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MINI REVIEW

Multi-drug resistant ESKAPE pathogens and the uses of plants as their antimicrobial agents

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Abstract

Infections by ESKAPE (*Enterococcus* sp., *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Enterobacter* spp.) pathogens cause major concern due to their multi-drug resistance (MDR). The ESKAPE pathogens are frequently linked to greater mortality, diseases, and economic burden in healthcare worldwide. Therefore, the use of plants as a natural source of antimicrobial agents provide a solution as they are easily available and safe to use. These natural drugs can also be enhanced by incorporating silver nanoparticles and combining them with existing antibiotics. By focussing the attention on the ESKAPE organisms, the MDR issue can be addressed much better.

Keywords Antibiotics · Antimicrobial · ESKAPE · Multi-drug resistance · Plant · Pathogen

Introduction

The advent of new diseases and the difficulties in finding cures and treatments cause fear in society. As many pathogenic microorganisms such as bacteria and yeasts become resistant to medications, infectious illnesses have become a severe public health concern. Multi-drug resistance (MDR) is defined as acquired non-susceptibility to one or more antimicrobial agents from three or more antimicrobial categories (Bhatia et al. 2021). Among MDR pathogens, ESKAPE (*Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, *Enterobacter* sp.) pathogens have caused a major concern due to their resistance against antibiotics and other medicine (Čivljak et al. 2014; Baker et al. 2018) (Fig. 1).

These bacteria cause severe infections, morbidity and mortality (Okwu et al. 2019; Taha Yassin et al. 2020), in which 75.7–78.9% of total bacterial isolates from hospitals in Italy cause bloodstream infections (BSIs) (De Socio et al. 2019). Meanwhile, in the United States, the Centre for Disease Control and Prevention (CDC) projected that MDR pathogens cause almost 2 million diseases and 23,000 deaths/year (Okwu et al. 2019). Infections by MDR pathogens were higher in hospital-onset compared with community-onset (De Socio et al. 2019). Hospital-acquired infections afflict 4 to 20 individuals out of every 100 admitted to acute care hospitals (De La Rosa-Zamboni et al. 2018). These infections not only infect patients but also have negative consequences for healthcare workers and visitors who are either directly or indirectly infected and can spread the infection (Sirijan Santajit et al. 2016; Baker et al. 2018). With the current COVID-19 situation, an effective and faster solution is needed to overcome the problems and minimise the burden on healthcare systems. One of the milestones for lowering mortality and morbidity from illnesses caused by resistant bacteria is to monitor the epidemiology. Indeed, it provides useful preventative information and aids clinicians in empirically prescribing an efficient antibiotic medication (De Socio et al. 2019).

Antibiotics were one of the most important medical breakthroughs in the fight against bacterial illnesses. Penicillin was the first antibiotic to have a significant impact on human and animal health (Suroowan et al. 2019). Hundreds of antibiotics have been found so far and used as treatments for a variety of diseases caused by microorganisms. However, some of these antibiotics were becoming less or no longer effective in treating diseases due to pathogen resistance (Čivljak et al. 2014; Mulani et al. 2019; Suroowan et al. 2019; Benkő et al. 2020).

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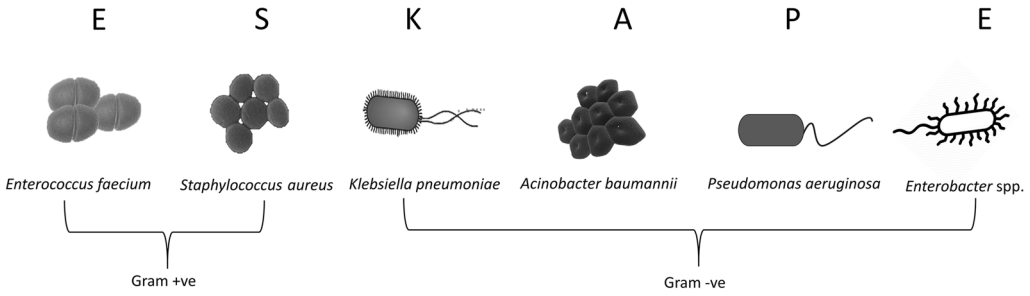

Fig. 1 ESKAPE multi-drug resistance bacteria

Apart from issues such as antibiotic abuse, which can lead to drug resistance, there are also concerns about the safety and toxicity of antibiotics, which limit their usage (Suroowan et al. 2019). Therefore, the use of plants as antimicrobial agents in antibiotics is promoted, as their efficacies are comparable to synthetic antibiotics while being far safer.

Plants are frequently employed in developing new medicine formulations because they contain a wide range of secondary metabolites. Secondary metabolites, often called phytochemicals, serve as a chemical defence against diseases and pathogens. These phytochemicals are appropriate as antibiotics due to their low to no side effects compared to other synthetic antibiotics and their ability to overcome pathogen resistance to existing antibiotics (Sieberi et al. 2020). Plant extracts have been tested against various pathogens in numerous studies such as *Curcuma longa* was effective in inhibiting *Bacillus cereus* and *Serratia* sp. (Dhiman et al. 2016), *Mentha piperita*, *Eucalyptus camaldulensis*, *E. citriodora*, *C. longa* were effective against *S. aureus*, (Sounouvou et al. 2021), *Skimmia anquetilia* showed antibacterial activity against *P. aeruginosa* (Nabi et al. 2022), and *Callistemon viminalis* extract was susceptible by *P. aeruginosa* and *S. aureus* (Chipenzi et al. 2020). These results have aided in developing new treatments for diseases, particularly those that have resisted conventional treatments. Plants have demonstrated their efficacy in evading and curing toxicity caused by toxic substances or medications via mechanisms such as pathogen entry inhibition, inhibition of replication enzymes and pathogen release blockage (Khan et al. 2021). The antibacterial effectiveness of plant extracts and derivatives has been helpful in developing innovative and helpful treatments for MDR-ESKAPE. This review examines plant extracts as potential therapies for ESKAPE infections, with the goal of resolving MDR issues.

