RESEARCH ARTICLE

NATURAL PRODUCTS AND TRADITIONAL MEDICINES FOR THE TREATMENT OF MULTIDRUG RESISTANT BACTERIA

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Abstract:

Multidrug resistant microorganisms (MDROs) have been responsible for numerous outbreaks of infectious epidemics, and pose a serious threat to global health. The lack of effective therapies for MDROs, coupled with a reduced number of antimicrobial drugs in the pharmaceutical pipeline to treat these infections, demonstrates the urgent need for research in this area. Of the resistant Gram-positive bacteria, methicillin-resistant *Staphylococcus aureus* (MRSA), multidrug-resistant *Pseudomonas aeruginosa* and multidrug-resistant tuberculosis (MDR-TB) continue to be the most problematic, however, reports of vancomycin-resistant *Staphylococcus aureus* (VRSA) infections are also increasing. For highly-resistant Gram-negative bacteria, vancomycin-resistant Enterococci (VRE), multidrug-resistant (MDR) carbapenemase-producing *Klebsiella pneumoniae* and MDR-*Acinetobacter baumannii* are most important, as these bacteria are often only susceptible to older antimicrobial agents, such as the polymyxins that have a higher adverse event profile. Taken together, these data demonstrate that there is an urgent need for new antibiotics and combinations of drugs to treat emerging MDR bacteria. Due to the lack of interest of pharmaceutical companies in the research and development of new antibiotics, research in the field of natural products has increased. Thus, there is an increasing body of scientific evidence suggesting that specific marine, fungal and medicinal plant extracts, as well as traditional medicine formulas and pure compounds are active against specific MDR-bacteria. Where active, these natural products should be further investigated for possible development as clinical agents. This review focuses on recently published data for natural products active against MDR bacteria and evaluates some of the in vitro data.

Key words: *Acinetobacter*, antibiotics, antimicrobial, botanicals, eathnomedicine, medicinal plants, methicillin-resistant *Staphylococcus aureus*, natural products, marine, multidrug resistant organisms, traditional medicine, Vancomycin-resistant Enterococci, *Klebsiella*

1.0 Introduction

The global emergence of multiple drug resistant pathogenic organisms (MDROs) continues to be a serious public health threat due to the lack of effective antimicrobial agents for treatment, and a paucity of new antibiotics in the pharmaceutical pipeline.[1-3] Globally, the increase in MDR infections has caused millions of deaths annually, with > 1M deaths annually due to resistant *Shigella* and *Mycobacterium tuberculosis.*[3] In the United States, MDR bacteria are responsible for > 23,000 deaths and ~ 2M life-threating infections annually, of which resistant *Clostridium difficile*, Enterobacter species, and *Neisseria gonorrhoeae* are now considered "urgent threats".[4-5] For example, *C. difficile* infections may cause life-threatening diarrhea in hospitalized patients, who have been recently treated with antibiotics.[4] In 2015, the Centers for Disease Control (CDC) reported that *C. difficile* was responsible for as many as 500,000 infections in the USA in a single year, causing ~15,000 deaths.[5] The CDC predicts that these numbers will continue to increase as the list of resistant bacteria continues to grow with *Staphylococcus aureus* resistance to methicillin and vancomycin, multidrug-resistant *Klebsiella pneumoniae*, vancomycin-resistant Enterococcus (VRE), as well as resistant *Pseudomonas aeruginosa*, *Acinetobacter baumannii* and *Mycobacterium tuberculosis*, all in need of more effective therapies. Thus, there is an urgent need for the research and development of new antimicrobial agents, and combinations of drugs, to treat these life-threatening infections.

1.1 Lack of interest in developing new antimicrobial agents

With so many drug resistant bacteria causing significant morbidity and mortality worldwide it is difficult to understand the lack of interest on the part of pharmaceutical companies to develop new antibiotics. Since 2004, < 2% of all new clinical drugs developed were antibiotics.[6] The reasons for the lack of interest in the research and development of new antibiotics appears to be economic. Antibiotics are less profitability than drugs used to treat chronic ailments; prescribing habits suggest that newer antibiotics would only be prescribed for resistant infections, thereby limiting initial investment returns; and the development of generics is always an issue.[2,6] Increased governmental regulation, economics and scientific challenges have also not been conducive to the development of new antibiotics.[2] Unfortunately, the bottom line is that new antibiotics, although they are critical to overall public health and welfare, are just not as lucrative of an investment when compared with other drugs. Thus, for the past 20 years only a few companies including, AstraZeneca, GlaxoSmithKline, Merck, Johnson & Johnson, and Pfizer/Wyeth have developed new antibiotics past the phase 1 clinical trial stage.[6] Interestingly, there has never been a successfully researched and developed antibiotic by any government agency, including the National Institutes of Health.[6] Thus, instead of the big Pharma taking the lead in this critical and seriously complicated issue, much of the development is being performed by small pharmaceutical and biotech companies, and academic institutions, with the exception of Japan, where the large pharmaceutical companies still play a central role in antibiotic development.[6] Therefore, there are plenty of opportunities for researchers interested in this topic to be involved at the academic level, as much of the scientific research on natural products is being performed in academic institutions.

