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REVIEW ARTICLE

Plant-derived antimicrobials to fight against multi-drug-resistant human pathogens

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Abstract Antibiotic resistance is becoming a pivotal concern for public health that has accelerated the search for new antimicrobial molecules from nature. Numbers of human pathogens have inevitably evolved to become resistant to various currently available drugs causing considerable mortality and morbidity worldwide. It is apparent that novel antibiotics are urgently warranted to combat these life-threatening pathogens. In recent years, there have been an increasing number of studies to discover new bioactive compounds from plant origin with the hope to control antibiotic-resistant bacteria. This review attempts to focus and record the plant-derived compounds and plant extracts against multi-drug-resistant (MDR) pathogens including methicillin-resistant *Staphylococcus aureus* (MRSA), MDR-*Mycobacterium tuberculosis* and malarial parasites *Plasmodium* spp. reported between 2005 and 2015. During this period, a total of 110 purified compounds and 60 plant extracts were obtained from 112 different plants. The plants reviewed in this study belong to 70 different families reported from 36 countries around the world. The present review also discusses the drug resistance in bacteria and emphasizes the urge for new drugs.

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Introduction

Approximately, 500,000 species of both identified and unidentified plants have been estimated on Earth. Among them, only 1–10% are being used as foods by animals and humans (Borris 1996; Cowan 1999). Plants are the key source for drugs and an alternative medicine for fighting against diseases since ancient times. Evidential specimens proved that Neanderthals living 60,000 years ago in present-day Iraq used plants such as hollyhock (Thomson 1978; Stockwell 1988; Cowan 1999) and these plants are still widely being used in ethnomedicine across the world. Interestingly, about 50% of all pharmaceutical products distributed in the United States have plant origin. Among which, very few are used as antimicrobials, since the microbial sources are widely relied upon (Cowan 1999). Nevertheless, since the arrival of antibiotics in the 1950s, the use of plant derivatives as antimicrobials has been literally non-existent. Researchers are interested in plant extracts as medicines as they are undisputable substitution for antibiotics prescribed by physicians (Cowan 1999). Besides, the public is becoming increasingly aware of problems with the overuse and misuse of antibiotics. In addition, many people are attracted in having more autonomy over their medical care (Cowan 1999). The self-medication with plant substances is common due to easy availability. The use of plant-derived natural products in medical treatments is attracting more attention due to its potential efficacy and no side effects (Cowan 1999). Indeed, plants are a rich source of valuable secondary metabolites, such as quinones, tannins, terpenoids,

alkaloids, flavonoids, and polyphenols that are used by plants as defence mechanisms against predation by microorganisms, insects, and herbivores. Some, such as terpenoids, give plants their odors; quinones and tannins are responsible for plant pigmentation. Many compounds including terpenoids are responsible for plant flavor and some of the herbs and spices, which are being used by humans to season foods, could yield useful medicinal compounds (Cowan 1999; Dixon 2001; Kyaw et al. 2012). The number of bioactive compounds derived from plants has been estimated to be at least 200,000 and it still represents only a fraction of the compounds produced by the plant species growing on Earth (Efferth and Koch 2011). Research interest on medicinal plants is being amplified in recent years, which is seen by the increase in the number of publications on plant-based pharmacological interactions and synergistic principles (van Vuuren and Viljoen 2011). This interest has led to the discovery of new/novel biologically active molecules by the researchers and pharmaceutical industries and the adoption of crude extracts of plants for self-medication by the general public. In this review, an effort is made to summarize one decade (2005–2015) of plant antimicrobials including the purified plant-based bioactive compounds, crude and partially purified plant extracts against MDR human pathogens including MRSA, MDR-*M. tuberculosis* and malarial parasites *Plasmodium* spp. This is by no means an exhaustive search of all plant-derived compounds and plant extracts during this past 10-year period. Nevertheless, the list provided in this review is impressive and illustrates the potential of plant antimicrobials against MDR human pathogens.

Drug resistance in bacteria: alarming need of new antibiotics

Antibiotic-resistant bacterial infections are already widespread on the globe (Golkar et al. 2014). In February 2017, World Health Organization (WHO) published its first ever list of antibiotic-resistant 'priority pathogens' that pose the greatest threat to human health. The first critical priority pathogens are carbapenem-resistant *Acinetobacter baumannii*, carbapenem-resistant *Pseudomonas aeruginosa* and carbapenem-resistant and extended spectrum beta-lactamase (ESBL) producing Enterobacteriaceae. The second level high priority pathogens are vancomycin-resistant *Enterococcus faecium*, methicillin-resistant *Staphylococcus aureus*, clarithromycin-resistant *Helicobacter pylori*, fluoroquinolone-resistant *Campylobacter* spp., fluoroquinolone-resistant Salmonellae and cephalosporin and fluoroquinolone-resistant *Neisseria gonorrhoeae*. These priority pathogens are resistant to multiple antibiotics and have in-built abilities to resist treatment and transfer along genetic material that leads other bacteria to become drug-resistant as well (http://www.who.int/mediacentre/news/releases/2017/bacteria-antibiotics-needed/en/, accessed on 09/05/2017). Therefore, new/novel antibiotics are desperately needed for battling these rapidly evolving pathogens. The production of new antibiotics has diminished progressively over the past 20 years, entrusting less possibilities to treat these drug-resistant pathogens (Ventola 2015). The treatment of infections caused by MDR pathogens is complicated and limited (Kanj and Kanafani 2011). Meanwhile, clinicians are still prescribing the existing drugs with appropriate dosage and combinations of various drugs for preventing and treating these super bugs (Safavi et al. 2016). Table 1 displays some of the WHO priority drug-resistant pathogens and their current antibiotics of choice for their treatment.