ESKAPE pathogens

The most prevalent bacteria with an antibiotic resistance profile included as a sentinel in surveillance systems are ESKAPE pathogens, which can be classified into several resistance groups (low-resistance; multi-drug and extremely drug resistant; pan-resistant bacteria) (Reale et al. 2017). Gram-negative isolates are *E. coli*, *K. pneumoniae*, *A. baumannii* and *P. aeruginosa*. Meanwhile, Gram-positive isolates are *S. aureus, E. faecium* and *E. faecalis*. The ESKAPE pathogens mainly were isolated from blood, urine, wound swabs, respiratory samples, etc., collected in hospital units (intensive care units (ICU), medical and surgical units) (Llaca-Díaz et al. 2012; Benkő et al. 2020; Pandey et al. 2021). Despite hospitals being the primary source, individuals having an impaired immune system, such as people with cardiovascular disorders, diabetes, chronic kidney, lung, as well as cancer patients, are the most affected (Founou et al. 2018). Pandey et al. (2021) isolated ESKAPE pathogens the most from urine samples (49.9%), followed by pus (22.3%), sputum (21.5%), blood (2.7%), semen (1.3%), high vaginal swab (0.7%), wound swab (0.4%), endotracheal tube (0.4%), ear swab (0.2%), broncho alveolar lavage (0.2%), suction tip (0.2%), and oral swab (0.2%). Based on gender, ESKAPE pathogens were recovered more from females, which were 249 (55%), while males were 203 (45%). Individuals categorised in 61–70 years old were the most infected (16%), followed by 21–30 years old (15%) (Pandey et al. 2021). A study by De Socio et al. (2019) found no significant difference in the hospital unit, gender, and patient age.

A study in a paediatric teaching hospital in Mexico isolated 94 MDR pathogens from the surgical and medical care units (De La Rosa-Zamboni et al. 2018). Another study by Llaca-Díaz et al. (2012) discovered that 65% of pathogens isolated from the ICU of a hospital in Monterrey, Mexico were in the ESKAPE group. Reale et al. (2017) found 2385 isolates, in which *E. coli* (38%) was the most frequent, followed by *P. aeruginosa* (15%), *K. pneumoniae* (14%), *S. aureus* (13%), *A. baumannii* (9%), *E. faecalis* (8%) and *E. faecium* (3%). Between 2011 and 2014, there was a 9% drop in MDR and pan-resistant isolates, particularly for *K. pneumoniae* and *E. coli*. Meanwhile, the hospital in Nepal isolated 90% MDR pathogens (Manandhar et al. 2020). A five-year study by Benkő et al. (2020) discovered that 72.22% of total isolates recovered from clinical specimens

were ESKAPE pathogens. Among 81 ESKAPE pathogens acquired from National Cancer Institute, Cairo University, 60 isolates were MDR, with *P. aeruginosa* and *K. pneumoniae* being the most dangerous, with fatality rates of 43% and 30%, respectively (El-Mahallawy et al. 2016). Table 1 lists the ESKAPE pathogens isolated from the hospital-onset.

Enterococcus faecium

Previously, *Enterococcus* were categorised as a section of the *Streptococcus* genus. Often found in chains or pairs, these Gram-positive bacteria live in the guts of animals and humans (Namikawa et al. 2017; Fiore et al. 2019). *Enterococcus* has more than 20 species, in which *E. faecium* and *E. faecalis* are the common species isolated from hospitals (Llaca-Díaz et al. 2012; Sirijan Santajit et al. 2016). *Enterococcus* can cause ulcerative colitis, inflammatory bowel disease, and Crohn's disease. Faecal samples from Crohn's disease patients consisted of more *E. faecium* than healthy individuals (Shiga et al. 2012). Usually, infections by *Enterococcus* are obtained internally, but cross-infection can occur through inanimate objects such as ear-probe thermometers, bedrails, hospital drapery, and nursing station keyboards (Sirijan Santajit et al. 2016; Fiore et al. 2019). Moreover, there was no report that clinical isolates of *Enterococcus* sp. be linked with human infection, but due to the environmental roughness, particularly of *E. faecalis* which builds tolerance to deadly doses of detergents and bile salts. Furthermore, 5–20% of *Enterococcus* are from community-acquired endocarditis. Both *E. faecalis* and *E. faecium* have demonstrated the best resilience to desiccation and hunger. Resistance to the popular hospital disinfectants chlorhexidine and chloroxylenol are similarly high in these two species (Fiore et al. 2019). However, *E. faecium* shows higher resistant to multiple antibiotics than *E. faecalis* (Namikawa et al. 2017). *Enterococcus* became the third most frequent nosocomial pathogen in the United States between 2011 and 2014, accounting for 14% of hospital-acquired infections, of which only 11% was recorded in 2007 (Fiore et al. 2019; Bhatia et al. 2021).

Staphylococcus aureus

Staphylococcus aureus is a Gram-positive coccal bacteria with clusters of cells that resemble grapes. It is a natural element of the skin flora, commonly isolated from the external portion of the nostrils and under the arm due to its non-stringent growth requirements (Pendleton et al. 2013). The general population has a high transmission rate, which can occur through direct contact or airborne. *Staphylococcus aureus* (64.4%) was the highest bacteria obtained from pus specimens since it had the ability to spread and cause a variety of diseases (Pandey et al. 2021). This pathogen was the most isolates in blood culture (64.5%), followed by wound or abscess specimen (30.9%), catheter-specimen urine (3.1%), and midstream urine (1.5%) (Benkő et al. 2020). Patients' blood cultures collected from hospitals in Italy between 2014 and 2018 found that *S. aureus* (26%) was the highest species that caused BSIs from 1858 isolates of ESKAPE pathogens (De Socio et al. 2019). Skin tissue infection and pyogenic lesions affecting multiple organs are known to be caused by *S. aureus* (Chakraborty et al. 2018; Yi Xin et al. 2021). During an infection, *S. aureus* isolates may use a variety of extracellular proteins. Haemolysins, proteases, hyaluronidase, and collagenase are secreted by nearly all strains, contributing to the host's opportunistic establishment through tissue breakdown for sustenance. Toxigenic shock syndrome is caused by the exotoxin TSST-1, which is produced by around 25% of *S. aureus*, while gastroenteritis is caused by enterotoxin. Panton-Valentine leukocidin is a pore-forming exotoxin that causes acute necrotising pneumonia. It is demonstrated by less than 5% of *S. aureus* but is concerned in the majority of community-acquired methicillin-resistant *S. aureus* (CA-MRSA) cases globally. Staphyloxanthin prevents neutrophils from producing reactive oxygen species and enhancing the survival of the cell. Moreover, the carotenoid pigment staphyloxanthin contains an intrinsic immuno-evasive mechanism in *S. aureus* and is in charge of *S. aureus* distinctive golden yellow colouration (Pendleton et al. 2013).

