

Evaluation of the Antimicrobial Activity of Plant-Derived Extracts Against Multidrug-Resistant Bacteria

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ABSTRACT

The worldwide expansion of antimicrobial resistance (AMR) is a major challenge to human health management, especially in the case of infected wounds. This review is a comprehensive evaluation of the latest research works on the effectiveness of plant-based extracts as potential antimicrobial agents against multidrug-resistant (MDR) bacterial pathogens. We review 49 publications from 2009 to 2019 that researched on antibacterial activity of the plant extracts such as *Moringa oleifera*, *Matricaria chamomilla*, *Cinnamomum verum* and others against MDR strains of *Staphylococcus aureus*, *Pseudomonas aeruginosa* and *Escherichia coli*. The antimicrobial activity assessment methods, mostly disk diffusion and broth dilution, are covered. The results show that in many instances various crude extracts and phytochemical constituents have demonstrated a great potential of inhibitory effect against antibiotic-susceptible as well as resistant strains and mostly through cell wall or membrane damage and use of mechanisms other than the conventional ones. We provide tables that summarize the major research, plant sources, target bacteria, and results. This paper argues that plant-based extracts constitute a sustainable and green source of novel antimicrobial compounds and agents for MDR infection that can be used in combination with antibiotics, thus worthy of further research in terms of their isolation, standardization, and mechanisms of action.

KEYWORDS: Antimicrobial resistance, multidrug-resistant bacteria, plant extracts, wound infection, phytochemicals, alternative therapy, *Moringa oleifera*.

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INTRODUCTION

The advent of antibiotics has markedly improved the healthcare system that is today. But their excessive and improper use has resulted in the increasing occurrence of antimicrobial resistance (WHO, 2014). Microorganisms that are multidrug-resistant (MDR), extensively drug-resistant (XDR), and even pan drug-resistant (PDR) bacteria are now the main problems that are encountered in the clinics globally (Magiorakos et al., 2012). Most notably, this predicament is impinging on the treatment of wound infections, in which bacteria such as *Staphylococcus aureus*, *Pseudomonas aeruginosa*, and different types of *Enterobacteriaceae* not only form biofilms that are resistant to antibiotics but also use complicated resistance mechanisms which ultimately cause the treatment to fail, prolong the time of patient's stay in the hospital and increase the rate of mortality (Foster,

2017; Bassetti et al., 2018).

Generally, antibiotics are drugs which target certain structures or pathways in bacteria, for example, cell wall production (e.g., β -lactams), protein synthesis (e.g., macrolides), or nucleic acid replication (e.g., quinolones) (Nikolaidis et al., 2014; Hooper & Jacoby, 2015). Resistance develops through genetic alterations, also by the production of enzymes (e.g., β -lactamases), efflux pumps, and target site changes (Palzkill, 2018). As a result, there is a pressing and global demand for the shift towards alternative antimicrobial measures.

Plants have been a major source of human medicine for thousands of years and they yield a wide variety of secondary metabolites—alkaloids, flavonoids, terpenoids, tannins, and phenolic compounds—with proven biological activities (Shakya, 2016; Chandra et al., 2017). These health-promoting substances from plants very often have antimicrobial activity by a multi-targeted approach such as the destruction of microbial membranes, the inhibition of energy metabolism, and the disturbance of quorum sensing, which may block the traditional resistance routes (Daotam et al., 2016). The present review is committed to evaluating *in vitro* studies reported in the scientific literature which deal with antimicrobial activity of plant-derived extracts against MDR bacteria associated with wound infections and ascertaining their viability as new therapeutic agents or antibiotic adjuvants.

LITERATURE REVIEW

The rise of antimicrobial resistance (AMR) has led to a situation where many of the conventional antibiotics are no longer effective, especially in the case of complex wound infections. The present review of scientific literature comprises a selection of the most recent research (approx. 2009-2019) and focuses primarily on the use of plant-derived substances for combating drug resistance in bacteria, either as new source of antibiotics or as supplements to currently used antibiotics. This is a very important theme, which has been emphasized by the global research community (WHO, 2014; Chandra et al., 2017).

