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What Makes Medicinal Plants Effective Against ESKAPE Pathogens? A Look at Updated Antibacterial Research

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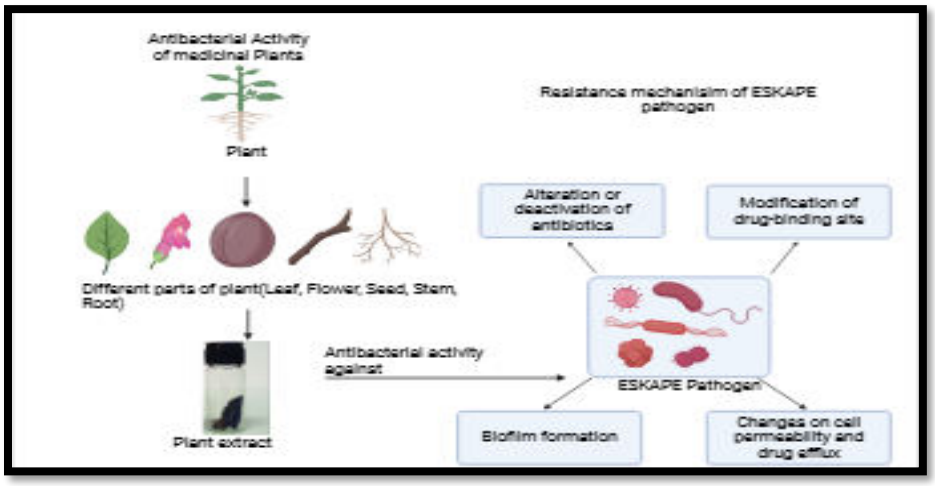
Abstract: Medicinal plants have garnered attention for their potential in combating ESKAPE pathogens (Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa, and Enterobacter species), a group of six multidrug-resistant bacteria that pose a severe threat to global health. Current antibacterial research has focused on the natural bioactive compounds including terpenoids, alkaloids, flavonoids, and phenolic compounds found in various medicinal plants, which exhibit a promising inhibitory effect against ESKAPE pathogens. These ESKAPE pathogens have the potential to "escape" from antibiotics and other conventional treatments through mechanisms including biofilm formation, target site modification efflux pump activation, and degradation of enzymatic antibiotics. These natural bioactive compounds target the cell walls, their membranes, intracellular components and the biofilm formation in bacteria, often increasing the bacterial susceptibility to antibiotics. This current review explores the most recent advancements in the antibacterial properties of medicinal plants and their potential to function as alternative or adjunctive treatments against ESKAPE pathogens and also genes enable various mechanisms, including degradation of antibiotic, activation of efflux pump, modification of target site, and biofilm formation. The continued exploration of naturally occurring bioactive compounds in medicinal plants is crucial for developing sustainable and effective strategies against growing threat of ESKAPE pathogens amid enhancing antibiotic resistance.

Keywords: Antimicrobial resistance, Antibiotics, Multidrug-resistance, ESKAPE pathogen, Bioactive compounds



1. Introduction

The search for alternative therapies for bacterial infections, especially those caused on by ESKAPE pathogens (*Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa*, and *Enterobacter* species), has become more intense due to the growing threat of antimicrobial resistance (AMR) worldwide. Because of their well-known tendency to "escape" the effects of traditional antibiotics, these opportunistic microorganisms pose serious therapeutic problems and required the development of innovative approaches to treatment. AMR has become as one of the 21st century's most urgent concerns to public health challenges globally. AMR arises from the evolution of microorganisms, such as bacteria, fungi, parasites, viruses, and to resistance to antimicrobial drugs, such as antibiotics, which are commonly used to treat these infections. Projections indicate that, in the absence of preventive actions, AMR may surpass all other global causes of mortality by 2050. Global, estimations indicate that the number of direct mortalities is associated with AMR surpassed 1.2 million in 2019. If suitable action is not taken to mitigate AMR, it is anticipated that this figure could rise to approximately 10 million deaths annually by 2050. [1] AMR is a public health issue that has made the treatment of multiple diseases more challenging, due to multidrug-resistance (MDR) gram –ve and gram +ve bacteria. Antimicrobial agents possess significant potential in controlling infectious diseases in animals and humans caused by microbial growth. [4] The improper use of antibiotics is the main cause of AMR, which has developed as a public health problem for health of animals and humans globally. Antimicrobials have significantly decreased mortality and morbidity rates because of their bactericidal and bacteriostatic actions and have saved millions of lives throughout human history. For 70 years, antimicrobials have reduced the mortality rate due to

infectious diseases. [21] AMR has become a major global environmental and public health concern, and more than two lakh people die from AMR each year, which is considered severely life-threatening and poses a severe risk to life. AMR is caused by five main factors that spread the disease: misuse and excess use of antimicrobial drugs, overuse of antimicrobials in agriculture, worldwide travel and trade, lack of development of new antimicrobial drugs, improper sanitation, and use of clean water. The WHO, in 2021 stated in a study that widespread antibiotic misuse and overuse contribute to AMR, which indicates that AMR is making COVID-19 patients' outcomes more challenging because of excessive overuse and abuse of antibiotics. AMR is one of the biggest challenges, a hidden threat for the future, and a global pandemic [2].A promising way to combat these infections is through medicinal plants,that contain an abundance of bioactive compounds like alkaloids, flavonoids, terpenoids etc. Compared to manufactured medications, numerous people think natural substances are less expensive and have less adverse effects. The combination of compounds with antibacterial and antioxidant properties will enhance the effectiveness of treatment. [38] Recent research has shown that medicinal plants are effective against ESKAPE pathogen that are resistant to drugs. The present investigation intends to examine the most recent studies on medicinal plants and assess how well they may work against ESKAPE infections. By comprehending how plant-derived antimicrobials help combat bacterial resistance, we may contribute to toward the development of novel, persistent, and effective medicinal approaches.