Multi-drug-resistant (MDR) pathogens: a threat to public health

The underuse, overuse, and misuse of antibiotics by humans are the selective pressure, which eventually lead to the development of antibiotic resistance in microbes (Davies and Davies 2010). Globally, emerging MDR pathogens also called as 'ESKAPE' organisms such as *Enterococcus* spp., *S. aureus*, *Klebsiella* spp., *A. baumannii*, *P. aeruginosa* and *Enterobacter* spp. are a serious threat now-a-days to public health (Boucher et al. 2009). MDR microorganisms can survive the treatment with antimicrobial drugs, thereby standard treatments become ineffective and infections persist, increasing the risk of spread to others. In general, MDR microbes are resistant to three or more antibiotics (Styers et al. 2006); however, strains of *Mycobacterium tuberculosis* are extremely drug-resistant (XDR) that are virtually resistant to all classes of antimicrobials (Gandhi et al. 2006). In 2012, WHO reported a gradual increase in resistance to HIV drugs, although not reaching critical levels (WHO 2012). Since then, further increase in resistance to first-line treatment drugs was reported, which might require using more expensive drugs soon (http://www.who.int/mediacentre/factsheets/fs194/en/, accessed on 18/08/2016). In addition, the Centre for Disease Control (CDC) estimates that each year, nearly 2 million people in the United States acquire an infection while in hospital, resulting in 90,000 deaths. More than 70% of the bacteria that cause these infections are resistant to at least one of the antibiotics commonly used to treat them (http://www.fda.gov/drugs/resourcesforyou/consumers/ucm143568.htm, accessed on 18/08/2016). The globally emerging antibiotic resistance, nevertheless, makes MDR microbes substantially difficult

Table 1 List of some WHO priority drug-resistant pathogens and their current antibiotics of choice for treatment

WHO priority drug-resistant pathogen	Currently using antibiotics	References
Carbapenem-resistant *A. baumannii*	Colistin, carbapenems, sulbactam, rifampin and tigecycline	Viehman et al. (2014)
Carbapenem-resistant *P. aeruginosa*	Ticarcillin-clavulanate, ceftazidime, aztreonam, imipenem, ciprofloxacin and colistin	Kanj and Kanafani (2011)
Carbapenem-resistant, ESBL-producing Enterobacteriaceae	Polymyxins, fosfomycin, carbapenems, tigecycline and aminoglycosides	Morrill et al. (2015)
Vancomycin-resistant *E. faecium*	Streptogramin, linezolid, daptomycin, oritavancin and tigecycline	Linden (2002)
Methicillin-resistant *S. aureus*	Vancomycin, trimethoprim-sulfamethoxazole, clindamycin, linezolid, tetracyclines and daptomycin	Kali (2015)
Clarithromycin-resistant *H. pylori*	Amoxicillin, esomeprazole, rabeprazole, omeprazole, metronidazole, levofloxacin and clarithromycin	Safavi et al. (2016)
Fluoroquinolone-resistant *Campylobacter* spp.	Erythromycin, ciprofloxacin and fluoroquinolones	Wieczorek and Osek (2013)

to control or kill and also builds them more stronger. It is clear that the currently available antibiotics are insufficient to control these superbugs and, hence, more research and novel antimicrobial sources are highly demanded.

Methicillin-resistant *S. aureus* (MRSA)

In this decade, the fastest evolving pathogen is MRSA. There has been a continuous increase in the incidence of MRSA worldwide. In the United States, current MRSA rates exceed 50% of all *S. aureus* infections and stand close to 90% in some Asian countries (Office for National Statistics 2005). The mortality rates for deaths involving MRSA have increased over 15-fold during the period 1993 to 2002 (Office for National Statistics 2005). MRSA has developed resistance to a number of antibiotics such as oxacillin, penicillin and amoxicillin. In some countries, over 60% of *S. aureus* cases in hospital intensive care units are now resistant to these first-line antibiotics (Laxminarayan and Malani 2007). MRSA has been categorized into two groups based on their infections such as hospital-acquired and community-acquired MRSA (HA-MRSA and CA-MRSA), which marginally differ in their genetic make-up.

HA-MRSA is a deadly pathogen and often infects hospitalized patients particularly those who are immunocompromised (Sheen 2010). HA-MRSA was first appeared in the United States in 1968 and showed resistance against β-lactam antibiotics and other various types of antibiotics (Chanda et al. 2010). The National Audit Office estimated that HA-MRSA was the primary factor in 5000 deaths per annum (National Audit Office 2000). CA-MRSA emerged in the community setting recovered from a clinical culture from a patient residing in the surveillance area, who had no established risk factors usually correlated with HA-MRSA (Chanda et al. 2010). The established risk factors include the isolation of MRSA two or more days after hospitalization; a history of hospitalization, surgery, dialysis, chronic diseases, or residence in a long-term care facility within 1 year before the MRSA-culture date; the presence of a permanent indwelling catheter or percutaneous medical device at the time of culture; or previous isolation of MRSA (Fridkin et al. 2005; Chanda et al. 2010). CA-MRSA often causes skin infection and severe infection resulting in fatal on certain occasions displaying resistance to β-lactam antibiotics, nevertheless susceptible to trimethoprim/sulfamethoxazole, clindamycin and tetracyclines (Deresinski 2005; Chanda et al. 2010).

