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Delineating the role of phytocompounds against anti-bacterial drug resistance–An update

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Abstract: Antibacterial resistance developed by bacteria due to the unlimited use of antibiotics has posed a challenge for human civilization. This kind of problem is not limited to India only, but it is a global concern. Nowadays, many treatments and medicines for bacterial diseases have been developed. However, they possess some drawbacks. Therefore, the alternative medicine has been used to target the drug resistant mechanisms and such medicines have less side effects which is becoming necessary. Natural products have traditionally or historically been of importance for the development of antibacterial agents and are also known to overcome bacterial drug resistance by directly targeting the drug resistance mechanisms in bacteria. In recent years, researchers have also focused on new drug discovery from plant-based research. They have looked on various phytocompounds as antibacterial agents. In the current review, we report various classes of secondary metabolites such as phenolic compounds, flavonoids, alkaloids, saponins, terpenes, quinones, and some essential oils that have been used as an antibacterial agent. In addition, we also discuss several mechanisms behind bacterial multi-drug resistance that are used during bacterial pathogenesis.

Introduction

Anti-bacterial drug resistance is a serious concern during the treatment of infectious bacterial diseases. Globally, about one-half of the human deaths are caused by infectious diseases and mainly bacterial diseases are of great concern. They can be transmitted from one person to another person by direct contact and indirectly transmitted through air, water, food, insect, and other environmental factors. Before 19th century, many bacterial diseases did exist and many people from the same village died because there was no cure for these diseases (Lederberg, 2000).

Nowadays, various drugs have been developed for bacterial disease treatments and they have potential benefits but they also possess some drawbacks. The larger use of anti-bacterial drugs and antibiotics leads to the development of drug resistance in bacteria, which has become one of the serious concerns in biomedical science (Lederberg, 2000). At present, the anti-bacterial drug resistance remains a challenge to the researchers worldwide. The continuous and excessive use of anti-bacterial drugs and antibiotics has led to the origin of the new drug resistant microbes known as 'superbug'. This is a result of adaptation or evolution of bacteria, which increases their potency to tolerate or degrade the drugs as compared to the parent strain (Chandra *et al.*, 2017). Many antibiotics were discovered in 19th and 20th centuries which majorly belong to the class of beta-lactam

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and glycol-peptides respectively. These antibiotics inhibit the peptidoglycan synthesis in bacteria. Some antibiotics inhibit the replication, transcription, or protein translation in bacteria (Kumar *et al.*, 2018). However, many of these antibiotics do not show any therapeutic effect against infectious bacterial diseases as a result of bacteria have developed the resistance. According to the World Health Organization (WHO) report (WHO, 2017), the list of antibiotic-resistant bacteria was presented based on the available evidence and priority. This list includes the species of different bacterial strains such as *Acinetobacter, Pseudomonas, Enterobacter, Enterococcus, Staphylococcus, Helicobacter, Neisseria, Salmonella, Campylobacter, Haemophilus*, and *Shigella* which were resistant to antibiotics like penicillin, ampicillin, fluoroquinolone, vancomycin, and carbapenem. Most of the diseases caused by these bacterial species were difficult to control by available anti-bacterial drugs (WHO, 2017). In the WHO 2002 report, the drug resistance was the emerging cause of deadly infectious diseases like tuberculosis, respiratory tract diseases, meningitis, and diarrhoea (WHO, 2002).

In 2016, Tsitsopoulos *et al.* (2016) demonstrated the nosocomial bloodstream infections (NBSI) due to the antibacterial drug resistance and analysed the neurosurgical patients for 10 years from 2003 to 2013. A total of 236 patients were identified with NBSI and 378 cases were recovered from the blood culture. In this case, Gram-negative bacteria were predominant compared to the Gram-positive bacteria. They found some common drug resistant bacteria such as *Staphylococci, Pseudomonas aeruginosa, Klebsiella pneumoniae*, and *Acinetobacter baumannii*, where *Staphylococcus aureus* was found resistant for methicillin. Likewise, *Acinetobacter baumannii* and *Pseudomonas aeruginosa* were found resistant for carbapenem. Similarly, in 2020, Naderi *et al.* (2020) also reported the pattern of antibacterial drug resistance of non-fermenting Gram-negative bacteria from Burn wound. It is a long-term major infection with thermal injuries associated with mortality. They examined a total of 100 samples of wounds, where *Acinetobacter baumannii* and *Pseudomonas aeruginosa* were identified to be the most common type of pathogens. *Pseudomonas aeruginosa* showed resistance against amikacin, imipenem, ciprofloxacin, gentamicin, ceftazidime, and piperacillin-tazobactam. Similarly, *Acinetobacter baumannii* showed 100% resistance for ceftazidime followed by other antibiotics such as imipenem, amikacin, ciprofloxacin, gentamicin, etc. *Escherichia coli* and *Staphylococcus aureus* were also reported in the drug resistance list against several antibiotics. Like, *Escherichia coli* showed resistance against ciprofloxacin, ampicillin, ceftriaxone, amoxicillin, and trimethoprim. While, *Staphylococcus aureus* exhibited resistance for erythromycin, trimethoprim-sulfamethoxazole, and methicillin. From the last 5-year periods (2012–2017), the augmentation in the antibacterial drug resistance rate against these two species was found to be a major global concern (Monteiro *et al.*, 2020).

According to the Centers for Disease Control and Prevention (CDC), more than 2 million people were affected by antibiotic-resistant bacteria each year (Pourmand *et al.*, 2017). Similarly, WHO states that the Global Antimicrobial Surveillance System (GLASS) provided an evidence for the occurrence of antibiotic-resistant bacterial infection in 500,000 people across 22 countries. Till now, total 52 countries have enrolled in GLASS. Out of 52, 40 countries have provided the information of the national surveillance system and furthermore, 22 countries gave the data on antibiotic resistant bacteria. The commonly reported bacterial strains were *Staphylococcus aureus, Klebsiella pneumoniae, Escherichia coli, Mycobacterium tuberculosis*, and *Staphylococcus pneumoniae*. Therefore, GLASS encouraged to each country for the surveillance of antibacterial drug resistance which will be helpful for their prevention as well as it will be useful in new drug discovery (WHO, 2019).

