. They are more efficient in cell walls and seeds degradation causing polyphenols to be released from cells. Also, the enzyme polyphenol oxidase, degrades polyphenols in water extracts but is inactive in methanol and ethanol. Moreover, water is a better medium for the growth of microorganisms than ethanol [80].

Although, methanol is more polar than ethanol but it is not frequently used for plant extraction due to its cytotoxic nature that may give incorrect results [81].

Extracts of medicinal plants are rich in phytochemicals. Phytochemicals or secondary metabolites are natural protective agents biosynthesized by plants against external stress and pathogenic attack. They are crucial for plant defences and survival. They have been divided into several categories: phenolics, alkaloids, steroids, terpenes, saponins, etc. They exhibit other bioactivities such as antimutagenic, anticarcinogenic, antioxidant, antimicrobial, and anti-inflammatory properties and are therefore responsible for the medicinal potential of plants (Table 2). Hence, from this review, anti-MRSA plants have antibacterial effect on MRSA strains and other medicinal/therapeutic uses as depicted in Table 2.
| Botanical name | Family       | Local/Common name          | Place of collection | Plant part used | Extracting Solvent | MIC /MBC (mg/ml) MRSA | MIC /MBC (mg/ml) VRSA | References |
|----------------|--------------|----------------------------|---------------------|----------------|--------------------|-----------------------|-----------------------|------------|
| *Acacia catechu* (L. f.) Willd | Fabaceae     | Cutch tree, black catechu  | Thailand            | Wood           | Ethanol            | 1.6–3.2/25            |                       | 55,56      |
| *Garcinia mangostana* L. | Clusiaceae   | Mangosteen                 | Thailand            | Fruit shell    | Ethanol            | 0.05–0.4/0.1–0.4      |                       | 55,57      |
| *Impatiens balsamina*    | Balsaminaceae| Garden balsam              | Thailand            | Leaf           | Ethanol            | 6.3/25                |                       | 55,58      |
| *Peltophorum ptercarpum* (DC.) | Fabaceae     | Yellow flame tree          | Thailand            | Bark           | Ethanol            | 0.1–0.8/6.3           |                       | 55,59      |
| *Psidium guajava* L.    | Myrtaceae    | Guava                      | Thailand            | Leaf           | Ethanol            | 0.2–1.6/6.3           |                       | 55,60      |
| *Punica granatum* L.    | Punicaceae   | Pomegranate                | Thailand            | Fruit shell    | Ethanol            | 0.2–0.4/1.6–3.2       |                       | 55,61      |
| *Uncaria gambir* (Hunter) Roxb. | Rubiaceae    | Gambier, White cutch       | Thailand            | Leaf, stem     | Ethanol            | 0.4–0.8/3.2           |                       | 55,62      |
| *Walsura robusta*       | Meliaceae    | Bonlichu                   | Thailand            | Wood           | Ethanol            | 1.6–3.2/25            |                       | 55,63      |
| *Swietenia mahagoni*    | Meliaceae    | Mahagoni                   | Malaysia            | Seed           | Ethanol            | 0.2–0.78/0.78–1.56    |                       | 64         |
| *Tinospora crispa*      | Menispermaceae| Patawali                   | Malaysia            | Stem           | Ethanol            | 0.4–0.78/0.78–1.56    |                       | 64         |
| *Butea monosperma* Lam. | Fabaceae     | Flame-of-the-forest        | India               | Leaf           | Ethanol            | 5.91/13.30            | 1.16/2.62            | 65         |
| *Callistemon rigidus* R.Br. | Myrtaceae    | Stiff bottlebrush          | India               | Leaf           | Methanol           | 0.00125–0.08          |                       | 66         |
| *Acacia albida* Del.    | Fabaceae     | Gawo                       | Nigeria             | Stem bark      | Methanol           | 3.0/4.0               |                       | 67         |
| *Anchomanes difformis* Engl. | Araceae     | Chakara                    | Nigeria             | Roots          | Methanol           | 4.0/5.0               |                       | 67         |
| *Boscia senegalensis* Del. | Capparidaceae| Anza                       | Nigeria             | Roots          | Methanol           | 5.0/6.0               |                       | 67         |
| *Moringa oleifera* Lam. | Moringaceae  | Zagale                     | Nigeria             | Leaf           | Ethanol            | 4.0/5.0               |                       | 67         |
| *Mormodica basalmina* Linn. | Cucurbitaceae| Garahuni                   | Nigeria             | Whole plant    | Methanol           | 4.0/5.0               |                       | 67         |
| *Nymphaea lotus* Linn.  | Nymphaeaceae | White lotus                | Nigeria             | Leaf           | Ethanol            | 5.0–10.0/10.0–30.0    | 5.0–10.0/10.0–30.0    | 68         |
| *Pavetta crassipes* K. Schum. | Rubiaceae    | Gadau                      | Nigeria             | Leaf           | Methanol           | 4.0/5.0               |                       | 67         |
| *Phyllanthus amarus* Schum. Thonn. | Euphorbiaceae| Geron tsuntsaye            | Nigeria             | Whole plant    | Methanol           | 4.0/5.0               |                       | 67         |