2. Rise of multidrug-resistant bacteria (MDR) and the need for new antimicrobials

The emergence of multidrug-resistant (MDR) bacteria is becoming more prevalent, a major universal health crisis. [29] These bacteria have evolved to resist multiple antibiotics, once highly effective at treating infections. The development of resistance is enhanced by the overuse and abuse of antibiotics, such as their prescription for viral diseases or usage in agriculture. MDR bacterial infections, such as those from *Klebsiella pneumoniae* or *Staphylococcus aureus*, result in more extended hospital stays, higher healthcare expenses, and higher death rates. So, there is an urgent demand for novel antimicrobials. Traditional antibiotics' efficacy is declining, and the pipeline for developing new drugs has slowed down due to expensive development costs, lengthy approval processes, and declining profits for pharmaceutical companies. The development of new antimicrobials and alternative therapies necessary to keep up with the rapid bacterial evolution and guarantee the efficacious treatment of infections in the

future. The development of antimicrobial drugs has long been the aim of research by medicinal chemists to minimize the death rate from diseases caused by microorganisms [28].

3. ESKAPE Pathogens

The ESKAPE pathogens are a group of six nosocomial pathogens: *Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii.* [34]ESKAPE pathogens include gram +ve and gram-ve bacterial species. [5] These pathogens can "escape" from the antimicrobials through different mechanisms. Globally, 1.30 million AMR-related deaths are reported per year, and around 80% of deaths are due to ESKAPE pathogens (including *Escherichia coli*). [11] The Centers for Disease Control (CDC), and Prevention categorizes the ESKAPE pathogens as urgent or significant threats to public health, while the World Health Organization (WHO) classified as high-priority or important pathogens.

Among ESKAPE organisms, *P. aeruginosa* and *A. baumannii* were categorized as critical priority organisms, whereas *E. faecium* and *S. aureus* were classified as high priority groups. The bacteria may develop multiple drug resistance by several mechanisms, including chemical alteration or breakdown of the drug, interfering with the antibiotic influx and efflux, modifications of drug targets, and more. In Table 1, we have discussed the antibiotic resistance mechanisms by ESKAPE pathogens and the genes involved in drug resistance of a particular ESKAPE pathogen.

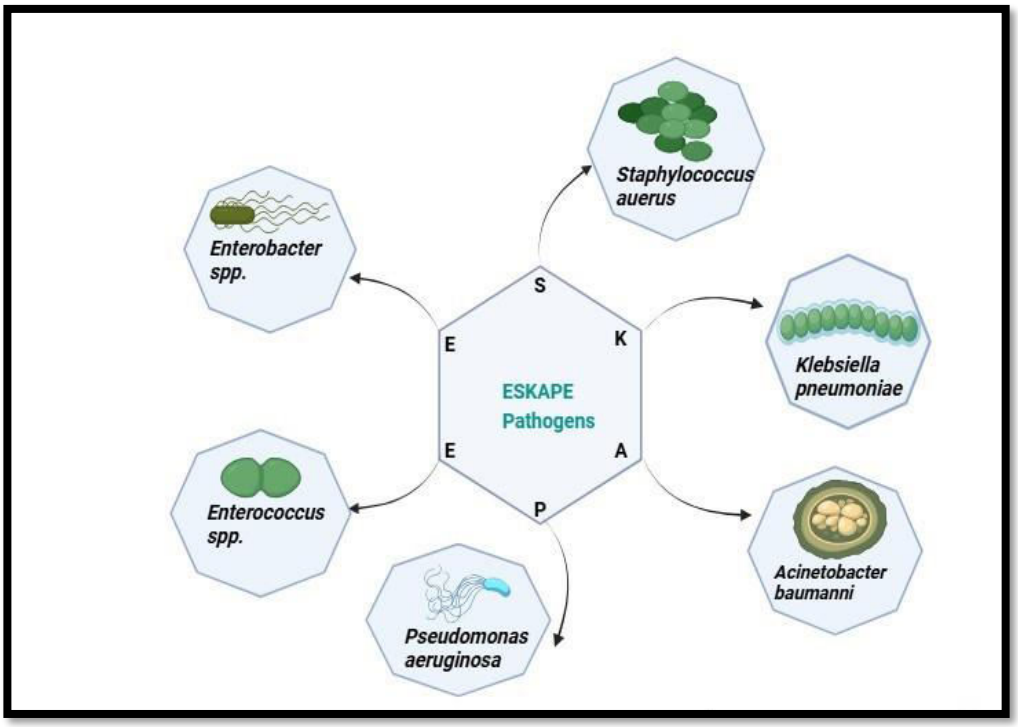


Figure1: The ESKAPE multiple drug-resistantbacteria groups, responsible for a different infection

Table 1: Genes involved in drug resistance of ESKAPE pathogen group

Sl no	Pathogen	Resistance to a different antibiotic	Genes involved in drug resistance	References
1	*Enterobacter* spp.	Cephalosporin, Aztreonam, Carbapenem, Imipenem, Etrapenem and Meropenem	*ampC, NDM-1,* orqep, *qnr,gyrA, gyrB, parC, Imp-1 aac (6')-1, bla_{SHV}, bla_{TEM}, bla_{CTX-M}, qnrA, qnrB and qnrS, blaOXA-48, ISEcpblaCTX-M-15, blaSHV blaoxa-1, pbp5, rmtE, pbp-3, bla-shv12, bla-mir*	[23], [51]
2	*Staphylococcus aureus*	Methicillin, Penicillin Oxacillin, Quinolones, Tetracycline, Vancomycin and Neomycin	*Pbp2, blaZ, mecA, fexA, lnu(A), (F), optrA, ermA, ereA-b, ter(A), aac (3')-Ia, aadA1, aph(3')-II, aph(3')IIIa, aacA-aphD, aadD, aac(6')Ie+aph(2", ant(4')Ia, ant(6)-Ia*	[23], [51]
3	*Klebsiella pneumoniae*	Amikacin, Cephalosporin Ceftotaxime, Meropenem Ciprofloxacin, Carbapenems, Ertapenem, Chloramphenicol, Mucins, Tigecycline, Ceftazidime-avibactam,Ampicillin, Cefepime, Cefoperazone, Ceftazidime, Gentamicin, Netilmicin, Piperacillin-tazobactam, Carbapenems, Penicillins, Monobactams, β-lactams, Lincosamide, Aminoglycosides, Streptogramins, Quinolones, Tetracyclines,	*Pbp2 and pbp4, sv-27, tem-116, blaKPC, blaNDM-1, blaTEM, blaCTX-M-15, blaOXA-4b, IntI, IntII, IntIII, aac(3)-II, aac(6')-Ib, AcrAB, KdeA, CepA, OmpK35, OmpK36, AmpR, Tem-116, ArmA, RmtB, RmtC, AcrAB, KdeA, CepA, OmpK35, OmpK36, blaOXA-48, ISEcpblaCtx-m -15, CTX-M-15, blaSHV blaoxa-1, blaOXA-48, blaSHVoqxA, oqxB, TEM-1, Shv -1, Shv -11, Shv-27, Shv-28, Shv -32, NDM-1, NDM-4, NDM-5, Oxa-10, Oxa-232, armA, aph(6)Id, aph(3*)Ib, aac(6')-Ib-cr, aph(3")-Ib, aph(6)-Id, aac(3)-Iid, armA,*	[12], [31], [51]