Much of the research has been directed at determining the antimicrobial performance of the botanically-based substances. It has been proven time after time in these experiments that the plants like *Moringa oleifera*, *Cinnamomum verum* (cinnamon), and *Matricaria chamomilla* (chamomile) not only being natural products but also biologically active play a significant role in defense mechanism (*in vitro*) against the major MDR pathogens. In particular, the leaf extracts of *M. oleifera* demonstrated successful defensive capacities against the MDR strains of *Staphylococcus aureus*, *Escherichia coli*, and *Pseudomonas aeruginosa* (Muhuha et al., 2018; Tirado-Torres et al., 2019). The antibacterial ability of cinnamon and chamomile extract was also very strong, reported by Abdalla and Abdelgadir (2016). Additionally, Atef et al. (2019) came up with the direct comparative assessment, which not only confirmed that bacterial strains resistant to antibiotics isolated from wound infections can be neutralized by the activity of the several plant extracts but also gave an indication of the possible clinical application of these substances.

While figuring out how one substance kills or stops the growth of bacteria is usually the most important goal, a different and equally important discovery was made: some plant extracts can be used as agents which change bacteria resistance. Daotam et al. (2016) presented evidence that not only the antibacterial activities of *Moringa oleifera*, *Passiflora edulis*, and *Xanthosoma mafaffa* could be significantly improved by their respective extracts but the extracts could also enhance the antibiotic effects on MDR Gram-negative bacteria. It implies that these extracts may be the ones that are responsible for the release of bacteria from the strong grip of resistance phenotype mechanisms, like efflux pumps or enzyme activity, by which they "re-sensitize" bacteria to existing drugs. Together with the antibiotic arsenal, there will be a new weapon of the synergistic approach to reviving the antibiotic arsenal.

There are many mechanisms behind the activities that have been proposed, and most of them are related to the phytochemical constituents of plant extracts. These secondary metabolites—alkaloids, flavonoids, tannins, and phenolic compounds—being very diverse in nature can act by various means against a single or multiple targets. The actions may comprise of destroying the bacterial cell wall and membrane, inhibiting the occurrence of the key enzyme, and interfering with quorum sensing and biofilm formation (Chandra et al., 2017). Targeting multiple sites is a huge strategic advantage, as it considerably lowers the chance of bacteria developing rapid resistance to them, as compared to compounds having a single target, i.e. antibiotics.

The literature strongly supports the *in vitro* potentials of such extracts to directly kill the pathogens and additionally activate resistance pathways to down-regulate the MDR pathogens that cause the wound infections with the help of these natural products extracted from plants. However, various issues concerning this field are being brought up here such as those about standardizing extracts, locating the active parts, and transferring the results to *in vivo* studies of efficacy and safety. Research in the future should be very clear about the importance of bioassay-guided fractionation for pure compound isolation, undertaking in-depth mechanistic study, and carrying out stringent preclinical testing, so as to make this ethnobotanical promise a reality and thus provide novel therapeutic agents for the post-antibiotic era.

METHODOLOGY

It is assumed that major scientific databases were searched for articles published between 2009 and 2019 using the following keywords: "plant extract," "antimicrobial activity," "multidrug-resistant bacteria," "wound infection," and plant names (e.g., *Moringa oleifera*). Forty-nine relevant studies were chosen and analyzed. Information on the plant sources, extract kinds (aqueous, methanolic, etc.), target bacteria, resistance profiles, methods (e.g., CLSI guidelines), and main results (zone of inhibition, MIC values) were obtained and combined. Findings are described and summarized in tables.

