



# Targeted Identification of Antibacterial Phytocompounds from Plant Extracts against Multidrug-Resistant Bacteria: A Systematic Review

Mohd Hasan Mujahid <sup>1</sup>, Tarun Kumar Upadhyay <sup>1\*</sup>, Vijay Jagdish Upadhye <sup>2\*</sup>

## Abstract

Extensive research on medicinal plants showed the presence of chemical entities that may be used to treat various ailments. These bioactive components can also be derived from multiple natural sources, including plants, microorganisms, animals, and marine organisms. The therapeutic action of these vigilant molecules (phytocompounds) has emerged as a new field to combat antimicrobial resistance development due to microbial resistance against chemically synthesized drugs. Problematic groups of multidrug-resistant (MDR) bacteria include vancomycin-resistant enterococci (VRE), Methicillin-resistant *Staphylococcus aureus* (MRSA), *Mycobacterium tuberculosis* (M. tb),  $\beta$ -lactamase-producing enteric bacteria (*Salmonella*, *E. coli*, etc) due to overuse and misuse of antibiotics leads to such state of emergence in communities and hospitals worldwide. Bacteria have remarkable mechanisms to evade and neutralize the effect of antimicrobial agents or antibiotic drugs through genes encoded at chromosomal, transposons, and R-plasmid levels. Through various mechanisms of action shown by bacterial species, in response to it selected screening of phytocompounds to

combat MDR bacteria that includes vernal strategies or approaches such as inhibition of MDR efflux pump, quorum sensing inhibition (QSI), phytochemical synergism with antibiotics, curb R-plasmid and its transfer, inhibit biofilm production, enzyme inactivation:  $\beta$ -lactamase. Considerable work has been done on the antimicrobial activity of plant extract, which led to the development of targeted screening of plant-derived phytocompounds and a system to test phytocompounds towards varied MDR strain bacteria for its efficacy will be the key to fight against such problematic situation. This review underlies various plant-derived phytochemicals and their mode of action towards different MDR bacterial species.

**Keywords:** Phytocompounds, Multidrug-resistant, Antibiotics, Antimicrobial resistance

## Introduction

Plants have abundant medicinal substances that show therapeutic potential for various diseases. The World Health Organisation (WHO) reported that about 80% of people depend on medicinal plants in underdeveloped countries (Mishra et al. 2013). It was found that only 28,187 medicinal species of plant are utilized by people out of 374,000 plant species for therapeutic use (Christenhusz and Byng 2016). Nowadays, it is a translation from synthetic drugs to naturally occurring compounds present in the form of secondary metabolites in plants, which are biosynthetically produced from primary metabolites such as carbohydrates and

**Significance** | Plant-derived phytocompounds are prominent in combating problematic multidrug-resistant (MDR) bacteria groups.

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amino acids. They can be categorized into different forms, such as terpenes, which have chemical constituents of carbon and hydrogen from mevalonic acid. Second, phenolics are formed from simple sugar and have hydrogen, oxygen, and benzene rings in their chemical structure. The third chemical compound is alkaloids, which include sulfur atoms, and the list also includes the members of flavonoids, coumarins, quinones, etc. (Khare et al. 2021; Harborne and Harborne 1984).

Systematic analysis by (Murray et al. 2022) found that the sub-Saharan region has a prevalence of antimicrobial resistance (AMR) is more serious in comparison to diseases like malaria and HIV (Human Immunodeficiency Virus). The World Health Organization (WHO), in a report describes antibiotic resistance and its fatality with a list of bacterial species (pathogens) which includes. First list critical pathogens: *Pseudomonas aeruginosa*, members of *Enterobacteriaceae* (*E. coli*, *Proteus*, *Klebsiella*, and *Serratia*), and *Acinetobacter baumannii*. Second list of high-priority groups: *Neisseria gonorrhoeae*, *Helicobacter pylori*, *Enterococcus faecium*, *Campylobacter spp.*, *Staphylococcus aureus*, and *Salmonellae*. The third group of medium-priority pathogens is *Haemophilus influenzae*, *Shigella spp.*, and *Streptococcus pneumoniae* (Asokan et al. 2019). There is an increased incidence of microbial drug or antibiotic resistance, becoming a serious global threat to human health. As multidrug-resistant (MDR) strains have created complications for pharmaceutical companies in drug development, these microbes are developing newer antibiotic-resistance mechanisms (Khare et al. 2021). Plant extracts have phytomolecules showing therapeutic potential used in powder or crude extract or even in purified form to show higher potency (Perumal Samy and Gopalakrishnakone 2010). Due to the exceptional therapeutic potential of phytochemicals, the FDA (Food and Drug Administration) has approved a few phytochemicals such as reserpine, paclitaxel, codeine, colchicine, and capsaicin to combat the MDR strains microbes (Kongkham et al. 2020). The efficacy and safety of phytochemicals made them an alternative to antibiotics. Varied phytochemicals such as terpenes (thymol, artemisinin, capsaicin, eugenol, and carvacrol), aldehydes (vanillin, and cinnamaldehyde), organosulfur compounds (allicin) and phenolic compounds (quercetin, curcumin, resveratrol, and apigenin) have antimicrobial (including antiviral, antifungal, antibacterial, and antiprotazoal). They also have immunomodulatory, antioxidant, and detoxification against mycotoxins, improving intestinal mucosa (Rossi et al. 2020). The rapid increase in the cases of antibiotic resistance poses a great threat to world health, with high rates of mortality, and morbidity also imposing a financial burden on the healthcare system. Hence, the WHO has approved the new medication practice towards antibiotic resistance (Diseases 2017; Razzaque 2021). Therefore, there is an urgent need for holistic screening of phytochemicals

towards multidrug-resistant (MDR) bacteria that develop resistance by acquiring new genetic markers or through mutation (Davies 1994). This review resumes the latest information, concepts, and progress by reviewing various articles regarding plant-derived phytochemicals and their effect on the varied MDR strains.

#### **Antibiotic toward Multi-drug resistance bacterial strain**

The available drugs (antibiotics) for bacterial infections have created chaos and a matter of concern worldwide due to their ineffectiveness towards the bacterial species. The bacterial strain has now become multidrug-resistant (MDR) due to various processes like resistance, hetero resistance, and tolerance that allow bacteria to withstand antibiotic treatment otherwise kill them (Pidcock 2012; Balaban et al. 2019), which can be seen in (Figure 1). Various strains of bacteria are creating emergence in communities and hospitals all over the globe. It includes enteric bacteria producing  $\beta$ -lactamase (*Klebsiella*, *E. coli*, *Shigella spp.*, *Salmonella*), vancomycin-resistant enterococci (VRE), Methicillin-resistant *Staphylococcus aureus* (MRSA), and *Mycobacterium tuberculosis* (M. tb) are problematic due to overuse and indiscriminate use of antibiotics (de Oliveira Santos et al. 2022).