1.2 Natural Products for the treatment of Multidrug Resistant Organisms

Plants, animal and marine natural products have always played a role in traditional medicine for millennia, and have made significant contributions to human health.[7-10] Man has used natural products derived from plants, marine organisms, fungi, animals and minerals to treat all diseases, including infectious diseases.[7-10] Review of the scientific and medical literature suggests that there are thousands of published papers describing the antimicrobial effects of bacteria, plant extracts, marine and fungal organisms. Data from the PubMed, Google Scholar and the Napralert databases (data from 1975 to 2017) suggest that there are as many as 68,000 reports describing the antimicrobial effects of natural products, and > 2000 reviews on the subject, including reviews on Actinomycetes, medicinal plants, marine products, fungi as antibacterial agents.[11-12] In terms of MDR organisms, there are almost 5000 reports in PubMed alone concerning the effects of natural products on a wide range of MDR organisms. The primary focus of these invesigations has been determining the in vitro antibacterial activities against methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-intermediate and resistant *S. aureus* (VISA and

VRSA), *Klebsiella pneumoniae*, vancomycin-resistant Enterococcus (VRE), as well as resistant *Pseudomonas aeruginosa* and *Mycobacterium* species.[13-19] For example, a recent review of plants used in traditional medicine from India suggests that there are ~120 plant families, and as many as 130,000 different plant species with medicinal effects, including activities against bacterial infections.[17] Many of these plant species have at least in vitro activity against MRSA, including *Acorus calamus, Lawsonia inermis, Hemidesmus indicus, Holarrhena antidysenterica, Punica granatum, Plumbago zeylanica, Camellia sinensis, Delonix regia, Terminalia chebula, Emblica officinalis* and *Terminalia belerica*.[17] However, one of the primary stumbling blocks to the progression of this research remains the same as it was almost 10 years ago, there is still a significant lack of rigorous animal studies or controlled clinical trials for naturally occurring antibiotics.[7,9] In addition, the methods used in many in vitro publications are not standardized, or are using old methods such as "zone of inhibition" instead of validated minimum inhibitory concentrations (MICs) and/or minimum bactericidal concentrations (MBCs). Other issues include high "active" concentrations at which natural products show efficacy, many at supra-physiological concentrations, that would not likely result in activity in vivo. This view will focus on the more recent data describing the in vitro of natural products as potential antibacterial agents for antibiotic resistant bacteria, including MRSA, VRSA, VRE, *Klebsiella*, *Pseudomonas* and *Mycobacterium* ssp. We will highlight some of the plants, fungi and marine organisms that have been recently tested and have in vitro activity against MDROs, that may be potential candidates for research and development as new drugs for the treatment of MDR bacteria.

2.0 Methicillin Resistant *Staphylococcus aureus* (MRSA)

Drug resistance of MRSA continues to be problematic worldwide, and is a serious threat even in community settings.[20] MRSA infections are commonly observed in skin, soft tissue, bone, joints, and in patients with indwelling catheters or prosthetic devices. Patients with MRSA tend to have poorer clinical outcomes than patients infected with methicillin-sensitive *S. aureus* strains. Serious MRSA infectious may lead to serious, life threating infective endocarditis (IE), septic arthritis, and osteomyelitis. Complications of these infections such as sepsis and septic resistance to first-line drugs are common in healthcare facilities and community clinics.[20] It has been suggested that patients presenting with MRSA infections are ~64% more likely to die than those with infections caused by methicillin susceptible *S. aureus*.[20] We have previously reported on numerous plant species also having in vitro effects against MRSA.[7,9] More recent data on some of the plant, marine and fungal species, as well as naturally occurring compounds that are active against MRSA are detailed in Tables 1 and 2.

TABLE 1. Plant and marine organisms and purified compounds with activity against methicillin-resistant Staphylococcus aureus (MRSA).