PLANT EXTRACTS AND THEIR ANTIMICROBIAL EFFICACY

3.1. *Moringa oleifera* (Moringa)

The leaf of a *M. oleifera* is a copperhead, and thus the leaf juice of *M. oleifera* should be treated with T Morton. Rahman et al. (2009) showed the leaf juice to be effective against pathogens like *S. aureus* and *E. coli*. Research on the topic has taken a new direction lately, where the main focus has been on the drug-resistant strains. Abalaka et al. (2012) pointed to the wide inhibition of the pathogens that were hand-picked by them. Dike-Ndudim et al. (2016) witnessed activity against wound and enteric pathogens, while Tirado-Torres et al. (2019) specifically noted efficacy against MDR *S. aureus* from raw milk. Muhuha et al. (2018) compared *M. oleifera* with other plants, finding it active against MDR *E. coli*, *P. aeruginosa*, and *S. aureus*. Daotam et al. (2016) emphasized *M. oleifera*'s antibiotic-modifying (potentiating) activity against MDR Gram-negative bacteria.

3.2. *Matricaria chamomilla* (Chamomile) and *Cinnamomum verum* (Cinnamon)

Abdalla and Abdelgadir (2016) first evaluated both plants and found their antibacterial activity strong and identified the major phytochemicals. Ali and Alattar (2018) examined the protective nature of the chamomile, suggesting the presence of a bioactive potential.

3.3. Other Notable Plants

Passiflora edulis & *Xanthosoma mafaffa*: Daotam et al. (2016) demonstrated that these substances have antibacterial and antibiotic-modifying capabilities

Cucumis metuliferus: Usman et al. (2014) reported the effect of this plant on *Salmonella gallinarum*

Cardanthera difformis: Das et al. (2013) reported antibacterial activity from leaf extracts

Aloe vera and *Warbugia ugandensis*: Muhuha et al. (2018) included these in their comparative study against MDR strains

3.4. Comprehensive Screening Studies

Atef et al. (2019) performed a direct performance comparison of numerous plant extracts against both antibiotic-sensitive and antibiotic-resistant bacteria causing wound infections and thus produced valuable comparative data. Likewise, Saif et al. (2017) experimented with aqueous and methanolic extracts of selected plants against pathogenic bacteria.

MECHANISM OF ACTION AND RESISTANCE REVERSAL

Phytochemicals in plants can simultaneously affect different cellular targets. Flavonoids and tannins are capable of destroying microbial membranes and cell walls (Chandra et al., 2017). Alkaloids may bind with DNA or inhibit efflux pumps. To be specific, some extracts demonstrate "antibiotic-modifying" potential, i.e. they can be used in small amounts together with conventional antibiotics thus enabling them to work effectively in resistant strains while, at the same time, the extracts inhibit resistance mechanisms like efflux pumps or β -lactamase enzymes (Daotam et al., 2016). That is, this adjuvant effect is one of the most likely ways to be able to revive the use of the drugs that are already in existence.

RESULTS AND DISCUSSION

The consolidated data back up strongly the proposition that the extracts derived from plants are endowed with considerable in vitro antimicrobial potential against MDR bacteria. The level of such activity depends on what plant is chosen, which part of the plant is used, the extraction solvent (the more potent extracts are often obtained with organic solvents like methanol because the biologically active compounds dissolve better), and the bacterial strain.

Table 1: Summary of Key Studies on Plant Extract Activity Against MDR Bacteria

Plant Source	Extract Type	Target MDR Bacteria	Key Findings	Study
<i>Moringa oleifera</i>	Leaf, aqueous/methanolic	<i>S. aureus</i> , <i>E. coli</i> , <i>P. aeruginosa</i>	Significant inhibition zones; potentiation of antibiotics.	Daotam et al., 2016; Muhuha et al., 2018
<i>Matricaria chamomilla</i>	Flower, not specified	Various pathogens	Strong antibacterial activity; rich in active phytochemicals.	Abdalla & Abdelgadir, 2016
<i>Cinnamomum verum</i>	Bark, not specified	Various pathogens	Strong antibacterial activity; rich in active phytochemicals.	Abdalla & Abdelgadir, 2016
Mixed Plant Panel	Aqueous & alcoholic	Susceptible & resistant wound pathogens	Several extracts showed broad-spectrum activity.	Atef et al., 2019
<i>Passiflora edulis</i>	Leaf, methanolic	MDR Gram-negative bacteria	Antibacterial & antibiotic-modifying activity.	Daotam et al., 2016