		Fluoroquinolones, Nitrofurantoin, Polymixins, Macrolids, Chlorhexidine, Rifampin, Colistin, Nalidixic acid and Tetracycline	*aad2, arr-2, arr-3, qnrB1, qnrB6, qnrS1, tetA, tetD, sul1, sul2, catB3, ant(3")-I, ant(2")-I dfrA, , dfrA5, dfrA14*	
4	*Acinetobacter baumannii*	Norfloxacin , Ofloxacin Ciprofloxacin, Imipenem Chloramphenicol and Nalidixic acid	*Pon A, mrcB, pbp4, fst1, tem, shv, GES, AdeA, tet(A), carO, omp22-23, ompA, Oxa-51, KPC, CarB, oprD, ctx-M, ade gene cluster, ant(3")-I, aac(3)i, aac(3')vi, ABUW_0982 of CHL gene cluster*	[5], [51]
5	*Pseudomonas aeruginosa*	Cefoxitin, Imipenem, Polymyxins, Piperacillin-tazobartum, Meropenem, Carbapenem, PolymyxinB, Gentamycin , Chloramphenicol and Quinolones	*mexR, nfxB, cmrA, fstI, opB, glpT, fusa1, ampD, parS, gryA, gyrB, parC and parE, OprD, OprH, MexAB-OprM, MexCD-OprJ, MexEF-OprN,MexXY-OprM, pslA, pslD, pbp2, pbp3, aac(6')Ib, , aadB, catB7, aphA1*	[26], [51]
6	*Enterococcus faecium*	Penicillin, Cephalosporin,Vancomycin, Tobramycin, Kanamycin, Gentamycin, and Chloramphenicol	*aac (6')-li, , aph(2")Ic, aph (3')-llla,aph(2")Ib, aph(2")Id, msrc, efmA, tet(m), pbp5, ant (6)-la, Van A to E , Van-G, ermB, catA7, catA8, catA9*	[26], [51]

4. Resistance mechanism in ESKAPE Pathogens

Antimicrobial resistance is mainly mediated by antimicrobial-resistant genes (ARGs) inherited in plasmids, chromosomal DNA, and transposons. Bacteria can also become resistant to various cellular gene alterations and mechanisms, like the alteration or deactivation of drugs, changes in drug binding sites, permeability changes in cells, and biofilm production.

4.1 Alteration or deactivation of antibiotics

The development of enzymes that degrade or neutralize antibiotics is a standard method by which ESKAPE bacteria exhibit drug resistance. These enzymes are categorized into two: one deactivates the active site of the antibiotic, and the other covalently alters the structural components of the drug or antibiotics to prevent interaction with target site of bacterial pathogen[20].

Production of β- Lactamases

Among the most prevalent mechanisms antimicrobial resistance gained by ESKAPE pathogen is the synthesis of enzymes that neutralizes or inactivates antibiotics. β-lactamases are from the α/β-hydrolase family. β-lactamases are classified into two categories based on the general features of the catalytic site and are separated. Serine β--lactamases use a serine in the active site to accomplish hydrolysis, whereas metallo- β-lactamases use 1or 2 divalent zinc atoms. [14] β-lactamases are the most common culprits among gram -ve bacteria responsible for cleaving β-lactam antibiotic rings. ESKAPE pathogens break down the β-lactam ring before targeting the penicillin-binding protein [5].

Aminoglycoside modifying enzymes (AMEs)

In ESKAPE pathogens, aminoglycoside resistance occurs through aminoglycoside-modifying enzymes. [5] Resistance is based on the generation of AMEs, which are further classified as aminoglycoside phosphor transferases, aminoglycoside nucleotidyltransferases, and aminoglycoside acetyltransferases. Resistance to aminoglycosides in the bacteria known as ESKAPE[52].

4.2 Modification of drug-binding sites

Resistant bacteria evade the effects of antibacterial drugs by altering their target sites through mechanisms like target enzyme modification, ribosome target site modification, and cell wall precursor alteration [23].

4.2.1. Target enzyme modification

Modifications in the target sites of the ESKAPE pathogen impede antibiotic binding, resulting in resistance to the respective drugs. [32] β-Lactam antibiotics inhibit the binding to PBP enzymes of bacteria that are present in the cell wall.

4.2.2. Ribosomal target site alterations

Many antibiotics exert antibacterial effects by targeting small and large ribosomal subunits (30S and 50S). Aminoglycoside antibiotics binds with a 16S rRNA component of the 30S subunit, which hinders the aminoacyl-tRNA association with the anticodon, eventually abrogating translation and its bactericidal effects. To resist most aminoglycosides, the 16S rRNA methyltransferases methylate either N7 of guanine (1405) or N1 of adenine (1408) of 16S rRNA. rRNAs (5S and 23S rRNA), as well as50S subunit of ribosomal proteins, are targeted by lincosamides, ketolides, streptogramin, and macrolides. Identical to 16S rRNAmethyltransferases, 23S rRNAmethyltransferases methylate antibiotics binding site resulting in elimination of antibiotic action. The methylation of 16S rRNA in gram –ve bacteria has developed as an innovative mechanism of resistance to aminoglycoside antibiotics described in *Pseudomonas aeruginosa* and *Acinetobacter baumannii*. To date, ten classes of 16S rRNA methyltransferases have been reported globally (like RmfA to RmfH, ArnA, and NmpA) [13].