#### **Antibiotic resistance**

Antibiotic resistance in the bacterial strain not only allows them to survive but also allows them to reproduce and grow. The most common indicator of antibiotic resistance is the minimum inhibitory concentration (MIC) rise. Higher resistance contributes to the higher MIC value. Antibiotic resistance can be inherited in the offspring of bacteria through gene transfer in the horizontal gene transfer in the resistance encoding genes (efflux pump and antibiotic inactivating enzymes encoding genes) and even through mutation (changing the antibiotic targets) that resistance passes to the bacterial population (Jacoby 2009; Du et al. 2018).

#### **Antibiotic persistence**

The bacterial (persisters) population survives due to their ability to growth arrest during exposure to fatal antibiotic (bactericidal) drugs, which are considered persistent, making them a heterogeneous population out of rest. Stress plays a big role in antibiotic resistance, and MIC is unaffected throughout the entire population since they are non-growers. This antibiotic persistence occurred throughout the population due to the genetic machinery to be persisters (Gollan et al. 2019). The prolonged antibiotic persistence by the bacterial population leads to the persisting of bacterial infection after the antibiotic treatment. Similar processes such as antibiotic resistance, implicated in immune evasion in the case of urinary tract infection (UTI) and biofilm formation (Mulvey et al. 2001; Lewis 2007).

#### **Antibiotic tolerance**

Antibiotic tolerance developed by the bacterial population makes them less susceptible to bactericidal antibiotics. There is an increase

in the duration of eradicating the bacterial population at a particular concentration of antibiotics. This occurred due to the diminished bacterial population being killed by the antibiotics as poor absorption of the drug with low target activity, leads to stress-induced reduced metabolism and growth (Fisher et al. 2017; Brauner et al. 2016). Antibiotic tolerance mechanism using extended production of  $\beta$ -lactamase by gram-negative bacteria has created a serious challenge for the antibiotics available in the market. The advent of plant metabolites can potentially obstruct the spread and growth of these harmful pathogenic microbes (Alam et al. 2022).

#### **Mechanism of antimicrobial resistance and way of secondary metabolites action**

The antimicrobial activity governed by agents, including bioactive molecules, has two mechanisms. Firstly, it can chemically interfere with the function or synthesis of vital biomolecules in the bacterium cell. Secondly, it can evade the conventional mechanism of antibacterial resistance. However, bacteria can naturally develop multiple antimicrobial resistance solely by selective pressures or acquire it from neighboring microbes (Magiorakos et al. 2012; Velayati et al. 2009). The pictorial representation of the mechanism of antimicrobial agents and resistance by microbes (Vaou et al. 2021) in (Figure 2).

#### **Pathogen resistance mechanism**

Antibiotic use and overuse have caused several harmful microorganisms to develop multi-drug resistance (MDR) (Zilberberg et al. 2014). Antibiotic resistance has been increased in low- and middle-income countries (LMICs). This is due to the poor diagnosis, uncontrolled use of antibiotics in animals and humans' case, unhygienic measures, and overproduction of meat and fish using antibiotics, leading to a higher overall infection burden and access to restricted costly second- or -third-party antibiotics (Laxminarayan et al. 2020). Antimicrobial resistance is a worldwide public health issue. At the molecular level, it is due to the resistance gene and its downstream products. This characteristic mechanism can be inherited or acquired from the rest of the pathogen, and as a result, these changes occur at the gene (DNA) level of bacteria and pass to offspring (Morar and Wright 2010). Various classes of phytochemicals such as alkaloids, terpenes phenols, and coumarins, have been used against antimicrobial resistance (AMR) (Khare et al. 2021). Bacteria can, however, resist antimicrobial agents via a variety of methods, as mentioned below.

#### **Structural modification of porins**

Porins are the protein structure found in the bacterial membrane that facilitates the diffusion of hydrophilic (water-loving) molecules across the hydrophobic (water-repellent) lipid bilayer of the outer membrane and primarily control the inflow of the antibiotics in microbes and these porin channels were initially identified in 1976 for *E. coli* (Pages et al. 2008; Nakae 1976). The number of porins in

bacteria is up to  $10^6$  copies per cell. This number varies based on environmental stimuli and has exclusion limits similar to the size of antimicrobial compounds (antibiotics), slowing the diffusion rate of these molecules and creating intrinsic resistance. (Achouak et al. 2001). This antibiotic resistance is generally found in gram-negative organisms such as *Pseudomonas* spp. and *Acinetobacter* spp. (Pages et al. 2008).