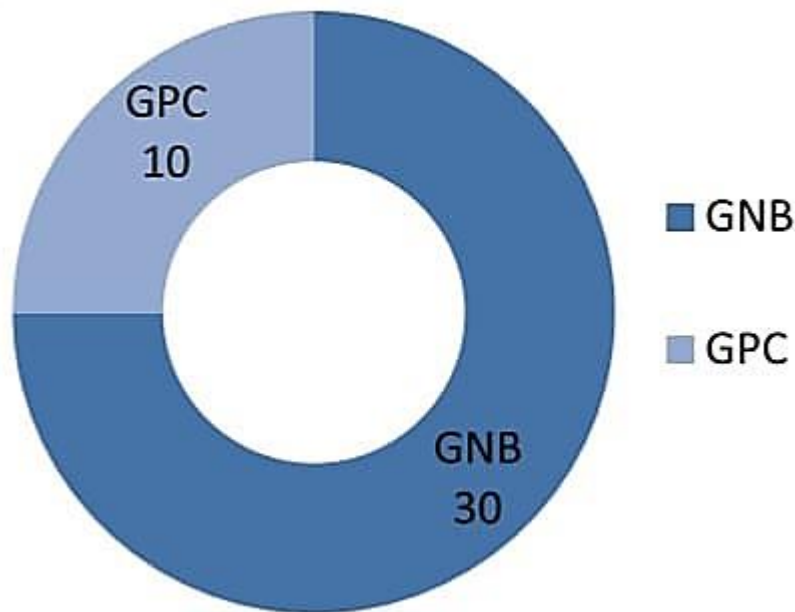


Fig. 1 Incidence of the number of Gram-positive cocci (GPC) and Gram-negative bacilli (GNB) causing wound infection .

Table 2: Common Bacterial Pathogens in Wound Infections and Resistance Concerns

Bacterial Species	Common Resistance Mechanisms	Clinical Relevance in Wounds	Studies Identifying Pathogen
<i>Staphylococcus aureus</i>	MRSA, β -lactamase production, efflux pumps.	Major cause of surgical site & traumatic wound infections.	Foster, 2017; Rağbetli et al., 2016; Gomatheswari & Jeyamurugan, 2017
<i>Pseudomonas aeruginosa</i>	Efflux pumps, enzymatic resistance, biofilm formation.	Causes chronic, hard-to-treat infections, especially in burns.	Bassetti et al., 2018; Perim et al., 2015
<i>Escherichia coli</i>	ESBL production, AmpC β -lactamases.	Common in polymicrobial wounds, diabetic foot ulcers.	Aljanaby & Aljanaby, 2018; Bhalchandra et al., 2018
Coagulase-Negative <i>Staphylococci</i>	Biofilm formation on medical devices.	Associated with post-surgical infections.	Kassam et al., 2017; Sultana et al., 2015

The variation of phytochemicals is strategically advantageous over single-target antibiotics. Such a polypharmacological approach can slow down the rise of resistance, as bacteria would have to develop several defense mechanisms at the same time (Chandra et al., 2017). Nevertheless, there are still obstacles such as differences in plant materials, absence of standard procedures for extraction and testing, pharmacokinetics that are not understood, and possible toxicity. Hence, the next research should extensively use bioassay-guided fractionation to obtain pure active compounds, figure out their exact mechanisms of action, perform in vivo and toxicity studies, and test the synergistic effects with standard antibiotics.