4.3. Cell wall precursor alterations

The cell wall precursors of bacteria may get altered, giving rise to resistant strains. The gram -ve bacteria have produced enzymes known as Lipid A-modification enzymes, which change the lipid A region of lipopolysaccharide(LPS) and enable the bacterial pathogen to elude host immune responses. The introduction of positively charged sugar groups such as N-Ara4N and phosoethanolamine (pETtN) is one form of alteration that can be caused by lipid A-modifying enzymes.

Acylation, fatty acyl chain deacylation, and hydroxylation are other different types of modification. [20] The development of modified peptidoglycan precursors (D-Ala-D-Ala termini are transformed to either D-Ala-D-lactate or D-Ala-D-Seine) displays subdued glycopeptide binding. By producing natural D-Ala-D-Ala precursors, D-carboxypeptidases, are removed from the host cell. [3] *Pseudomonas aeruginosa, Klebsiella pneumoniae*, and *Acinetobacter baumannii*, have shown resistance to polymyxin through the remodeling of the lipid A structure's outer membrane lipopolysaccharide. [37]

4.4. Changes in cell permeability and drug efflux

ESKAPE pathogens exhibit significant modifications in cell permeability and drug efflux mechanisms as major factors contributing to their antibiotic resistance. The leading causes of antibiotic resistance exhibited by ESKAPE pathogens are substantial alterations in cell permeability and drug efflux mechanisms. These adaptations include decreased cell wall permeability, loss of porins, and overexpression of different efflux pumps, which collectively hinders the therapeutic efficiency of antibiotics. Developing effective strategies to tackle infections caused by these resistant pathogens needs an

understanding of mechanisms. Porins are a protein found in the gram –ve bacteria's outer membranes. Efflux pumps are bacterial membrane proteins that release antibiotics from intracellular compartments. The majority of efflux pumps act as multidrug transporters, increasing multidrug resistance and also releasing a variety of drugs. The efflux pump family has five members: the major facilitator superfamily, ATP binding cassette family, multidrug and toxic chemical extrusion family, resistance nodulation division family, and the small multidrug resistance family. [22] Efflux pumps perform on identifying and eliminating antibiotics, such as β-lactams, fluoroquinolones, and aminoglycosides.

4.5. Biofilm formation

Another massive challenge in the inhibition of ESKAPE pathogen growth is their rapid tendency to form biofilms. In the ESKAPE pathogen, biofilm formation is an outcome of bacterial cells adhering to surfaces, proliferating, and producing an extracellular matrix that serves as protection. Biofilm-forming bacteria have shown a greater resistance to antibiotics than their planktonic state. [23]

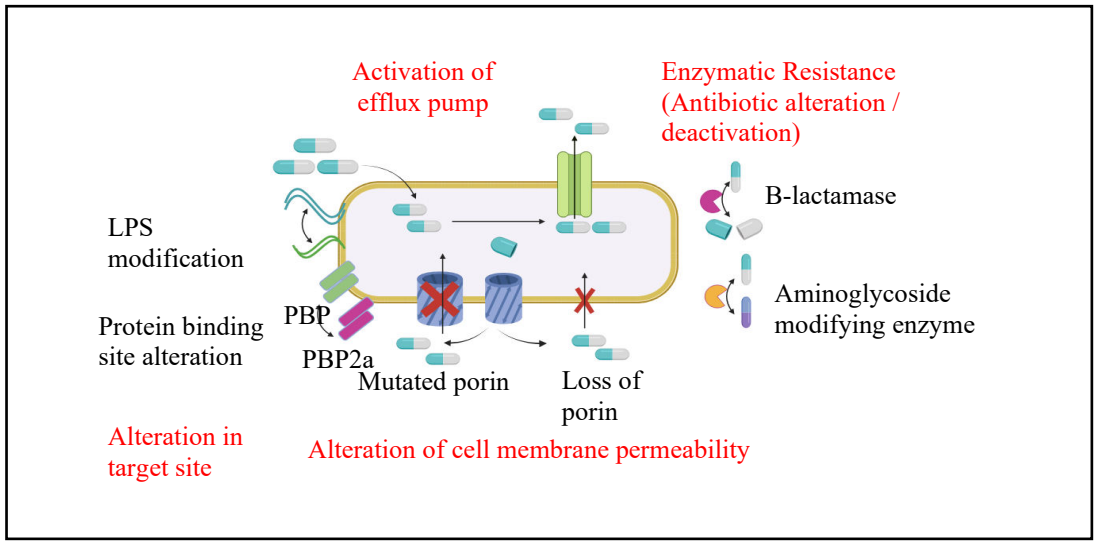


Figure2: The antibiotic resistance mechanism in ESKAPE pathogen

5. Role of medicinal plants in combating antimicrobial resistance of ESKAPE pathogen

Medicinal plants are used as the primary form of traditional medical practice, especially in the developing world. [33] Herbal remedies have been used since ancient times, as identified by archeological discoveries suggesting medicinal herbs as early as the Paleolithic era, approximately 60,000 years ago.[9] According to a World Health Organization (WHO) statistics analysis, around 80% of the world's population uses

traditional medicine for major healthcare by utilizing plants. The WHO classifies a medicinal plant as a species that exerts a pharmacological effect when applied to humans.[8]Exploring novel antibiotics derived from natural sources is essential for addressing the socio-economic and health impacts of multidrug-resistant microbes.