Infections by *S. aureus* are often lethal and usually treated by cephalosporins (e.g. cefazolin) and oxacillin. Patients with serious infections of *S. aureus* will get parenteral penicillinase-resistant penicillins (e.g.nafcillin) or first- or second-generation cephalosporins (e.g. cephalexin, in combination with clindamycin or quinolones). Trimethoprim-sulfamethoxazole (TMP-SMX), doxycycline and rifampin are some of the other antibiotics available (Yi Xin et al. 2021).

Methicillin-resistant *S. aureus* (MRSA) is a common bacteria that causes nosocomial and CA-MRSA. Since it was first identified in 1961, it has caused various deadly infections, such as severe pneumonia, endocarditis, and septic shock (Chakraborty et al. 2018). Infection of livestock or humans exposed to infected animals is known as livestock-associated MRSA (LA-MRSA) (Nemati et al. 2008). MRSA transmission from animals to humans was reported through direct contact with the animals and ingestion of meat or other food products as a result of insufficient hygiene standards in several situations (Chakraborty et al. 2018; De La Rosa-Zamboni et al. 2018). MRSA infection transmission patterns could be similar in raw food, prepared food products (such as meat and fish), and among humans. Therefore, special attention during meals preparation is required in public hospitals and retail food because they are meant for patients

Table 1 Reported cases of ESKAPE pathogens isolated from hospitals

Location	Year	No. of isolates									Total isolates	References
		E. faecium	*E. faecalis*	*Entero-coccus* spp.	*S. aureus*	*K. pneumo-niae*	*A. baumannii*	*P. aeruginosa*	*E. coli*	*Entero-bacter* spp.		
Perugia, Italy	2014–2018	130 (7%)	–	–	473 (25%)	315 (17%)	61 (3%)	131 (7%)	–	117 (6%)	1110	De Socio et al. (2019)
Mexico	2013–2016	–	4 (4%)	–	21 (22%)	41 (44%)	4 (4%)	7 (7%)	15 (16%)	2 (2%)	94	De La Rosa-Zamboni et al. (2018)
Calabria, Italy	2011–2014	68 (3%)	199 (8%)	–	316 (13%)	341 (14%)	205 (9%)	362 (15%)	894 (38%)	–	2380	Reale et al. (2017)
uMgungund-lovu district, South Africa	2017	–	–	–		6 (25%)	8 (33%)	7 (29%)		3 (13%)	24	Founou et al. (2018)
Nepal	2018	25 (6%)	–	–	151 (33%)	149 (33%)	39 (9%)	84 (19%)	–	4 (1%)	452	Pandey et al. (2021)
Monterrey, Mexico	2011–2012	35 (3%)	121 (9%)	–	241 (31%)	192 (15%)	268 (21%)	242 (19%)	90 (7%)	97 (8%)	1286	Llaca-Díaz et al. (2012)
Kathmandu, Nepal	2012–2018	–	–	–	–	532 (25%)	382 (18%)	–	719 (33%)	520 (24%)	2153	Manandhar et al. (2020)
Szeged, Hungary	2014–2019	–	–	471 (11%)	561 (13%)	664 (16%)	31 (1%)	181 (4%)	2194 (52%)	119 (3%)	4221	Benkő et al. (2020)
Cairo, Egypt	2012	–	–	7 (9%)	19 (23%)	30 (37%)	8 (10%)	7 (9%)	–	10 (12%)	81	El-Mahallawy et al. (2016)
Wuhan, China	2007–2014	10 (19%)	–	–	10 (19%)	7 (13%)	18 (34%)	5 (9%)	–	3 (6%)	53	Song et al. (2014)
Selangor, Malaysia	–	–	–	3 (3%)	20 (20%)	12 (12%)	21 921%)	22 (22%)	1 (1%)	22 (22%)	101	Phoon et al. (2018)
Guilin, China	2014–2018	–	–	–	–	3850 (24%)	2418 (15%)	2711 (17%)	7142 (44%)	–	16,121	Zhong and He (2021)

who are at a high risk of contracting *S. aureus*-related infections (Chakraborty et al. 2018).

Klebsiella pneumoniae

Klebsiella pneumoniae is in the family Enterobacteriaceae, which is a non-fastidious and encapsulated Gram-negative bacillus. Infections caused by *Klebsiella* species are the most common bacterial pathogens encountered in the hospital. Infections can be through contact with an infected host, or they can be endogenous (Sirijan Santajit et al. 2016). Sources of *Klebsiella* spp. that caused bacteraemia in the United Kingdom and Ireland were from genitourinary tract (23%), gastrointestinal tract (17%), and line-associated (14%) (Livermore et al. 2008). In the urine specimen from the Nepalese hospital, 44.8% of major organisms isolated were *K. pneumoniae* (Pandey et al. 2021). The thick capsule that acts as an antiphagocytic agent and fimbrial adhesins cause *K. pneumoniae* to be genetically infectious and capable of severe infection. The capsule is made up of two layers of polysaccharide fibres: the internal layer forms thick, solid stacks aligned to the external membrane, and the external layer forms a very thin, arbitrary net-like gathering primarily parallel to the surface of the cell (Pendleton et al. 2013).

Acinetobacter baumannii

Acinetobacter baumannii is a Gram-negative, non-fermentative coccobacillus that causes infections in the respiratory and urinary systems, among other places. It can survive for an extended time on human hands, resulting in high incidences of nosocomial infections cross-contamination (Sirijan Santajit et al. 2016). This pathogen is increasingly found in hospitalised patients in ICUs and intubated patients with urinary tract and intra-abdominal infections, exhibits geographic variability in prevalence, and frequently poses therapeutic dilemmas to clinicians due to its resistance profile (Karlowsky et al. 2017). A study done in José Eleuterio González University Hospital, Mexico, found that *A. baumannii* was the highest pathogen in respiratory specimens (18.8%) compared to other specimens such as catheters, blood, and urine (Llaca-Díaz et al. 2012).