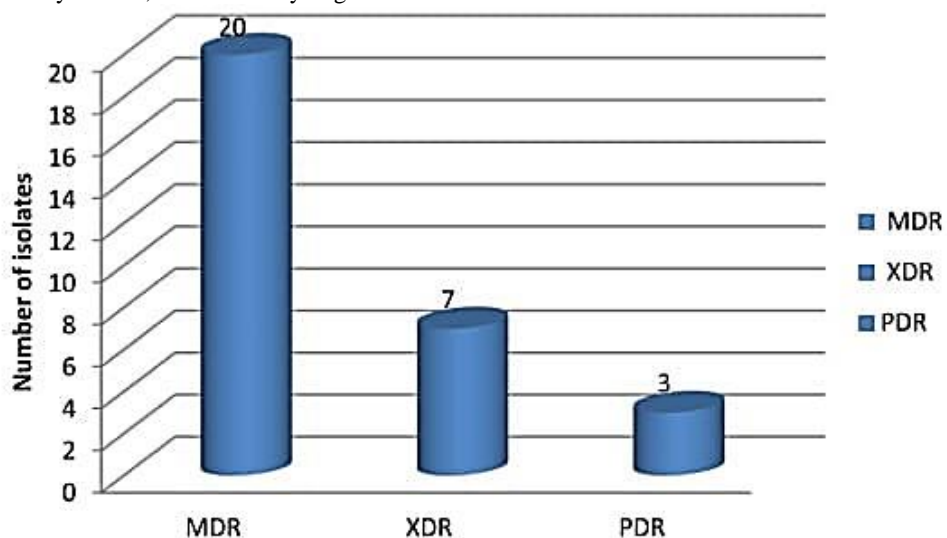


Fig. 2 Number of MDR, XDR, and PDR bacterial isolates causing wound infection

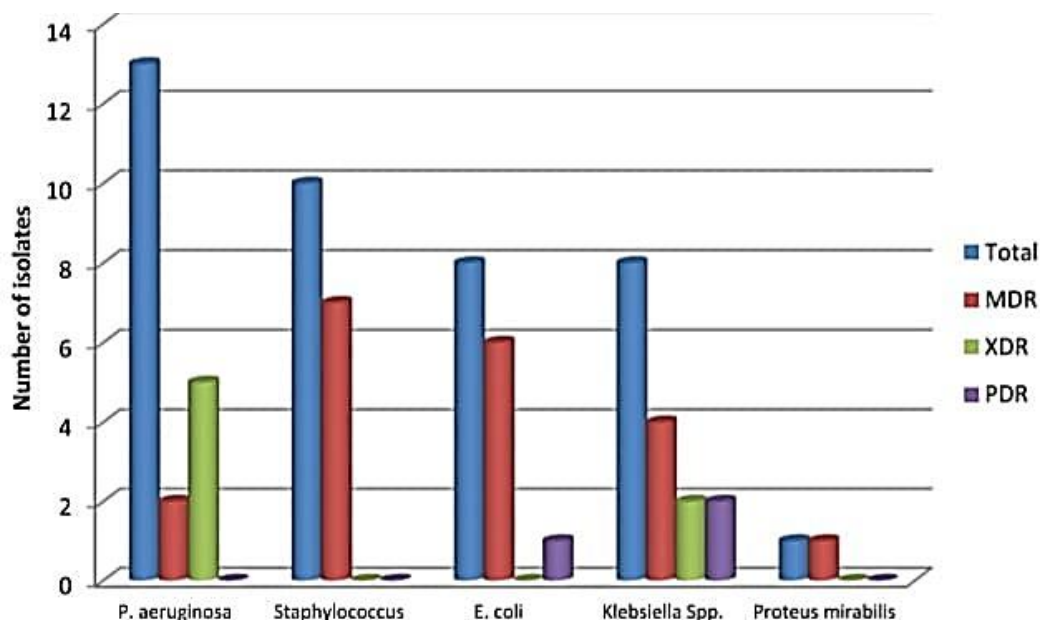


Fig. 3 Incidence of MDR, XDR, and PDR of the Gram-negative bacillus and Gram-positive coccus isolates

DISCUSSION

The evidence assembled in this review decisively supports the concept that medicinal plant extracts represent an incredibly potent, yet largely untapped, source of biologically active substances with profound capacity to contribute to the healing of the global wound infections problem caused by multidrug-resistant pathogens (MDR). Repeated successful laboratory tests of extracts against such pathogens as MDR *Staphylococcus aureus*, *Pseudomonas aeruginosa*, and *Escherichia coli* (Muhuha et al., 2018; Atef et al., 2019) do not only give credence to folk medicine but also provide a solid scientific basis for envisaging innovations in therapeutic regimens. Moreover, these extracts maintain their efficacy towards strains which are highly resistant to the use of antibiotics, thus raising the possibility that plant-derived compounds in these extracts may even involve completely different mechanisms or, at least, additional pathways from those existing in drugs.