Thus, for the development of a new class of antibiotics, there is a prerequisite to understand the relation between the human-associated bacteria and the mechanisms behind the pathogenesis of infectious diseases. Presently, researchers attempt to fight against these drug resistant pathogens and to eliminate them at rapid pace. Currently, the use of traditional medicine or phytomedicine has drastically increased because phytomedicinal compounds are natural, inexpensive, non-toxic, and able to overcome the drug resistance problem easily. Some phytocompounds alone or in combination with antibiotics have shown a good therapeutic efficacy against antibacterial drug resistance by targeting different mechanisms that bacteria generally use to develop resistance. Some phytocompounds also inhibit the bacterial biofilm formation which is responsible for drug resistance in bacteria. Therefore, it is imperative to prevent the resistance developing mechanisms in bacteria and there is need of continuous search for discovering novel antibacterial drugs that have less side-effects. Nowadays, traditional medicine which is described in Ayurveda, Sushruta Samhita and Charak Samhita is largely explored by researchers all over the world. The traditional medicines have numerous medicinal properties with negligible side-effects. Therefore, the market size of their usage is continuously increasing day-by-day. In this review, we have comprehensively discussed different types of natural phytocompounds like phenolic, tannins, coumarins, alkaloids, flavonoids, terpenes, etc., and their therapeutic role in the elimination of anti-bacterial drug resistance condition. These phytocompounds are elaborated in brief using suitable examples. Further, we described different mechanisms of anti-bacterial drug resistance that are targeted by natural phytocompounds. Besides it, recent challenges and future perspectives in this research area are also discussed.

Phytocompounds and Anti-Bacterial Drug Resistance

Traditionally, medicinal plants are regarded as a treasure of phytocompounds that have excellent therapeutic properties. The crude phytoextracts or purified phytocompounds show good antibacterial activity by which they can inhibit the bacterial growth or completely kill the bacterial pathogens. In recent years, the use of phytomedicine has increased tremendously. Nowadays, the antibacterial drug resistance is a serious threat to humans. It is speculated that we would soon run out of antibiotics because bacteria get evolved and later develop resistance to the antibiotics that are being continuously used. Therefore, natural products are a good

source for new anti-bacterial drug discovery. In the past two decades, many researchers have focused on natural products and ethnomedicines for the discovery of new antibacterial drugs. The active phytocompounds isolated from the medicinal plants which are responsible for bactericidal and bacteriostatic actions are flavonoids, terpenes, alkaloids, tannins, lignans, phenols, saponins, and other secondary metabolites as listed in Tab. 1 and shown in Fig. 1. The essential oil of some of the medicinal plants also shows the antibacterial activity and prevents the bacterial drug resistance.

Phenolic Compounds

Phenolic compounds are a large class of secondary metabolites which contain benzene ring with a hydroxyl group. In 2019, Jafri *et al.* (2019) reported that *Streptococcus mutans* displayed a resistance to azithromycin, ampicillin, vancomycin, and ceftriaxone antibiotics. For inhibiting this anti-bacterial drug resistance, they used eugenol (4-allyl-2-methoxyphenol), which is a phenolic compound extracted from the essential oil of *Syzygium aromaticum*. Also, the eugenol exhibited the

TABLE 1

Phytocompounds with their plant sources and antibacterial activity

Name of phytocompounds	Sources	Antibacterial activity	MIC/MBC/BIC/ MLC/*SIC*	References
Phenolic compounds				
Eugenol	*Ocimum gratissimum**	*Streptococcus mutans*	100 µg/mL	Jafri *et al.*, 2019
Garcinoic acid	*Garcinia kola*	*Staphylococcus aureus, Enterococcus faecalis, Escherichia coli, Pseudomonas aeruginosa*	25–100 µg/mL	Viault *et al.*, 2021
Honokiol	*Magnolia officinalis, Magnolia obovate*	*Staphylococcus aureus*	191.62 mg/g	Lovecká *et al.*, 2020
Scopoletin	*Morinda citrifolia*	*Staphylococcus aureus*	100 µg/mL	De La Cruz-Sánchez *et al.*, 2019
Curcumin + Meropenem	*Curcuma longa**	*Streptococcus pyogenes, Staphylococcus aureus, Acinetobacter baumannii, Pseudomonas aeruginosa, Klebsiella pneumoniae* and *Escherichia coli*	128 to 512 µg/mL	Yasbolaghi Sharahi *et al.*, 2020
Thymol and Hydroquinone	*Camellia sinensis*	*Pseudomonas aeruginosa, Salmonella typhimurium, Escherichia coli, Staphylococcus aureus, Staphylococcus capitis, Corynebacterium diphtheria*	8–20 mg/C^3	Sultan *et al.*, 2020
Flavonoids				
Quercetin	*Triplaris gardneriana*	*Staphylococcus aureus, Bacillus subtilis, Salmonella choleraesuis*	9.967 ± 1.01 mg/g	Macêdo *et al.*, 2019
Luteolin	*Lonicera japonica**	*Trueperella pyogenes*	78 µg/mL	Guo *et al.*, 2020
Morin	*Maclura pomifera**	*Escherichia coli, Enterococcus hirae*	250 µg/mL	Woźnicka *et al.*, 2017
Artonin I	*Morus mesozygia*	*Staphylococcus aureus*	20 µg/mL	Farooq *et al.*, 2014
Baicalein	*Scutellaria baicalensis**	*Staphylococcus aureus*	0.0043 mM	Yan *et al.*, 2020
Hesperetin	*Cordia sebestena*	*Bacillus subtilis, Staphylococcus aureus* and *Pseudomonas aeruginosa*	25–100 µL	Prakash *et al.*, 2020
Kaempferol	*Croton piauhiensis*	*Escherichia coli, Pseudomonas aeruginosa*, and *Staphylococcus aureus*	128 µg/mL	Cruz *et al.*, 2020
Alkaloids				
Berberine	*Berberis sp.*	*Streptococcus agalactiae*	78 µg/mL	Peng *et al.*, 2015
Sanguinarine	*Macleaya cordata**	*Providencia rettgeri*	7.8 µg/mL	Zhang *et al.*, 2020
Quinine	*Cinchona sp.*	*Escherichia coli, Staphylococcus aureus, Pseudomonas aeruginosa*, and *Bacillus subtilis*	0.25–0.5% w/v	Antika *et al.*, 2020
Carvacrol	*Zataria multiflora*	*Staphylococcus aureus* and *Escherichia coli*	0.031–1 mg/mL	Pourhosseini *et al.*, 2020
Thalicfoetine	*Thalictrum foetidum*	*Bacillus subtilis*	3.12 µg/mL	Ding *et al.*, 2019

(Continued)

Table 1 (continued).