Pseudomonas aeruginosa

The facultative anaerobe, Gram-negative and rod-shaped *P. aeruginosa*, is found in the digestive tracts of humans. It is a common nosocomial, opportunistic bacterium that can cause serious infections with a high death rate. It is most commonly found in sewage and hospitals (Mane et al. 2020). It was also the most isolates detected from sputum specimens in a Nepalese hospital (Pandey et al. 2021). Clinical specimens collected in the ICU of the José Eleuterio González University Hospital, Mexico, showed that *P. aeruginosa* was the most detected in urine (23.3%), followed by catheter (15%), respiratory (14.5%), blood (10.3%) and other (9.9%) (Llaca-Díaz et al. 2012). Saleem and Bokhari (2020) isolated 81% *P. aeruginosa* from 108 patients' samples with wound infections, burn injuries and bacteremia from primary hospitals of Islamabad and Rawalpindi. Out of these, 36% were MDR. Carriage rates in the general population are modest, but they are higher among hospital patients who are immunocompromised. This bacteria is antibiotic-resistant, which makes it a hazardous and dreaded pathogen. Due to its adaptive antibiotic resistance, it is also one of the most important bacterium species.

Enterobacter sp.

Enterobacter species are Gram-negative, non-fastidious and in rods shape that is occasionally encapsulated (Sirijan Santajit et al. 2016). One of the most common members of the *Enterobacteriaceae* family is *E. coli.* De Socio et al. (2019) found that the most isolated pathogen from patients' blood culture was *E. coli* (34%), besides other *Enterobacter* sp. (6.3%). Rectal colonisation with third-generation cephalosporin-resistant *Enterobacter cloacae* was discovered in nine patients (Eichel et al. 2020). Out of 143 clinical samples collected from three hospitals in Northeast Iran, 20.97% *E. cloacae* was isolated (Rizi et al. 2021). This pathogen can cause severe illness in immunocompromised patients (Sirijan Santajit et al. 2016). *Enterobacter* spp. is a vital nosocomial pathogen that causes infections in the lower respiratory tract, ophthalmic, digestive tract, skin and soft-tissue, urinary tract, intra-abdominal, endocarditis, septic arthritis, and osteomyelitis (Rizi et al. 2021).

Multi-drug resistance of ESKAPE pathogen

ESKAPE pathogens are typical sources of nosocomial infections in seriously ill and immunocompromised patients, and they are known for their medication resistance mechanisms (Sirijan Santajit et al. 2016). Antimicrobial resistance genes can be found on transposons, plasmids, or chromosomes of bacteria. Antimicrobial resistance is caused by antibiotic's inactivation or alteration, modification of antibiotic's binding sites, efflux pumps activation to eliminate the antibiotic, and changes in the outer membrane permeability through porin loss to hinder effective antibiotic's entrance (Walsh 2000; Blair et al. 2015; González-Bello 2017) (Fig. 2). The common drug resistance of the certain pathogens is MRSA, vancomycin-resistant *S. aureus* (VRSA), vancomycin-intermediate *S. aureus* (VISA), vancomycin-resistant *Enterococci* (VRE), multi-drug-resistant *S. pneumoniae* (MDRSP),

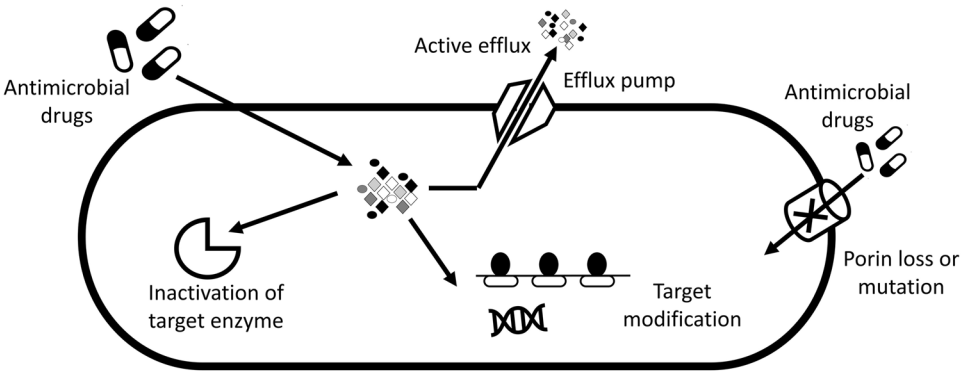

Fig. 2 Multi-drug resistance mechanism

extended-spectrum β-lactamases (ESBLs) producing Gram-negative bacilli, multi-drug-resistant *A. baumannii*, and carbapenem-resistant *Enterobacteriaceae* (CRE) (Okwu et al. 2019). Carbapenem-resistant *P. aeruginosa* (CRPA), carbapenem-resistant *A. baumanii* (CRAB), and other carbapenem-resistant *E. coli* (CREC) and carbapenem-resistant *K. pneumoniae* (CRKP) are categorised as priority 1 (critical) on the list of World Health Organization (WHO) priority pathogens for new antimicrobials resistance research and development (Zhen et al. 2019).

Gram-negative isolates (*K. pneumoniae*, *E. coli*, *P. aeruginosa*, and *A. baumannii*) were resistant to ampicillin, ciprofloxacin, meropenem, tigecycline or colistin. Meanwhile, Gram-positive isolates (*S. aureus*, *E. faecalis*, and *E. faecium*) were resistant to the first-choice penicillins (oxacillin for *S. aureus* and ampicillin for *E. faecium* and *E. faecalis*), tigecycline, linezolid, daptomycin (only for *S. aureus*) or vancomycin (Reale et al. 2017). Chakraborty et al. (2018) observed that non-clinical and clinical MRSA isolates were resistant to cefoxitin, oxacillin, penicillin, and methicillin but vulnerable to vancomycin. A study by Reale et al. (2017) found that the highest Gram-negative species resistance to ≥ 1 molecule in ≥ 3 classes of antibiotics was *A. baumannii* (52/61 = 85% of cases), followed by *K. pneumoniae* with 17% (13/78) isolates and *P. aeruginosa* with 10% (8/78) isolates. Only two isolates among 215 isolates of *E. coli* (1%) were included in groups 2 plus 3. Both were unaffected to ampicillin but vulnerable to meropenem, tigecycline and colistin, while one was unaffected to ciprofloxacin. On the other hand, *S. aureus* was the most Gram-positive included in group 2 plus 3 with 10% (9/91) of cases. *E. faecium* was included in group 2 plus 3 in 8% (1/13) of cases, resistant to ampicillin but susceptible to linezolid, tigecycline and vancomycin. Only 2% (1/51) of *E. faecalis* isolates were included in groups 2 plus 3 with conserved susceptibility to ampicillin, linezolid, tigecycline and vancomycin. According to Fiore et al. (2019), due to both inherent and developed antibiotic resistance, *Enterococci* have a restricted response to antibiotics. Cephalosporins, lincosamides, aminoglycosides, and streptogramins are innately resistant to *Enterococci*. *Enterococci* with intrinsic resistance are unquestionably well positioned to acquire additional resistances on mobile genetic components.

