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REVIEW ARTICLE

Herbal based inhibitors against efflux pumps in antibiotic resistant bacteria: A mini review

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ABSTRACT
Multidrug efflux pumps pose a threat through developing antibiotic resistance patterns in bacteria. A number of efflux pumps in antibiotic or multidrug resistant bacteria have been characterized which exerts the role in antibiotic extrusion from the cellular interior. To combat efflux pumps, there is an urgent need of efflux pump inhibitors to reduce or reverse the antimicrobial resistance in bacteria. Therefore, plant-derived compounds screened against pathogenic and antimicrobial drug-resistant bacteria were determined as potential efflux pump inhibitors. Still, the research is being carried out with immense zeal to explore potent and broad-spectrum efflux pump inhibitors from plant sources.
Key words: *Antibiotic resistance, Bacteria, Efflux pump, Efflux pump inhibitors, Plants*

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INTRODUCTION

Pathogenic microorganisms are the main entities to cause a range of ailments in humans, and therefore are believed to be a major factor of mortality and morbidity [1]. Physicians recommend a particular antibiotic/drug for curing diseases caused by microorganisms. Though, improper use of antibiotics has led to the development of antibiotic resistance patterns in microorganisms revealing significant health associated risk factors and posed a threat globally regarding human health [2]. The two important aspects including mutation in chromosomal genes and the trait of horizontal gene transfer result in development of intrinsic resistance in microorganisms towards antibiotics [3]. In addition to intrinsic resistance, bacteria can also develop resistance to antibiotics by several mechanisms such as modifying antibiotic targets, poor penetration of antibiotics in bacterium and inactivation of antibiotics by hydrolysis [4]. However, the most important intrinsic drug resistance has been analyzed due to the presence of the expression of drug efflux pumps [5].

The assembled protein complexes localized in bacterial membrane take part in construction of drug efflux pumps, and the fully active or overexpressed efflux pump extrude the antibacterial drug/antibiotics and toxins. Furthermore, the efflux pumps show the capability to decrease the antimicrobial drug concentration inside the bacterial cells to the sub-toxic level [6]. Drug efflux pumps show crucial roles in pathogenesis and virulence of bacteria, and also considered as an important constituent for biofim formation [7]. Even the importance of efflux pumps in bacterial pathogenesis and development of multidrug-resistant is well studies, still there are presently no inhibitors developed against drug efflux pumps in clinical uses [5]. Antibiotic resistance of bacteria coupled with the detrimental side effects of several antibiotics [8] have led to the investigation of novel antimicrobial substances from alternative sources [9]. Many bioactive compounds from natural resources have exhibited strong antimicrobial activity with antibiotics in a synergistic way and hence played the role of potent efflux pump inhibitors [10]. Medicinal plants having potential antimicrobial properties may serve as a natural pool of new and efficient efflux pump inhibitors [11]. Numerous reports are available on evaluating plants or herbal based compounds for antimicrobial activities, but limited reports deciphered the role of crude extract and pure

molecules of plants against multidrug-resistant or extensive drug-resistant microbial strains and other mechanisms of antimicrobial action targeted by plant derived bioactive compounds or products [12]. Capsaicin, catechol, gingerol, pinene, reserpine, resveratrol, and others are some important phytochemicals that have shown their activity as potential efflux pump inhibitors [9, 13, 14, 15]. But the ongoing and future studies are focused to explore more and novel phytochemicals as an efflux pump inhibitor for reversing the efflux pump mediated antimicrobial-resistant in bacteria. The present review provides a brief introduction of bacterial efflux pumps responsible for developing the pattern of antibiotic resistance and the inhibition of efflux pumps by herbal- based products.