Organism/compound	Family	Extract/compounds	MIC/MBC	Reference
Alstonia boonei	Apocynaceae	Leaf, bark/Echitamine, echitamidine, voacangine, akuammidine, N- α-formylechitamidine, N- α-formyl-12-methoxyechitamidine	128 µg/mL	21, 22
Benzylisoquinolone alkaloids	Various	Tetrandrine and demethyltetrandrine	64-128/256-1024 µg/mL	23
Berberine	Various	N/A	32-128/64-256 µg/mL	24
Bobgunnia madagascariensis		Methanol	23-47 µg/mL	25
Caesalpinia sappan	Leguminosae	Protosappanins A and B	64 (PsA) and 128 (PsB) mg/L	26
Cassia obtusifolia	Fabaceae	Whole plant extract	64 µg/mL	22
Cinnamomum altissimum and Cinnamomum impressicostatum	Lauraceae	Aqueous	19.5/39 µg /mL	27
Cissus populnea	Vitaceae	Methanol	94-375 µg /mL	25
Curcuma longa/curcumin	Cucurbitaceae	Ethyl acetate/curcumin	0.125-2 mg/mL	28
Cynodon dactylon	Poaceae	Chloroform	63 µg/mL	10
Cytisus striatus	Fabaceae	Ethyl acetate/isoflavones	1 mg/mL	29
Erythrina senegalensis		Methanol	12-23 µg/mL	25
***Hypericum japonicum/* Isojacareubin**	Hyperiaceae	80% ethanol/ isojacareubin	4-16 /16-64 µg/mL	30
Juncus inflexus	Juncaceae	Jinflexin B, juncusol, juncuenin D, and dehydrojuncuenin B	12.5-100 µg/mL	31
Lannea acida	Anacardiaceae	Methanol	94-1500 µg/mL	25
Magnolia officinalis/ Magnolol/honokiol	Magnoliaceae	Magnolol/honokiol	16-64 mg/mL	32
Nuphar japonicum	Nymphaeaceae	Dried rhizomes/6,6′-dihydroxythiobinupharidine	1–4 µg/mL	33
Paullinia pinnata	Sapindaceae	Stem Extract	64 µg/mL	34
Penicillium radicum FKI-3765-2	Trichocomaceae	Rugulosin A -C	0.125-64 µg/mL	35
Piper betle	Piperaceae	Leaves/Ethanol	78-156 µg/mL	36
Piper sarmentosum	Piperaceae	Alcohol	50/100 mg/ml	37
***Plagiochasma intermedium, Reboulia hemisphaerica/*ricardin C**	Aytoniaceae	Ricardin C	4-8 mg/mL	38
Premna resinosa	Lamiaceae	Dichloromethane	31.25 µg /mL	39
Rotheca myricoides [syn. Clerodendrum myricoides]	Lamiaceae	Methanol	31.25 µg /mL	40
Salvia miltiorrhiza	Lamiaceae	TCM	128-256 mg/L	41
Tabernaemontana alternifolia	Apocynaceae	Aqueous	600-800 µg/ml.	42
Tetradium rutacarpa/evocarpine	Rutaceae	Evocarpine	8-128 µg/mL	43
Tieghemella heckelii	Sapotaceae	Aqueous, ethanol, ethyl acetate,	45-97 µg/mL	44

		ethanol,		
Talaromyces wortmannii	Asphodeloideae	Flavomannin/talaromannin/emodin/skyrin	2-16 µg/mL	45
Tetradium ruticarpum/evocarpine	Rutaceae	Evocarpine	8-128 µg/mL	43
Tripterygium wilfordii	Celastraceae	Tripteryols B (±)-5,4'-dihydroxy-2'-methoxy-6',6″-dimethypyraro-(2″,3″:7,8)-6-methyflavanone, ((2S)-5,7,4'-trihydroxy-2'-methoxy-8,5'-di(3-methyl-2-butenyl)-6-methylflavanone.	2.95-8.59 µg/mL 1.06-2.60 µg/mL	46
Urtica dioica	Urticaceae	Butanol	16.33 mg/mL	47
Waltheria lanceolata	Sterculiaceae	Methanol	47-188 µg/mL	25
***Zanthoxylum nitidum*/coumarins**	Rutaceae	Coumarins	8-64 µg/mL	48

EO = essential oil
TCM = Traditional Chinese medicine

Table 2. Marine organisms and naturally occurring compounds with activity against MRSA and

Marine organisms	Extract/compounds	Concentration	Reference
Actinomycete NPS8920	Lipoxazolidinones A -C	1–2 µg/mL	49
***Alteromonas rava* SANK 73390**	Thiomarinols A-G	< 0.01 µg/mL	50
Bacillus sp.	Bogorol A	2-10 µg/mL	51
Bacillus sp. MK-PNG-276A	Loloatins A-D	0.5–8 µg/mL	52
Marinispora sp.	Marinomycins A, B and D	0.13-0.25 µM	52
Marinispora species NPS12745	Lynamicins A - E	1–3 µg/mL	53
Pestalotia sp. strain CNL-365	Pestalone	37 ng/mL	54
Pseudomonas sp. F92S91	Alpha-pyrones	2–4 µg/mL	55
Pseudomonas sp. strain AMSN	2,4-diacetylphloroglucinol	1–8 µg/mL	56
***Pseudomonas fluorescens* NCIMB 10586**	Pseudomonic acids A and C	NS	57
***Pseudoalteromonas phenolica* O-BC30**	Phenolics	1–4 µg/mL	58
Streptomyces sp. CNQ-418	Marinopyrroles A and B	<0.2 µM	59
Streptomyces strain, AM045	Actinomycin V	0.1~0.4 µg/mL	60
Streptomyces sp. HKI0381	Abyssomicin E	NS	61
***Streptomyces platensis* TP-A0598**	TPU-0037-A - D	3–13 µg/mL	62
Streptomyces lydicus	Lydicamycin	6 µg/mL	63
Streptomyces strain N1-78-1	BE-43472 A -D	0.11–0.45 µM	64, 65
Verrucosispora AB-18-032	Abyssomicin C	4–13 µg/mL	66, 67