#### **Enzymatic inactivation**

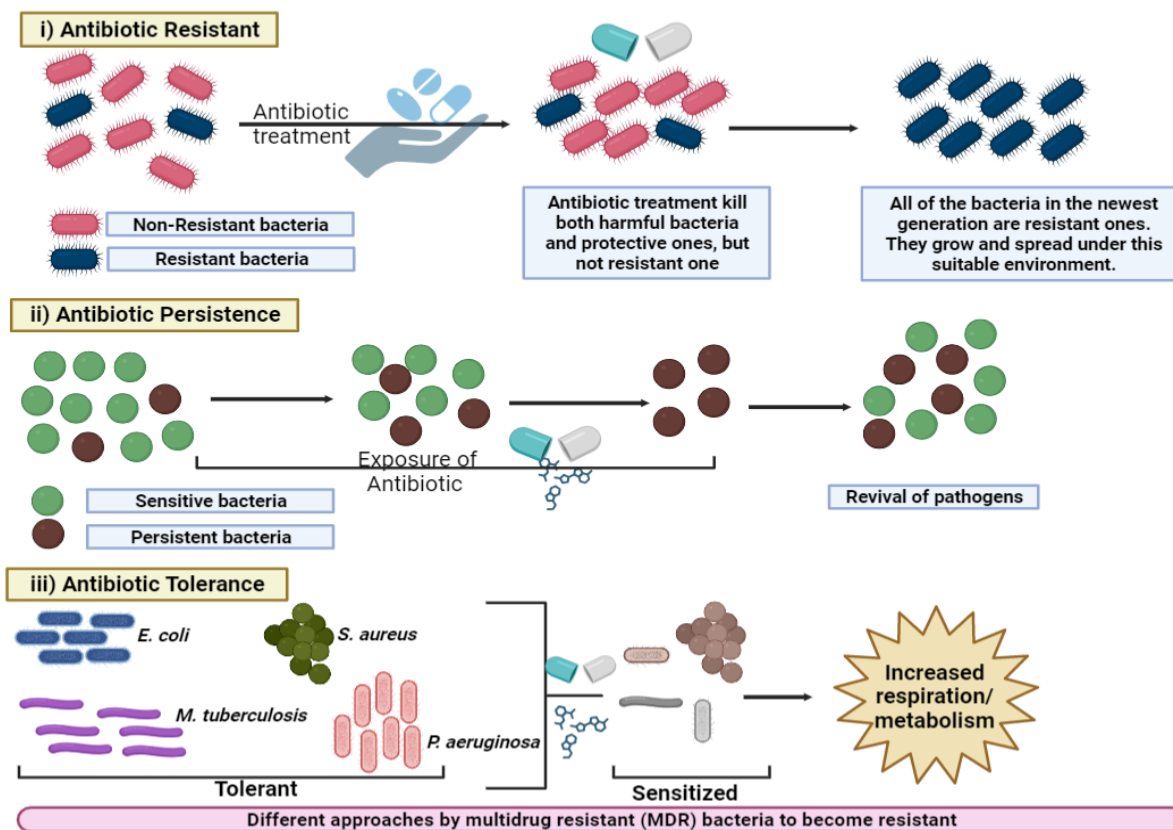
The mechanism of bacterial resistance towards antibiotics is remarkable, where the bacterial cell function is specific to fend off the effect of the toxic material or substance. Antibiotic inactivation using enzymes such as aminoglycosides in Gram-negative bacteria and  $\beta$ -lactamase modification are the key resistance enzymes (Fernández and Hancock 2012). At the genetic level, the intracellular targets have a modification (mutation). As they cannot attach to ribosomes, these changed products have a far decreased affinity for RNA and have prevented the creation of proteins (Shaw et al. 1993; Över et al. 2001).

#### **Efflux Pump (EP)**

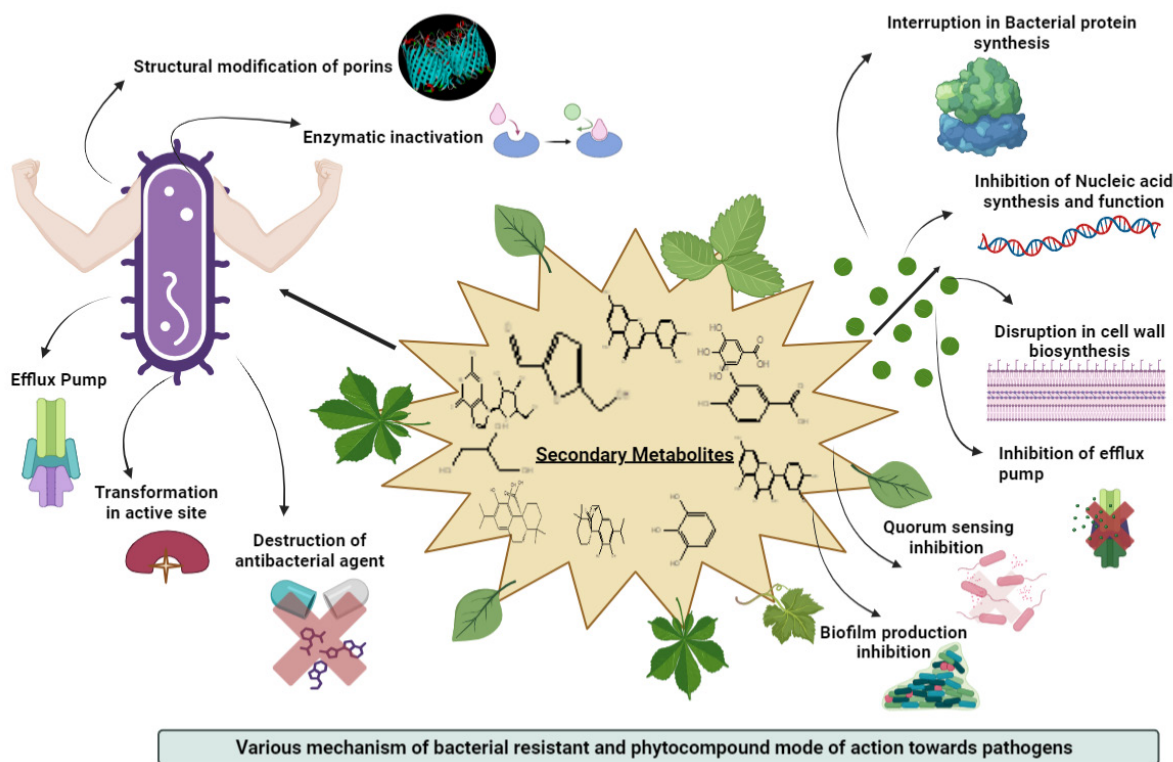
Antibiotic efflux was first identified in 1980 for tetracycline resistance found in enterobacteria (Levy 1992). Efflux pumps play a significant role in the antimicrobial resistance (AMR) towards antibiotics and act as an intrinsic resistance in the bacterial cell membrane. They actively pump out various compounds, including antibiotics, from the inner environment of the cell to the outside, contributing to bacterial multi-drug resistance (MDR). The intracellular concentration of the toxic material becomes lesser through EP and leads to resistance. Additionally, EPs can increase the pathogenicity of the bacteria directly or indirectly (Aygül 2015). There are varied numbers of gram-positive, gram-negative, and fungal species such as *Candida albicans*, *Staphylococcus aureus*, *Acinetobacter baumannii*, and *Pseudomonas aeruginosa* that exhibit antibiotic resistance through the EPs mechanism (P Tegos et al. 2011). It is a cause for worry to develop efflux pump inhibitors to treat MDR. Since a single multi-drug efflux pump may export many drugs (Nishino et al. 2021). Phyto-therapeutics eventually serve as a prospective pharmacological adjunct for pharmaceutical corporations as an inhibitor of efflux pumps (Khosravani et al. 2020). For example, the alkaloids and phenolic substances, block the efflux pumps of *E. coli* (Dwivedi et al. 2019).