Staphylococcus aureus is one of the most critical human pathogens causing wide range of infections from mild skin diseases to life-threatening endocarditis (Chambers 2001). After identifying the evidential occurrence of methicillin resistance among *S. aureus* strains, vancomycin and quinolones antibiotics have been used as alternative drugs of choice as staphylococcal infections therapy (Tiwari et al. 2009). Nevertheless, over a decade, most of the *S. aureus* strains including MRSA developed resistance to many commonly used fluoroquinolones by acquiring a rapid mutation in the genes encoding for target enzymes and expression of the efflux pump (Tanaka et al. 2000; Gade and Qazi 2013). Looking at the widespread development of fluoroquinolones resistance in *S. aureus* (FRSA), potential antibiotics are required and demand more awareness in public health care and community settings.

Table 2 Plant-derived compounds and plant extracts reported during 2005–2015 against multi-drug-resistant pathogens

Compound/extract	Plant	Source	Target	Reported country	References
Aqueous alkaloid, organic alkaloid and non-alkaloid	*Rhazya stricta*	Leaves	MRSA	Saudi Arabia	Khan et al. (2016)
Aqueous, chloroform, ethanol and hexane	*Alkanna tinctoria*	Leaves	MRSA, MDR-*Acinetobacter baumannii*, *E. coli* and *P. aeruginosa*	Pakistan	Khan et al. (2015)
Dehydroabietic acid	*P. elliottii*	Resin-oil	MDR-*Staphylococcus epidermidis*, *S. capitis*, *S. haemolyticus, E. faecium* and *E. faecalis*	Brazil	Leandro et al. (2014)
Dichloromethane, methanol, petroleum ether, chloroform, ethyl acetate, acetone, ethanol and water	*Lantana camara* L.	Leaves	MRSA, VRE, MDR-*A. baumannii*, *P. aeruginosa, Streptococcus pyogenes, Citrobacter freundii, Proteus mirabilis* and *P. vulgaris*	India	Dubey and Padhy (2013)
Petroleum ether, acetone, methanol, ethanol and water	*Butea monosperma* Lam.	Leaves	MRSA, VRSA	India	Sahu and Padhy (2013)
Ethanol and water	*Anthocephalus cadamba* and *Pterocarpus santalinus*	Leaves and bark	MDR-*Acinetobacter* sp., *P. aeruginosa, C. freundii* and *Proteus* sp.	India	Dubey et al. (2012)
Ethanol	*Rhus coriaria*	Seeds	MDR-*P. aeruginosa*	Palestine	Adwan et al. (2010)
(+)-Lyoniresinol-3 alpha-*O*-beta-D-glucopyranoside	*Lycium chinense* Mill.	Roots and bark	MRSA	China	Lee et al. (2005)
Baicalin	*Scutellaria baicalensis* Georgi.	NA	Synergistic effect with β-lactam-resistant strains of *S. aureus*, synergies between baicalein, tetracycline, β-lactams and ciprofloxacin against MRSA and inhibit MRSA-pyruvate kinase	China	Chan et al. (2011)
Sophoraflavanone G, 7,9,2′,4′-tetrahydroxy-8-isopentenyl-5-methoxychalcone	*Sophora flavescens*	Roots	MRSA, VRE	China	Cha et al. (2009), Lee et al. (2010)
Chloroform and chloroform + HCl	*Andrographis paniculata*	NA	MRSA	India	Roy et al. (2010)
Hexane	*Sclerocarya birrea*	Seeds	MRSA	Malaysia	Mariod et al. (2010)
Cold and hot aqueous and ethanol	*Terminalia chebula* Retz.	Dried seedless ripe fruits	MRSA, trimethoprim-sulphamethoxazole-resistant uropathogenic *E. coli*	India	Bag et al. (2009)
20-Hydroxyecdysone	*Achyranthes japonica*	Roots	MRSA	South Korea	Kim et al. (2009)
Aqueous and ethanol	*Fabiana bryoides, F. densa, F. punensis, Baccharis boliviensis, Chuquiraga atacamensis, Parastrephia lepidophylla, P. lucida,* L. *phyliciformis, Frankenia triandra, Chiliotrichiopsis keidelii*	Aerial parts	MRSA, MSSA, MRSCN, MSSCN and MDR-*E. faecalis*	Argentina	Zampini et al. (2009)