Table 2. Anti-bacterial activity of selected medicinal plants against ESKAPE pathogen

SI No	Medicinal Plants	Parts used	Extract prepared in	Anti-bacterial activity against ESKAPE Pathogen	Reference
1	*Moringaoleifera and Metricariarecutita*	Leaves and Flowers	Water, Ethanol and Methanol	*Escherichia coli, Staphylococcus aureus, Pseudomonas aeruginosa, Klebsiella* spp.	[25]
2	*Vernoniaauriculifera*Hiern	Aerial parts	Ethanol	*Escherichia coli, Enterbacteraerogenes, Klebsiellapneumoniae, Pseudomonas aeruginosa, Staphylococcus aureus*	[24]
3	*Bergenia ligulate*	Rhizome	Methanol	*Staphylococcus aureus, Escherichia coli*	[41]
4	*Newbouldialaevis and* *Dracaena arborea*	Leaves	Methanol	*Staphylococcus aureus, Pseudomonas aeruginosa, Klebsiella pneumonia*	[49]
5	*Cameliasinensis*L., *Aloe secundiflora*Engl.and*Sennadidymobotrya*(Fres.) Irwin &Barneby	Leaves	Methanol, Petroleum ether, Dichloromethane and Water	*Escherichia coli, Pseudomonas aeruginosa, Methicillin Resistant Staphylococcus aureus, Klebsiella pneumoniae, Staphylococcus aureus,*	[38]
6	*Punica granatum* L.	Peel	Hydro-alcoholic	*Enterococcus faecium, Staphylococcus aureus, Klebsiella*	[44]

				pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa, Enterobacter spp.	
7	*Abelmoschus esculentus*	Fruit	Hexane, Chloroform, Ethyacetate and Ethanol	*Staphylococcus aureus, Escherichia coli, Klebsiella pneumoniae, Pseudomonas aeruginosa*	[10]
8	*Mangifera indica*	Leaves , Stem and Barks	Methanol	*Staphylococcus aureu, Methicillin Resistant Staphylococcus aureus*	[17]
9	*Peganumharmala*	Seed	n-Butanol	*Multidrug-resistantPseudomonasaeruginosa*strain (P1 and P2)	[27]
10	*Thalictrumrhynchocarpum*	Root	Crude extract, n-Hexane Fraction, Chloroform Fraction and Methanol Fraction	*Klebsiella pneumoniae, Pseudomonas aeruginosa, Staphylococcus aureus, Escherichia coli*	[16]
11	*Terminaliachebula*	Seed	Aqueous, Alcohol and Acetone	*Staphylococcus aureus , Klebsiella pneumoniae, Pseudomonas aeruginosa*	[35]
12	*Azadirachtaindica and Carica papaya*	Leaves	Ethanol	*Staphylococcus aureus*	[45]
13	*Syncarpiahillii*	*Leaf*	*Methanol*	*Enterococcus faecalis* (QUT code 1105), *Pseudomonas aeruginosa* (ATCC 27853)	[40]
14	*Kitaibeliavitifolia*	Aerial part	Ethanol	*Klebsiella* spp., *Escherichia coli* (ATCC 25922), *MRSA (1726, 1063), Acinetobacter* spp. strain 1578	[30]
15	*Gymnemainodorum*	Leaf	Distilled water	*Vancomycin-resistant Enterococcus faecium*	[39]
16	*Cassia alata* L.	Root, leaf	Ethyl acetate	*Staphylococcus aureus*	[48]

17	*Hibiscus sabdariffa* L.	Flower	Methanol	*Staphylococcus aureus* (ATCC 25923), *Pseudomonas aeruginosa* (RCMB008001), *Escherichia coli* (RCMB004001)	[35]
18	*Terminaliaphanerophlebia* Engl. & Diels and T*erminaliasambesiaca* Engl. & Diels	Leaf	Methanol and Aqueous	*Staphylococcus. aureus, Escherichia coli , Klebsiellapneumoniae*	[19]
19	*Lanneacoromandelica*	Bark	Methanol, Ethanol and Aqueous	*Methicillin-resistant Staphylococcus aureus*	[18]
20	*Skimmiaanquetilia*	Root	n-Hexane, Ethyl acetate, and Methanol	*Pseudomonas aeruginosa* (MTCC424), *Klebsiella pneumonia* (MTCC139), *Staphylococcus aureus* (MTCC96), *E. coli* (MTCC739)	[36]
21	*Paederiafoetida* L.	Leaf	Ethanol	*Methicillin-resistant Staphylococcus aureus and Staphylococcus aureus,*	[43]
22	*Epilobium angustifolium* L.	Aerial parts	Aqueous	*Staphylococcus aureus , Acinetobacter baumannii, Escherichia coli, Klebsiella pneumoniae, Pseudomonas aeruginosa,*	[15]
23	*Curcuma longa*	Rhizome	Ethanol	*Staphylococcus aureus*	[47]
24	*Indigoferaheteranth a*	Root, Flower, Leaves and Bark	Methanol and Aqueous	*Escherichia coli* (MTCC 739), *Staphylococcus aureus* (MTCC 96), *Pseudomonas aeruginosa* (MTCC1688), *Klebsiella pneumoniae* (MTCC 432)	[6]
25	*Ailanthus altissima*	Leaf	Methanol	*Escherichia coli* (ATCC 25922), *Pseudomonas aeruginosa* (ATCC 27853), *Staphylococcus aureus* (ATCC 25923)	[7]

6. Challenges and considerations of medicinal plants against ESKAPE pathogens

Medicinal plants are being explored increasingly for their significant potential to combat ESKAPE pathogens, but several are fraught with challenges and considerations. Antibiotic resistance in high levels among ESKAPE pathogens complicates the treatment efforts, which results in the need for effective alternate treatments. The medicinal plant use has been related to poor cultivation, collection practices, poor storage facilities, lack of standardization during preparation, and adulteration of essential compounds, ultimately affecting the development of novel antimicrobials. Factors like the harvesting season, plant sections used, cultivation area, and processing type can affect the concentrations and mechanisms of different compounds in plant extracts. Therefore, comparing the many research data on the antimicrobial activity of medicinal plant extracts may be challenging due to the plant extract's composition varying on the basis of regional climate and ecological conditions. The complete information on the composition of plant extracts is also an inherent difficulty, as these plant extracts contain several complex components to interpret. The isolation of a particular compound with the appropriate antimicrobial activity can take a long period and may require many plant samples.