Name of phytocompounds	Sources	Antibacterial activity	MIC/MBC/BIC/ MLC/*SIC*	References
Benzyl isothiocyanate	*Salvadora Persica**	*Escherichia coli* and *Salmonella enterica*	200 µg/mL	Patel *et al.*, 2020
Terpenes/Terpenoids				
Citral	*Cymbopogon citratus**	*Staphylococcus aureus*	75–150 µg/mL	Gupta *et al.*, 2017
Mansumbinone, 3,4-seco-mansumbinoic acid, Sesquiterpenes (β-elemene (3) and T-cadinol)	*Commiphora myrrha*	*Staphylococcus aureus*, *Salmonella enterica*	4–256 µg/mL	Rahman *et al.*, 2008
β-caryophyllene	*Commiphora gileadensis**	*Bacillus cereus*	2.5% (v/v)	Moo *et al.*, 2020
α-pinene, Camphene, β-pinene, 3-carene, Limonene, Bornyl acetate, β-caryophyllene, and Borneol	*Schinus terebinthifolius Raddi, Piper cernuum, Citrus sinensis, Abies koreana, Blumea balsamifera**	*Staphylococcus aureus, Escherichia coli*	0.3–1.2 µg/mL	Allenspach *et al.*, 2020
α-Pinene, Camphene, β-Pinene, Myrcene, Carene, p-Cymene, Limonene, γ-Terpinene, Fenchone, Linalool, Camphor, cis-Verbenol, Borneol, Terpinen-4-ol, Verbenone, Carvone	*Lavandula pedunculata subsp. Atlantica*	*Staphylococcus aureus, Escherichia coli, Enterobacter aerogenes, Pseudomonas aeruginosa, Klebsiella pneumoniae, Klebsiella oxytoca, Salmonella spp., Acinetobacter baumannii, Enterobacter cloacae*	3.13–25 mg/L	Sayout *et al.*, 2020
Myrcene, Limonene, Geraniol, Linalool, Nerol	*Humulus lupulus, Ocimum canum**	*Escherichia coli, Salmonella enterica*, and *Staphylococcus aureus*	0.420–1.598 mg/mL	Wang *et al.*, 2019
Gedunin	*Azadirachta indica*	*Xylella fastidiosa*	1.30 mg/mL	Ribeiro *et al.*, 2008
Quinones				
Alizarin, Anthraquinone	*Rubia cordifolia, Morinda officinalis**	*Staphylococcus aureus* and *Staphylococcus epidermidis*	>1 mg/mL	Lee *et al.*, 2016
Purpurin (1, 2, 4-trihydroxyanthraquinone)	*Rubia tinctorum**	*Staphylococcus aureus, Bacillus subtilis, Escherichia coli, Pseudomonas aeruginosa*	62.5 µg/mL	Kharlamova *et al.*, 2020
Emodin, Ventilagolin	*Ventilago denticulata*	*Bacillus cereus, Staphylococcus aureus, Escherichia coli* and *Pseudomonas aeruginosa*	25 µg/mL, 200–400 µg/mL	Molee *et al.*, 2018
Xanthones				
Alpha-mangostin	*Garcinia mangostana*	*Staphylococcus epidermidis*	0.875 µg/mL	Sivaranjani *et al.*, 2019
Garmoxanthone	*Garcinia mangostana*	*Staphylococcus aureus*	3.9 µg/mL	Wang *et al.*, 2018

Note: *The sources of different phytocompounds given in the table but their purified form was purchased and used in the study. MIC–Minimum Inhibitory Concentration, SIC–Sub-Inhibitory Concentration, MLC–Minimum Lethal Concentration, BIC–Biofilm Inhibitory Concentration, MBC–Minimum Bactericidal Concentration.

concentration-dependent biofilm inhibition activity in the bacterial drug-resistant population. It showed 36.37% growth inhibition in *S. mutans* and the cell viability of bacteria decreased from 6.4 to 3.8 CFU/mL (Jafri *et al.*, 2019). Some of the phenolic compounds are discussed in brief which are as follows.

Tannins

Tannins are large polyphenolic compounds containing both carboxyl and hydroxyl groups. This is an abundant organic compound found in many plants. Tannins possess an astringent property and cause dry and puckery feeling when taken orally. It is also used to clean the skin and tighten the skin pore. For example-Persimmon fruit is a rich source of tannins, found in many countries. The extract of persimmon fruit has shown a strong antibacterial activity against Methicillin-Resistant *Staphylococcus aureus* (MRSA) (Liu *et al.*, 2019). Generally, Tannins are a good source of tannic acid. Like, *Psidium guajava* is a rich source of tannins, which has good antibacterial activity (Biswas *et al.*, 2013).

Coumarins

Coumarins are found in many medicinal plants. It is basically a phenolic compound used in the pharmaceutical industries for medicinal uses. For example-Scopoletin is the best example of coumarins that is found in *Morinda citrifolia* seeds. It exhibits a strong antibacterial activity with a MIC value of 100 µg/mL against the MRSA (de La Cruz-Sánchez *et al.*, 2019).