Table 2 continued

Compound/extract	Plant	Source	Target	Reported country	References
Limonoids	*Swietenia mahagoni*	Seeds	MRSA, MDR-Group A haemolytic *S. aureus*, *Streptococcus pneumoniae, Haemophilus influenza, E. coli, Klebsiella pneumonia, Salmonella typhi* and *S. paratyphi*	Bangladesh	Rahman et al. (2009)
Water	*Punica granatum*	Pomegranate rind	MRSA, MSSA, PVL-positive-CA-MSSA	London	Gould et al. (2009)
Commercial extract (NA)	*Olea europaea*	Leaves	MRSA	Australia	Sudjana et al. (2009)
Ellagic acid, norwogonin, chebulagic acid, chebulinic acid, corilagin and terchebulin	*Rosa rugosa, Scutellaria baicalensis* and *Terminalia chebula*	Commercial plant powder	MDR-*A. baumannii*	USA	Miyasaki et al. (2013)
Triterpenes	*Planchonia careya*	Leaves	MRSA, VRE	Australia	McRae et al. (2008)
Butanol	*Retama raetam*	Flowers	MRSA	Tunisia	Hayet et al. (2008)
Ethanol	*Atuna racemosa*	Seeds	MRSA	USA	Buenz et al. (2007)
Methanol	*Callistemon rigidus*	Leaves	MRSA	India	Gomber and Saxena (2007)
Diterpenoids	*Croton tonkinensis*	Leaves	MRSA	Vietnam	Giang et al. (2006)
Aqueous and 80% ethanol	*Rosa damascena, Melissa officinalis* and *Mentha longifolia*	Aerial parts and flowers	MRSA	Palestine	Abu-Shanab et al. (2006)
Aqueous and ethanol	*Terminalia avicennioides, Bridella ferruginea, Ageratum conyzoides, Phyllanthus discoideus, Ocimum gratissimum* and *Acalypha wilkesiana*	Leaves and bark	MRSA	Nigeria	Akinyemi et al. (2005)

MRSA methicillin-resistant *S. aureus*, *MDR* multi-drug-resistant, *VRE* vancomycin-resistant enterococci, *VRSA* vancomycin-resistant *S. aureus*, *MSSA* methicillin-sensitive *S. aureus*, *MRSCN* methicillin-resistant *Staphylococcus* coagulase negative, *MSSCN* methicillin-sensitive *Staphylococcus* coagulase negative, *PVL-positive-CA-MSSA* Panton-Valentine leukocidin positive community-acquired MSSA, *NA* not accessed

Vancomycin-resistant *Enterococcus* (VRE)

Vancomycin-resistant *Enterococcus* (VRE) is another current threat in emerging drug-resistant pathogens in hospitals worldwide (Johnstone et al. 2017). Approximately, 66,000 healthcare-associated enterococcal infections are reported in the United States every year. Out of them, approx. 20,000 are vancomycin-resistant infections with about 1300 deaths attributes to VRE infections (Centre for Disease Control 2013). Hospital incurred Enterococci infections are resistant to several drugs including daptomycin, linezolid, penicillin and cephalosporins, and their progressive resistance has been

Table 3 Plant-derived compounds and plant extracts reported during 2005–2015 against MDR-*M. tuberculosis*

Compound/extract	Plant	Source	Reported country	References
20% Ethanol	*Prunella vulgaris* L.	Whole plant	China	Lu et al. (2011)
Dihydro-β-agarofuran sesquiter penes	*Celastrus vulcanicola*	Dried leaves	Spain	Torres-Romero et al. (2011)
n-hexane, ethanol, ethyl acetate, *n*-butanol, and methanol extracts	*Flourensia cernua*	Whole plant	Mexico	Molina-Salinas et al. (2011)
70% ethanol	*Allium sativum*	Cloves	Pakistan	Hannan et al. (2011), Dini et al. (2011)
6α-7-Dehydro-*N*-formylnornantenine; *E*/*Z*-*N*-formylnornantenine; 7,9-dimethoxytariacuripyrone; 9-methoxytariacuripyrone; aristololactam I; β-sitosterol; stigmasterol; 3-hydroxy-α-terpineol	*Aristolochia brevipes*	Roots	Mexico	Navarro-Garcia et al. (2011)
Bisbenzylisoquinoline alkaloids	*Tiliacora triandra*	Roots	Thailand	Sureram et al. (2012)
Alcohol	*Humulus lupulus*	Whole plant (stems, leaves and roots)	Iran	Serkani et al. (2012)
Essential oil	*Citrus* sp.	NA	USA	Crandall et al. (2012)
Obtusifoliol	*Struthanthus marginatus*	Aerial parts	Brazil	Leitao et al. (2013)
3-*O*-*n*-acil-lup-20(29)-en-3β,7β,1 5α-triol	*Struthanthu sconcinnus*	Leaves	Brazil	
(−) Licarin A	*Aristolochia taliscana*	Roots	Mexico	Leon-Diaz et al. (2013)
Ethanol extract	*Hypericum* sp.	Aerial parts	Portugal	Nogueira et al. (2013)
Ursolic and oleanolic acids	*Chamaedorea tepejilote*	Aerial parts	Mexico	Jimenez-Arellanes et al. (2013)
Maritinone and 3,3′-biplumbagin	*Diospyros anisandra*	Stem and bark	Mexico	Uc-Cachon et al. (2014)
70% Ethanol and water eluted part of ethanol extract	*Ranunculi ternati* Radix	Whole plant	China	Zhang et al. (2015)
Water, methylene chloride, ethanol, *n*-hexane and ethyl acetate extracts	*Andrographis paniculata, Annona muricata, Centella asiatica, Pluchea indica* and *Rhoeo spathacea*	Whole plant and dried leaves	Indonesia	Radji et al. (2015)
Diterpenoids including ent-kaurane, kaurane and grayanane	*Croton tonkinensis*	Whole plants or leaves	South Korea	Jang et al. (2016), Gupta et al. (2010)
Water extract	*Acalypha indica* L.	Leaves	India	
	Adhatoda vasica	Leaves	India	
	Allium cepa	Bulbs	India	
	Allium sativum L.	Cloves	India	
Pure gel of *Aloe vera*	*Aloe vera* L.	Pure gel	India	Gupta et al. (2012)
Ethyl *p*-methoxycinnamate	*Kaempferia galanga*	Rhizome	India	Lakshmanan et al. (2011)
Piperine	*Piper nigrum* L.	Seeds	India	Birdi et al. (2012)
5,10-Pentadecadiyn-1-ol, a-curcumene, hydroxyjunipene, cycloisosativene, valencine and selino 3,7 (11)-diene	*Vetiveria zizanioides*	Fresh roots	India	Gupta et al. (2012)
Alkaloids, flavonoids	*Urtica dioica*	Leaves	India	Singh et al. (2013)