Scientific research of novel extracts from plants is challenging because of their variability and vast complexity. Plant extracts might contain 100 or even 1000 different compounds in variable amounts, and it is essential to identify the compounds responsible for a particular biological action. One of the biggest obstacles in developing novel antimicrobials has been translating *in vitro* research to *in vivo* tests and human medical trials. Only the medicinal plant extracts that inhibit the growth of microbes at low or moderate minimum inhibitory concentration values deserve the ultimate attention, and further investigation in this area can help to understand the process. Although extracts from various medicinal plants have shown inhibitory effects against these pathogens, ensuring these natural products' safety, effectiveness, and appropriate use are crucial. Another challenge in developing antimicrobials derived from medicinal plants is inadequate funding for research, which results in a lack of high-quality research on understanding the structure-activity relationship with particular compounds[50]. Therefore, further investigation is essential to address these challenges and enhance the therapeutic application of medicinal plants.

7. Conclusion and Future Aspects

The need for novel therapeutic strategies has been highlighted by the rising incidence of antibiotic resistance, especially in ESKAPE pathogen. With their wide range of bioactive compounds, including terpenoids, alkaloids, flavonoids, and phenolics, medicinal plants present a promising way to address this global issue. These natural substances have a variety of antibacterial properties, including as altering efflux pumps, preventing biofilm formation, disrupting bacterial cell membranes, and interfering with quorum sensing. By

reducing the chance of resistance development, phytochemicals' capacity to target several resistance pathways at once positions medicinal plants as effective substitutes or supplementary drugs to traditional antibiotics. While medicinal plants hold considerable promise in the fight against ESKAPE pathogens, several challenges associated with their use must be carefully addressed to ensure they can effectively contribute to combating the rising antibiotic resistance issues. With the increasing risk posed by multidrug-resistant ESKAPE pathogens, investment in exploring and developing novel plant anti-infectives is critical. Current studies are often limited to in vitro experiments, with insufficient validation in animal models and clinical trials. To harness the full potential of medicinal plants, future research must focus on: isolation and characterization of bioactive compounds, molecular mechanisms through which plant compounds interact with ESKAPE pathogens, synergistic approaches, in vivo and clinical validation and creation of stable, bioavailable, and cost-effective formulations (e.g., nano-drug delivery systems). In summary, medicinal plants offer an enormous and mainly unexplored resource for antimicrobial compounds that could help combat the escalating threat posed by ESKAPE bacteria. Plant-based medicines have the potential to become a key component of future antimicrobial efforts by bridging the gap between traditional knowledge, contemporary science, and technological innovation. In order to turn this promise into practical therapeutic treatments and ultimately support international efforts to fight antibiotic resistance and protect public health, cooperation between researchers, the pharmaceutical industry, and policymakers will be essential.

Abbreviation: Nil

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8. References

1. Ahmed, S.K., Hussein, S., Qurbani, K., Ibrahim, R.H., Fareeq, A., Mahmood, K.A., & Mohamed, M.G. (2024). Antimicrobial resistance: impacts, challenges, and future prospects. Journal of Medicine, Surgery, and Public Health.2, 100081.

2. Alotaibi, G. (2024). Prevalence, pandemic, preventions and policies to overcome antimicrobial resistance. Saudi Journal of Biological Sciences.31(8), 104032.
3. Arredondo-Alonso, S., Top, J.,Corander, J.,Willems, R.J.,&Schürch, A.C. (2021). Mode and dynamics of vanA-type vancomycin resistance dissemination in Dutch hospitals. Genome medicine.13, 1-8.
4. Asghar, A., Khalid, A., Baqar, Z., Hussain, N.,Saleem, M.Z.,SairashRizwan, K. (2024). An insights into emerging trends to control the threats of antimicrobial resistance (AMR): an address to public health risks. Archives of Microbiology. 206(2),72.
5. Badar, L., Ibrahim, A. (2024). Exploring the Strategies to Combat Antimicrobial Resistance in ESKAPE Pathogens; A Comprehensive Review. Microbiological & Immunological Communications.3(1), 43-72.
6. Bhat, S.A., Zargar, M.I., Wani, S.U., Mohiuddin, I., Masoodi, M.H., Shakeel, F., Ali, M., & Mehdi, S.(2024). In-vitro evaluation of Indigoferaheterantha extracts for antibacterial, antifungal and anthelmintic activities. Journal of Pharmaceutical Health Care and Sciences. 10(1), 7.
7. Boukhibar, H.,Laouani, A., Touzout, S.N.,Alenazy, R.,Alqasmi, M., Bokhari, Y., Saguem, K., Ben-Attia, M., El-Bok, S., &Merghni, A. (2023). Chemical Composition of Ailanthus altissima (Mill.) Swingle Methanolic Leaf Extracts and Assessment of Their Antibacterial Activity through Oxidative Stress Induction. Antibiotics. 12(8), 1253.
8. Cedillo-Cortezano, M., Martinez-Cuevas, L.R., López, J.A., Barrera López, I.L., Escutia-Perez, S.,&Petricevich, V.L. (2024). Use of medicinal plants in the process of wound healing: a literature review. Pharmaceuticals. 17(3), 303.
9. Chaachouay, N., Zidane, L. (2024). Plant-Derived Natural Products: A Source for Drug Discovery and Development. Drugs and Drug Candidates.3 (1), 184–207.
10. Chan, S.M., Fong, V.Y., Koo, S.Y., Singh, T.R., Tang, E.H.,Thoo, L.T., Sit, N.W., (2022). Antibacterial activity of selected medicinal plants from Malaysia. Asian Pacific Journal of Science and Technology.27(1), 1-10.
11. Christiana, A.E.,Theolyn, C.,S'thebe,W.N.,Yamkela, D., Saheed, S. (2024). ESKAPE pathogens and associated quorum sensing systems–New targets for novel antimicrobials development. Health Sciences Review.11, 100155.
12. Cireșă, A.,Tălăpan, D., Vasile, C.C., Popescu, C., Popescu, G.A. (2024). Evolution of Antimicrobial Resistance in Klebsiella pneumoniae over 3 Years (2019–2021) in a Tertiary Hospital in Bucharest, Romania. Antibiotics.13(5), 431.
13. De Oliveira, D.M., Forde, B.M., Kidd, T.J., Harris, P.N., Schembri, M.A., Beatson, S.A., Paterson, D.L., Walker, M.J. (2020). Antimicrobial resistance in ESKAPE pathogens. Clinical microbiology reviews. 33(3), 10-128.