Continued on next page
| Botanical name          | Family      | Local/Common name    | Place of collection | Plant part used                  | Extracting Solvent | MIC /MBC (mg/ml) MRSA | MIC (mg/ml) VRSA | References |
|-------------------------|-------------|----------------------|---------------------|----------------------------------|--------------------|------------------------|-----------------|------------|
| Vernonia blumeoides Hook. f. | Asteraceae  | Bagashi              | Nigeria             | Aerial part                      | Ethanol            | 4.0/5.0                |                 | 67         |
| Curcuma xanthorrhiza    | Zingiberaceae | Java ginger         | Indonesia           | Rhizome                          | Ethanol            | 0.5/ND                 |                 | 69         |
| Kaempferia pandurata Roxb. | Zingiberaceae | Temu kunci, fingerroot | Indonesia           | Rhizome                          | Ethanol            | 0.3/ND                 |                 | 69         |
| Senna alata             | Fabaceae    | Candle bush          | Indonesia           | Leaf                             | Ethanol            | 0.5/ND                 |                 | 69         |
| Mallotus yunnanensis Pax et. Hoffm. | Euphorbiaceae | -                  | China               | Tender Branches & leaves(TBL)    | Ethanol            | 0.008–0.032/0.064–0.26 |                 | 70         |
| Skimmia arborescens Anders. | Rutaceae  | Japanese skimmia     | China               | TBL                              | Ethanol            | 0.016–0.064/0.13–0.26 |                 | 70         |
| Cyclobalanopsis austroglauca Y.T. Chang | Fagaceae | Oak                  | China               | TBL                              | Ethanol            | 0.016–0.064/0.13–0.51 |                 | 70         |
| Manglietia hongheensis Y.m Shui et. W.H. Chen. | Magnoliaceae | Magnolia            | China               | TBL                              | Ethanol            | 0.008–0.13/0.032–0.51 |                 | 70         |
| Brandisia hancei Hook.f. | Scrophulariaceae | -                  | China               | Whole plant                      | Ethanol            | 0.032–0.064/0.13–0.26 |                 | 70         |
| Evodia daniellii (Benn) | Rutaceae    | Bebe tree            | China               | TBL                              | Ethanol            | 0.032–0.064/0.064–0.26 |                 | 70         |
| Schima sinensis (Hemscl. et. Wils) Airy-shaw. | Theaceae | Schima               | China               | TBL                              | Ethanol            | 0.016–0.064/0.064–0.26 |                 | 70         |
| Garcinia morella Desr. | Clusiaceae  | Gamboge              | China               | Whole plant                      | Ethanol            | 0.016–0.064/0.064–0.26 |                 | 70         |
| Meliosma squamulata Hance. | Lauraceae | -                    | China               | TBL                              | Ethanol            | 0.032–0.064/0.13–0.26 |                 | 70         |
| Curculigo orchioides Gaertn. | Hypoxidaceae | Golden eye-grass     | China               | Whole plant                      | Ethanol            | 0.26–0.51/0.51–>2.05  |                 | 70         |
| Euonymus fortunei (Turcz.); Hand. Mazz. | Celastraceae | Spindle, Winter creeper | China               | Vane                            | Ethanol            | 0.51/1.02–>2.05       |                 | 70         |

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| Botanical name                     | Family             | Local/Common name          | Place of collection | Plant part used | Extracting Solvent | MIC /MBC (mg/ml) MRSA | MIC /MBC (mg/ml) VRSA | References |
|-----------------------------------|--------------------|----------------------------|---------------------|-----------------|--------------------|------------------------|------------------------|------------|
| *Alnus nepalensis* D. Don.        | Betulaceae         | Nepalese alder             | China               | TBL             | Ethanol            | 0.26–1.02/1.02–>2.05  | 70         |
| *Illicium simonsii* Maxim.        | Illiciaceae        | -                          | China               | TBL             | Ethanol            | 0.51–1.02/1.02–>2.05  | 70         |
| *Blumea balsamifer* (Linn.) D.C.  | Asteraceae         | Sambong                    | China               | Whole plant     | Ethanol            | 0.064–0.26/0.26–1.02  | 70         |
| *Machilus salicina* Hance         | Lauraceae          | Liu ye run nan             | China               | TBL             | Ethanol            | 0.51–1.02/1.02–>2.05  | 70         |
| *Schisandra viridis* A.c.Smith.   | Schisandraceae     | Magnolia vine              | China               | Vane            | Ethanol            | 0.064–0.26/0.26–1.02  | 70         |
| *Selaginella tamariscina* (Seauv.) Spring. | Selaginellaceae | Little club moss           | China               | Whole plant     | Ethanol            | 0.51–1.02/1.02–>2.05  | 70         |
| *Celastrus orbiculatus* Thunb.    | Celastraceae       | Chinese bittersweet        | China               | Vane            | Ethanol            | 0.51–1.02/1.02–>2.05  | 70         |
| *Polygonum molle* D. Don.         | Polygonaceae       | Knotweed                   | China               | Whole plant     | Ethanol            | 0.26–0.51/1.02–>2.05  | 70         |
| *Carex prainii* C.B. Clarke       | Cyperaceae         | Sedges                     | China               | Whole plant     | Ethanol            | 1.02–2.05/2.05–>2.05  | 70         |
| *Embelia burmif.*                | Myrsinaceae        | Baberung, Vidanga          | China               | Leaves          | Ethanol            | 0.51–1.02/1.02–>2.05  | 70         |
| *Melianthus major* L.             | Melianthaceae      | Giant honey flower         | South Africa        | Leaves          | Ethanol            | 0.78/3.12              | 71         |
| *Melianthus comosus* Vahl         | Melianthaceae      | Honey flower               | South Africa        | Leaves          | Ethanol            | 0.39/1.56              | 71         |
| *Dodonaea angustifolia* (L.f.) Benth | Sapindaceae       | Sticky hopbush, sand olive | South Africa        | Leaves          | Ethanol            | 0.59/ 1.17             | 71         |
| *Withania somnifera* L.           | Solanaceae         | Ashwagandha, Winter cherry | South Africa        | Roots & leaves  | Ethanol            | 1.56/> 6.25            | 71,72,73   |
| *Quercus infectoria* Olivier      | Fagaceae           | “Machika or Oak galls”     | South Africa        | Nutgalls        | Ethanol            | 0.4–3.2/3.2–6.3        | 74         |
| *Thymus vulgaris* L.              | Lamiaceae          | Thyme                      | Peru                | Leaves          | Essential oil      | 0.057/ND               | 75,76      |

Key: ND- Not done; MIC- Minimum inhibitory concentration; MBC- Minimum bactericidal concentration; VRSA- Vancomycin-resistant *S. aureus*
Table 2. Anti-MRSA plants with their phytochemical contents and medicinal uses.