Table 3 continued

Compound/extract	Plant	Source	Reported country	References
Plumericin and iso-Plumericin	*Plumeria bicolor*	Bark	India	Kumar et al. (2013)
Emodin	*Ventilago madraspatana*	Stem and bark	India	Basu et al. (2005)
Diospyrin	*Diospyros montana*	Stem and bark	India	Dey et al. (2014)
Andrographolide	*Andrographis paniculata*	Whole plant	India	Prabu et al. (2015)
Aqueous, boiling water and methanol extracts	*Punica granatum*	Fruit	India	Dey et al. (2015)

discovered across the world posing an alarming concern (Simeon et al. 2006; Johnstone et al. 2017).

Table 2 summarizes 15 plant-derived compounds and 40 plant extracts reported during 2005–2015 against MDR pathogens including MRSA, VRE, Trimethoprim–sulphamethoxazole-resistant uropathogenic *Escherichia coli* and various MDR Gram-negative and MDR Gram-positive human pathogens. This list clearly demonstrates the substantive and ongoing role of plant-derived compounds against MRSA and other MDR pathogens. A total of 43 plants are reviewed in Table 2; they are belonging to 23 different families. Interestingly, out of the 43 plants, 42 are angiosperms excluding the Brazilian *Pinus elliottii* (Leandro et al. 2014). Results show that both angiosperms and gymnosperms harboring potential antimicrobials against MDR pathogens; nevertheless, angiosperms are widely studied against MDR pathogens.

Multi-drug-resistant tuberculosis (MDR-TB)

Tuberculosis (TB) is an extremely notorious and infectious disease caused by *Mycobacterium* spp., particularly *M. tuberculosis*. TB is the second most fatal disease after HIV, accountable for human deaths across the globe according to the World Health Organization (WHO 2014). Around 6.1 million TB patients have been reported in the year 2013, of these, about 5.7 million (93%) cases were new (WHO 2014). About 9.6 million people were reported ill due to TB in 2014, of which approximately 1.5 million died (WHO 2014; Pandit et al. 2015). This disease is highly progressive in Asia and Africa, and more than 80% of all TB cases were reported from these two continents (Zager and McNerney 2008). Evidently, the *M. tuberculosis* is acquiring resistance against conventional drugs, thus frightening the global health community (Zignol et al. 2006). MDR-*M. tuberculosis* requires treatment courses that are much longer and less effective than those for non-resistant *M. tuberculosis*. Extensively drug-resistant TB (XDR-TB, defined as MDR-TB plus resistance to any fluoroquinolone and any second-line injectable drugs) has been identified in 100 countries, in all regions of the world (http://www.who.int/mediacentre/factsheets/fs194/en/, accessed on 18/08/2016). In this review, we have outlined plant-derived compounds and plant derivatives having significant anti-mycobacterial activity against MDR-TB reported during 2005–2015 (Table 3). Table 3 covers a total of 34 plants belonging to 26 different families and all are angiosperms. A total of 36 purified compounds and 20 plant extracts were reported during 2005–2015 against MDR-*M. tuberculosis*. These data obviously revealed that the plant-derived antimicrobials have a unique competence, as well as alternative and novel solutions to control these deadly MDR- and XDR-TB.

Malaria: a current public health concern

Malaria is a complex deadly blood disease with ravaging effects in the world (Onguéné et al. 2013). Approximately, half of the world's population is at risk of malaria and that 1–2 million annual deaths can be attributed to malaria alone (Vogel 2010; WHO 2012; Onguéné et al. 2013). There were approximately 245 million cases of malaria in 2006 and 3.3 billion people were at risk of the disease. Among them, about 1 million deaths were mostly of children under the age of five (Oliviera et al. 2009). Currently, there are 109 malarious countries and territories, of which, 45 are within the African region (WHO 2008). A total of four protozoan species of the genus *Plasmodium* (*P. falciparum*, *P. malariae*, *P. ovale*, and *P. vivax*) are the causative agents for this infection, although majority of fatal cases are caused by *P. falciparum* (Nogueira and Lopes 2011). Currently, malaria has been treated with

Table 4 Plant-derived compounds and plant extracts reported during 2005–2015 for anti-plasmodial activity