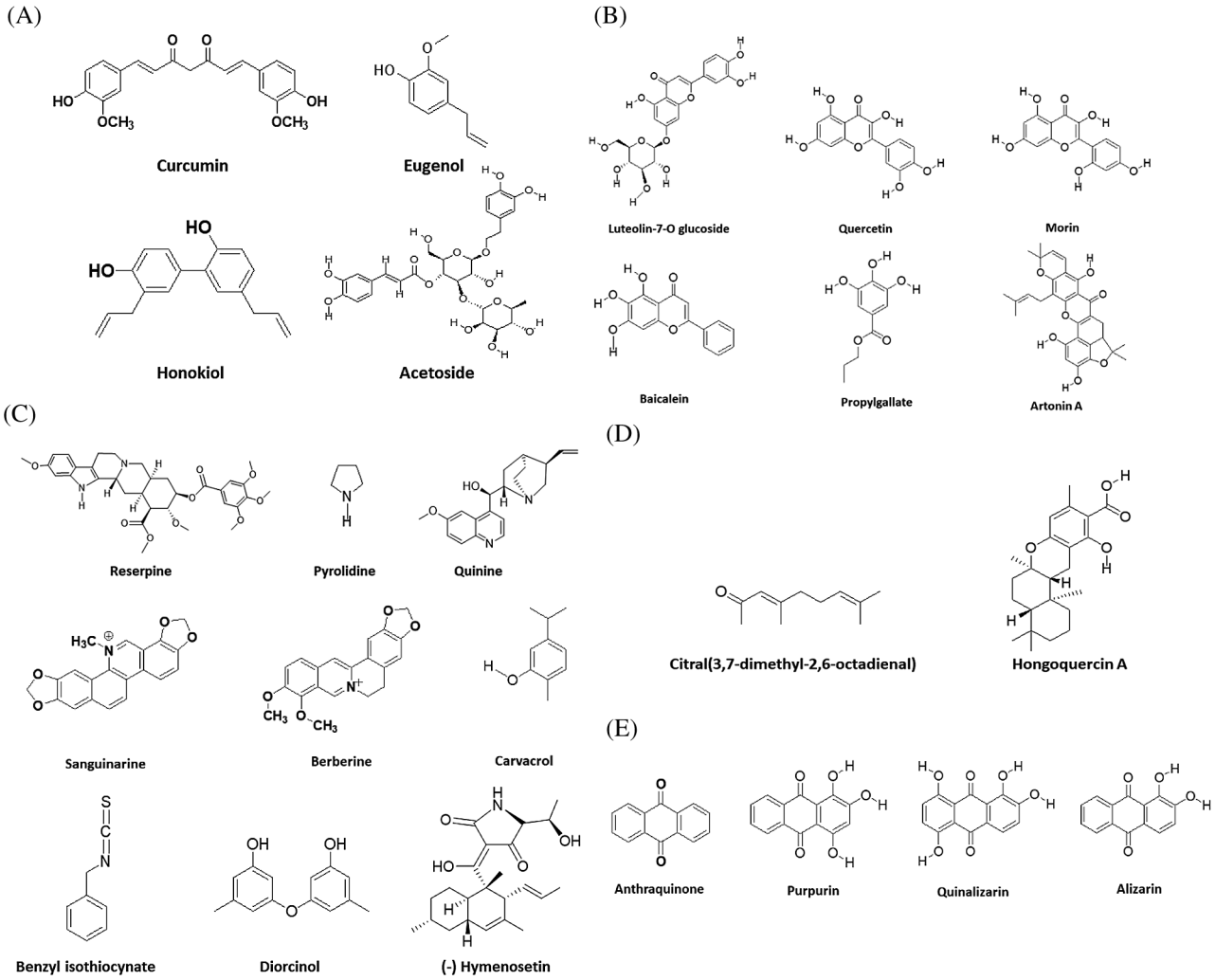

FIGURE 1. Chemical structure of phytocompounds known for inhibiting anti-bacterial drug resistance (A) Phenolics, (B) Flavonoids, (C) Alkaloids, (D) Terpenes, and (E) Quinones.

Lignans

Lignans are a group of polyphenolic compounds found in various medicinal plants. For example–8-hydroxypinoresinol, a lignin compound isolated from *Strombosia grandifolia*. This compound has shown the potent antibacterial activity against *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Escherichia coli*, and *Salmonella typhi*. In disk diffusion method, the zone of inhibition was measured to be between 11 and 17 mm for this compound in different bacterial culture. The MIC and MBC values of 8-hydroxypinoresinol was calculated and the MIC values was found between 0.73 and 3.0 mg/mL and the MBC values were 1.5 mg/mL (Ekalu *et al.*, 2019). Lignans are also present in *Sesamum indicum* honey which showed a strong antibacterial activity against *Escherichia coli, Salmonella typhimurium*, and *Vibrio cholerae* (Das *et al.*, 2015; Kumar and Singh, 2015).

Flavonoids

Flavonoids are an important class of plant secondary metabolites. These compounds are commonly found in the leaves, flowers, seeds, and other parts of the medicinal plants. In 2018, Chew *et al.* (2018) reported that the flowers of the *Bauhinia kockiana* have potent antibacterial activity against MRSA. They confirmed the presence of the flavonoids in the flower of this plant during phytochemical analysis. They found gallic acid and methyl gallate in the flowers of *Bauhinia kockiana* plant and showed a strong antibacterial activity with changes in cell membrane structure, cell membrane fluidity, and cell membrane attachment. In 2013, Mun *et al.* (2013) used curcumin, a natural flavonoid which has numerous traditionally well-known medicinal values. They determined the synergistic antibacterial effect of curcumin against MRSA by standard microdilution method. In 2015, Abreu *et al.* (2015) demonstrated the synergistic antibacterial effect of five different flavonoids with antibiotics against *Staphylococcus aureus*. The examples of some other flavonoids are quercetin, kaempferol, myricetin, luteolin, licochalcone, and flavones. These compounds also exhibited potent antibacterial activity (Farhadi *et al.*, 2019).

Alkaloids

Alkaloids are nitrogen-containing phytocompounds present in the flowering plants and rarely in gymnosperms. Alkaloids have strong antibacterial medicinal property as these natural compounds can inhibit the biofilm formation in bacterial population. In 2016, Abreu *et al.* (2016) studied the antibacterial

effect of some alkaloids like quinine, pyrrolidine, and reserpine in the presence of few antibiotics against biofilm forming bacteria *Staphylococcus aureus*. Their results showed a significant reduction in the biofilm formation and reduced the antibacterial drug resistance developed by this bacterium to the antibiotics. In 2015, AL-Ani *et al.*, (2015) reported the synergistic bactericidal activity of sanguinarine, berberine, carvacrol, and benzyl isothiocyanate alkaloids with bee venom and some antibiotics against multi-drug resistant Gram-positive and Gram-negative bacteria. In 2015, Peng *et al.* (2015) showed the strong antibacterial activity of berberine alkaloid (isolated from *Berberis sp.*) against *Streptococcus agalactiae*. This alkaloid can intercalate with DNA, disrupt the bacterial cell membrane structure, and increase the cell membrane permeability in bacteria.