While many of these plant, marine, and fungi species have weak activity against MRSA as determined by MICs above 25 µg/mL, a few species stand out, having MICs below 10 µg/mL. For example, extracts from the fungus, *Penicillium radicum* FKI-3765-2, and its active metabolite Rugulosin A (MIC 0.125 µg/ml); the aquatic plant, *Nuphar japonicum* extracts and the isolated active constituent 6,6′-dihydroxythiobinupharidine (MIC range 1-4 µg/ml); *Hypericum japonicum*, and its active chemical constituent isojacareubin (MIC range 4-16 µg/ml); *Talaromyces wortmannii* and its active constituent flavomannin (MIC 2 µg/ml); and *Tripterygium wilfordii* and its active chemical constituent tripteryol B (MIC range 1-8 µg/ml) all have good activity

against various MRSA strains (Table 1). In addition, to many plant and fungal species, there are more than 3,000 naturally occurring compounds isolated and identified from marine organisms, some with exceptional MRSA activities (Table 2). Compounds derived from marine actinomycetes are especially prevalent. However, it has been suggested that the recovery of microorganisms from the ocean may not mean that the organism is 'marine', as some organisms may be wash-in components from the terrestrial environment.[68] None the less, the marine environment contains novel microflora that remain a comparatively untapped resource for antimicrobial chemical constituents.[68] For an in-depth review of marine natural products with antibiotic activities against MRSA, see the excellent review published by Rahman and co-workers.[68] The organisms listed in Tables 1 and 2 are just some of the examples of hundreds of naturally occurring organisms and purified compounds, many with excellent activity against MRSA. These and many more represent examples of naturally occurring compounds that may also be potential candidates for research and development as clinical anti-MRSA agents.

2.2 Vancomycin Intermediate and Resistant *Staphylococcus aureus* (VRSA)

By the 1990s, MRSA had become one of the most pervasive infections worldwide. As a consequence, the use of vancomycin, a glycopeptide antibiotic that was the primary treatment for severe MRSA infections, increased dramatically.[69] However, the increased use of vancomycin to treat MRSA, led to increasing numbers of clinical isolates with reduced susceptibility to vancomycin.[69] The National Committee for Clinical Laboratory Standards (NCCLS) that sets standards to describe sensitivity and resistance for bacterium and antibiotics has defined vancomycin resistance.[69] According to the NCCLS, staphylococci with an MIC for vancomycin of ≤ 4 µg/mL are sensitive, while strains with an MIC for vancomycin of 8-16 µg/mL are defined as intermediate sensitive (vancomycin-intermediate *S. aureus*, VISA), and isolates having an MIC of vancomycin ≥ 32 µg/mL are designated resistant (VRSA). Although these standards are followed in the USA and Canada, in Japan, staphylococci with an MIC of 8 µg/mL are considered VRSA.[69]

In 1997, the first VISA strain was identified in Japan, indicating the beginning of resistance to vancomycin, and was heralded as the "doomsday bug" because of the lack of effective treatments available.[70-71] Between the years 2002-2006, the first patients with VRSA were reported in the United States.[72] All of the isolated VRSA strains were vanA positive and had an MIC for vancomycin of 512 µg/mL. Each of the infected patients had a medical history of MRSA, as well as an enterococcal infection, and most had received vancomycin therapy prior to the development of VRSA.[72] The staphylococci isolated from these patients contained the mecA gene for methicillin resistance, as well as a vanA gene that was identical to that of vancomycin-resistant *Enterococcus faecalis* (VRE), suggesting a gene transfer from *Enterococcus* to the staphylococci.[72] VRSA is now found in every country worldwide. Thus, in a very short period of time (from 1997 to 2002) *S. aureus* went from an organism that was completely susceptible to standard of care antibiotics, to one that was completely resistant to treatment.[69] Considering the significant morbidity and mortality of VRSA infections, the search for new safe and effective antimicrobial agents for VRSA should be high priority worldwide.

Reviews of the scientific literature show that there are >100 published reports of medicinal plants with in vitro activity against VISA and VRSA. Table 3 is a summary of some of the tested plant species with in vitro activity against VISA and VRSA.

Table 3. Naturally occurring extracts and compounds from plant, fungi and marine species with activities against vancomycin resistant *Staphylococcus aureus* (VRSA).

Organism/compound	Family	Extract/compounds	MIC/MBC	Reference
Achillea millefolium	Compositae	Aqueous alcohol	1.0 mg/mL	73
Achyrocline satureioides	Compositae	Achyrofuran	0.07 µg/ml	74
Allium ascalonicum	Amaryllidaceae	Aqueous alcohol	128 µg/mL	73
Armoracia rusticana	Brassicaceae	Isothiocyanates	666 µg/mL	75
Chrysophyllum albidium	Sapotaceae	Hexane	0.63–10 mg/ml	76
Nymphae lotus	Nymphaceae	Ethanol	5-80 mg/mL	77
Plectranthus amboinicus/ carvacrol	Lamiaceae	Carvacrol	10.25 mg/mL/0.5 mg/mL	78
Rosmarinus officinalis	Lamiaceae	Alcohol	0.156 mg/mL/0.312 mg/mL	79
Salvia miltiorrhiza	Lamiaceae	Cryptotanshinone	2 µg/mL/4 µg/mL	80
Tabernaemontana alternifolia	Apocynaceae	Aqueous stem bark	600–800 µg/mL	81

While the in vitro data for most of these plant extracts and pure compounds is weak, as many of them have MICs for VRSA above 25 µg/mL, there are again a few plant extracts and purified compounds with excellent activity against VRSA. These include extracts from *Achyrocline satureioides* (Compositae), and its isolated active compound, achyrofuran (VISA MIC 0.07 µg/ml)[74]. Also, the traditional Chinese herbal medicine, *Salvia miltiorrhiza* (Lamiaceae) and its active constituent, cryptotanshinone that had an MIC of 2 µg/mL and an MBC of 4 µg/mL.[80] In addition, cryptotanshinone had synergistic effects when combined with vancomycin in VRSA strains, suggesting that combinations of cryptotanshinone and vancomycin may be feasible for the clinical management of VRSA.[80] Thus, there are a number of natural products or natural product/antibiotic combinations that might be feasible for the development of new treatments for both VISA and VRSA.