| Medicinal Plant       | Phytochemical content                                                                 | Medicinal uses                                                                                      | References |
|-----------------------|---------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------|------------|
| *Acacia catechu*      | tannins, flavonoids, amino acids, saponins, triterpenoids                              | Cold, cough, diarrhea, piles, fever, ulcers, boils, etc                                             | 82, 83     |
| *Garcinia mangostana* | Xanthones and phenolics (tannins)                                                     | skin infections, wounds, dysentery, urinary disorders, cystitis and gonorrhoea                        | 84, 85     |
| *Impatiens balsamina* | flavonoids, triterpenoids, glycosides, fatty acids & alkaloids                         | diuretic, emetic, laxative, demulcent and tonic                                                     | 86         |
| *Peltophorus ptercarpum* | fatty acids, amino acids, terpenoids, phenolics, flavonoids, alkaloids, steroids etc. | stomatitis, insomnia, skin troubles, constipation, ringworm, insomnia, dysentery, muscular pains, sores, and skin disorders | 87         |
| *Psidium guajava*     | Tannins, Steroids, Alkaloids, glycosides, vitamins, carbohydrates                     | diarrhea, sore throat, vomiting, stomach upset, vertigo etc.                                         | 88         |
| *Punica granatum*     | Tannins, Alkaloids, glycosides, vitamins, carbohydrates, flavanoids, saponins, triterpenoids | sore throats, coughs, urinary infections, digestive disorders, skin disorders, arthritis, expel worms | 89         |
| *Uncaria gambir*      | tannins, catechin, gambiriins                                                         | wounds and ulcers, fevers, headaches, gastrointestinal illnesses, bacterial/fungal infections, diarrhea, sore throat | 90, 91     |
| *Walsura robusta*     | Sesquiterpenoid 10-nitro-isodauc-3-en-15-al, 10-oxo-isodauc-3-en-15-al                 | Antibacterial, antimicrobial, astringent, diarrhea                                                  | 92, 93     |
| *Swietenia mahagoni*  | Alkaloids, terpenoids, anthraquinone, cardiac glycosides, saponins, phenols, flavonoids, etc | Hypertension, diabetes, malaria, amoebiasis, cough, chest pain, tuberculosis, antibacterial        | 64, 94     |
| *Tinospora crispa*    | Triterpenes, flavones o-glycosides (apigenine), picroretoside, berberine, palmatine, picroretine & resin | Fever, jaundice, hyperglycemia, wounds, intestinal worms, skin infections, antibacterial activity    | 64         |
| *Butea monosperma*    | Tannins, Saponins, Alkaloids, Glycosides, Carbohydrates                                | hepatoprotective, antidiabetic, antihelmintic, antimicrobial, antitumour, antiulcer, inflammatory diseases, wound healing, etc | 65         |
| *Callistemon rigidus* | Tannins & phenolic compounds, Lipids & fats, Steroids, Alkaloids, Saponins, Terpenoids | Treatment of cough, bronchitis and respiratory tract infections                                      | 66, 95     |

*Continued on next page*
| Medicinal Plant         | Phytochemical content                                                                 | Medicinal uses                                                                                             | References |
|------------------------|---------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------|------------|
| *Acacia albida*        | Alkaloids, tannins, saponins, phenols, flavonoids                                      | respiratory infections, skin infections, digestive disorders, malaria and other fevers, toothache in humans and eye infections in livestock. | 96         |
| *Anchomanes difformis* | Alkaloids, tannins, saponins                                                          | cough, respiratory diseases, dysentery                                                                      | 97,98      |
| *Boscia senegalensis*  | Alkaloids, anthraquinone, cardiac glycosides, saponins, phenols, tannins, flavonoids  | Anticancer and ulcer swellings                                                                               | 98         |
| *Moringa oleifera*     | anthraquinone, cardiac glycosides, saponins, phenols, tannins, flavonoids              | Asthma, eye infections, migraine, headache, febrifuge, abortifacient                                        | 98         |
| *Mormodica basalmina*  | resins, alkaloids, flavonoids, glycosides, steroids, terpenes, cardiac glycoside, saponins | anti-HIV, anti-plasmodial, anti-diarrheal, anti-septic, anti-bacterial, anti-viral, anti-inflammatory, anti-microbial, etc | 99         |
| *Nymphaea lotus*       | phenols, tannins, saponins, alkaloids and steroids                                      | aphrodisiac, anodyne, astringent, cardiotonic, sedative, analgesic and as anti-inflammatory agent.           | 68,100     |
| *Pavetta crassipes*    | flavonoids, sugars, tannins, saponins, glycosides, alkaloids and polyphenols           | respiratory infections and abdominal disorders, gonorrhoea, cough remedy                                     | 101,102    |
| *Phyllanthus amarus*   | lignans, flavonoids, hydrolysable tannins (ellagitannins), polyphenols, triterpenes, sterols and alkaloids. | used in the problems of stomach, genitourinary system, liver, kidney and spleen. It is bitter, astringent, stomachic, diuretic, febrifuge and antiseptic | 103         |
| *Vernonia blumeoides*  | glycosides, saponins, alkaloids, tannins, flavonoids, steroids/terpenes                | treatment of various human ailments including parasitic (malaria) and infectious diseases                     | 104         |
| *Curcuma xanthorrhiza* | Alkaloids, terpenoids, cardiac glycosides, saponins, phenols, flavonoids, coumarin     | Treatment of liver damage, hypertension, diabetes, and cancer.                                              | 105,106    |
| *Kaempferia pandurata* | Flavonoids, such as pinostrobin, pinocembrin, alpinetin, cardamonin, etc              | Treatment of cough, stomach distended, diuretic, anti-anthelmintic, uterus inflammation, vaginal infection    | 107,108    |
| *Senna alata*          | flavonoids, tannic acid, anthocyanin, alkaloids, quercetin and coumarins               | Antimicrobial, antifungal, ringworm, asthma, aphthose ulcers                                               | 109         |
| *Mallotus yunnanensis* | Polyphenols, tannins, flavonoids, coumarins, various terpenoids                        | hepatitis, sore, otitis media, stomach and duodenal ulcer, enlarged spleen and boils swelling, hematuria leukorrhea and traumatic bleeding | 70         |