In Gram-negative bacteria, the production of β-lactamase has been considered the primary mechanism of resistance. Extended-spectrum β-lactamases (ESBLs) are enzymes that can hydrolyse and therefore inactivate β-lactam antimicrobials such as cephalosporins, monobactams, penicillins, and carbapenems. The ESBLs are plasmid-mediated and are naturally linked with MDR phenotype that confers resistance to entire β-lactams excluding cephamycins and carbapenems (Rizi et al. 2021). Multiple enzymes derived from ESBLs have been detected and grouped into several structural and evolutionary families, including OXA, GES, CTX-M, BES, TEM, PER, SHV, VEB, and TLA (Manandhar et al. 2020). In recent years, a large number of β-lactamase *K. pneumoniae* isolates have been advanced, breaking down the chemical structure of lactam-consisting medicines like cephalosporins, carbapenems, and penicillin (Pendleton et al. 2013). At first, carbapenems were applied for most difficult Gram-negative infections, but the emergence of CRKP has resulted in large-scale epidemics in the United States due to serine carbapenemase, a broad-spectrum class A that is able to disseminate interspecies. In New Delhi, the advent of the metallo-β-lactamase-1 among *K. pneumoniae*, and later *E. coli* has increased the occurrence of carbapenem-resistance and may foretell the clinical expendability of β-lactams, aminoglycosides, and fluoroquinolones (Pendleton et al. 2013). There was also a report on *A. baumannii* isolates that produced carbapenemase that transported imipenem metallo-lactamases (bla_{IMP}) and oxacillinase serine-lactamases (bla_{OXA}), which showed resistance to imipenem and colistin. The resistance genes combination avoid the effects of most standard compounds of antibiotics. Carbapenem-resistant *Enterobacteriaceae* are becoming well-known sources of sporadic and epidemic infections in Europe and the United States (Sirijan Santajit et al. 2016). These strains are resistant to almost all antibiotics, excluding polymyxins, tigecycline, and colistin (Boucher et al. 2009; Sirijan Santajit et al. 2016). Many *P. aeruginosa* strains have an inherent lower vulnerability to numerous antibiotics and a proclivity to

produce resistance during treatment, particularly carbapenem-resistant (mostly imipenem) strains. Synthesis of chromosomal AmpC combined with alteration of porin is the typical resistance mechanism of *P. aeruginosa* towards imipenem. Low synthesis of AmpC enzyme by the pathogen can cause fewer carbapenem drugs to be hydrolysed, thus resulting in not very resistance towards carbapenem. However, high AmpC combined with reduced permeability of outer membrane porin and/or overexpression of efflux pump enhances the resistance of pathogen towards carbapenem (Sirijan Santajit et al. 2016).

Overuse of these antibiotics began in 1948, resulting in the advent of *Staphylococcus* strains that produced β-lactamase in which clinical *Staphylococcus* isolates (65–85%) became penicillin G resistance. MRSA is frequently caused by the methicillin-resistant *S. aureus* horizontally acquiring the mecA gene. Penicillin-binding protein (PBP2a) is expressed by this gene, which decreases affinity for β-lactam (Pendleton et al. 2013; Okwu et al. 2019; Yi Xin et al. 2021). Over the last two decades, more than 80% of cases have been reported in hospitals and communities regarding infections by β-lactamase-producing *Staphylococcus* species. Incidence of MRSA infections was first reported in the 1960s, and 25–50% of MRSA were isolated from total *S. aureus* isolates. Isolates collected from the hospital in Italy recorded an increase for *S. aureus* from 5% in 2011 to 10% in 2014 (Reale et al. 2017). In Malaysia, nosocomial infections by MRSA from 2012 to 2018 increased from 17.7% to 19.4%. Studies from hospitals in Thailand found instances of 60.9% MRSA from 92 clinical *S. aureus* isolates. However, all the MRSA isolates were susceptible to vancomycin (Dechayont et al. 2021). Due to the rising occurrence of MRSA infections, cephalosporins and penicillins are no longer effective against *Staphylococcal* infections. Vancomycin is commonly used as the first antibiotic to treat infections by MRSA, while linezolid is another option. Nevertheless, the rise of MRSA strains with lower susceptibility to vancomycin and linezolid and greater resistance to both has limited their use in clinical settings. As a result, second and third-line antibiotics are now commonly used in combinations, which are often more expensive and harmful (MOH 2022).

Aminoglycosides were synergistic with β-lactams used as the standard of care for *Enterococcus* infections. Antibiotic with β-lactam such as penicillin does not affect *E. faecium* (Pendleton et al. 2013). A surge of nosocomial infections by *Enterococcus* resistant to ampicillin and vancomycin has been reported in recent years, including intra-abdominal infections, urinary tract infections, endocarditis, and bacteremia. Kanamycin is an aminoglycoside bacteriocidal antibiotic used to treat Gram-negative bacterial infections, such as *K. pneumoniae*, *E. coli*, and *Serratia marcescens* (Patra et al. 2016). However, aminoglycoside resistance in *Enteroccous* was discovered a few years later, which was attributed to plasmid-borne resistance component acquisition. Enzymes that can modify aminoglycoside, particularly a bifunctional enzyme, offer high-level resistance to aminoglycosides, and mobile elements providing this feature have diffused across the *Enterococcus* (Fiore et al. 2019). The rate of resistance of *P. aeruginosa* towards aminoglycoside is also a concern (Boucher et al. 2009).

Vancomycin was first launched in the late 1950s, but the antibiotic has limited use for patients with β-lactam infections and allergies due to its narrow spectrum and intravenous administration. Vancomycin was useful for aminoglycoside-resistant *Enterococcus* in the late 1970s and early 1980s, and it quickly became a popular alternative therapy. However, vancomycin resistance initially appeared in Europe and later in the United States in the mid-1980s (Fiore et al. 2019). By 2002, *E. faecium* isolates resistant to vancomycin increased up to 61% in North America (Pendleton et al. 2013). Vancomycin-resistant *Enterococcus* is now widely distributed, with some hospitals recording that up to 80% of *E. faecium* isolates are resistant to the antibiotic (Fiore et al. 2019). There are five main types of resistances (VanA, VanB, VanC, VanD, VanE) in which VanA resistance is most rampant and deliberates high-level resistance to all glycopeptides by changing the cell wall precursors terminal sequence, thus decreasing their binding attraction (Pendleton et al. 2013). *Enterococcus* resistant to vancomycin has a gene that encodes a potential enterococcal surface protein (esp), which is surface-expressed, and esp-positive strains help create thicker biofilms (Pendleton et al. 2013).