Terpenes

Terpenes constitute the large class of phytocompounds which contain five-carbon isoprene units. It is the primary ingredient of essential oil and has numerous medicinal properties. Terpenes group has approximately 30,000 compounds, in which around 400 are monoterpenes. The derivatives of monoterpenes such as nitrogen-containing terpenoids showed the significant antibacterial activity against *Staphylococcus aureus* and *Bacillus subtilis* (Kozioł *et al.*, 2020). In 2017, Gupta *et al.* (2017) discussed about Citral (3, 7-dimethyl-2,6-octadienal) monoterpene which is present in the essential oil of many medicinal plants. Citral exhibited a bactericidal activity in combination with norfloxacin against drug-resistant *Staphylococcus aureus*. This compound inhibited the drug resistance by closing the efflux pump, damaging the bacterial cell membrane, and changing the membrane potential. Hence, Citral is a strong anti-staphylococcal agent but in combination with antibiotic, it reduces the antibiotic drug resistance. In 2019, Costa *et al.* (2019) discussed about Limonene, a monoterpene found in the essential oil of many plant species. This compound has strong antibacterial activity against both Gram-positive and Gram-negative bacteria.

Saponins

Saponins are glycosides which contain steroid linked to the carbohydrate moieties by a glycosidic bond. It has a detergent property. In 2019, Lall *et al.* (2019) discussed about the saponins. They extracted these glycosides from *Argania spinosa* plant and they observed a potent antibacterial activity against *Cutibacterium acnes* and *Prevotella intermedia* bacteria. In 2019, Fleck *et al.* (2019) reported about *Quillaja saponaria* plant which is a rich source of saponin. They showed a high antibacterial activity against *Salmonella typhimurium, Staphylococcus aureus*, and *Escherichia coli*.

Quinones

Quinones have numerous biological and pharmacological activities. In 2016, Lee *et al.* (2016) described about quinones and their inhibitory role in biofilm formation. These quinones were anthraquinones, alizarin, purpurin and quinalizarin. These phytocompounds prevented the antibacterial drug resistance induced by infectious bacteria. During the post-transcriptional analysis, they found that Alizarin repress the *rbf, spα*, and *psmα* genes responsible for biofilm formation and they also found the expression of *cid/led* genes responsible for reducing the biofilm formation.

Essential Oil and Other Phytochemicals

In the last few decades, health care system gradually moved towards the use of traditional medicines and plant-based drugs. Most of the research communities are trying to learn from nature for the discovery of new drugs based on the medicinal plants. In 2016, Moussaoui and Alaoui (2016) showed the antibacterial activity of the essential oils of five medicinal plants such as *Thymus willdenowii*, *Chrysanthemum coronarium, Origanum compactum, Origanum majorana*, and *Melissa officinalis* against 10 bacterial strains. They observed a synergistic effect of essential oils with the antibiotic. This study unequivocally demonstrated that these bacterial strains show antagonistic effect when treated with antibiotics alone but the combination of antibiotics with the essential oils resulted in the synergistic effect and reduced the antibacterial drug resistance.

In 2017, Mishra *et al.* (2017) described the antibacterial activity of the crude extract of some medicinal plants against multi-drug resistant bacteria. In this study, the crude extracts of nine medicinal plants namely *Azadirachta indica, Anogeissus acuminate, Boerhaavia diffusa, Bauhinia variegate, Soymida febrifuga, Punica granatum, Terminalia chebula, Tribulus terrestris* and *Tinospora cordifolia* were tested against 11 multidrug-resistant bacteria, isolated directly from the urine samples of the urinary tract infected patients. These bacteria were resistant to 17 antibiotics. This study highlighted that these three plants namely *Anogeissus acuminate, Punica granatum* and *Soymida febrifuga* contain stigmasterol and luteolin-7-O glucoside as major phytocompounds, due to which they possess a potent antibacterial activity against multi-drug resistant bacteria. In 2015, Kouidhi *et al.* (2015) demonstrated the antibacterial drug resistance in the dental care which was developed due to the biofilm forming bacteria like *Streptococcus, Lactobacillus, Actinomycetes*, and other Gram-negative/Gram-positive bacteria within the oral cavity. They used different plant extracts to prevent the biofilm formation in the dental cavities. In this study, the extracts of total 21 medicinal plants containing numerous phytocompounds exhibited the strong antibacterial activity against the multi-drug resistant bacteria via the inhibition of biofilm formation. In 2015, Tankeo *et al.* (2015) reported the antibacterial activity of different phytoextracts of *Polyscias fulva, Newbouldia laevis, Beilschmedia acuta*, and *Clausena anisate* against different bacterial strains like *Pseudomonas aeruginosa, Klebsiella pneumoniae, Escherichia coli*, and *Enterobacter aerogenes*. Among these extracts, the phytoextract of *Beilschmedia acuta* plant showed better potency against multi-drug resistant bacterial infection. Similarly, in 2016, Barreto *et al.* (2016) examined the use of aminoglycosides isolated from *Anadenanthera colubrine* plant along with antibiotics against the multidrug-resistant bacteria and they observed the inhibition of the drug efflux pump which reduced the drug resistance in bacteria. Further, in 2015, Fankam *et al.* (2015) revealed that the extracts of *Allanblackia gabonensis, Combretum mole*, and

Gladiolus quartinianus increased the antibacterial activity against the drug-resistant Gram-negative bacteria and these extracts inhibited the drug-resistant mechanisms in the tested bacteria.

In 2017, Zacchino *et al.* (2017a) comprehensively discussed the combinations of 17 antibiotics with phytocompounds. They showed the synergistic action of antibiotics with natural products in the prevention of bacterial biofilm formation. Further, some of the natural products such as kibdelomycin, hymenosetin, hunanamycin, batumin, tetarimycin, artonin, baulamycin, viridicatumtoxin, hongoquercin, diorcinol, baicalein, propylgallate, honokiol, and acteoside are active phytocompounds with good antibacterial activity. These natural products are the best candidates for the new antibacterial drug discovery (Moloney, 2016; Zacchino *et al.*, 2017b). In 2017, Chandra *et al.*, collected the data on the use of plant based medicinal compounds for controlling the antibacterial drug resistance. This study concluded that active phytocompounds such as quinones, alkaloids, flavonoids, coumarins, terpenoids, tannins, lignans, glucosinolates, and essential oils participate in modulating the drug resistance (Chandra *et al.*, 2017). As plants are the major source of derived phytocompounds for therapeutic use, however most of the higher plants have not been explored completely. Out of near 3 lakh species of higher plants, only 6% plants have been investigated pharmacologically for their medicinal values and about 15% based on the phytochemical analysis (Borges *et al.*, 2016). Thus, natural products are the best sources for the new drug discovery in order to overcome the antibacterial drug resistance condition. These products inhibit such condition by targeting key signaling pathways which are described in detail in the next section.