Continued on next page
| Medicinal Plant       | Phytochemical content                                                                 | Medicinal uses                                                                 | References |
|-----------------------|---------------------------------------------------------------------------------------|--------------------------------------------------------------------------------|------------|
| *Skimmia arborescens* | alkaloids, coumarins, triterpenoids, phenols                                          | HBV (skimmianine), rheumatoid, paralysis, beriberi, and containing toxic substances | 70         |
| *Cyclobalanopsis austroglauca* | None                                                                              | astringing sores, carbuncles, dysentery, hemostasis and vaginal discharge       | 70         |
| *Manglietia hongheensis* | Alkaloids                                                                          | vomiting, diarrhea, dysentery, constipation and geriatric hacking cough        | 70         |
| *Brandisia hancei*     | hydroxytyrosol derivatives and glycosides                                           | jaundice, boils, swelling, tuberculosis injury, hematemesis, osteomyelitis, periostitis, rheumatism and pain | 70         |
| *Evodia daneillii*     | alkaloids, flavonoid glycosides, flavaprin, limonoids                               | diarrrhea, abdominal pain and vomiting                                          | 70         |
| *Schima sinensis*      | benzoquinone, tannins, phenols, lignans, flavonoids, triterpenoids                  | furuncle and swelling                                                          | 70         |
| *Evodia canelli*       | phenols (gambogic acid), flavonoids (xanthones), triterpenoids                      | wound rot, carbuncle, tinea, ulcer and sore, anthelminthic and containing toxic substances | 70         |
| *Meliosma squamulata*  | Triterpenoids                                                                      | scabies, carbuncle boils swollen poison, hemorrhoids, enterobiasis, beriberi, rheumatoid, and snake bite | 70         |
| *Curculigo orchoides*  | triterpenoids, lignans, flavonoids, alkaloids, steroids                             | diarrhea, ulcer, pus and muscles atrophy                                        | 70         |
| *Euonymus fortune*     | alkaloids, triterpenoids, flavonoids                                               | chronic diarrhea, dysentery, dispersing blood stasis and traumatic bleeding     | 70         |
| *Alnus nepalensis*     | tannins, triterpenoids, flavonoids, phenols                                        | bleeding of the nose, enteritis and dysentery                                    | 70         |
| *Illicium simonsii*    | terpenoids, lignans, flavonoids, phenols                                           | scabies, bladder hernias, mixed cropping of edible spices and containing toxic substances | 70         |
| *Blumea balsamifera*   | flavonoids, simple terpenoids                                                       | anti-rheumatism, ringworm and sores, dysentery, detoxification and snake bite  | 70         |
| *Machilus salicina*    | alkaloids, lignans                                                                 | carbuncle, furunculosis and sore pain                                            | 70         |
| *Schisandra viridis*   | lignans, triterpenoids, organic acids                                              | urticaria, herpes zoster, rheumatism and analgesia                              | 70         |

Continued on next page
| Medicinal Plant        | Phytochemical content                                                                 | Medicinal uses                                                                 | References |
|------------------------|----------------------------------------------------------------------------------------|---------------------------------------------------------------------------------|------------|
| Selaginella tamariscina| flavonoids, phenol glycosides, trehalose                                               | inflammation, pharyngolaryngitis and bacteriostasis                              | 70         |
| Celastrus orbicularis  | sesquiterpene, flavonoids                                                               | dysentery, multiple abscess, Herpes zoster, detoxification, inflammatory, cellulites and snake bite | 70         |
| Polygonum molle        | tannins, flavonoids, alkaloids                                                          | carbuncle, swollen abscess, fistula and scrofula                                  | 70         |
| Carex prainii          | alkaloids, polyphenols, flavonoids                                                       | antipyresis, diuretic and chyluria                                               | 70         |
| Embelia burm           | quinones, triterpenoids, flavonoids                                                      | heat clearing and detoxicating, pharyngitis, dysentery, diarrhea, furuncle ulcer, skin itching, swelling and pain of hemorrhoids, etc | 70         |
| Melianthus major       | quercetin 3-O-β-galactoside-6-gallate, kaempferol 3-O-α-arabinopyranoside               | wound healing and sores                                                           | 71,110     |
| Melianthus comosus     | Triterpenoids                                                                           | wound healing, sores, skin inflammation, snakebite                                | 110,111,112|
| Dodonaea angustifolia  | diterpenoids, flavonoids                                                                 | skin infections and irritations, inflammation, tuberculosis and pneumonia         | 110,113    |
| Withania somnifera     | withanolides, alkaloids, chlorogenic acid, glycosides, glucose, tannins, and flavonoids | anti-inflammatory, antimicrobial, antitumour, anti-convulsant, sedative            | 72,73      |
| Quercus infectoria     | tannin, saponin, gallic acid and ellagic acid                                           | hemorrhages, chronic diarrhea, dysentery, Skin disease, sore throat               | 114,115,116|
| Thymus vulgaris        | alkaloids, carbohydrates and glycosides, flavonoid, resins, saponins, tannins, sterols and triterpenes | headache, fevers, ulcers, arthritis, microbial infections even cancers             | 117        |
The therapeutic properties of these medicinal plants obtained from their phytochemicals could be employed for drug development [118]. The antibacterial (anti-MRSA) activity of these plants is attributed to their phytochemical contents. For instance, flavonoids complex with bacterial cell wall, extracellular and soluble protein while tannins inactivate microbial adhesions, enzymes and cell envelop proteins [55,67–69,119].

Although, these anti-MRSA plants are likely promising candidates for drug development for MRSA infections, it has been reported that most plants contain potentially toxic, mutagenic, and/or carcinogenic substances. Therefore, it is highly recommended that medicinal plants undergo a critical sequential antimicrobial, pharmacological, and toxicology screening to ascertain their safety and selection as good candidates for novel drug development [77,79,120].

5. Conclusion

*S. aureus* is a common microorganism that is widely spread in the human population with many being asymptomatic carriers. It can also cause life-threatening infections and its strains have evolved into MRSA and strains with reduced vancomycin susceptibility (VISA, hVISA and VRSA). These strains cause infections and diseases that are either difficult to treat or resistant to the empiric antibiotics usually prescribed for treatment. The globe is running short of drugs/antibiotics available for therapy as a result of infections associated with this organism.

Many research studies have reported that some medicinal plants in different countries have anti-MRSA activities due to their phytochemical contents. These plants can be employed as alternative candidates for drug development to halt or/and control the infections of multi-drug resistant *S. aureus*. However, there is a need for further studies to adequately determine the safety and clinical efficacy of anti-MRSA plants to man.

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Conflict of interest

All the authors have declared no conflict of interest in this short review.

References

1. Magiorakos AP, Srinivasan A, Carey RB, et al. (2012) Multidrug-resistant, extensively drug-resistant and pandrug-resistant bacteria: an international expert proposal for interim standard definitions for acquired resistance. *Clin Microbiol Infect* 18: 268–281.

2. Basak S, Singh P, Rajurkar M (2016) Multidrug resistant and extensively drug resistant bacteria: A study. *J Pathog* 2016: 4065603.