14. de Souza, J., Vieira, A.Z., Dos Santos, H.G., et al. (2024). Potential involvement of beta-lactamase homologous proteins in resistance to beta-lactam antibiotics in gram-negative bacteria of the ESKAPEE group. BMC genomics. 25(1), 508.
15. Dreger, M., Adamczak, A.,Foksowicz-Flaczyk, J. (2023). Antibacterial and Antimycotic Activity of Epilobium angustifolium L. Extracts: A Review. Pharmaceuticals.16(10), 1419.
16. Dubale, S.,Kebebe, D.,Zeynudin, A., Abdissa, N., &Suleman S. (2023). Phytochemical screening and antimicrobial activity evaluation of selected medicinal plants in Ethiopia. Journal of experimental pharmacology. 31, 51-62.
17. Ekamgue, B.,Mbaveng, A.T.,Seukep, A.J.,Matieta, V.Y.,Kuete, J.R.,Megaptche, J.F.,Guefack, M.G.,Nayim, P.,&Kuete, V. (2023). Exploring Mangiferaindica (Anacardiaceae) leaf and bark methanol extracts as potential adjuvant therapy in the management of multidrug-resistant Staphylococcus aureus. Investigational Medicinal Chemistry Pharmcology.6(2), 84.
18. Ferdous, R.N.,Nebir, S.S., Das, P.K.,Prova, A.H.,Moniruzzaman, M., Khan, M.S., Rokeya, B., Asna, S.M. (2022). Antimicrobial activity of Lanneacoromandelica bark extracts against methicillin-resistant Staphylococcus aureus. BIRDEM Medical Journal. 12(3),201-6.
19. Florenca, C., Tiwana, G., Grant, G.D., Cock, I.E., Cheesman, M.J. (2024). Phytochemical analysis and antibacterial properties of Terminaliaphanerophlebia and Terminaliasambesiaca leaf extracts. South African Journal of Botany.174, 9-22.
20. Gauba, A., Rahman, K.M. (2023). Evaluation of antibiotic resistance mechanisms in gram-negative bacteria. Antibiotics.12(11),1590.
21. Howard, S.J., Hopwood, S., Davies, S.C. (2014). Antimicrobial resistance: a global challenge. Science translational medicine. 6(236), 236ed10.
22. Huang, L., Wu, C., Gao, H., Xu, C., Dai, M., Huang, L., Hao, H., Wang, X., Cheng, G. (2022). Bacterial multidrug efflux pumps at the frontline of antimicrobial resistance: an overview. Antibiotics.11(4), 520.
23. Jain, A., Kumar Oli, A., Kulkarni, S., D Kulkarni, R., Chandrakanth, K. (2024). A review on drug resistance patho-mechanisms in ESKAPE bacterial pathogens. Novel Research in Microbiology Journal. 8(3), 2435-2451.
24. Jepkoech, C.,Omosa, L.K.,Nchiozem-Ngnitedem, V.A., Kenanda, E.O.,Guefack, M.G., Mbaveng, A.T., Kuete, V., Heydenreich, M. (2022). Antibacterial secondary metabolites from VernoniaauriculiferaHiern (Asteraceae) against MDR phenotypes. Natural Product Research. 36(12), 3203-6.
25. Keita, K.,Darkoh, C., Okafor, F. (2022). Secondary plant metabolites as potent drug candidates against antimicrobial-resistant pathogens. SN Applied Sciences. 4(8), 209.

26. Kelly, J.B., Nolan, A.C.,Zeden, M.S. (2024). How can we escape the ESKAPEs: Antimicrobial resistance mechanisms and what lies ahead?.PLoS pathogens. 20(6), e1012270.
27. Khadraoui, N., Essid, R.,Jallouli, S., Damergi, B., Ben Takfa, I., Abid, G.,Jedidi, I., Bachali, A., Ayed, A.,Limam, F., &Tabbene, O. (2022). Antibacterial and antibiofilm activity of Peganumharmala seed extract against multidrug-resistant Pseudomonas aeruginosa pathogenic isolates and molecular mechanism of action. Archives of Microbiology. 204(2), 133.
28. Khatoon, H., Faudzi, S.M. (2024). Exploring quinoxaline derivatives: An overview of a new approach to combat antimicrobial resistance. European Journal of Medicinal Chemistry.276, 116675.
29. Kumar, N.R.,Balraj, T.A.,Kempegowda, S.N.,Prashant, A. (2024). Multidrug-resistant sepsis: A critical healthcare challenge. Antibiotics. 13(1), 46.
30. Kurćubić, V.S., Raketić, S.V.,Mašković, J.M.,Mašković, P.Z.,Kurćubić, L.V., Heinz, V., & Tomasevic, I.B. (2023). Evaluation of Antimicrobial Activity of Kitaibeliavitifolia Extract against Proven Antibiotic-Susceptible and Multidrug-Resistant (MDR) Strains of Bacteria of Clinical Origin. Plants.12(18), 3236.
31. Li, Y., Kumar, S., Zhang, L. (2024). Mechanisms of Antibiotic Resistance and Developments in Therapeutic Strategies to Combat Klebsiella pneumoniae Infection. Infection and Drug Resistance. 1107-19.
32. Mancuso, G., Midiri, A., Gerace, E., Biondo, C. (2021). Bacterial antibiotic resistance: the most critical pathogens. Pathogens.10(10), 1310.
33. Marković, M.S.,Pljevljakušić, D.S.,Matejić, J.S.,Nikolić, B.M.,Zlatković, B.K.,Rakonjac, L.B.,Djokić, M.M.,Papović, O.M., & Stankov Jovanović, V.P. (2024). Traditional uses of medicinal plants in Pirot District (southeastern Serbia). Genetic Resources and Crop Evolution. 71(3), 1201-20.
34. Miller, W.R., Arias, C.A. (2024). ESKAPE pathogens: antimicrobial resistance, epidemiology, clinical impact and therapeutics. Nature Reviews Microbiology.1-9.
35. Mohammed, F.R., Hussein, K.A., & Abboud, Z.H. (2024). Evaluation of Some Medicinal Plant Crude Extracts (Aqueous, Ethanol, and Acetone) Against Several Pathogenic Bacteria. Medical Journal of Babylon.21(Suppl 1), S88-95.
36. Nabi, M., Tabassum, N., Ganai, B.A. (2022). Phytochemical screening and antibacterial activity of Skimmiaanquetilia NP Taylor and Airy Shaw: A first study from Kashmir Himalaya. Frontiers in Plant Science.13, 937946.
37. Nguyen, A.H., Hood, K.S.,Mileykovskaya, E., Miller, W.R., Tran, T.T. (2022). Bacterial cell membranes and their role in daptomycin resistance: A review. Frontiers in Molecular Biosciences. 9, 1035574.