Mechanisms Behind Antibacterial Drug Resistance

Antibiotics have been largely used in the treatment of the bacterial infections. These antibiotics can be classified as broad or narrow spectrum depending on whether it targets the wide-range or specific groups of bacteria respectively. In current scenario, the pharmacological activity of these antibiotics became limited due to their excess and unwanted use against bacteria.

Globally, a large population of the drug-resistant bacteria is continuously increasing. These bacteria are existing in nature due to their continuous evolutionary process and adaptation. In recent time, the antibacterial drug resistance has become a major clinical challenge and worldwide concern. To meet this challenge, traditional medicines are being used which delivers a promising solution in the clinics without any toxic side-effects. Phytomedicines are well-known pharmacological compounds that can directly target the antibacterial drug resistance mechanisms. Some of these mechanisms are described in detail as follows.

Expression of Efflux Pump

The efflux pump is a key mechanism which is present in almost all the drug-resistant bacteria. In bacteria, the efflux pump helps in reducing the concentration of toxic substances like drugs that kill the bacteria. These pumps also regulate the quorum sensing signals (Soto, 2013). The efflux pumps are found in both Gram-positive and Gram-negative bacteria. The overexpression of more than one efflux pumps lead to the antibacterial drug resistance in clinics. Based on the bacterial cell membrane composition and type of drug molecules, the efflux pumps get activated (Chandra *et al.*, 2017). These multidrug efflux pumps are classified into five different families as shown in Fig. 2.

- **Multidrug-Antimicrobial Extrusion protein (MATE):** MATE is also known as multidrug and toxic compound extrusion transporter. Such pump is usually found in both Gram-positive and Gram-negative bacteria. ArcAB, MdtK are the few examples of MATE found in *E. coli* and MepA protein is present in *Staphylococcus aureus* (Sun *et al.*, 2014). These transporters usually lead to the efflux of several cationic drugs such as fluoroquinolones, aminoglycosides (Soto, 2013).
- **Resistance-Nodulation-Division (RND) protein:** RND transporters are mostly found in the Gram-negative bacteria. It is a type of efflux pump which majorly leads to the drug resistance in bacteria. For example- MexAB-OprM, MexCD-OprJ, MexEF-OprN, and MexXY are RND family proteins which are commonly present in *Pseudomonas aeruginosa* (Gupta *et al.*, 2017). In 2014, Sun *et al.* (2014) reported ArcAB-ToIC, AcrD, AcrEF, CusCFBA, MtdABC, and MtdEF efflux pumps which are present in *Escherichia coli*. Similarly, other bacteria also have different types of efflux pump such as CmeABC (*Campylobacter jejuni*), AdeABC (*Acinetobacter baumannii*), and AmeABC (*Agrobacterium tumefaciens*). Likewise, *Neisseria gonorrhoeae* has FarAB and MtrCDE. *Salmonella typhimurium* has ArcAB, ArcD, ArcEF, MdsABC, and MdtABC efflux pumps. Also, *Pseudomonas putida* has SrpABC, TgtABC, and ArpAB type of efflux pumps. These RND proteins efflux many antibiotics such as chloramphenicol, novobiocin, and β-lactams.
- **Small Multidrug Resistance (SMR)/Drug Metabolite Transporter (DMT) protein:** SMR transporters are present in the inner membrane of Gram-negative bacteria. For example–NepAB, EbrAB, and SsmE are present in *Arthronobacter nicotinovorans*, *Bacillus subtilis*, and *Serratia marcescens* respectively. Likewise, EmrE is present in *Pseudomonas aeruginosa* and *Escherichia coli* (Blanco *et al.*, 2016; Srinivasan *et al.*, 2009). These DMT proteins actively pump the methylamine, ciprofloxacin, amikacin, cefepime, and many others drugs which are known to cause drug resistance in bacteria.
- **ATP Binding Cassette (ABC) proteins:** ABC transporters bind to the small drug molecules and efflux them outside the bacterial cell through ATP hydrolysis. The ABC pump is present in both Gram-positive and Gram-negative bacteria which actively export the macrolides. Also, this transporter led to the biofilm formation in *Listeria monocytogenes* bacteria (Soto, 2013). MacABCsm and MacAB are some of the examples of ABC protein, present in *Stenotrophomonas maltophilia* and *Salmonella typhimurium* bacteria respectively. ABC proteins are also