Moreover, vancomycin is no longer the preferred drug to treat MRSA infections since the occurrence of VRSA and VISA (Pendleton et al. 2013; Okwu et al. 2019). In the mid-1990s, VISA was discovered in Japan and spread throughout Asia, Europe, and the United States, posing a global health threat. Since the majority of VISA strains are also resistant to teicoplanin, the phrase glycopeptide-intermediate *S. aureus* can be applied interchangeably to describe this more comprehensive resistance profile. VISA strains have emerged due to vital changes in composition and thickness of the cell wall, which 'trap' vancomycin and reduce penetration to the active site. On the other hand, VRSA is substantially less common, resulting from the interspecies transmission of VRE genetic resistance determinants. Both resistance genes, mecA and VanA, are found in multi-drug-resistant VRSA isolates, and resistance is imparted through the same pathways as MRSA and VRE (Pendleton et al. 2013).

In 2000, linezolid was the first oxazolidinone antibiotic permitted by the Food and Drug Administration (FDA) as an alternative to vancomycin to treat MRSA infections by inhibiting the protein synthesis of Gram-positive bacteria (Pendleton et al. 2013; Yi Xin et al. 2021). However, in 2001, VRE strains resistant to linezolid were discovered in the United States and a year later in the United Kingdom due to a mutation of G2576U in the 23S ribosomal ribonucleic acid (rRNA) subunit. It also was discovered the strains in Thailand had evolved the

cfr methyltransferase on a plasmid, resulting in methylation of A2503 in the 23S rRNA, increasing their resistance (Fiore et al. 2019).

Tigecycline effectively controls Gram-positive and Gram-negative organisms, for example, *Acinetobacter* and MRSA. In 2005, the FDA approved the use of tigecycline for cSSSI and severe intra-abdominal infections. Despite the fact that community-acquired pneumonia trials fulfilled primary end objectives, ventilator-associated pneumonia and hospital-acquired pneumonia study was a failure, leaving tigecycline's function in treatment undetermined (Boucher et al. 2009). Glycylcycline tigecycline has successfully treated VRE alone or combined with other antibiotics. It inhibited the protein synthesis of Gram-negative and Gram-positive bacteria (Pendleton et al. 2013). Still, resistance has emerged. The occurrence of tigecycline resistance in *E. faecalis* and *E. faecium* from 2007 to 2015 were found due to the mutations in different efflux pumps. There were also mutations in the ribosomal protein subunit, *rpsJ* found in *E. faecium*, although this mutation has not yet been functionally verified (Fiore et al. 2019).

Chloramphenicol is originally derived from *Streptomyces venezuelae* and is regarded as a wide-spectrum antibiotic besides tetracyclines, inhibiting bacteria's protein synthesis. High dependence on chloramphenicol to treat typhoid fever, infection in the central nervous and rickettsia in patients who have β-lactams allergic in the developing countries due to its low cost and easy to manufacture, increasing the Gram-positive bacteria resistance to chloramphenicol up to 100% in some African countries. In developed countries, it has been banned since it can cause serious adverse effects, such as fatal aplastic anaemia and grey baby syndrome in newborns and premature babies (Čivljak et al. 2014; Baker et al. 2018). The antibiotic still shows its efficacy against Gram-positive such as MRSA (74%) and *E. faecium* (83%), but less favourable against Gram-negative bacteria such as *A. baumannii* and *P. aeruginosa,* in which the success rate of treatment is only 0–20%. Meanwhile, susceptibility rates for *Enterobacter* spp. and *K. pneumoniae* were slightly higher. This susceptibility was reduced in the presence of other antibiotic resistance, such as carbapenems or cephalosporins. Chloramphenicol is rarely studied on *A. baumannii* because it has been known to be ineffective against it in the past, but in recent investigations, the majority of *A. baumannii* showed chloramphenicol resistance with rates of resistance ranging from 80 to 100% (Čivljak et al. 2014).

Plant extract as antimicrobial agents for ESKAPE pathogens

Plant extract contains various primary and secondary metabolites that have been actively studied for their antimicrobial properties. Primary metabolite such as myristic acid, which is a common form of saturated fatty acid, has been shown to be effective against *S. aureus* (Narasimhan et al. 2006). The secondary metabolites, quercetin-7-O-methyl ether and isoorientin, were isolated from *Rhynchosia beddomei* Baker and reported to have antimicrobial properties against *P. aeruginosa* and *S. aureus* (Rammohan et al. 2019). Furthermore, Song et al. (2021) reported that isopentenylated flavonoids such as α-mangostin and isobavachalcone were effective against antibiotic-resistant *E. faecium* and *S. aureus*.

The in vitro screening of the plant extract provides critical data to select crude plant extract with antimicrobial potential for further investigation (Mathekga and Meyer 1998). It was suggested that a good antimicrobial activity is indicated by a minimum inhibitory concentration (MIC) value less than 100 µg/mL, a moderate antimicrobial activity has MIC value of 100 to 500 µg/mL, while a weak antimicrobial activity has MIC of 500 to 1000 µg/mL, and MIC greater than 1000 µg/mL is deemed inactive (Gado et al. 2021). The list of plants in which the crude extract exhibits antimicrobial properties against ESKAPE pathogens is given in Table 2.

Development of current herbs in the treatment

The decline of the effectiveness of antibiotics against ESKAPE has pushed forward the development of plant-based alternative treatments such as the combination of antibiotics with plant-based adjuvant and using antibacterial agents from green synthesised nanoparticles.

Combination of antibiotics with plant-based adjuvant

Although plant-based antimicrobial products show great potential, their antimicrobial action is small compared to classic antibiotics. Therefore, plant extract or plant's active substances can be used in combination with antibiotics to either block the bacteria's main resistance mechanism or enhance the drug's antimicrobial action (González-Bello 2017).