Compound	Plant	Source	Reported country	References
17-*O*-acetyl,10-hydroxycorynantheol	*Strychnos usambarensis*	Leaves	Belgium	Cao et al. (2011)
Alstonine	*Picralima nitida*	Fruits	USA	Okunji et al. (2005)
Methyl uguenenoate, furoquinoline and maculosidine	*Vepris uguenensis*	Roots	South Africa	Cheplogoi et al. (2008), Kiplimo (2012)
Evoxine, arborinine and xanthoxoline	*Teclea gerrardii*	Roots, bark and fruits	South Africa	Waffo et al. (2007), Tchinda et al. (2009)
N-isobutyldeca-2,4-dienamide	*Hugonia castaneifolia*	Root and bark	Tanzania	Baraza et al. (2008)
Pipyahyine	*Beilschmiedia zenkeri*	Bark	France	Lenta et al. (2009)
Cryptoquindoline	*Cryptolepis sanguinolenta*	Stems	Ghana	Barku et al. (2012)
Clerodane and labdane diterpenoids	*Nuxia sphaerocephala*	Leaves	Sudan	Mambu et al. (2006)
16-Oxolabda-8(17),12(*E*)-dien-15-oic acid, methyl-14,15-epoxylabda-8(17), 12(*E*)-Diene-16-oate and Turraeanin A	*Turreanthus africanus*	Seeds	Cameroon	Ngemenya et al. (2006)
3-Deoxyaulacocarpin A, Zambesiacolactones A and B, aulacocarpin A	*Aframomum zambesiacum*	Seeds	Cameroon	Kenmogne et al. (2006)
Galanal B, galanolactone, (*E*)-8,17-epoxylabd-12-ene-5,16 dial and (*E*) Labda-8,12-diene-15,16 dial	*Aframomum arundinaceum*	Seeds	Cameroon	Wabo et al. (2006)
7α-Obacunylacetate, 7α-acetoxydihydronomilin, 22-hydroxyhopan-3-one and 24-methylene cycloartenol	*Entandrophragma angolense*	Stem and bark	Cameroon	Bickii et al. (2007)
7-Deacetoxy-7-oxogedunin, Ekeberin C1–C3 and acyclic triterpenes	*Ekebergia capensis*	Stem and bark	Japan	Murata et al. (2008)
Bisnorterpenes	*Salacia madagascariensis*	Roots	USA	Thiem et al. (2005)
Cassane furanoditerpenes	*Caesalpinia volkensii*	Root and bark	Kenya	Ochieng et al. (2012)
Abietane diterpenes	*Plectranthus* spp.	Leaves	South Africa	Van Zyla et al. (2008)
Ferruginol	*Fuerstia africana*	Aerial parts	USA	Koch et al. (2006)
13-Epi-dioxiabiet-8(14)-en-18-ol	*Hyptis suaveolens*	Leaves	South Africa	Chukwujekwu et al. (2005)
Sesquiterpenes	*Acanthospermum hispidum*	Flowers, leaves and stems	Belgium	Ganfon et al. (2012)
Vernangulides A, B, Vernodalol and Vernodalin	*Vernonia angulifolia*	Aerial parts	Denmark	Pedersen et al. (2009)
Urospermal A-15-O-acetate	*Dicoma tomentosa*	Whole plant	Belgium	Jansen et al. (2012)
Artemisinin	*Artemisia annua*	Seeds	Italy	Reale et al. (2008)
Dehydrobrachylaenolide	*Dicoma anomala* subsp. *gerrardii*	Roots stocks	South Africa	Becker et al. (2011)
Okundoperoxide	*Scleria striatinux*	Roots	Cameroon	Efange et al. (2009)
Coloratane sesquiterpenes	*Warburgia ugandensis*	Stem and bark	Austria	Wube et al. (2010)
Beilshmiedic acid derivatives	*Beilschmiedia cryptocaryoides*	Bark	Germany	Talontsi et al. (2013)
3-Hydroxy-20(29)-lupen-28-ol	*Schefflera umbellifera*	Leaves	South Africa	Mthembu (2007)
Pristimerin	*Maytenus senegalensis*	Root and bark	Sudan	Khalid et al. (2007)

Table 4 continued

Compound	Plant	Source	Reported country	References
Pentacyclic triterpenes	*Nuxia sphaerocephala*	Leaves	Sudan	Mambu et al. (2006)
Lupeol and Lupeyl docosanoate	*Hymenocardia acida*	Bark and stems	Nigeria	Mahmout et al. (2008), Ajaiyeoba et al. (2008)
Betulinic acid	*Hypericum lanceolatum*	Stem and bark	Cameroon	Zofou et al. (2011)
3-Friedelanone	*Psorospermum glaberrimum*	Stem and bark	Germany	Lenta et al. (2008)
3-*O*-betulinic acid *p*-coumarate	*Baillonella toxisperma*	Stem and bark	Cameroon	Mbah et al. (2011)
2β,3β,19α-Trihydroxy-urs-12-20-en-28-oic acid	*Kigelia africana*	Stem and bark	Cameroon	Zofou et al. (2012)
Cucurbitacins B, D and 20-epibryonolic acid	*Cogniauxia podolaena*	Stem and bark	Congo	Banzouzi et al. (2008)

quinine, chloroquine, mefloquine and artemisinin among other drugs (Onguéné et al. 2013). However, the protozoans have developed resistance in many countries of the world over time towards the influential factors: poor hygienic conditions, poorly managed vector control programmes and no approved vaccines so far (White 2004).