3.0 Vancomycin resistant Enterococci

Enterococci are Gram-positive, facultative anaerobes that are well known to have the ability to survive under harsh conditions.[82-83] Prior to the 1980's Enterococci were classified as enteric Gram-positive cocci in the genus, *Streptococcus*, but then they later were re-categorized into their own genus, *Enterococcus*.[82-83] There are more than twelve different *Enterococcus* species, however only two are predominant human pathogenic infections, namely *E. faecalis* and *E. faecium*.[82] Enterococci are now a common cause of nosocomial infections worldwide, and have long been recognized as an important cause of bacterial endocarditis.[82-83] In the United States, enterococci are the second most common bacteria recovered from catheter-associated infections of the bloodstream and urinary tract, and from skin and soft-tissue infections.[82] These bacteria are able to survive in hospital environments because they are not generally susceptible to commonly used antibiotics, and because they can actively acquire resistance to common antibiotics through the process of mutation or through the transfer of genetic materials via plasmids and transposons.[82] Enterococci have a high tolerance to both β-lactam and glycopeptide antibiotics, and treatment normally requires one of these antibiotics in combination with an aminoglycoside. However, the synergistic bactericidal effects between the aminoglycosides and β-lactams

or glycopeptide antibiotics may be lost if there is high resistance to either antibiotic. Until recently, vancomycin was the primary antibiotic consistently used for the management of infections caused by MDR enterococci. However, Vancomycin-resistant enterococci (VRE) now pose a global threat to public health and are emerging as some of the most common antimicrobial-resistant pathogens causing nosocomial infections.[83-84] VRE infections have been associated with increased length of hospital stays and mortality. The World Health Organization (WHO) has deemed VRE to be of high importance in the "Global Priority list of antibiotic-resistant bacteria to guide research, discovery and development of new antibiotics".[85] The major objective of developing this WHO list was to guide the prioritization of incentives and funding, and help align research and development priorities for antibiotics with public health needs.[85] VRE ranks in the high priority category on the list. WHO also recommends that there should be a new emphasis on the discovery and development of novel antibiotics specifically active against multidrug- and extensively drug-resistant Gram-negative bacteria.[85] As a consequence, there has been an increased effort to test natural products against Enterococci, including VRE, see Table 4.

Table 4. Plant, fungal, and marine organism extracts with activities against drug resistant Enterococcus faecalis, Pseudomonas aeruginosa, and Klebsiella pneumoniae.

Plant/compound	Family	Bacterial Strain	Concentration	Reference
Aframomum citratum	Zingiberaceae	*MDR-Enterobacter, Klebsiella pneumonia*	512-1024 µg/mL	86
Allanblackia gabonensis	Clusiaceae	*MDR-Enterobacter, Klebsiella pneumonia, Pseudomonas aeruginosa*	64-1024 µg/mL	87
Arnebia euchroma/ butyryl alkannin	Boraginaceae	*VRE*	3.13 to 6.26 µg/mL	88
Beilschmiedia acuta	Lauraceae	*MDR-Enterobacter, Klebsiella pneumonia, Pseudomonas aeruginosa*	16-256 µg/mL	89
Beilschmiedia cinnamomea	Lauraceae	*MDR-Enterobacter, Klebsiella pneumonia, Pseudomonas aeruginosa*	64-1024 µg/mL	86
Bobgunnia madagascariensis	Caesalpinaceae	VRE	23–47 µg/mL	25
Cistus ladaniferus	Cistaceae	MDR Enterobacter serogenes EA289	0.05 to 0.8 mg/mL.	90
Clausena anisata	Rutaceae	*MDR-Enterobacter, Klebsiella pneumonia, Pseudomonas aeruginosa*	128-256 µg/mL	89
Combretum molle	Combretaceae	*MDR-Enterobacter, Klebsiella pneumonia, Pseudomonas aeruginosa*	256-1024 µg/mL	86