3. Health Research and Educational Trust (HRET). (2017) Multidrug-resistant organisms. Infection change package. Available from: http://www.hret-hiin.org.
4. Nii-Trebi NI (2017) Emerging and neglected infectious diseases: Insights, advances and challenges. *Bio Med Res* 2017: 5245021.

5. Adwan GM, Abu-Shanad BA, Adwan KM (2009) In vitro activity of certain drugs in combination with plant extracts against *Staphylococcus aureus* infections. *Afric J Biotechnol* 8: 4239–4241.

6. World Health Organization (WHO). WHO publishes list of bacteria for which new antibiotics are urgently needed, 2017. Available from: http://who.int/mediacentre/news/releases/2017/bacteria-antibiotics.

7. Gardete S, Alexander Tomasz A (2014) Mechanisms of vancomycin resistance in *Staphylococcus aureus*. *J Clin Invest* 124: 2836–2840.

8. Kali A (2015) Antibiotics and bioactive natural products in treatment of Methicillin-resistant *Staphylococcus aureus* (MRSA): A brief review. *Pharmacogn Rev* 9: 29–34.

9. Kaur DC, Chate SS (2015) Study of antibiotic resistance pattern in methicillin-resistant *Staphylococcus aureus* with special reference to newer antibiotic. *J Global Infect Dis* 7: 78–84.

10. Arunkumar V, Prabagaravarthan R, Bhaskar M (2017) Prevalence of Methicillin-resistant *Staphylococcus aureus* (MRSA) infections among patients admitted in critical care units in a tertiary care hospital. *Int J Res Med Sci* 5: 2362–2366.

11. McGuinness WA, Malachowa N, DeLeo FR (2017) Vancomycin Resistance in *Staphylococcus aureus*. *Yale J Biol Med* 90: 269–281.

12. Subramani R, Narayanasumy M, Feussner KD (2017) Plant-derived antimicrobials to fight against multidrug-resistant human pathogens. *3 Biotech* 7: 172.

13. Conly JM, Johnston BL (2002) Vancomycin–intermediate *Staphylococcus aureus*, hetero-vancomycin–intermediate *Staphylococcus aureus* and vancomycin-resistant *Staphylococcus aureus*: The end of the vancomycin era? *Pulsus: The Canadian J Infect Dis* 13: 282–284.

14. Taiwo SS (2011) Antibiotic-resistant bugs in the 21st century: A public health challenge. *World J Clin Infect Dis* 30: 11–16.

15. Onemu OS, Ophori EA (2013) Prevalence of multidrug-resistant *Staphylococcus aureus* in clinical specimens obtained from patients attending the University of Benin Teaching Hospital, Benin City, Nigeria. *J Nat Sci Res* 3: 154–159.

16. Kobayashi SD, Malachowa N, DeLeo FR (2015) Pathogenesis of *Staphylococcus aureus* abscesses. *Am J Pathol* 185: 1518–1527.

17. Kong C, Neoh H, Nathan S (2016) Targeting *Staphylococcus aureus* toxins: A potential form of anti-virulence therapy. *Toxins (Basel)* 8: 72.

18. Weinstein RA, Fridkin SK (2001) Vancomycin–intermediate and –resistant *Staphylococcus aureus*: What the infectious disease specialist needs to know. *Clin Infect Dis* 32:108–115.

19. Appelbaum PC (2006) The emergence of vancomycin–intermediate and vancomycin-resistant *Staphylococcus aureus*. *Clin Microbiol Infect* 12: 16–23.

20. Loomba PS, Taneja J, Mishra B (2010) Methicillin- and Vancomycin-resistant *Staphylococcus aureus* in hospitalized patients. *J Global Infect Dis* 2: 275–283.

21. Pinho MG, Filipe SR, De Lencastre H, et al. (2001) Complementation of the essential peptidoglycan transpeptidase function of penicillin-binding protein 2 (PBP2) by the drug resistance protein PBP2A in *Staphylococcus aureus*. *J Bacteriol* 183: 6525–6531.
22. Lee JH (2003) Methicillin (Oxacillin)- resistant Staphylococcus aureus strains isolated from major food animals and their potential transmission to humans. *Appl Environ Microbiol* 69: 6489–6494.

23. Harkins CP, Pichon B, Doumith M, et al. (2017) Methicillin-resistant Staphylococcus aureus (MRSA) emerged long before the introduction of methicillin into clinical practice. *Genome Biol* 18: 130.

24. Johnson AP (2011) Methicillin-resistant Staphylococcus aureus (MRSA): The European landscape. *J Antimicrob Chemother* 66: 43–48.

25. Okwu M, Bamgbala S, Aborisade W (2012) Prevalence of nasal carriage of Community-associated Methicillin-resistant Staphylococcus aureus among healthy primary school children in Okada, Nigeria. *J Nat Sci Res* 2: 61–65.

26. Adhikari R, Pant ND, Neupane S, et al. (2017) Detection of Methicillin-resistant Staphylococcus aureus (MRSA) and determination of Minimum Inhibitory Concentration (MIC) of vancomycin for S. aureus isolated from pus/wound swab samples of the patients attending a tertiary care hospital in Kathmandu, Nepal. *Can J Infect Dis Med Microbiol* 2017: 2191532.

27. Rodríguez-Noriega E, Seas C, Guzmán-Blanco M, et al. (2010) Evolution of methicillin-resistant Staphylococcus aureus in Latin America. *Int J Infect Dis* 14: 7.

28. Otto M (2017) Next-generation sequencing to monitor the spread of antimicrobial resistance. *Genome Med* 9: 68.

29. Sit PS, Teh CS, Idris N, et al. (2017) Prevalence of Methicillin-resistant Staphylococcus aureus (MRSA) infection and the molecular characteristics of MRSA bacteremia over a two-year period in a tertiary teaching hospital in Malaysia. *BMC Infect Dis* 17: 274.

30. Milheiroço C, Oliveira DC, deLencastre H (2007) Update to the multiplex polymerase chain reaction strategy for assignment of mec element types in Staphylococcus aureus. *Antimicrob Agents Chemother* 51: 3374–3377.

31. Okwu MU, Mitsan O, Oladeinde B, et al. (2016) Staphylococcal cassette chromosome mec (SCCmec) typing of methicillin-resistant staphylococci obtained from clinical samples in south-south, Nigeria. *World J Pharm Pharmaceut Sci* 5: 91–103.