38. Ningsih, I.Y.,Sulistyono, I.R.,Hafizha, Z.,Robiyanto, A.,Puspitasari, E.,Dianasari, D., Hidayat, M.A. (2024). Antibacterial and antioxidant activities of Eleutherineamericana (Aubl.) Merr. leaves extract growing in different cultivation sites. Research Journal of Pharmacy and Technology.17(11), 5597-4.
39. Odongo, E.A.,Mutai, P.C.,Amugune, B.K.,Mungai, N.N.,Akinyi, M.O.,Kimondo, J. (2023). Evaluation of the antibacterial activity of selected Kenyan medicinal plant extract combinations against clinically important bacteria. BMC Complementary Medicine and Therapies.23(1),100.
40. Ounjaijean, S., Somsak, V., Saki, M.,Mitsuwan, W.,Romyasamit, C. (2024).Antibacterial, Antibiofilm, and Antioxidant Activities of Aqueous Crude Gymnemainodorum Leaf Extract against Vancomycin-Resistant Enterococcus faecium. Microorganisms.12(7),1399.
41. Perera, M.M., Dighe, S.N.,Katavic, P.L., Collet, T.A. (2022). Antibacterial potential of extracts and phytoconstituents isolated from Syncarpiahillii leaves in vitro. Plants.11(3), 283.
42. Rolta, R., Goyal, M., Sharma, S.,Bharaj, D., Salaria, D., Upadhyay, N.K., Lal, U.R., Dev, K., Sourirajan, A. (2022). Bioassay Guided Fractionation of Phytocompounds from Bergenialigulata: A synergistic approach to treat drug resistant bacterial and fungal pathogens. Pharmacological Research-Modern Chinese Medicine.3:100076.
43. Santajit, S.,Tunyong, W.,Horpet, D.,Binmut, A., Kong-Ngoen, T.,Wisessaowapak, C.,Thavorasak, T.,Pumirat, P.,Indrawattana, N. (2024). Unveiling the Antimicrobial, Anti-Biofilm, and Anti-Quorum-Sensing Potential of Paederiafoetida Linn. Leaf Extract against Staphylococcus aureus: An Integrated InVitro–In Silico Investigation. Antibiotics.13(7), 613.
44. Scaglione, E., Sateriale, D.,Mantova, G., Di Rosario, M.,Continisio, L., Vitiello, M., Pagliarulo, C., Colicchio, R., Pagliuca, C., Salvatore, P. (2024). Antimicrobial efficacy of PunicagranatumLythraceae peel extract against pathogens belonging to the ESKAPE group. Frontiers in Microbiology. 15,1383027.
45. Sehim, A.E., Amin, B.H., Yosri, M., Salama, H.M., Alkhalifah, D.H., Alwaili M.A.,AbdElghaffar, R.Y. (2023). GC-MS Analysis, Antibacterial, and Anticancer Activities of Hibiscus sabdariffa L. Methanolic Extract: In Vitro and In Silico Studies. Microorganisms. 11(6), 1601.
46. Shil, A.,Shuvo, M.N., Sultana, H., Alam, N., Himel, M.K. (2023). Effect of traditional medicinal plants on the pathogenic potential of the versatile pathogen Staphylococcus aureus. Jahangirnagar University Journal of Biological Sciences. 73-86.
47. Sultan, S., Sultan, I., Nawaz, Y., Tanvir, F., &Rehman, S. (2023). Study of Antibacterial Properties of Turmeric Extract Against Salmonella typhi and Staphylococcus aureus. Phytopharmacological Communications.3(2), 101-108.

48. Toh, S.C., Lihan, S., Bunya, S.R., &Leong, S.S. (2023). In vitro antimicrobial efficacy of Cassia alata (Linn.) leaves, stem, and root extracts against cellulitis causative agent Staphylococcus aureus. BMC complementary medicine and therapies.23(1), 85.
49. Uchenna, H.,Ezema, J.N.,Chinaka, C.B.,Imanyikwa, O.E.,Ukhureigbe, O.M., Ezugwu, I.A., Chukwuma, S.T., & Eze, E.A. (2024). Evaluation of Antibacterial Effects of Newbouldialaevisand Dracaena arborea Methanol Extracts against Some Multidrug Resistant'ESKAPE'Pathogens Isolated from Hospital Environments. Tropical Journal of Natural Product Research. 8(7).
50. Vaou, N., Stavropoulou, E.,Voidarou, C.,Tsigalou, C.,Bezirtzoglou, E. (2021). Towards advances in medicinal plant antimicrobial activity: A review study on challenges and future perspectives. Microorganisms. 9(10), 2041.
51. Venkateswaran, P., Vasudevan, S., David, H., Shaktivel, A., Shanmugam, K., Neelakantan, P., Solomon, A.P. (2023). Revisiting ESKAPE Pathogens: Virulence, resistance, and combating strategies focusing on quorum sensing. Frontiers in cellular and infection microbiology. 13, 1159798.
52. Wang, N., Luo, J., Deng, F., Huang, Y., Zhou, H. (2022). Antibiotic combination therapy: a strategy to overcome bacterial resistance to aminoglycoside antibiotics. Frontiers in Pharmacology. 13:839808.