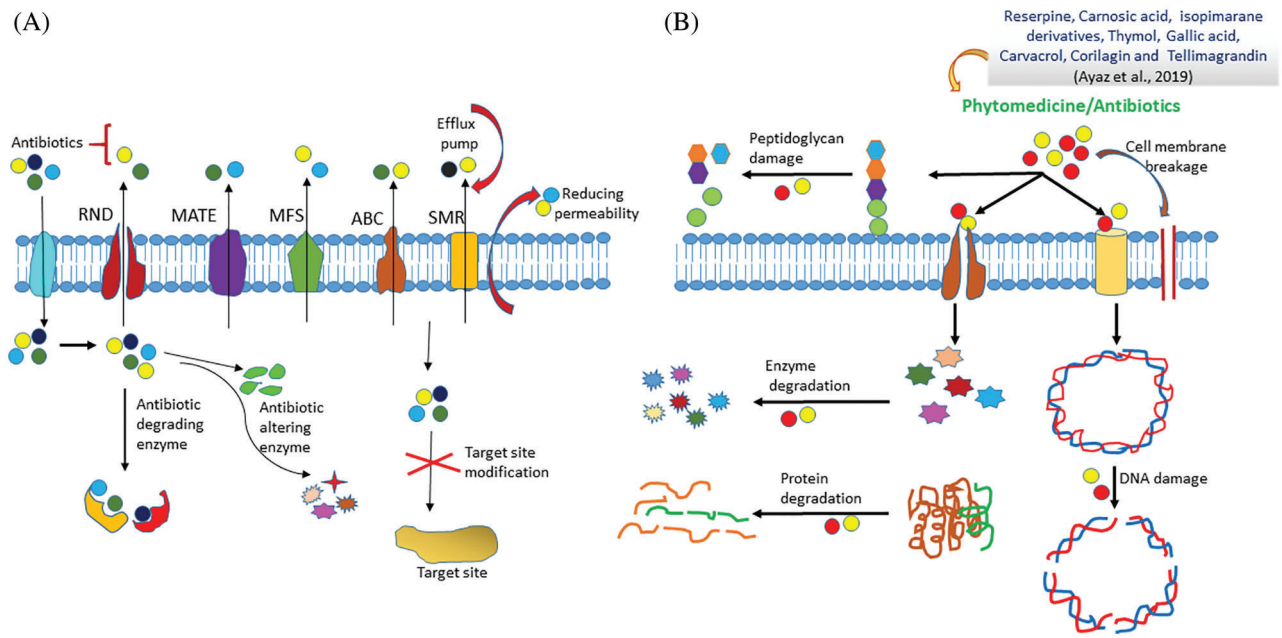

FIGURE 2. Mechanism of drug resistance in resistant and non-resistant bacterial cell.

overexpressed in most of the drug resistant bacteria (Lin *et al.*, 2014).

- **Major Facilitator Superfamily (MFS):** MFS membrane proteins are the largest group of transporters, present in both Gram-positive and Gram-negative bacteria. In Gram-positive strains, MFS proteins have been shown to export cetrimide and acriflavine whereas in Gram-negative bacteria, these proteins have been shown to export the novobiocin and nalidixic acid. The MFS superfamily contains numerous types of efflux pumps like Bmr and Blt in *Bacillus subtilis*, EmrAB and EmrKY in *Escherichia coli*, QacA and NorA in *Staphylococcus aureus*, and PmeA in *Streptococcus pneumoniae* (Soto, 2013).

From ancient times, the herbal products have been used to cure several bacterial infections. The herbal medicine has the potential to directly target the bacterial drug-resistant mechanisms. Like, 4', 5'-*O*-decaffeoylquinicacid (4', 5'-ODCQA) isolated from *Artemisia absinthium*, showed the strong antibacterial activity by directly targeting the MFS transporters in *Staphylococcus aureus, Bacillus cereus*, and *Enterococcus faecalis* (Fiamegos *et al.*, 2011). In 2018, Shin *et al.*, discussed about several flavonoids like myricetin, epigallocatechin, and robinetin which directly inhibit the DNA synthesis whereas, quercetin blocks the ATPase activity in *Escherichia coli* by binding with GyrB protein (Shin *et al.*, 2018). Similarly, other phytocompounds such as reserpine, gallotannin, curcumin, piperine, chalcones, berberine, and carnisic acid directly inhibit the ABC efflux pump (Shriram *et al.*, 2018). Likewise, phytocompounds such as sarothrin, capsaicin, lanatoside, cathecol, olympicin, daidzein, lysergol, and ursolic acid also inhibit the efflux pump in many pathogenic bacterial strains (Prasch and Bucar, 2015).

Inactivation and Modification of Antibacterial Agents

This is another mechanism in which the antibacterial agents become inactive by its modifications which takes place by the drug-resistant bacteria. Generally, antibiotics target the bacteria at different levels such as inhibition of DNA and protein synthesis and prevention of bacterial cell wall formation. These antibiotics such as aminoglycosides, macrolides, chloramphenicol, ampicillin, novobiocin can be modified or degraded by the bacterial hydrolytic enzymes like transferases and β-lactamase. Also, bacteria can utilize other mechanisms like redox process, enzymatic hydrolysis, and group transfer to degrade these antibiotics. For example-Metallo-β-lactamase is present in *Pseudomonas aeruginosa, Escherichia coli*, and *Klebsiella pneumoniae*. Cephalosporinases is found in *Enterobacter sp.* and penicillinase is found in *Staphylococcus aureus*. These enzymes can degrade or alter the chemical structure of antibiotics (Bush and Fisher, 2011). Usually, the inactivation of antibiotics takes place by phosphorylation, acetylation, and adenylation of the drug molecule using phosphoryl transferases, nucleotidyl transferases, and acetyltransferases enzymes. Hence, bacteria have potential to inactivate the antibacterial agents and become resistant for that particular drug (Borges *et al.*, 2016; Chandra *et al.*, 2017).

Modification in the Target Site of Antibacterial Agent

The modification in the target site is also an important mechanism by which pathogenic bacteria prevent the drug to reach their target site. Mutation is the main factor for the modification of the drug target site. Usually, antibiotics such as chloramphenicol, streptomycin, and tetracycline block protein synthesis in the pathogenic bacteria by targeting 23S rRNA of the 50S ribosomal subunit. Due to mutation in 23S rRNA, *Enterococcus sp.* shows resistance against oxazolidinones. Also, the mutation in 16S rRNA induce the resistance in bacteria against aminoglycosides. However, the drug resistance in *Mycobacterium tuberculosis* occurs due to the mutation in the ribosomal protein S12 encoding *rpsL* gene (Chandra *et al.*, 2017). It has been shown that post-transcriptional or post-translational modifications lead to

the changes in the target site of antibiotics responsible for antibiotic resistance in bacteria (Kuiper and Conn, 2014). Bacteria can also alter the binding sites of drug molecules. The spontaneous mutations in the chromosome also lead to the alternation in the amino acids sequence by which the encoded protein sequence changes. These mutations also modify the recombination sites in the bacteria by which they become drug resistant (Borges *et al.*, 2016). For example - Penicillin, a β-lactam antibiotic, targets the penicillin-binding protein (PBP) which is a transpeptidase found in the bacterial cell wall. A mutation in PBP leads to the changes in the binding site of penicillin and causes resistance in bacteria (Cabot *et al.*, 2016).