Dichrostachys glomerata	Mimosaceae	MRD- *Enterobacter; Klebsiella pneumonia*	512-1024 µg/mL	86
Ecteinascidia turbinate isolated Cyanobacterium	Unknown	*VRE*	0.11–0.45 µM	64
Echinops giganteus	Asteraceae	*MDR-Enterobacter, Klebsiella pneumonia, Pseudomonas aeruginosa*	512-1024 µg/mL	86
Entada abyssinica	Fabaceae	*Klebsiella pneumoniae* ATCC11296 Kp55	128 µg/mL µg/mL	
Erythrina senegalensis	Fabaceae	*MDR-Enterobacter*	12-24 µg/mL	25
Erythrina sigmoidea/ neobavaisoflavone	Fabaceae	*MDR-Enterobacter, Klebsiella pneumonia, Pseudomonas aeruginosa*	8 µg/mL	92
Fagara xanthozyloïdes	Rutaceae	*MDR-Enterobacter, Klebsiella pneumonia, Pseudomonas aeruginosa*	256-1024 µg/mL	86
Garcinia mangostana	Clusiaceae	VRE	3.13- 6.25 µg mL	93
***Holarrhena antidysenterica*/conessine**	Apocynaceae	MDR Pseudomonas aeruginosa	40 mg/mL	94
Khaya senegalensis	Meliaceae	*Aminoside-RE*	94 µg mL	25
Mondia whitei	Periplocaceae	*MDR-Enterobacter, Klebsiella pneumonia, Pseudomonas aeruginosa*	1024 µg/mL	86
***Nauclea pobeguiinii*/resveratrol**	Rubiaceae	VRE	32 µg/mL/16 µg/mL	95
Newbouldia laevis	Bignoniaceae	*MDR-Enterobacter, Klebsiella pneumonia, Pseudomonas aeruginosa*	126-256 µg/mL	89
***Nuphar japonicum*/6,6′-dihydroxythiobinupharidine**	Nymphaeaceae	VRE	1–4 µg/mL	33
Olax subscorpioidea	Olacaceae	*MDR-Enterobacter, Klebsiella pneumonia*	256-1024 µg/mL	86
Piper betle	Piperaceae	VRE	19 µg/mL	36
Polyscias fulva	Araliaceae	*Enterobacter, Klebsiella pneumonia, Pseudomonas aeruginosa*	126-256 µg/mL	89
Solanum melongena	Solanaceae	*Enterobacter, Klebsiella pneumonia, Pseudomonas*	512-1024 µg/mL	86

		aeruginosa		
Tripterygium wilfordii/ Tripteryols B	Celastraceae	*Pseudomonas aeruginosa, VRE*	2.95-8.59 μg/mL	96
Uapaca togoensis	Euphorbiaceae	*Aminoside-RE*	94 μg/ml	25, 97
Waltheria lanceolata	Sterculiaceae	*Aminoside-RE*	94 μg/ml	25
Ximenia americana	Olaeaceae	*Aminoside-RE*	94 μg/ml	25
Xylopia aethiopica	Annonaceae	*Klebsiella pneumoniae* ATCC11296 Kp63	64 μg/mL	86

VRE = Vancomycin-resistant Enterococcus faecalis

From these results in Table 4, *Arnebia euchroma* extracts and the active antibacterial compound, butyryl alkannin, inhibited the growth of VRE in vitro with an MIC range of 3.13 to 6.26 μg/mL, suggesting excellent activity.[88] Also, *Garcinia mangostana* (Clusiaceae) and *Nuphar japonicum* (Nymphaeceae) inhibited the growth of VRE with MICs of 3.13-6.25 μg mL and 1–4 μg/mL, respectively, also indicating excellent activity.[33,93] Furthermore, the traditional Chinese herbal medicine, *Tripterygium wilfordii* and its active constituent, Tripteryols B, inhibited the growth of VRE with an MIC range of 2.95-8.59 μg/mL.[96] There are also numerous compounds isolated and identified from marine organisms, with exceptional activity against VRE (see Table 4), particularly compounds derived from marine Actinomycetes. Thus, along with plant extracts, marine organisms are an excellent and untapped source of novel biomolecules with activities against both MRSA and VRE that may be useful for further research and development of new treatments for these infections.

3.1 Drug resistant *Klebsiella pneumonia, Pseudomonas aeruginosa* and *Acinetobacter baumannii*

While infections caused by Gram-positive bacteria may be more prevalent in hospital settings, the Gram-negative Enterobacteriaceae, have by far the highest mortality rate.[99-104] Bacteria from the genus *Klebsiella* are some of the most commonly isolated bacteria from patients in the intensive care units (ICUs) of hospitals.[99-100] *Klebsiella pneumoniae* (KP) is a major cause of bacteremia, pneumonia, and neonate infections, and resistance of KP to carbapenem has spread to globally.[99-100] In fact, KP is now the most common carbapenemase-producing Enterobacteriaceae (CRKP) globally, causing significant morbidity and mortality.[100] Currently, there are few antibiotics available for the treatment of CRKP infections, and therefore the research and development of new agents to treat CRKP is also a global priority. Along with KP, *Pseudomonas aeruginosa* is also an important cause of nosocomial infections.[99] The antibiotics currently used to treat *P. aeruginosa*, include penicillins, cephalosporins, carbapenems, and fluoroquinolones, particularly ciprofloxacin.[99] The aminoglycosides have been used in combination with other drugs for the treatment of serious pseudomonal infections, but are not recommended as single entity treatment.[99-101] Like KP, *P. aeruginosa* has become an MDR pathogen associated with high morbidity and mortality.[101] MDR *P. aeruginosa* causes a wide range of life threating infections including pneumonia, sepsis and urinary tract infections.[101] Treatment for MDR *P. aeruginosa* is difficult due to the broad range of antibiotic resistance. Numerous MDR efflux pumps have been identified in MDR *P. aeruginosa*, including MexAB-OprM, MexCD-OprJ, MexEF-OprN, and MexXY-OprM.[101-103] MexAB-OprM is an efflux pump for numerous antibiotics including fluoroquinolones, β-lactams, tetracycline, macrolides, chloramphenicol, novobiocin, trimethoprim, and sulphonamides.[101-103] Thus, along with KP, MDR-*P. aeruginosa* is a serious life threatening infectious agent in