32. Amirkhiz MF, Rezaee MA, Hasani A, et al. (2015) Staphylococcal cassette chromosome typing of Methicillin-resistant Staphylococcus aureus (MRSA): An eight year experience. *Arch Pediar Infect Dis* 3: e30632.

33. Rodvold KA, McConeghy KW (2014) Methicillin-resistant Staphylococcus aureus therapy: Past, present and future. *Clin Infect Dis* 58: S20–S27.

34. Clinical and Laboratory Standards Institute (2006) Performance standards for antimicrobial susceptibility testing, CLSI approved standard M100-S16, Wayne, PA.

35. Tenover FC, Robert C, Moellering RC (2007) The rationale for revising the Clinical and Laboratory Standards Institute vancomycin minimal inhibitory concentration interpretive criteria for Staphylococcus aureus. *Clin Infect Dis* 44:1208–1215.

36. Howden BP, Davies JK, Paul DR, et al. (2010) Reduced vancomycin susceptibility in Staphylococcus aureus including vancomycin-intermediate and heterogeneous vancomycin-intermediate strains: Resistance mechanisms, laboratory detection and clinical implications. *Clin Microbiol Rev* 23: 99–139.

37. Dhanalashmi TA, Umapathy BL, Mohan DR (2010) Prevalence of methicillin, vancomycin and multidrug resistance among Staphylococcus aureus. *J Clin Diagn Res* 6: 974–977.
38. Fridkin SK (2001) Vancomycin-intermediate and resistant Staphylococcus aureus. What infectious disease specialists need to know. *Clin Infect Dis* 32: 108–115.

39. Appelbaum PC (2007) Reduced glycopeptides susceptibility in Methicillin-resistant Staphylococcus aureus (MRSA). *Int J Antimicrob Agents* 30: 398–408.

40. Hiramatsu K, Hanaki H, Ino T, et al. (1997) Methicillin-resistant Staphylococcus aureus (MRSA) clinical strain with reduced vancomycin susceptibility. *J Antimicrob Chemother* 40: 135–136.

41. Gardete S, Tomasz A (2014) Mechanisms of vancomycin resistance in Staphylococcus aureus. *J Clin Invest* 124: 2836–2840.

42. National Committee for Clinical Laboratory Standards (NCCLS) (2007) Performance standards for antimicrobial susceptibility testing; 15th Informational supplement M100-S15, NCCLS Wayne, PA.

43. National Committee for Clinical Laboratory Standards (NCCLS) (2007) Methods for antimicrobial susceptibility tests for bacteria that grow aerobically; 5th ed. Approved standards, M7-A5, NCCLS Wayne, PA.

44. Centre for Disease Control and Prevention (CDC) (2002) Staphylococcus aureus resistant to vancomycin- United States. *Morb Mortal Weekly Rep (MMWR)* 51: 565–567.

45. Chang S, Sievert DM, Hageman JC, et al. (2003) Infection with vancomycin-resistant Staphylococcus aureus containing the van A resistance gene. *N Engl J Med* 348: 1342–1347.

46. Okwu MU, Okorie TG, Mitsan O, et al. (2014) Prevalence and comparison of three methods for detection of Methicillin-resistant Staphylococcus aureus (MRSA) isolates in tertiary health institutions in Nigeria. *Can Open Biol Sci* 1: 1–12.

47. Ravensbergen SJ, Berends M, Stienstra Y, et al. (2017) High prevalence of Methicillin-resistant Staphylococcus aureus (MRSA) and ESBL among asylum seekers in the Netherlands. *PLoS One* 12: e0176481.

48. Stefani S, Chung DR, Lindsay JA, et al. (2012) Methicillin-resistant Staphylococcus aureus (MRSA): Global epidemiology and harmonisation of typing methods. *Int J Antimicrob Agents* 39: 273–282.

49. Vaez H, Tabaraei A, Moradi A, et al. (2011) Evaluation of methicillin resistance Staphylococcus aureus isolated from patients in Golestan province north of Iran. *Afri J Microbiol Res* 5: 432–436.

50. Akanbi BO, Mbe JU (2013) Occurrence of methicillin- and vancomycin-resistant Staphylococcus aureus in University of Abuja Teaching Hospital, Abuja, Nigeria. *Afri J Clin Exper Microbiol* 14: 10–13.

51. Goud R, Gupta S, Neogi U, et al. (2011) Community prevalence of methicillin- and vancomycin-resistant Staphylococcus aureus in and around Bangalore, southern India. *Rev Soc Bras Med Trop* 44: 309–312.

52. Alo M, Ugah U, Okoro N (2013) Epidemiology of vancomycin-resistant Staphylococcus aureus among clinical isolates in a tertiary hospital in Abakaliki, Nigeria. *Amer J Epidemiol Infect Dis* 1: 24–26.

53. Abdallah EM (2016) Medicinal plants as an alternative drug against Methicillin-resistant Staphylococcus aureus (MRSA). *Int J Microbiol Allied Sci* 3: 35–42.

54. Mahady GB (2005) Medicinal plants for the prevention and treatment of bacterial infections. *Curr Pharmaceu Design* 11: 2405–2427.
55. Voravuthikunchai SP, Kitpipit L (2005) Activity of medicinal plant extracts against hospital isolates of Methicillin-resistant Staphylococcus aureus (MRSA). *Clin Microb Infect* 11: 493–512.

56. Invasive Species Compendium- CABI (2018) Available from: https://www.cabi.org/isc/datasheet/2184.

57. Invasive Species Compendium- CABI (2018) Available from: https://www.cabi.org/isc/datasheet/24882.

58. Invasive Species Compendium- CABI (2018) Available from: https://www.cabi.org/isc/datasheet/28765.

59. Invasive Species Compendium- CABI (2018) Available from: https://www.cabi.org/isc/datasheet/39510.

60. Invasive Species Compendium- CABI (2018) Available from: https://www.cabi.org/isc/datasheet/45141.

61. United States Department of Agriculture (USDA) (2018) National resources conservation service. Available from: https://plants.usda.gov/core/profile?symbol=PUGR2.