Researchers currently put their research efforts on new antimalarial agents, mainly focusing on natural origin and the development of phytomedicines (Onguéné et al. 2013). Table 4 reviews the plant-derived compounds including alkaloids, terpenoids and triterpenoids for antimalarial properties. A total of 59 anti-plasmodial compounds including a potent antimalarial drug artemisinin were reported from different plants documented during 2005–2015 (Table 4). Notably, Table 4 displays a total of 35 plants belonging to 21 families under angiosperms showing antimalarial activity. The data summarized in the Table 4 highlight the rich diversity of plant natural products that manifest to be a promising source for the development of antimalarial agents.

Drug discovery from plants

The concept of 'the active principle' in medicine first reported in the fifteenth century; however, pure compounds isolated from the plant extracts were reported in the late eighteenth and earlier nineteenth century (Houghton 2001). It is important to note that plant-derived pure compounds had the similar effect as the plant extract and thus been promptly substituted in many cases as the important ingredient in medicines (Houghton 2001). Codeine and narcotine were the first natural compounds isolated from *Papaver somniferum*. Since then, numbers of compounds have been isolated from plants and many of these remain in extensive use in medicine as drugs (Houghton 2001; Lahlou 2013). Some of the prominent plant-derived commercially proven drugs, sources, brand names and their medicinal uses are shown in Table 5. Plant-derived molecules including secondary metabolites that demonstrate medicinal properties may act by similar or different mechanisms. The mode of antimicrobial action is similar between plant-derived quinones (bind to adhesions, inactivate enzymes and complex with cell wall) and flavonoids (bind to adhesions and complex with cell wall). However, polyphenols and tannins (enzyme inhibition, substrate deprivation, membrane disruption and metal ion complexation), terpenoids and essential oils (membrane disruption) and alkaloids (intercalate into cell wall) antimicrobial actions are varied in their mode of action (Pandey and Kumar 2013).

A total of 112 plants were studied during the period 2005–2015 of which, 110 purified bioactive compounds and 60 plant-derived extracts were reported and displayed significant antibacterial, antitubercular, and antimalarial activities (Tables 2, 3, 4). Totally, 40 and 20 plant extracts were reported for antibacterial and antitubercular activities, respectively, during this period (Tables 2, 3, 4). Although these plant extracts showed same therapeutic effects as pure compounds, further investigation of structural elucidation would afford novel chemical structures and new drugs. Plants reviewed in this study are reported from 36 countries around the world. Out of 112 plants, 41.96, 25.00, 10.71, 11.60, 8.90 and 1.78% were reported from Asia, Africa, Europe, North America, South America and Oceania, respectively (Fig. 1). Asia, the highest number (20) of plants, is reported for India for antibacterial and antitubercular activities in the period 2005–2015. Besides, the 112 plants revised in this study belong to 70 different plant families and 99% of them are angiosperms, which is displaying the

Table 5 Some of the drugs obtained from plants

Drug	Brand/trade name	Plant source	Medicinal use
Amitriptylin	Amitrip, Elavil, Levate	*Hypericum perforatum* L.	Mental illnesses, migraines, fibromyalgia
Midazolam	Versed, Dormicum, Hypnovel	*Hypericum perforatum* L.	Anesthesia, procedural sedation, trouble sleeping
Nevirapine	Viramune	*Hypericum perforatum* L.	Antiretroviral therapy to treat HIV/AIDS
Paroxetine	Paxil, Pexeva, Seroxat, Brisdelle, Rexetin	*Hypericum perforatum* L.	Antidepressant drug
Cyclosporine	Neoral, Sandimmune	*Hypericum perforatum* L.	Rheumatoid arthritis, Psoriasis, Crohn's disease, Nephrotic syndrome
Tacrolimus	Prograf, Advagraf, Protopic	*Hypericum perforatum* L.	Immunosuppressive drug
Simvastatin	Zocor	*Hypericum perforatum* L.	Lipid-lowering medication
Alprazolam	Xanax, Niravam	*Piper methysticum* G. Forst.	Anxiety disorders
Atropine	Atropen	*Atropa belladonna*, *Hyoscyamus* spp., *Datura* spp.	Antispasmodic for gastrointestinal tract, Pupil enlargement in eye
Pilocarpine	Isopto Carpine, Salagen	*Pilocarpus jaborandi*	Glaucoma Treatment, Pupil contraction in eye
Indinavir	Crixivan	*Hypericum perforatum* L.	Antiretroviral therapy to treat HIV/AIDS
Sertraline	Zoloft	*Hypericum perforatum* L.	Antidepressant drug
Scopolamine	Transdermscop, Kwells	*Atropa belladonna*, *Hyoscyamus* spp., *Datura* spp.	Preoperative Sedative, Antiemetic in travel sickness
Caffeine	Vivarin, Cafcit, Alert	*Coffea arabica, Thea sinensis*	Psychoactive drug, Central nervous system (CNS) stimulant
Digoxin	Lanoxin	*Digitalis lanata*	Improvement in force of contraction to remedy congestive heart failure
Ephedrine	Bronkaid, Primatene	*Ephedra* spp.	Relief of asthma and hay fever
Paclitaxel	Taxol	*Taxus brevifolia*	Chemotherapy medication used to treat number of types of cancer
Quinine	Qualaquin, Quinate, Quinbisul	*Cinchona* spp.	Antimalarial drug
Carbamazepin	Tegretol	*Plantago* sp.	Epilepsy, Neuropathic pain
Clopidogrel	Plavix	*Ginkgo biloba*	Heart disease, stroke
Reserpine	Raudixin, Serpalan, Serpasil	*Rauwolfia* spp.	Antipsychotic, Antihypertensive drug
Phenelzin	Nardil, Nardelzine	*Panax ginseng*	Antidepressant and anxiolytic drug
Vinblastine	Velban	*Catharanthus roseus*	Chemotherapy medication used to treat number of types of cancer
Prednisolon	Orapred, Prelone, PediaPred, Millipred	*Glycyrrhiza glabra*	Allergies, inflammatory conditions, autoimmune disorders
Hydrocortisone	Cortef, Solu-Cortef	*Glycyrrhiza glabra*	Thyroiditis, rheumatoid arthritis, dermatitis, asthma