urgent need of new treatments. The data in Table 4 outlines some of the active extracts and pure compounds from plants, fungi and marine organisms that are active against KP and *P. aeruginosa*.

Along with KP and *P. aeruginosa*, *Acinetobacter baumannii* is also a serious cause nosocomial infections and associated with high rates of morbidity and mortality.[104] *Acinetobacter baumannii* (AB) is a significant cause of bacteremia, pneumonia, meningitis, urinary tract and wound infections, and also of significant concern due to drug resistance.[105-106] The wound infections caused by AB often inflitrate skin and deep soft tissue leading to osteomyelitis, bacteremia and other life-threating complications.[105] In addition, AB is the most common Gram-negative bacillus isolated in traumatic injuries to extremities and from patients who suffered traumatic injuries, particularly those obtained during emergency situations such as war or earthquakes.[105-106] Thus, AB has been characterized as a novel and a rapidly emerging clinical pathogen that possesses a variety of antimicrobial resistance mechanisms.[106] Due to increasing antibiotic resistance rates, multi-drug (MDR-AB) and extensively-resistant *A. baumannii* (XDR-AB) have become a serious threat particularly to immune compromised patients.[106] The available treatments for treating MDR-AB and XDR-AB are extremely limited, and there has been a renewed interest in the older antimicrobial agents such as rifampin and minocycline.[106-107] However, like CRKP, MDR- and XDR-AB are also high priority for the research and development of new antimicrobial agents for the management of these infections.

A number of reviews have already outlined the isolation and characterization of naturally occurring plant-based compounds with activity against AB up to 2015.[108-109] The review by Miyasaki detailed the wide range of naturally occurring compounds that were active against AB[108], and the excellent review by Tiwari et al.,[109] has detailed the naturally occurring compounds from plant extracts that have potent antibacterial activities against carbapenem resistant strains of AB. In addition, Abdulhaq[110] has outlined the antibacterial effects of essential oils from Arabian plants with activity against AB and XDR-AB (Table 5). For example, the essential oils of *Acacia arabica*, *Combretum aculeatum*, *Eucalyptus camaldulensis*, *Hibiscus sabdariffa*, and *Rosmarinus officinalis* are active against AB and XDRAB in concentrations below 10 µg/mL (Table 5).[110] Furthermore, Intorasoot et al.,[111] have also reported activities of essential oils from common spice plants against AB and MDR-AB. Interestingly, essential oils have been used for thousands of years to manage wounds healing and many of these naturally occurring essential oils appear to speed wound healing, as well as inhibit the growth of a wide range of MDR bacteria.[110-111] Thus, there may be an opportunity to develop the most active essential oils alone or in combination with antibiotics for the management of MDR- and XDR-AB.

Table 5. Naturally occurring essential oils from plants from Arabia used to treat MDR-AB and wounds.

Organism/compound	Family	Extract/compounds	MIC/MBC	Reference
Acacia nilotica [syn. A. Arabica]	Leguminosae	Essential oil	<0.39 µg/mL/1.56 µg/mL	Abdulhaq, 2017
Combretum aculeatum	Combretaceae	Essential oil	0.78 µg/mL/0.78 µg/mL	Abdulhaq, 2017
Hibiscus sabdariffa	Malvaceae	Essential oil	1.56 µg/mL/3.13 µg/mL	Abdulhaq, 2017
Peganum harmala	Nitrariaceae	Essential oil	<0.39 mg/mL/0.78 µg/mL	Abdulhaq, 2017
Rosmarinus officinalis	Laminaceae	Essential oil	3.13µg/mL/3.13µg/mL	Abdulhaq, 2017
Tamarix aphylla	Tamariaceae	Essential oil	12.5 µg/mL/12.5 µg/mL	Abdulhaq, 2017