62. Globinmed (2018) Available from: https://www.globinmed.com/index.php?option.

63. Arefin K, Rahman M, Uddin MZ, et al. (2011) Angiosperm flora of Satchari Natural Park, Habiganj, Bangladesh. *Bangl J Plan Taxon* 18: 117–140.

64. Al-Alusin NT, Kadir FA, Ismali S, et al. (2010) In vitro interaction of combined plants: Tinospora crispa and Swietenia mahagoni against Methicillin-resistant Staphylococcus aureus (MRSA). *Afri J Microbiol Res* 4: 2309–2312.

65. Sahu MC, Padhy RN (2013) In vitro antibacterial potency of Butea monosperma Lam. against twelve clinically isolated multidrug resistant bacteria. *Asian Pac J Trop Dis* 3: 217–226.

66. Gomber C, Saxena S (2006) Anti-staphylococcal potential of Callistemon rigidus. *Centr Euro J Med* 2: 79–88.

67. Aliyu AB, Musa AM, Abdullahi MS, et al. (2008) Activity of plant extracts used in Northern Nigerian traditional medicine against Methicillin-resistant Staphylococcus aureus (MRSA). *Nig J Pharmaceu Sci* 7: 1–8.

68. Akinjogunla OJ, Yah CS, Eghafona NO (2010) Antibacterial activity of the leave extracts of Nymphaea lotus (Nymphaeaceae) on Methicillin-resistant Staphylococcus aureus and Vancomycin-resistant S. aureus isolated from clinical samples. *Annals Biol Res* 1: 174–184.

69. Wikaningtyas P, Sukandar EY (2016) The antibacterial activity of selected plants towards resistant bacteria isolated from clinical specimens. *Asian Pac J Trop Biomed* 6: 16–19.

70. Zuo GY, Zhang XJ, Yang CX, et al. (2012) Evaluation of traditional Chinese medicinal plants for anti-MRSA activity with reference to the treatment record of infectious diseases. *Molecules* 17: 2955–2967.

71. Heyman HM, Hussein AA, Meyer JJ, et al. (2009) Antibacterial activity of South African medicinal plants against Methicillin-resistant Staphylococcus aureus (MRSA). *Pharmaceu Biol* 47: 67–71.

72. Uddin Q, Samiulla L, Singh VK, et al. (2012) Phytochemical and pharmacological profile of Withania somnifera Dunal: A review. *J Appl Pharmaceu Sci* 2: 170–175.

73. Nefzi A, Abdallah RA, Jahnoun-Khiareddine H, et al. (2016) Antifungal activity of aqueous and organic extracts from Withania somnifera L. against Fusarium oxysporium f. sp. radicis-lycopersia. *J Microb Biochem Tech* 8: 144–150.

74. Sucilathangam G, Gomatheswari SN, Velvizhi G, et al. (2012) Detection of antibacterial activity of medicinal plant Quercus infectoria against methicillin-resistant Staphylococcus aureus (MRSA) isolates in clinical samples. *J Pharmaceu Biomed Sci* 14: 8.
75. Imelouane B, Amhamdi H, Wathelet JP, et al. (2009) Chemical composition and antimicrobial activity of essential oil of thyme (Thymus vulgaris) from Eastern Morocco. *Int J Agric Biol* 11: 205–208.

76. Armas JR, Quiroz JR, Roman RA, et al. (2016) Antibacterial activities of essential oils from three medicinal plants in combination with EDTA against MRSA. *British Microbiol Res J* 17: 1–10.

77. Anyanwu MU, Okoye RC (2017) Antimicrobial activity of Nigerian medicinal plants. *J Intercul Ethnopharmacol* 6: 240–259.

78. Abouzeed YM, Elkahem A, Zgheel F (2013) Antibacterial in-vitro activities of selected medicinal plants against methicillin-resistant Staphylococcus aureus (MRSA) from Libyan environment. *J Environ Anal Toxicol* 3: 194.

79. Van Vuuren SF (2008) Antimicrobial activity of South African medicinal plants. *J Ethnopharmacol* 119: 462–472.

80. Lapornik B, Prosek M, Wondra AG (2005) Comparison extracts prepared from plant by-products using different solvents and extraction time. *J Food Eng* 71: 214–222.

81. Tiwari P, Kumar B, Kaur M, et al. (2011) Phytochemical screening and extraction: A review. *Int Pharmaceu Sci* 1: 98–106.

82. Singh KN, Lal B (2011) Notes on traditional uses of Khair (Acacia catechu Willd.) by inhabitants of Shivalik Range in Western Himalaya. *Ethnobot Leafl* 10: 109–112.

83. Lakshmi T, Aravind Kumar S (2011) Preliminary phytochemical analysis and in vitro antibacterial activity of Acacia catechu Willd bark against Streptococcus mitis, S. sanguis and Lactobacillus acidophilus. *Int J Phyomed* 3: 579–584.

84. Obolskiy D, Pischel I, Siriwasanatametanon N, et al. (2009) A phytochemical and pharmacological review. *Phytother Res* 23: 1047–1065.

85. Karim AA, Azlan A (2012) Fruit pod extracts as a source of nutraceuticals and pharmaceuticals. *Molecules* 17: 11931–11946.

86. Shah KN, Verma P, Suhagia B (2017) A phyto-pharmacological overview on jewel weed. *J Appl Pharmaceu Sci* 7: 246–252.

87. Jash SK, Singh RK, Majhi S, et al. (2013) Peltophorum pterocarpium: Chemical and pharmacological aspects. *Int J Pharmaceu Sci Res* 5: 26–36.

88. Joseph L, George M, Singh G, et al. (2016) Phytochemical investigation on various parts of Psidium guajava. *Annals Plant Sci* 52: 1265–1268.

89. Satheesh KB, Suchetha KN, Vadisha SB, et al. (2012) Preliminary phytochemical screening of various extracts of Punica granatum peel, whole fruit and seeds. *Nitte Univer J Healt Sci* 2: 34–38.

90. Taniguchi S, Kuroda K, Doi K, et al. (2007) Revised structures of gambiriins A1, A2, B1, and B2 chalconeflavan dimmers from gambir (Uncaria gambir extract). *Chem Pharm Bull* 55: 268–272.

91. Amir M, Mujeeb M, Khan A, et al. (2012) Phytochemical analysis and in vitro antioxidant activity of Uncaria gambir. *Int Green Pharma* 6: 67–72.