#### **Transformation in the Active site**

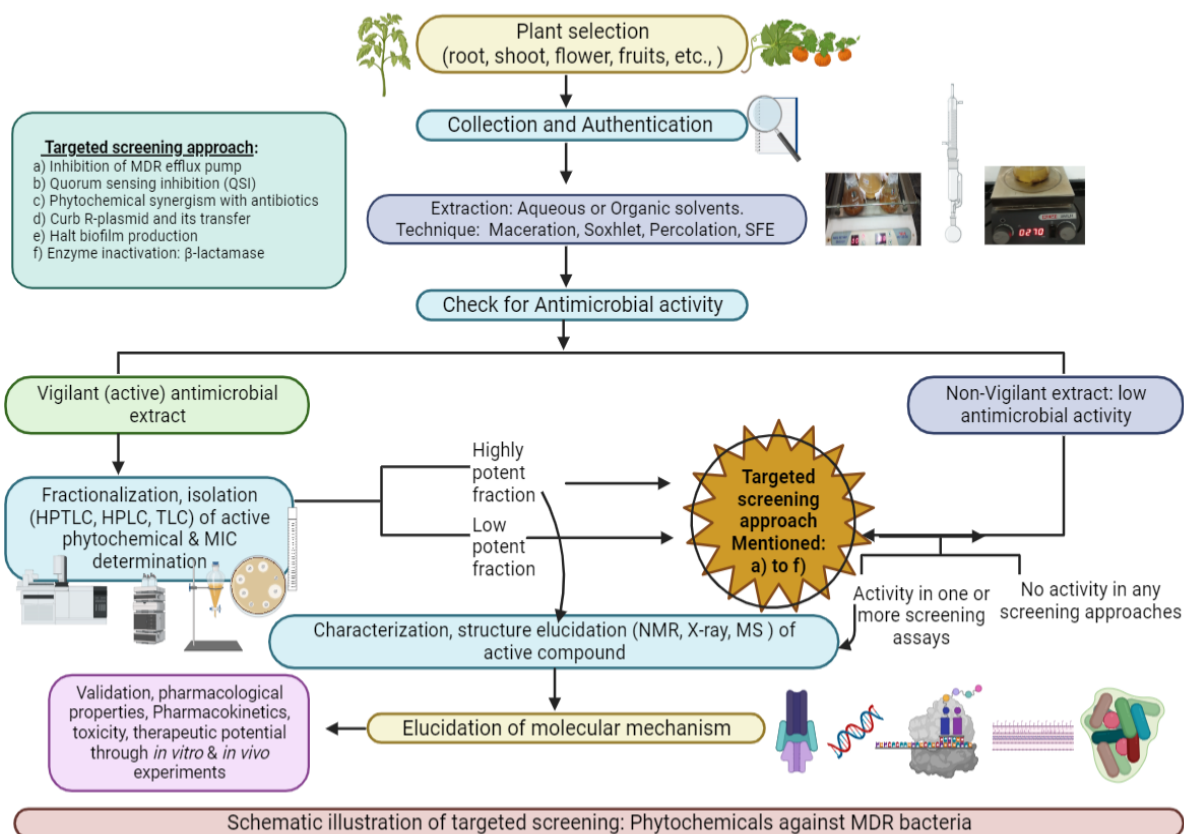
Another mechanism the bacterial machinery employs to evade the antibiotic effect is to change the conformation of the binding site of the drug receptor and decrease the drug's affinity (Munita and Arias 2016). Drugs such as Vancomycin (glycopeptide) and daptomycin (lipopeptide) work by preventing cell wall synthesis and depolarizing the cell membrane. While gram-negative bacteria have developed an intrinsic resistance to these drugs due to thick lipopolysaccharide (LPS) coating (Randall et al. 2013).



**Figure 1.** Systematic illustration of different approaches adopted by multidrug-resistant strain bacteria towards the exposure of antibiotics to become resistant.



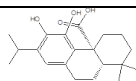
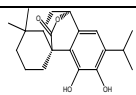
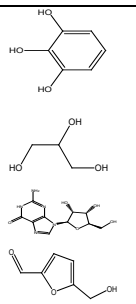
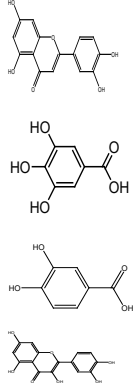
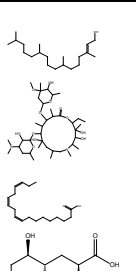
**Figure 2.** Pathogen resistance mechanisms and antimicrobial agent phytocompounds action of mechanism.

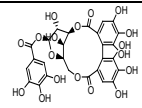
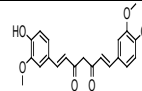
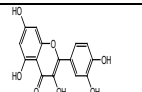
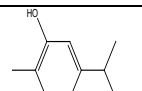
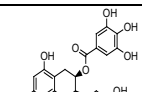
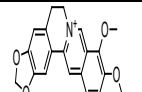
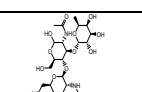
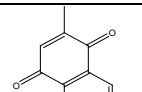


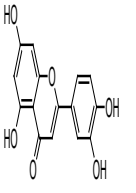
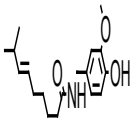
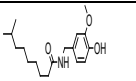
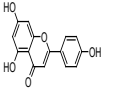
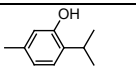
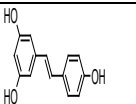
**Figure 3.** Various targeted screening approaches of plant-derived phytochemicals towards multiple-drug resistance (MDR) bacteria.



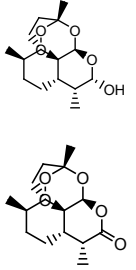
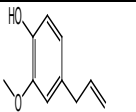
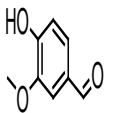
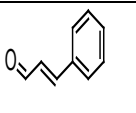

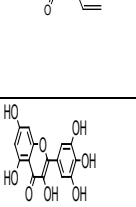
**Table 1.** Representation of various phytochemicals synergistic effect with antibiotics and way of mechanism of action.