The plant represents a promising source of antibiotic adjuvant in combating the ESKAPE pathogen. An example of a plant that shows good potential as an antibiotic adjuvant is *Bauhinia forficata* Link (Fabaceae). Although the ethanolic extract of *B. forficate* had no antibacterial activity against *S. aureus*, the extract was able to regulate the resistance of norfloxacin, which eventually increased

Table 2 Plant extract with antimicrobial activities against ESKAPE pathogens

Scientific name	Parts used	Extraction process of plant extract			Minimum inhibitory concentration (µg/mL)						References
		Solvent	Temperature (°C)	Extraction time (h)	*A. b*	*E. f*	*E. s*	*K. p*	*P. a*	*S. a*	
Brachychiton acerifolium (A. Cunn. ex G.Don) F.Muell	Leaves	Acetone	NA	24	ND	ND	160[a]	**80**	310	310	Gado et al. (2021)
		Ethanol	NA	24	ND	ND	160[a]	**80**	310	310	
Brachychiton bidwillii Hook	Leaves	Acetone	NA	24	ND	ND	**80**[a]	**80**	630	250	Gado et al. (2021)
Blighia unijugata Baker	Leaves	Acetone	NA	24	ND	ND	**80**[a]	**80**	**80**	630	Gado et al. (2021)
		Ethanol	NA	24	ND	ND	310[a]	**80**	**80**	630	
		Cold water	NA	24	ND	ND	310[a]	**80**	310	310	
Camellia sinensis	NA	Methanol	Room temperature	72	ND	ND	ND	ND	ND	500 ± 200[b]	Bataineh et al. (2021)
Carya illinoinensis	Leaves	Methanol	Room temperature	24	ND	ND	ND	ND	1750	875	Javan bakht Dalir et al. (2020)
Dracaena loureiroi Gagnep	Wood	Ethanol	Room temperature	72	ND	ND	ND	ND	ND	**0.625**	Dechayont et al. (2021)
Glycyrrhiza glabra	NA	Methanol	Room temperature	72	ND	ND	ND	ND	ND	900 ± 500[b]	Bataineh et al. (2021)
Kirkia wilmsii Engl	Leaves	Methanol	NA	24	ND	ND	160[a]	**80**	630	**40**	Gado et al. (2021)
		Acetone	NA	24	ND	ND	**80**[a]	**80**	310	160	
Lavandula stoechas	Flowers	Ethanol	Room temperature	48	**35.9**	**17.95**	–[b]	–	**35.9**	**17.95**	Canlı et al. (2019)
Loxostylis alata A. Spreng. ex Rchb	Leaves	Methanol	NA	24	ND	ND	**40**[a]	**80**	160	160	Gado et al. (2021)
		Acetone	NA	24	ND	ND	**40**[a]	**80**	160	160	
		Ethanol	NA	24	ND	ND	**80**[a]	**80**	160	160	
		Cold water	NA	24	ND	ND	160[a]	**80**	160	160	
Noltea africana (L.) Rchb. f	Leaves	Acetone	NA	24	ND	ND	**80**[a]	**80**	630	310	Gado et al. (2021)
Pogostemon cablin (Blanco) Benth	Leaves	Ethanol	Room temperature	72	ND	ND	ND	ND	ND	**0.625**	Dechayont et al. (2021)
Protorhus longifolia Bernh. (Engl.)	Leaves	Methanol	NA	24	ND	ND	160	**80**	160	40	Gado et al. (2021)
		Acetone	NA	24	ND	ND	**40**	**40**	**40**	160	
		Ethanol	NA	24	ND	ND	**80**	**40**	**80**	310	
Tiliacora triandra Diels	Leaves	Ethanol	Room temperature	72	ND	ND	ND	ND	**5**	ND	Dechayont et al. (2021)
Trillium govanianum Wall. ex D. Don	Rhizome	Ethanol	Room temperature	48	ND	ND	ND	400	200	400	Verma et al. (2021)
Sedum takesimense	Aerial	Ethanol	Room temperature	30	ND	ND	ND	ND	1024	512	Jeong et al. (2021)

NA not available, *ND* not determine, *A. b* stands for *A. baumannii*, *E. f* stands for *E. faecium*, *E. s* stands for *Enterobacter* spp., *K. p* stands for *K. pneumonae*, *P. a* stands for *P. aeruginosa*, *S. a* stands for *S. aureus*

Values in bold indicate promising activity (MIC < 100 µg/mL)

[a]MIC value for *E. cloacae*

[b]MIC value for *E. aerogenes*

– No inhibition

norfloxacin efficacy by inhibiting NorA (de Sousa et al. 2021).

Cha et al. (2014) reported that cryptotanshinone from *Salvia miltiorrhiza* Bunge demonstrated strong antibacterial activity against MRSA and VRSA. This compound also exhibited synergistic bacterial properties when combined with oxacillin, ampicillin, and vancomycin. Similarly, methanol crude extract from *Lobelia inflata* has been shown to have weak antibacterial activity on multi-drug-resistant *S. aureus*. The combination of *L. inflata* extract with norfloxacin or tetracycline showed better antibacterial activity with a fourfold reduction in MIC rather than antibiotic alone (Oyedemi et al. 2020). In another study, the MIC values of 1,2,4,6-tetra-O-galloyl-β-glucose isolated from *S. takesimense* towards MRSA was found to be 16–256 µg/ml, in which this value reduced significantly after being combined with antibiotics, suggesting that the combination of the compound isolated from *S. takesimense* with the antibiotics synergistically inhibit the methicillin-resistant *S. aureus* growth (Jeong et al. 2021).

A study by Abreu et al. (2017) reported the synergistic effect of luteolin and the potentiation effect of nonantibacterial phytochemicals extracted from *Cytisus striatus* against *S. aureus* when used in combination with antibiotics. It was shown from the study on the ciprofloxacin potentiation and NorA efflux pump inhibition for structurally different isoflavonoids that the antibacterial and antibiotic-potentiation compounds are very structure-dependent. Table 3 shows the compounds from plants used in combination with antibiotics and the effect on ESKAPE pathogen.

Antibacterial agents from green synthesised nanoparticle

The vast amount of phytochemicals in plant extract makes it an attractive reducing and capping agent for the green synthesis of nanoparticles. The plant phytochemicals responsible for nanoparticle bioreduction includes flavones, terpenoids, ketones, aldehydes, carboxylic acid, and carbohydrate (Walsh 2000). The green synthesis of nanoparticles using plant extract could be conducted at room temperature and at a neutral pH without a complicated experimental setup, making it an eco-friendly, easy, and economical process.