92. Li H, Tang GH, Yu Z, et al. (2013) A new carotene sesquiterpene from Walsura robusta. *Chin J Nat Med* 11: 84–86.
93. Quattrochi U (2014) Common names, scientific names, eponyms, synonyms and etymology. In: Taylor and Francis Group, CRC World dictionary of medicinal and poisonous plants, New York: CRC Press, 3938.
94. Bhurat MR, Bavaskar SR, Agrawal AD, et al. (2011) Swietenia mahogany Linn- A phytopharmacological review. *Asian J Pharmaceut* 1: 1–4.
95. Danga YS, Esimone CO, Nukenine EN (2014) Larvicidal and phytochemical properties of Callistemon rigidus R. Br. (Myrtaceae) leaf solvent extract against three vector mosquitoes. *J Vector Borne Dis* 51: 216–223.
96. Almahy HA, Nasir OD (2011) Phytochemical and mineral content of the leaves of four Sudanese Acacia species. *J Stored Prod Posthar Res* 2: 221–226.
97. Oyetayo VO (2007) Comparative studies of the phytochemical and antimicrobial properties of the leaf, stem and tuber of Ankanomases diffimos. *J Pharmcol Toxicol* 2: 407–410.
98. Osuntokun OT (2015) Bioactivity and phytochemical screening of Nigerian medicinal plants growing in Ondo and Ekiti states against bacterial isolates from paediatrics hospital. *J Advan Med Pharmaceut Sci* 4: 1–14.
99. Thakur GS, Bag M, Samodiya BS, et al. (2009) Momordica balsamina: A medicinal and neutraceutical plant for health care management. *Curr Pharmaceut Biotech* 10: 667–682.
100. Afolayan AJ, Sharaibi OJ, Kazeem MI (2013) Phytochemical analysis and in vitro antioxidant activity of *Nymphaea* lotus L. *Int J Pharmaco* 9: 297–304.
101. Bello IA, Ndukwe GI, Audu OT, et al. (2011) A bioactive flavonoid from *Pavetta crassipes* K. Schum. *Org Med Chem Lett* 1: 14.
102. Bariweni MW, Ozolua RI (2017) Neuropharmacological effects of the aqueous leaf extract and fractions of *Pavetta crassipes* (K. Schum.) Rubiaceae in mice. *J Pharm Pharmacog Res* 5: 278–287.
103. Patel JR, Tripathi P, Sharma V, et al. (2011) Phyllenthus amarus: Ethnomedicinal uses, phytochemistry and pharmacology: A review. *J Ethnopharmacol* 138: 286–313.
104. Aliyu AB, Musa AM, Abdullahi MS, et al. (2011) Phytochemical screening and antibacterial activities of *Vernonia ambiguia*, V. Blumeoides and V. oceephala (Asteraceae). *Acta Pol Pharm* 68: 67–73.
105. Halim MR, Tan MS, Ismail S, et al. (2012) Standardization and phytochemical studies of *Curcuma xanthorrhiza* Roxb. *Int J Pharm Pharmaceu Sci* 4: 606–610.
106. Salleh NA, Ismail S, Abhalim MR (2016) Effects of *Curcuma xanthorrhiza* extracts and their constituents on phase II drug-metabolizing enzymes activity. *Pharmacog Res* 8: 309–315.
107. Chahyadi A, Hartati R, Wirasutisna K, et al. (2014) Boesenbergia pandurata Roxb., an Indonesian medicinal plant: Phytochemistry, biological activity, plant biotechnology. *Proc Chem* 13: 13–37.
108. Yadnya-Putra AA, Chahyadi A, Elfishmi (2014) Production of panduratin A, cardamomin and sitosterol using cell cultures of Fingerrot (Boesenbergia pandurata (Roxb.) Schlechter). *Biosci Biotech Res Asia* 11: 43–52.
109. Adelowo F, Olateji O (2017) An overview of the phytochemical analysis of bioactive compounds in *Senna alata*. *Amer J Biochem Eng* 2: 7–14.
110. Mabona U, Van Vuuren SF (2013) Southern African medicinal plants used to treat skin diseases. *South Afri J Bot* 87: 175–193.
111. Kelmanson JE, Jäger AK, van Staden J (2000) Zulu medicinal plants with antibacterial activity. *J Ethnopharmacol* 69: 241–246.

112. Yakov F (2006) In vitro 5-lipoxygenase and antioxidant activities of South African medicinal plants commonly used topically for skin diseases, (thesis). Johannesburg: University of Witwatersrand, Faculty of Health Sciences.

113. Omosa LK, Amugune B, Ndunda B, et al. (2014) Antimicrobial flavonoids and diterpenoids from Dodonaea angustifolia. *South Afri J Bot* 91: 58–62.

114. Vaidya V, Mahendrakumar CB, Bhise K (2013) Preliminary phytochemical screening of Quercus infectoria Oliv. for treatment of skin diseases. *J Med Plants Res* 7: 2019–2027.

115. Shrestha S, Kaushik VS, Eshwarappa RS, et al. (2014) Pharmacognostic studies of insect gall of Quercus infectoria Olivier (Fagaceae). *Asian Pac J Trop Biomed* 4: 35–39.

116. Magbool FA, Elnima EI, Shayoub ME, et al. (2018) Preliminary phytochemical screening of Quercus infectoria galls. *World J Pharm Pharmaceut Sci* 7: 77–87.

117. Nema SS, Tohamy MA, El-Banna HA, et al. (2015) Phytochemical and pharmacological studies of ethanolic extract of Thymus vulgaris. *World J Pharm Pharmaceut Sci* 4: 1988–2001.

118. Chew YL, Chan EW, Tan PL, et al. (2011) Assessment of phytochemical content, polyphenolic composition, antioxidant and antibacterial activities of leguminosae medicinal plants in Peninsular Malaysia. *BMC Compl Altern Med* 11: 12.

119. Cowan MM (1999) Plant products as antimicrobial agents. *Clin Microbiol Rev* 12: 564–582.

120. Eze C, Iroha IR, Eluu SC, et al. (2017) Comparative studies on the antibacterial activities of leaf extracts of Azadirachta indica and Psidium guajava and antibiotics on methicillin- and vancomycin-resistant Staphylococcus aureus. *Pharmaceu Biol Eval* 4: 155–161.

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