S. No.	Phytochemicals/ crude extracts	PubChem Id	Structure	Source: Plant extract	Synergistic combined: Antibiotic	Targeting bacterial strain	Mechanism	Reference
1.	Carnosic acid	65126		<i>Rosmarinus officinalis</i> L.	Gentamicin, tetracycline, kanamycin, ciprofloxacin, and tobramycin	MRSA (Methicillin-resistant <i>Staphylococcus aureus</i> ), G <sup>+</sup> cocci	Act through efflux modulator via dissipating membrane potential	(Vázquez et al. 2016; Barni et al. 2012; Ojeda-Sana et al. 2013)
2.	Carnosol	442009		<i>Salvia officinalis</i> L. (sage)	Aminoglycosides	<i>E. faecalis</i> and <i>Enterococcus faecium</i>	Aminoglycoside-modifying enzyme or low aminoglycoside permeation into enterococcal cells	(Horiuchi et al. 2007)
3.	Crude ethanolic extract (Pyrogallol, Glycerin, Guanosine, and Hydroxymethylfurfurole)	1057, 753, 135398635, 237332		<i>Punica granatum</i> rind (PGR)	Gentamicin, ciprofloxacin, ceftazidime, meropenem, ciprofloxacin, cefoxitin, and levofloxacin	<i>Klebsiella pneumoniae</i>	Pyrogallol compound's action mechanism through enzyme inhibition by oxidized compounds	(Rafiq et al. 2017; Kumar and Vijayalakshmi 2011; Lima et al. 2016)
4.	Crude extract (luteolin, gallic acid, protocatechuic acid, and quercetin)	5280445, 370, 72, 5280343		<i>Grape pomace</i>	Tetracycline, β-lactam, chloramphenicol, quinolone, and fluoroquinolone.	<i>E. coli</i> , and <i>S. aureus</i> strains.	Changed the permeabilization of both the outer and inner membranes	(Sanhueza et al. 2017; Eumkeb et al. 2012)
5.	Crude ethanolic extract (3,7,11,15-Tetramethylhexadec-2-en-1-ol, Methylhexopyranoside, Linolenic acid, and 3-Deoxy-d-mannonic acid)	5366244, 2269, 5280934, 152990		<i>Lantana camara</i> L.	Streptomycin, Tetracyclin, Ciprofloxacin, Norfloxacin, and Nalidixic acid	Multi-drug resistant <i>S. dysenteriae</i> , <i>E. coli</i> , and <i>S. paratyphi</i>	-	(Ahmad and Beg 2001; Anand et al. 2018; Mansoori et al. 2020)

6.	Corilagin	73568		<i>Arctostaphylos uva-ursi</i>	Cefmetazole, and oxacillin	Methicilli-resistant <i>S. aureus</i> (MRSA)	Probably as a result of the altered target of penicillin-binding protein (PBP2a)	(Shimizu et al. 2001)
7.	Curcumin	969516		<i>Curcuma longa</i>	Colistin, polymyxin B, tetracycline, and ciprofloxacin	Methicillin-resistant <i>S. aureus</i> (MRSA), and polymyxin-resistant <i>K. pneumoniae</i>	Inhibition of the NorA efflux pump	(Itzia Azucena et al. 2019; de Assis Souza et al. 2013; Taghavifar et al. 2022; Jaberi et al. 2018)
8.	Quercetin	5280343		<i>Rubus fruticosus</i>	Amoxicillin	Amoxicillin-resistant <i>Staphylococcus epidermidis</i> (ARSE) strain	Inhibiting $\beta$ -lactamase activity, increasing cytoplasmic membrane (CM) permeability, cytoplasmic and peptidoglycan membrane disruption, level of protein amide I and II increased, and decreased fatty acid (FA) in bacterial cells	(Zahoor et al. 2020; Siriwong et al. 2016)
9.	Carvacrol (Monoterpene)	10364		<i>Thymus and Oregano family of herbal plants</i>	penicillin or clindamycin	<i>S. pyogenes</i> ,	Cell membrane damage, increasing permeability of cell membrane	(Vinciguerra et al. 2019; Wijesundara et al. 2021)
10.	(-)-Epigallocatechin gallate (EGCG)	65064		<i>Camellia sinensis</i> (Tea)	$\beta$ -Lactams	Methicillin susceptible <i>Staphylococcus aureus</i> (MSSA) and MRSA	Creating interference with the cell wall integrity material peptidoglycan	(Zhao et al. 2001)
11.	Berberine hydrochloride (BBR)	12456		<i>Berberis vulgaris, Phellodendron amurense, and Coptis chinensis</i>	Erythromycin, linezolid, and cefoxitin	Methicillin-resistant <i>Staphylococcus aureus</i> (MRSA)	Inhibiting the NorA pump will enhance the effects of the antibiotics	(Herrmann et al. 2016; Imenshahidi and Hosseinzadeh 2016; Wojtyczka et al. 2014; Ettefagh et al. 2011)
12.	Bromelain	44263865		<i>Ananas comosus</i>	Tetracycline, and amoxicillin	<i>Streptococcus mutans, E. faecalis, Aggregatibacter actinomycetemcomitans</i>	It breaks down the peptide connections in bacterial cell wall.	(Varilla et al. 2021; Dighe et al. 2010; George et al. 2014)
13.	Plumbagin	10205		<i>Plumbago zeylanica L.</i>	Gentamicin	Carbapenem-resistant <i>Klebsiella pneumoniae</i> (CRKp)	Increasing TCA efflux and PMF (proton motive force)	(Muralidharan et al. 2018; Chen et al. 2020)