3.2 Drug resistant *Mycobacterium tuberculosis*

Infections caused by *Mycobacterium tuberculosis* (MTb) also continue to be a serious threat to public health worldwide.[114-115] It is estimated that there are > 10 million new cases and 1.5 million deaths annually due to MTb infections alone.[114-117] The continued prevalence of MTb is associated with the increase in HIV/AIDS, a lack of new antibiotic therapies, poor use of anti-TB drugs, as well as the emergence of multi-drug resistant (MDR-TB) and extensively drug resistant (XDR-TB) strains.[115] During the last forty years, resistant strains of MTb have evolved from single drug resistance, to MDR and extensively drug resistant (XDR), and finally now to totally drug resistant (TDR) strains, due to the sequential accumulation of resistance mutations.[116] WHO estimates that, in 2014, there were about 480,000 new cases of multidrug-resistant tuberculosis (MDR-TB), of which only about 25% were detected and reported.[118] MDR-TB requires longer treatment and, treatment tends to be less effective. Of the MDR-TB cases in 2014, WHO estimates that only one half of these patients were successfully treated.[118] MDR-TB strains are now reported to be the cause of ~480 thousand cases of MTb and > 200,000 deaths as these strains are resistant to the most commonly used TB drugs, isoniazid and rifampicin.[115] Extensively drug-resistant tuberculosis (XDR-TB), a form of tuberculosis that is resistant to at least four of the core anti-TB drugs, has now been identified in over 100 countries.[118] An estimated 9.7% of people with MDR-MTb have XDR-TB, and XDR-MTb mortality can be as high as 40-50%, particularly in cases where the patients are also infected with HIV.[119-120] Reviews from the scientific and medical literature suggest that there are hundreds of plant, marine and fungal species worldwide that have been tested for activity against MTb, and many naturally occurring compounds have been isolated and identified with activity against MTb, MDR-TB and XDR-TB.[115,120-121] Table 6 is an overview of some of the more recent work in the field from plant, marine and fungal species, as well as isolated natural compounds with promising activity against MDR- and XDR-TB. Interestingly, numerous naturally occurring compounds with excellent activity against MDR-TB, with MICs below 5 µg/mL (Table 6). These natural products could be used as the basis for further research in animal and human studies, or in mechanistic studies.

Table 6. Naturally occurring extracts and compounds from plant, fungi and marine species with activities against MDR and XDR-MTb.

Organism/compound	Family	Extract/compounds	MIC/MBC	Reference
Artemisia capillaris	Compositae	Ursolic acid and hydroquinone	12.5-25 µg/mL	123-124
Caesalpinia sappan	Leguminosae	3-deoxysappanchalcone	3.125-12.5 µg/mL	125
Citrullus colocynthis	Cucurbitaceae	Ursolic acid and cucurbitacin E 2-0-β-d-glucopyranoside	31.2–125 µg/mL	126
Cynanchum atratum	Apocynaceae	(-)-Deoxypergularine	12.5 µg/mL	127
Diospyros anisandra	Ebenaceae	Plumbagin, maritinone and 3,30-biplumbagin	1.56-3.33 mg/mL	128
Kaempferia galanga	Zingiberaceae	Ethyl p-methoxy-cinnamate	0.485 mM	129
Lentzea kentuckyensis	Pseudonocardiaceae	Lassomycin	0.41 to 1.65 µM	130
Marine fungi	Unidentified	Vermelhotin	1.5- 12.5 µg/mL	131
Marine Streptomyces	Actinomycetes	Cyclomarin A	0.3 µM	130

***Nonomuraea* spp**	Actinomycetes	Ecumicin	0.16-0.62 µM/1.5 µM	130
Plumeria rubra [syn P. bicolor]	Apocynaceae	Plumericin and isoplumericin	1.2-2.6 µg/mL	132
Pterolobium stellatum	Leguminosae	Chloroform	0.078 mg/mL	133
Tiliacora triandra	Menispermaceae	Tiliacorinine, 20-nortiliacorinine and tiliacorine	0.7 to 6.2 µg/mL	134

4.0 Conclusion

Globally, antimicrobial resistance is occurring in both Gram-positive and Gram-negative bacteria, and new efforts have been initiated to harmonize the description and classifications of these bacteria to assure that surveillance data can be reliably collected across countries.[135] Due to resistance to more than one antibiotic, the treatment of multidrug-resistant infections is more difficult and complicated, and may require multiple rounds of antibiotic therapies. Infections caused by MDROs may lead to inadequate or delayed antimicrobial therapy, and tend to be associated with poorer patient outcomes.[1-4,135] To make matters worse, despite the growing need for new antibiotics for the increasing numbers of MDROs, only a few new antibiotics have been approved for clinical use in the past 20 years.[2]

Of the resistant Gram-positive bacteria, both MRSA and MDR-MTb are now commonly seen. However, more recently, there has been increasing reports of VISA and VRSA, as well as VRE, MDR-KB, *Pseudomonas* and *Acinetobacter* species. All of these bacteria represent serious threats to public health as they are often only susceptible to some of the older and more toxic antibiotics such as the polymyxins, making treatment choices difficult and causing serious adverse events.[1-4,136-137] The lack of new antimicrobial agents in development to address MDROs is a significant problem as many pharmaceutical companies choose not to develop these drugs due to the lack of financial return on investments. As a consequence, the potential use of natural products against MDROs has been the focus of intensive research, and thousands of natural products have been tested against these organisms, some with excellent results. In this work, we have shown that for many of these MDROs, there are extracts and pure natural compounds with significant activity against MDR bacteria that could be potentially developed as clinical agents to treat these infections. In addition, there are many reports of natural products having additive or synergistic effects with antibiotics against MDROs that could perhaps extend the life of common antibiotics. While there are challenges to the development of natural products, novel strategies in antibiotic development and potentially new drug combinations have put natural products back in the forefront of the MDRO crisis and will hopefully lead to a new era in antibiotic development.[2]

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