therapeutic potential. Houghton (2001) reported that 25% of the drugs prescribed by physicians in the developed countries are obtained from flowering plants, angiosperms. Among the 70 families recorded, plants from Apocynaceae, Lamiaceae and Asteraceae showed antibacterial, antitubercular, and antimalarial activities, while plants from Acanthaceae, Lythraceae, and Euphorbiaceae disclosed antibacterial and antitubercular activities. However, plants from Fabaceae and Meliaceae exhibited antibacterial and antimalarial activities, but plants belonging to Celastraceae, Rutaceae, Hypericaceae and Zingiberaceae demonstrated antitubercular and antimalarial activities. The plant-derived extracts mentioned in this review were from various organic solvent extracts including aqueous extracts (Tables 2, 3). Furthermore, the total number of purified compounds given in this review is not an exact number reported in the mentioned period because we also have provided the class of compounds which may contain number of derivatives. Nevertheless, the data collected in this review impose and focus the value of plant antimicrobials against the lethal MDR pathogens including malarial parasites.

Future perspectives

Plants are the renowned natural laboratories for producing structurally unique, diverse and complex natural products. Besides the plants, extensive efforts are also being

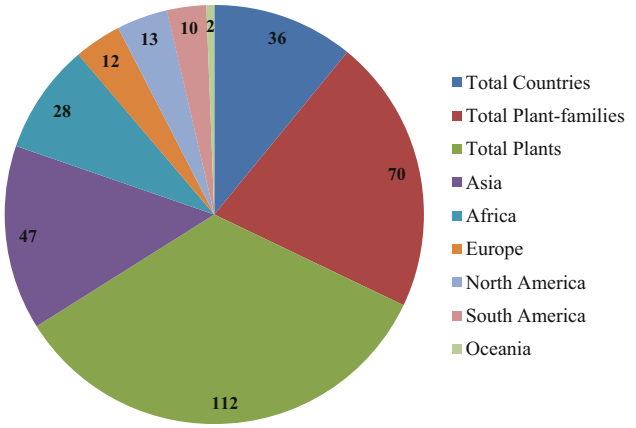

Fig. 1 Plants reported from worldwide during 2005–2015 for antibacterial, antitubercular and antimalarial activities

undertaken on microorganisms and other organisms from another living world, such as the oceans (Subramani and Aalbersberg 2013; Malve 2016) for pharmaceutically important biomolecules. However, in plants particularly angiosperms, only less than 10% have been screened for natural products discovery (Houghton 2001). Therefore, there is an immense scope for more fascinating bioactive compounds from flowering plants that will yield new/novel drugs. To access this hidden treasure, more integrative approach with various natural product discovery tools will be the key for success in discovery of phytomedicines. The complex and rich chemical diversity in plants pave to the isolation of natural products which is tough and laborious. Therefore, the significant application of tools such as high-performance liquid chromatography coupled to mass spectrometry (HPLC–MS), liquid chromatography–mass spectrometry (LC–MS), liquid chromatography–nuclear magnetic resonance–mass spectrometry (LC–NMR–MS), capillary NMR (cap-NMR) spectroscopy, LC–solid phase extraction (SPE)–NMR along with bioassay-guided fractionation and high-throughput bioassays will accelerate the access of plant-derived natural products. However, the substantial use of medicinal plants for drug discovery programme endangers their existence, so farming of medicinal plants must be instigated for assuring the future accountability (Lahlou 2013).

Conclusion

The use of herbs and herbal products has widely been accepted in our modern way of life and it is estimated that about 80% of the world's population still rely on traditional medicines for their primary health care. The significance of plant-derived natural products and their extracts used by the lay community has been realized and documented since ancient time. Interestingly, researchers and clinicians pay great attention to plant-derived secondary metabolites because of their antibiotic activity without conferring any antibiotic resistance. Hence, plant-based antimicrobials have widely been used as preventative and curative solutions against multi-drug-resistant pathogens. Globally emerging MDR and XDR pathogens are a serious concern. On the other hand, most of the chemically synthesised antibiotics can cause adverse side effects and are very expensive. Therefore, these days, there is an increasing inclination towards the use of an alternative source of medicines, particularly the medicinal plants. Several plant species have already been widely reported showing potential medicinal properties. However, the emerging new infections, diseases and rapid evolution of pathogens urge the researchers for further exploration into nature for novel natural products. Plants are certainly playing a dynamic role to control antibiotic-resistant bacterial infections. However, these plant-derived active principles should be taken for further research to translate this knowledge into potential therapeutic drugs.

Compliance with ethical standards

Conflict of interest No conflict of interest was declared.

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