14.	Luteolin	5280445		<i>Eclipta alba</i>	Amoxicillin	Amoxicillin-resistant <i>Escherichia coli</i> (AREC)	Modification in the outer and inner membrane, inhibition of peptidoglycan and protein, reduction in the activity of $\beta$ -lactamase	(Shaikh and Sathaye 2011; Eumkeb et al. 2012)
15.	Capsaicin	1548943		<i>Capsicum annuum</i> (chili peppers) fruit	Ciprofloxacin	<i>S. aureus</i> SA-1199B	Ability to lessen <i>S. aureus</i> SA-1199B's infiltration into macrophages	(Kalia et al. 2012)
16.	Dihydrocapsaicin (DHC)	107982		<i>Capsicum annuum</i> (chili peppers) fruit	Rifampicin	<i>M. smegmatis</i>	Potent efflux pump inhibition.	(Prasch et al. 2019)
17.	Apigenin	5280443		<i>Justicia gendarussa</i> (Brum.f)	Gentamicin, vancomycin, ampicillin, and erythromycin	<i>Porphyomonas gingivalis</i> , <i>Streptococcus mutans</i> , <i>Streptococcus ratti</i> , <i>Streptococcus cricetid</i> , <i>Actinobacillus actinomycetemcomitans</i> , <i>Streptococcus gordonii</i> , <i>Fusobacterium nucleatum</i> , <i>Porphyomonas gingivalis</i> .	Membrane modification, induces cell wall permeability, and inhibition in the glycopeptide to halt cell wall synthesis and improve the potency of the antimicrobial agents.	(Cha et al. 2016; Kumar et al. 2018; Okano et al. 2017)
18.	Thymol	6989		<i>Thymus vulgaris</i> L.	Chloramphenicol, streptomycin, gentamicin,	<i>S. typhimurium</i> , <i>Acinetobacter baumannii</i> , and <i>Pasteurella aerogenes</i>	Alter the cell membrane, and target the ribosomal (30S) subunit leads to a misread of the mRNA triplets	(Gan et al. 2023; Zeng et al. 2020; Madigan et al. 2003)
19.	Resveratrol	445154		<i>Veratrum grandiflorum</i> O. Loes.	Polymyxin B, Colistin	MDR <i>P. aeruginosa</i> , <i>K. pneumoniae</i> , <i>E. coli</i> , <i>Citrobacter braakii</i> , <i>Enterobacter cloacae</i> , <i>Stenotrophomonas maltophilia</i>	Antibiofilm activity	(Qi et al. 2022; Cannatelli et al. 2018)



20.	Artemisinin (ARS) derivative dihydroartemisinin	68827, 3000518		<i>Artemisia</i> spp. ( <i>A. annua</i> , <i>A. abyssinica</i> , and <i>A. absinthium</i> )	Colistin, rifampicin, ethambutol, isoniazid, amikacin	<i>M. tuberculosis</i> H37Ra, and <i>M. bovis</i> BCG	Induced increasing level of peroxides treated with drug pair	(Zhou et al. 2022; Patel et al. 2019; Rana et al. 2013)
21.	Eugenol	3314		<i>S. aromaticum</i>	Colistin, cefotaxime, and ciprofloxacin	<i>E. coli</i> , <i>C. albicans</i> , <i>S. mutans</i> , ESBL-QR Enterobacteriaceae	RT-PCR analysis showed down-regulation of <i>mcr-1</i> gene, down-regulation of the efflux pump, $\beta$ -lactamase gene inhibition, and overexpression of porin	(Wang et al. 2018b; Jafri et al. 2019; Dhara and Tripathi 2020b)
22.	Vanillin	1183		<i>Vanilla planifolia</i>	Imipenem, gentamicin, tetracycline, erythromycin, and norfloxacin	MDR strains of <i>P. aeruginosa</i> 24, <i>E. coli</i> 06, and <i>S. aureus</i> 10,	Through the inhibition efflux pump or by the elimination of plasmids	(Gallage and Møller 2015; Choi et al. 2013)
23.	Cinnamaldehyde	637511		<i>Cinnamomum</i> (cinnamon bark oil)	Colistin, ciprofloxacin, and cefotaxime	<i>P. aeruginosa</i> (MDR-PA), ESBL-QR Enterobacteriaceae	Cell death occurred due to damage to bacterial cell membranes, and leakage in cytoplasmic substances. RT-qPCR revealed it altered the gene expression of porins ( <i>ompF</i> , <i>ompC</i> , etc), antibiotic-resistant gene ( <i>blaSHV</i> , <i>QnrB</i> , etc), and efflux pump genes ( <i>acrB-K. pneumoniae</i> , and <i>acrB-E. coli</i> )	(Shreaz et al. 2016; Bakkali et al. 2008; Dhara and Tripathi 2020a)
24.	Allicin (diallylthiosulfinate)	65036		<i>Allium sativum</i> L. (garlic)	Oxytetracycline, ciprofloxacin, levofloxacin, azithromycin, and rifaximin	<i>E. coli</i> , and <i>Bacillus subtilis</i>	Biofilm reduction, and protein denaturation	(Bhattacharya et al. 2022; Borlinghaus et al. 2014)
25.	Myricetin	5281672		<i>Myrica rubra</i> ( <i>Myrica rubra</i> (Lour.)	Vancomycin and oxacillin	<i>Vancomycin intermediate-resistant S. aureus</i> (VISA) strains, and <i>methicillin resistant S. aureus</i> (MRSA)	Inhibition of functional membrane microdomains (FMMs) on $\beta$ -lactams	(Song et al. 2021; Pinto et al. 2020)

Phytochemicals play their role indirectly to modulate the various processes to halt AMR or MDR through synergistically combining with antibiotics (Li et al. 2018), antibiofilm properties (Uddin Mahamud et al. 2022), and immunomodulatory effect (Al-Hatamleh et al. 2020).

### **Destruction of antibacterial agent**

The bacterial species can also render the efficacy of the antibacterial agent through the deactivation or degradation of drug material. Bacterial machinery can produce enzymes in a targeted manner to break down the antibacterial compounds. Such as the  $\beta$ -lactamase enzyme produced by the bacteria that inactivate and hydrolyze the  $\beta$ -lactam ring present in antibiotics like penicillin, carbapenems, and cephalosporins, which is essential for the antibiotic's activity (Blair et al. 2015; Dever and Dermody 1991).

### **Antibacterial Phytochemical Action Mechanism**

These phytochemicals are organic substances found in plants and have a bactericidal nature. As there are various ways these bioactive compounds halt the growth and survival of bacteria. Here are a few typical ways that antibacterial phytochemicals work.

#### **Interruption in bacterial protein synthesis**

Plant-derived phytoconstituents can interrupt bacterial protein synthesis through various measures. It is a practical approach to target phytochemicals towards the protein machinery "ribosomes" on a specific site. It prevents the progression along m-RNA (messenger RNA) synthesis during the translation process, inhibiting the new protein formation. Allicin is an organosulfur, and its mechanism includes protein synthesis inhibition, DNA synthesis inhibition, and sulfhydryl-dependent enzyme inhibition (Reiter et al. 2017).