Mechanism of Plasmid Efflux

In bacteria, the transfer of genetic material occurs by the process of horizontal transfer which is mainly of three types: conjugation, transformation, and transduction. If the genetic material transfers from one species to other species of bacteria, then it is vertical gene transfer and if the transfer occurs from the parent to the progeny, then it is horizontal gene transfer. Generally, the resistant genes transfer in bacteria from the parent to the progeny by the process of conjugation using pilus. In 2017, Chandra *et al.* (2017) investigated about the pheromone–responsive plasmids which are constituted of mobile genetic elements that facilitate the transfer of antibiotic-resistant genes.

Together, the antibacterial drug resistance is a major and serious global issue which persists due to one or more drug resistance mechanisms. To encounter this, there is an urgent need to develop novel antibacterial drugs which can target the bacteria in multiple ways. At the same time, the development of plant-based medicines to combat the antibacterial drug resistance is still at underway.

Recent Challenges and Future Prospective

As of today, the development of new antibacterial drug to prevent the bacterial drug resistance is a major challenge. Many pharmaceutical companies take part in the synthesis of the new antibacterial drug but due to the drug resistance problem, these drugs are no longer effective. Therefore, developing new drugs which can fight against antibacterial drug resistance is the need of the hour. Currently, many pharmaceutical companies and academic institutes have invested major resources for the research and development of new antibacterial drugs and few others are using natural compounds as medicines but it is still a big challenge. The invention of new technologies on day by day gives a better hope for developing the effective drugs against these drug resistant pathogens. For instance, the nanotechnology-based techniques have revolutionized the field biomedicine as drug delivery systems. Due to the advent of nano-carriers, several parameters such as drug solubility, permeability, blood circulation time, and therapeutic efficiency of poorly water-soluble drugs and phytocompounds have been improved. Moreover, the site-specific drug delivery is achieved due to the introduction of actively targeted nanoparticles. The physical entrapment or stimuli-responsive conjugation of these anti-bacterial drugs could be possible inside the nanoparticles. However, some metal nanoparticles display potent bactericidal activity. When these metal nanoparticles were conjugated with phytocompounds then it could become an ideal choice for the development of new antibacterial drug which have prevented the bacterial drug resistance. In 2018, Lakshminarayanan *et al.* (2018) reported that both metallic and non-metallic nanoparticles show antibacterial activity and target the drug resistant mechanisms of bacteria. Especially, non-metallic nanoparticles such as lipid-based and polymer-based nanoparticles were used as a carrier for the delivery of antimicrobial drugs to increase their therapeutic efficacy and reduce the systemic cytotoxicity. It is worthy to mention that the numbers of publications on nanoparticles based antimicrobial drugs have drastically increased from 2002 to 2017. In 2018, Hussain *et al.* (2018) synthesized the antibiotic loaded nanoparticles against bacterial infections for improving the antibacterial activity of antibiotics. In 2018, Escárcega-González *et al.* (2018) demonstrated the antibacterial activity of silver nanoparticles synthesized using the medicinal plant *Acacia rigidula* against Gram-positive and Gram-negative bacterial strains. Thus, the synthesis of nanoparticles using medicinal plants and their derivatives, as reducing and stabilizing agents has led to the advancements in the biomedical science field.

The synergistic combinatorial therapeutic effects of antibiotics with one or more phytochemicals are the perspective for decreasing the bacterial drug resistance (Ayaz *et al.*, 2019). In 2018, Cheypratub *et al.* (2018) displayed the antibacterial activity of *Cyperus rotundus* extract with ampicillin against the ampicillin resistant strain *Staphylococcus aureus*. This combination increased the cytoplasmic permeability of the bacteria. In 2018, Vambe *et al.* (2018) reported that the mixed phytoextracts of seven medicinal plants (*Solanum panduriforme, Prunus africana, Protea caffra, Searsia lancea, Cucumis myriocarpus, Bolusanthus speciosus*, and *Ekebergia capensis*) exhibited strong antibacterial activity. On the other hand, some phytocompounds showed the inhibitory effects against bacterial drug resistance as listed in Tab. 1. Reserpine, pyrrolidine, quinine, morin, quercetin, alizarin, and anthraquinones have been reported as an antibacterial compound against *Staphylococcus aureus* (Abreu *et al.*, 2016; Lee *et al.*, 2016). Similarly, cinnamaldehyde displayed the strong antibacterial activity against *Aeromonas hydrophila* with a MIC value of 256 and 512 μg/mL (Yin *et al.*, 2020). Further, eugenol also showed the potent antibacterial activity against *Salmonella typhimurium, Mycobacterium tuberculosis*, and *Listeria monocytogenes* (Jafri *et al.*, 2019). In addition, carvacrol, benzyl isothiocyanate, sanguinarine, and berberine are also reported as antibacterial phytocompounds against *Staphylococcus aureus, Streptococcus thermophilus, Enterococcus casseliflavus*, and *Mycobacterium sp.* (AL-Ani *et al.*, 2015), where these phytocompounds also prevent the bacterial drug resistance. Similarly, artonin and baulamycin showed a potent antibacterial effect against *Bacillus subtilis, Listeria sp., Enterococcus sp.*, and *Staphylococcus aureus* (Moloney, 2016).

Conclusions

Medicinal plants are nature's gift to humans and they are well known for their antimicrobial, antioxidant, anti-inflammatory, antipyretic, and anticancer properties. Due to these properties, medicinal plants have been used in a wide range of biomedical applications. Most of the pharmaceuticals available in the market are known for treating bacterial diseases. However, these bacteria can develop resistance against these pharmaceuticals and cannot be killed so easily. There are several bacterial diseases like tuberculosis and pneumonia where, the complete treatment is not available due to the development of continuous drug resistance. Therefore, the concept of using traditional medicine to overcome such bacterial drug resistance is the solution at present. The medicinal plants have active phytocompounds such as flavonoids, alkaloids, terpenes, saponin, glycosides, polyphenols, and others, which have involved in the inhibition of drug resistance mechanism. These phytocompounds directly target the drug resistant mechanisms in bacteria and form the base for researchers to search for new antibacterial drugs. Moreover, the relations between the antibiotics, phytocompounds, and the cocktail of extracts increase the potential to fight against drug resistant bacterial pathogens. This review concludes that several phytocompounds were discussed in this paper that directly target the bacterial drug resistance mechanisms and in recent years, traditional medicine has gained more popularity and been the focus area of research due to the fewer side effects and promising efficacy results.

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