EFFLUX PUMPS: STRATEGY OF BACTERIA FOR ANTIBIOTIC RESISTANCE

Bacteria contain special sets of protein commonly known 'efflux pumps', which show the role in expelling of substrates (particularly antibiotics) from the interior of the cellular environment to the outer environment and thus impart antibiotic resistance pattern in efflux pump bearing bacteria [16]. Efflux pumps are energy-dependent and based on their energy deriving mechanisms the efflux pumps can be classified in two broad categories a) primary efflux pump: derive energy from active hydrolysis of ATP, and b) secondary efflux pumps: derive energy from chemical gradients that formed by either protons or ions (such as sodium). Advancement in molecular biology gave a pace in the characterization of numerous kinds of efflux pumps in both Gram positive bacteria (such as *Clostridium difficile***,** *Enterococcus* spp**,** *Listeria monocytogenes***,** methicillin-resistant *Staphylococcus aureus* **(**MRSA**)** and *Streptococcus pneumoniae*) and Gram-negative bacteria (such as *Escherichia coli, Acinetobacter baumannii, Campylobacter jejuni, Klebsiella pneumoniae, Neisseria gonorrhoeae, Salmonella* spp*, Stenotrophomonas maltophilia, Pseudomonas aeruginosa and Vibrio cholera***)** [17, 18]. Furthermore, the microbial efflux pumps have the five super families such as 1) 'NorM', 'multi-antimicrobial extrusion protein family (MATE)', 2) 'QacA' major facilitators (MFS), 3) 'LmrA', 'ATP-binding cassettes (ABC)', 4) 'MexAB', 'QacC' 'small multidrug resistance family (SMR)', 5) 'resistance-nodulation cell division (RND)' [15, 19]. The types of efflux pumps are mainly responsible for causing drug resistance pattern in bacteria. The efflux transporters present in the cytoplasmic membrane are responsible for developing drug resistance in Gram-Positive Bacteria. On the contrary, the efflux pumps in Gram-negative bacteria are more complexed because of the multilayered cell envelop and construct a tripartite protein channel where extrusion of drugs takes place. Efflux pumps of bacteria can be either specific/selective or non-specific/non-selective in regards to the extrusion of drugs. TetA and AbaF have considered as specific as these selectively expel particular antibiotics (such as tetracycline and fosfomycin, respectively) [20]. Nonselective type of efflux pumps targets numerous classes of antibiotics rather than a specific type of antibiotic. For instance, NorA, MexAB-OprM, and BmrA extrude different classes of antibiotics, disinfectants, detergents, and dyes, and have been considered as MDR efflux pumps. Most of the efflux pumps are chromosomally encoded (such as NorA, NorB, MepA and MdeA of ***S.*** *aureus*) and generate intrinsic resistance towards a number of antibiotics in bacteria. On the other hand, some of the efflux pumps are plasmid-encoded (such as QacA/B of *S. aureus) and transposons encoded (such as* 'MefA' and 'MefB' of *Streptococcus* spp.), and give trasferable mode of antibiotic resistance in bacteria [21, 22].

NEED OF EFFECTIVE EFFLUX PUMP INHIBITOR: AN APPROACH TO REVERSE ANTIBIOTIC RESISTANCE

To explore the novel efflux pump inhibitors is worthwhile to circumvent the problem associated with antibiotic resistance. Efflux pump inhibitors are the special compounds showing the capacity to reduce or reverse the antibiotic resistance [23]. Efflux pump inhibitors mainly inhibit the activity of efflux pumps by adapting particularly one or more mechanisms to dispel drug transport. Moreover, efflux pump inhibitor might show its activity due to various mechanisms such as 1) Interfering in genetic regulation: down-regulation of gene expression pertaining to efflux pump, 2) Inhibition of assembly of efflux pump and blocking of pumps to evade substrate binding at the active site, 3) Abolishing energy metabolism needed to the proper functioning of efflux pumps [15, 24]. The present review is particularly focused on plant-based efflux pump inhibitors (EPIs), which are biomolecules or secondary metabolites derived from plants, and their inhibitory action against bacterial efflux pumps. Efflux pump inhibitors can be employed as an adjunct in a combination of antibiotics and thus could be attributed to improving the antibacterial activity of normal dose of antibiotic against bacteria bearing efflux pumps [9]. However, to use an efflux pump inhibitors commercially following things can be consider such as (a) the newly explored or synthesized EPIs must not be antibacterial, otherwise the trait of antibacterial activity of EPIs will lead to select the mutant strain, b) The EPIs should not target any eukaryotic efflux pump and possess

pharmacological benefits without showing any toxicity (c) The production and use of EPIs should be economically reason [24].