#### **Inhibition of nucleic acid synthesis and function**

Nucleic acid synthesis can be interrupted in MDR bacterial strains by certain phytochemicals such as polyphenols, resveratrol, curcumin, genistein, allicin, etc., and have a role in disease prevention and cellular functions. Polyphenols such as tannins, flavonoids, and phenolic acids are secondary metabolites with antibacterial and antibiofilm properties (Suganya et al. 2022). Resveratrol in the presence of copper ions has prooxidant activity and can cause DNA damage (Hwang and Lim 2015). Curcumin((1E,6E)-1,7-bis-(4-hydroxy-3-methoxyphenyl)) is the main active component of the *Curcuma longa* (turmeric), a plant that belongs to the ginger family (Kocaadam and Şanlıer 2017). Furthermore, it has been found that curcumin associated with bacterial DNA causes a bacteriostatic effect (Zheng et al. 2020). An isoflavonoid called genistein is mostly present in leguminous plants. It was found that severe inhibition of DNA and RNA synthesis in the case of *Vibrio harveyi* (Gram-negative) bacteria within 15 minutes with morphological changes (formation of filamentous cells) after the addition of isoflavone was found in the bacterial culture at a concentration of 0.1 mM (Ulanowska et al.

2006). It was found that allicin prevents bacteria from synthesizing DNA, RNA, and protein. While the effect on RNA synthesis is severely affected (Feldberg et al. 1988). A study by (Son et al. 2006) found that allicin effect on the drug-resistant and drug-sensitive strain of *Mycobacterium tuberculosis* (*M. tb*) a minimum inhibitory concentration (MIC) was found and a significant anti-mycobacterial action towards multifarious strains including multiple drug resistance (MDR) and extensively drug-resistant (XDR).

#### **Disruption in cell wall biosynthesis**

Phytochemicals are bioactive compounds found in the arsenal of problematic strains of bacteria. It can prevent bacteria from properly constructing the cell wall, an essential step in their development and survival. The structure of the cells lost its typical spherical form and developed abnormally elongated shapes with ruptured or torn cell walls (Wijesundara et al. 2021). Household spice *Allium sativum* (garlic) contains "Allicin," an organosulfur or sulfur-containing phytochemical containing at least one carbon-sulfur link. Including allicin, many more sulfur-containing phytochemicals, such as glucosinolates, isothiocyanate, and thiosulfonates, and many have been identified. The mechanism demonstrates that allicin generally suppresses the activity of the cell wall biosynthesis enzyme known as MurA (Laddomada et al. 2016; Barbieri et al. 2017). A polyphenolic compound (-)-epigallocatechin gallate (EGCG) is catechin only found in the leaves of *Camellia sinensis* (Green tea) (Cabrera et al. 2006) have antimicrobial activity and inhibit cell wall synthesis. Tannins (tannic acid) are polyphenolic compounds and have antibacterial activity towards Gram-positive ( $G^+$ ) and Gram-negative ( $G^-$ ) bacterial species and show bacteriostatic effect rather than bactericidal effect (Boakye et al. 2016). It was found that tannins impede the development of bacteria through varied methods, including disruption of the cell membrane, iron chelation, blockage of the fatty acid synthetic pathway, and suppression of cell wall formation (Farha et al. 2020).

#### **Inhibition of efflux pump**

Efflux pumps generally transport proteins through which various biomolecules travel inside the bacterial cell. MDR strain bacteria (or superbugs) can retard numerous antimicrobial compounds including antibiotics and thus reduce the effectiveness of the drug. However, many attractive bioactive compounds reverse multi-drug resistance by acting as efflux pump inhibitors (EPIs), thus ameliorating the effect of antimicrobial agents (Ohene-Agyei et al. 2014). Resveratrol (RSV; trans-3,4',5-trihydroxystilbene) is a polyphenolic compound found in foods such as red wine, grapes, and peanuts in higher amounts (Guthrie et al. 2017). As an efflux pump inhibitor, the resveratrol enhanced the chlorhexidine sensitivity towards *A. baumannii* due to increased ethidium bromide accumulation (EtBr) (Singkham-In et al. 2020). RSV

controls the growth of *E. coli* by inhibiting the AcrAB-TolC pump. Hence RSV may function as an efflux pump inhibitor and act as a potential drug to combat antibiotic resistance by lowering the drug resistance and raising the intracellular concentration of antibiotic compounds (Zhang et al. 2020). Curcumin a bioactive compound obtained from turmeric can inhibit the NorA efflux pump in *Staphylococcus aureus* and reduce antibiotic resistance (Jaberi et al. 2018). Another natural phenolic compound Silybin (flavonolignan) found in the seeds of milk thistle, inhibits the MRSA's efflux mechanism by targeting the NorA gene and reduces the bacteria's resistance to antibiotics (Wang et al. 2018a).

#### **Quorum sensing inhibition (QSI)**

Quorum sensing (QS) is a cell-cell communication system developed by bacteria to coordinate between them related to gene expression and behaviour. It led bacteria to control gene expression on a large level rather than individual cells. Autoinducers (AIs) are the fundamental regulatory molecules for QS that release, create, and respond to external signaling molecules (Papenfort and Bassler 2016). Increased knowledge of QS has led to developing QSI as a therapeutic targeted approach to fight against bacterial infection and lessen antibiotic resistance. The phytochemicals can disrupt the communication or coordination between the bacterial population. This technique blocks or inhibits the signaling molecules AIs involved in QS, lowering bacterial pathogenicity (virulence) and inhibiting biofilm formation. (Gao et al. 2003). A phytoconstituent pyrogallol with its analogues present in *Embllica officinalis* shows antagonist behaviour towards autoinducer-2 (AI-2) (Ni et al. 2008). Extracts of numerous plants such as *T. capensis*, *P. nigra*, *R. officinalis*, *L. nobilis*, *P. alba*, and *J. sambac*, have been found to exhibit anti-quorum sensing ability and to diminish the production of violacein (Brackman et al. 2009).