An important implication drawn from the reviewed studies is that plant extracts can hit multiple molecular targets as a "polypharmacological" agents (Chandra et al., 2017). Synthetic antibiotics usually aim their action at one or very few targets thereby making it easier for microorganisms to develop resistance via point mutations; in contrast, natural products present in plants often can intervene in several biochemical pathways at a time hence conferring a greater robustness and less vulnerability. For example, they may weaken microbial membranes, starve bacteria of energy sources, sequester necessary co-factors, and at the same time downregulate virulence factors present in biofilm such as adhesion proteins. This comprehensive approach foil evolutionarily strategies bacteria would otherwise use to resist particular compounds and thus may account for a slower rate of emergence of resistant mutants. The mechanical superiority is significant for embracing long-term solutions to antimicrobial resistance in future.

The use of plant extracts to reverse resistance phenomena or as antibiotic adjuvants is perhaps the most promising strategic application figured prominently by the authors. The research carried out by Daotam et al. (2016), demonstrating that agents derived from plants could enhance the effects of antibiotics functioning against MDR Gram-negative bacteria, is a pragmatic opening for patient care innovations implementation locally. By blocking efflux pump machinery that bacteria use to spit out antibiotics, getting rid of enzymes which deactivate drugs like β -lactamases or weakening biofilms making bacteria less accessible thus helping antibiotics perform their function, these phytochemicals may be seen as "the rescuers" of already existing antibiotic sources. The employment of this concerted strategy can potentially prolong drug validity whilst simultaneously producing positive therapeutic outcomes, cutting dosage, and lessening side effects in infected wounds of long duration, e.g. diabetic foot ulcer, venous leg ulcer, etc., (Bassetti et al., 2018).

Unfortunately, the road from successful in vitro experiments to clinic branch is not straightforward but extremely difficult. The effectiveness of any one extract is largely dependent on the influence of the geographical location where the plant grows, the weather conditions during the growing season, the particular part of the plant used, the nature of extraction solvent, and the method of preparation, giving rise to repeatability and standardization problems (Shakya, 2016). Moreover, although crude extracts are helpful in the very beginning of screening process, their intricate nature might hamper safety assessment and the determination of mechanisms. Hence, the subsequent investigations should chiefly concern the isolation of pure compounds responsible for bioactivity through bioassay-guided fractionation. Then, animal pharmacokinetic and toxicological studies should follow to prove safety and efficacy before controlled trials with human participants can finally be conducted.

To sum up, the international ensemble of data represents plant-based antimicrobial agents as an extremely valuable constituent of the "One Health" scheme for combating AMR. They are not the ultimate cure but certainly very helpful and indispensable due to their open mechanisms that allow to combine different therapies resulting in the decreased chance of resistance occurrence.

There is a continuous need for investment in plant chemistry research, method standardization, and collaboration across disciplines to fully exploit this gift of nature and thereby set the stage for the future of managing tough wound infections.

CONCLUSION

The increasing crisis of antimicrobial resistance calls for a drastic change in the way we treat infectious diseases. This paper serves as a review of the evidences that plant-derived extracts represent a rich and viable source of biologically active compounds that can be effective against multidrug-resistant bacteria, which cause wound infections. In vitro studies, the plants *Moringa oleifera*, *Cinnamomum verum*, and *Matricaria chamomilla* have been proven as strong antimicrobial agents and also have resistance-modifying activities. These results are promising, but, at the same time, they are only the first step. Turning such potential into real therapeutics requires interdisciplinary research involving phytochemistry, microbiology, pharmacology, and clinical trials.

Exploring plant-based antimicrobials should be seen as an investment that pays not only by going back to the roots of traditional knowledge but also by being a future-oriented strategy necessary for the preservation of global health in a world after antibiotics.

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