HERBAL BASED EFFLUX PUMP INHIBITORS

Microorganisms exert antimicrobial drug resistance, and hence such trait makes microorganisms stronger to sustain for ample period which obviously results in the development of various infectious and other diseases in human beings [25]. Therefore, herbal-based drugs or phytotherapy may provide as an alternative to synthetic antimicrobial drugs to protect against infectious diseases caused by pathogenic microorganisms. Plants are a natural source of antimicrobial substances in the form of 'phytochemicals', therefore plants can be used as a drug for inhibition of bacteria exerting antibiotic resistance patterns including efflux pumps [2]. Using plant-based drugs can reveal the foremost step for abolishing threat engendered by increasing antibiotic resistance in microorganisms [26]. Phytochemicals include a wide spectrum of 'chemical adjuvants' which have been determined to synergistically enhancement of antibiotics efficiency up to many folds. 'Reserpine' isolated from the root portion of *Rauwolfia serpentina*, is determined as a promising efflux pump inhibitor against efflux pumps of the RND and MFS superfamily [13]. The activity of efflux pump inhibitor of 'piperine' and its derivative (piperidine) has been depicted against *Staphylococcus aureus* and *Mycobacteria* spp. [27]. Moreover, piperine also decreased the minimum inhibitory concentration (MIC) of ethidium bromide in *Mycobacterium smegmatis* and indicated its potential application as an effective efflux pump inhibitor [28]. 'Geraniol' (monoterpenoid alcohol), extracted from *Helichrysum italicum*, has been found to decline the minimum inhibitory concentration of chloramphenicol in *Enterobacter aerogenes* expressing tripartite efflux pump such as 'AcrAB-TolC', and also described to change the drug resistance pattern in numerous Gram-negative bacteria [29]. Phenolic diterpenes including 'carnosic acid' and 'carnosol' (extracted from *Rosmarinus officinalis*), have been analyzed as Efflux pump inhibitors as these compounds enhanced the effectiveness of antibiotics (such as tetracycline and erythromycin) against *Staphylococcus aureus* expressing the ABC transporters such as TetK and MsrA efflux pumps [30]. 'Lysergol' extracted from *Ipomoea muricata* (L.) inhibited the ABC pump (YojI) of *Escherichia coli* [31]. The sap extracted from *Acer saccharum* was also depicted as an effective efflux pump inhibitor against strains of *Escherichia coli*, *Proteus mirabilis* and *Pseudomonas aeruginosa* [32]. 'Resveratrol' is a phytoalexin which previously assumed to be efflux pump inhibitor against strain of *Mycobacterium smegmatis* [33] and furthermore this compound was determined to make twofold influx of ethidium bromide into the bacterial cells and impaired the metabolic activities of *Acrobacter* strains [34]. Two more plant derived important compounds such as thymol and carvacol served as potential efflux pump inhibitors against food-borne pathogens [35]. 'Capsaicin' (as efflux pump inhibitor) inhibited the NorA efflux pump and also reduced the virulence of *Staphylococcus aureus* [36]. Bioactive phytochemicals such as Berberine and Palmatine were determined as efflux pump inhibitor in strain of *Pseudomonas aeruginosa* [37]. Coumarin (isolated from Mesua ferrea) was confirmed as a promising efflux pump inhibitor against NorA-over producing strain of *Staphylococcus aureus* [38]. p-Coumaric acid and its derivatives acted as potential molecules for efficient inhibition of RND efflux pump in *Pseudomonas aeruginosa* [39]. 'Ellagic' and 'tannic acids' as adjuvants or efflux pump inhibitors improved the activity of aminocoumarin antibiotics against the multidrug-resistant strain of *Acinetobacter baumannii* [40]. Gallotannin isolated from *Terminalia chebula* fruit showed efflux-pump inhibitory effect as one of the probable mechanisms of antibacterial action against multidrug resistant uropathogenic *Escherichia coli* [41]. Essential oils from three plant sources (such as *Salvia fruticosa*, *Salvia officinalis* and *Salvia sclarea*) were found to reduced the MIC (minimum inhibition concentration) of tetracycline and efflux/extrusion of antibiotic, and also estimated to decreased the Tet(K) gene expression in the strain of *Staphylococcus epidermidis* [42].

CONCLUSION

Reversal of antibiotic resistance is the foremost need for reducing the risk of antibiotic resistance in pathogenic bacteria. The overexpression of efflux pumps in bacteria results in antimicrobial resistance via extrusion of the substrate such as antibiotics. Therefore the role of efflux pump inhibitor becomes imperative to defend against multidrug-resistant bacteria for reducing the risk of antibiotic resistance. Plants in the form of natural sources of 'phytochemicals' provide an impetus to induce the anti-efflux pump activity against microorganisms as most of the bioactive phytochemicals acted as potential efflux pump inhibitors. Therefore, the exploration of novel and herbal based efflux pump inhibitors are needed to exemplify the splendid role of phytochemicals in resuming the currently used antibiotics.

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