#### **Biofilm production inhibition**

Antibiotic resistance and biofilm production are closely related processes, are the research subjects of various researchers, and are linked with the phenotypic traits of bacterial pathogens (Whelan et al. 2020). The term "biofilm" refers to a microbial colony attached to some biotic or abiotic substratum and enclosed within it and self-produced extracellular polymeric substances (EPS) such as protein, polysaccharide, and DNA matrix (Costerton 1999). This shield of biofilm makes the bacteria very resistant to antimicrobial therapies as they are protected from various stresses such as pH changes, dehydration, harmful radiation, and antibiotic substances and promotes bacterial persistence and survival in the environment (Dufour et al. 2010; Flemming 2016). MDR strain bacteria pose a great threat to the care system as they produce biofilm and show resistance to various antibiotics such as in the case of *Enterobacteriaceae* extended spectrum of produces  $\beta$ -lactamases (ESBLs) and also the extended intrinsic chromosomal AmpC  $\beta$ -lactamases (Poole 2004; Wiedemann 1986). Biofilm production can

be inhibited or disrupted through the anti-adhesion activity of plant-derived phytochemicals that can interfere with the various stages of biofilm production and act as a natural biofilm production inhibitor (Klančnik et al. 2021). Quorum sensing (QS) plays a significant role in the development of infectious diseases brought on by bacteria. Hampering the biofilm formation through bioactive compounds produced by plants and prokaryotes leads to the reduction of quorum sensing, termed quorum quenching (QQ) (Kalia 2013). It was found that polyphenolic compounds such as epigallocatechin gallate (EGCG) and catechins found in green tea inhibit the adhesion property of bacteria to a substratum and hence reduce biofilm production (Xu et al. 2012).

#### **Methods for Targeted Screening of Phytochemicals against MDR Bacteria**

Targeted screening of phytochemicals refers to analyzing a group of plant extracts with bioactive compounds that show pharmacological, therapeutic, or other ailments' treatment, and these biological activity qualities are known as targeted screening of phytochemicals. This is important as the bacteria are continuously evolving new resistance mechanisms, due to mutation or acquirement of the new genes through varied processes such as transduction, transformation, and conjugation, and the majority of the resistance in bacterial populations is due to multi-resistance encoding genes to one or antibiotics by R-plasmid (Davies 1994). Plant-based drugs are widely utilized by people all around the world and are well explored by the different tribal and traditional groups and the knowledge about the benefits of plants just passes from generation to generation without any records. These traditional medicines (TM) are regularly used by 3300 million people around developing nations (Pan et al. 2013). The therapeutic value lies in the extracts prepared through these medicinal plants, and various ethnic groups rely on these TM to preserve their health and well-being (Noorhosseini et al. 2020). Plant samples are collected from garden areas or the available natural habitats (Hamilton 2004). The essential step in separating and recovering bioactive compounds from plants is extraction. Various methods are employed to obtain efficient extracts using different solvent materials ranging from aqueous to organic and non-polar solvents touching the targeting analytes and the optimum size must be less than 0.5 mm (Scientific 2013). Various conventional methods are used to extract crude and powdered extracts such as maceration, infusion, percolation, digestion, infusion, and soxhlet. Advanced techniques are also available that have higher yield percentages and use fewer solvents for extraction, such as pressurized liquid extraction (PLE), microwave-assisted extraction (MAE), supercritical fluid extraction (SFE), etc. These methods are classified as "Green Extraction" methods because they offer benefits over conventional procedures, such as good yield, rapid extraction time, low energy use, a small quantity of organic or hazardous solvent, and are simple to run

(Khoddami et al. 2013). Afterward, the extracts are checked for the MDR strain bacteria (antimicrobial) for their efficacy through the mentioned different approaches for the inhibition of microbial growth by phytochemicals as discussed above that include mainly, a) Inhibition of MDR efflux pump, b) Quorum sensing inhibition (QSI), c) Phytochemical synergism with antibiotics, d) Halt R-plasmid and its transfer, e) Inhibit biofilm production, f)  $\beta$ -lactamase enzyme inhibition. Extracts having an active antimicrobial property with low MIC (minimum inhibitory concentration) and shown efficacy towards the mentioned a) to f) approaches can further be fractionalized, isolated, and characterized using sophisticated techniques like HPTLC (high-performance liquid chromatography), HPLC (high-performance liquid chromatography), TLC (thin layer chromatography), MS (mass spectrometry), and for the structural elucidation of phytochemical technique like NMR (nuclear magnetic resonance), X-rays, etc. Further, *in vitro* and *in vivo* studies for elucidating molecular mechanisms for the mode of action, pharmacokinetics, toxicity, pharmacological, and pharmacodynamics studies were assessed and can be visualized in (Figure 3).

#### Targeting Antibiotic resistance through the Synergistic Effect of Antibiotics and Bioactive compounds

Worldwide there is an upsurge in antimicrobial resistance (AMR) in both Gram-negative and Gram-positive which has created an alarming situation for the healthcare system. The bacteria known as ESCAPE, which stands for *Acinetobacter baumannii*, *Enterobacter* species, *Pseudomonas aeruginosa*, and *Klebsiella pneumoniae*, have risen with large cases of AMR and may act as a major source of life-threatening nosocomial infection (or hospital infection) (Santajit and Indrawattana 2016). Phytochemicals with tiny molecular weights (MW<500) are known as phytoalexins and have lower antibacterial activity than conventional antibiotics. The phenomena of bacteria's sensitivity to an antibiotic's killing (bactericidal) or growth-inhibiting (bacteriostatic) effects can be managed using synergistic interaction between the natural bioactive compounds and antibiotics can be depicted in (Table 1). The combined properties of these two substances enhance the therapeutic impact and are greater than the individual effects (Chung et al. 2011). The synergistic effect of antibiotics with the naturally derived phytochemicals generally decreased antibiotics' minimum inhibitory concentration (MIC), thus making them more susceptible to these drugs (Coutinho et al. 2009).

#### Conclusion and Future Perspective

To fight against microbial illnesses, plants produce a wide range of chemical molecules known as phytochemicals or bioactive compounds. Phytochemicals can be used in place of standard drugs at a lower cost to overcome chemoresistance. Standard medicine is

accessible in the clinic, but the process is costly and has a high risk of complications. A significant task in developing new phytochemicals is transitioning from *in vitro* research to *in vivo* investigations and, eventually, to human clinical trials. Clinical trials should be done to determine the efficacy, safety, bioavailability, pharmacokinetics, and interaction of these bioactive substances and their formulation with the internal biomolecules. It is critical to remember that the participants' health comes first and to assess the immediate and long-term detrimental impacts and results of these phytochemicals. Substantial scientific study is required in safety, efficacy, and pharmacokinetics to develop medicines based on phytochemicals. Research has demonstrated that the bioactive substances in plant extracts and how they interact with common drugs can reduce drug resistance and have therapeutic benefits. Considering these facts, phytochemicals can be utilized in place of traditional medications, such as antibiotics.

#### Author contributions

T.K.U. conceptualized. T.K.U., V.J.U., and M.H.M. designed, M.H.M. and T.K.U. reviewed, wrote and edited the manuscript. All authors approved the final version of the manuscript.

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The authors have no conflict of interest.

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