In a study conducted by Javan bakht Dalir et al. (2020), silver nanoparticles synthesised using plant extract had higher microbial inhibition than the plant extract used in the green synthesis process. This could be due to the silver nanoparticles' small size, enabling better penetration through the bacterial cells than the plant extract (de Sousa et al. 2021). Studies have suggested that the silver nanoparticles may be attached to the cell wall's surface and bacterial cell's membrane and inhibit the bacteria's respiratory enzymes (Cha et al. 2014; Oyedemi et al. 2020). It was also suggested that the antibacterial activity of silver particles are due to three steps mechanism. Initially, silver nanoparticles are attached to the bacteria's cell wall, where the positively charged silver nanoparticles interact with the negatively charged bacterial cell wall and disrupt the bacteria's function (e.g. respiration). Silver nanoparticles caused further damage inside the bacteria by interacting with compounds containing sulfur and phosphorus, destroying their activity. The silver nanoparticles also interact with DNA, hampering the bacteria's replication ability, resulting in the bacteria's death (Morones

Table 3 Compounds from plants used in combination with antibiotics

Plant name	Antimicrobial activity against	Properties of adjuvant	Antibiotic	Minimum inhibitory concentration (µg/mL)		References
				Alone	Combination	
Bauhinia forficata Link (Fabaceae)	*S. aureus*	Ethanolic extract	Norfloxacin	64[a]	8	(de Sousa et al. 2021)
Cytisus striatus	Methicillin-resistant *S. aureus*	Apigenin	Ciprofloxin	> 120[b]	10–60	(Abreu et al. 2017)
		Daidzein	Erythromycin	> 120[b]	30	
		Genistein	Ciprofloxin	> 120[b]	15–60	
		Luteolin	Ciprofloxin	> 120[b]	30–60	
			Erythromycin	> 120[b]	30–60	
			Ciprofloxin	30-120[b]	60	
			Erythromycin	30-120[b]	3.5–60	
S. takesimense	Methicillin-resistant *S. aureus*	1,2,4,6-tetra-O-galloyl-β-glucose	Ampicillin	16[b]	2	(Jeong et al. 2021)
			Oxacillin	16[b]	2	
			Clavulanic acid	16[b]	8	

[a]MIC value for antibiotic

[b]MIC value for plant-based adjuvant

Table 4 Nanoparticles from green synthesis with antimicrobial activities against ESKAPE pathogens

Type of nano-particles	Source of plant extract	Extraction process of plant extract			Characteristics of nano-particles		Antimicrobial activity against	References
		Solvent	Temperature (°C)	Extraction time	Shape	Size (nm)		
Copper indium disulfide	*Azadirachta indica*	Double distilled water	80	20 min	Rod	17.21 ± 0.28	*S. aureus* (MIC = 625 µg/mL) *E. aerogenes* (MIC = 1250 µg/mL) *P. aeruginosa* (MIC = 1250 µg/mL)	Giri et al. (2021)
	Aloe vera	Double distilled water	80	20 min	Plate	16.83 ± 0.26	*S. aureus* (MIC = 300 µg/mL) *E. aerogenes* (MIC = 300 µg/mL) *P. aeruginosa* (MIC = 300 µg/mL	Giri et al. (2021)
	Curcuma longa	Double distilled water	80	20 min	Plate	17.59 ± 0.35	*S. aureus* (MIC = 625 µg/mL) *E. aerogenes* (MIC = 1250 µg/mL) *P. aeruginosa* (MIC = 625 µg/mL	Giri et al. (2021)
	Cocos nucifera	Double distilled water	80	20 min	Rod	16.27 ± 0.19	*S. aureus* (MIC = 625 µg/mL) *E. aerogenes* (MIC = 625 µg/mL) *P. aeruginosa* (MIC = 2500 µg/mL	Giri et al. (2021)
	Ocimum sanctum	Double distilled water	80	20 min	Plate	18.06 ± 0.23	*S. aureus* (MIC = 625 µg/mL) *E. aerogenes* (MIC = 625 µg/mL) *P. aeruginosa* (MIC = 1250 µg/mL	Giri et al. (2021)
Copper oxide	*Cassia fistula*	Distilled water	60	30 min	Spherical	43.8	*K. pneumoniae* (zone of inhibition = 15 ± 0.58 mm)	Naseer et al. (2021)
	Melia azedarach	Distilled water	60	30 min	Semi-spherical	28.2	*K. pneumoniae* (zone of inhibition = 13 ± 0.46 mm)	
Magnesium oxide	*Pterocarpus marsupium* Roxb	Distilled water	100	30 min	Spherical	5–20	*S. aureus* (MIC = 22 ± 0.168 µg/mL)	Walsh (2000)
Silver	*C. illinoinensis*	Methanol	Room temperature	24 h	Spherical	12–30	*S. aureus* (MIC = 128 µg/mL) *P. aeruginosa* (MIC = 32 µg/mL)	Javan bakht Dalir et al. (2020)
	Eucalyptus citriodora	Ethanol	Room temperature	168 h	Spherical	17.51	*A. baumannii* (MIC_{90} = 0.04 µg/mL) *K. pneumoniae* (MIC_{90} = 0.04 µg/mL) *P. aeruginosa* (MIC_{90} = 0.04 µg/mL) *S. aureus* (MIC_{90} = 0.09 µg/mL)	Ammulu et al. (2022)

Table 4 (continued)

Type of nano-particles	Source of plant extract	Extraction process of plant extract			Characteristics of nano-particles		Antimicrobial activity against	References
		Solvent	Temperature (°C)	Extraction time	Shape	Size (nm)		
	Spondias mombin	Ethanol	37 °C	7 days	Spherical	17	*S. aureus* (zone of inhibition = 22 mm) *E. cloacae* (zone of inhibition = 21 mm) *K. pneumoniae* (zone of inhibition = 0.33 mm) *P. aeruginosa.* (zone of inhibition = 21 mm)	Samuggam et al. (2021)
Zinc oxide	*Amaranthus caudatus*	Deionised water	80 °C	20 min	Spherical	NA	*E. aerogenes* (zone of inhibition = 9 mm)	Jeyabharathi et al. (2017)
	Aristolochia indica	Double distilled water	60 °C	20 min	Quasi-spherical	22.5	*S. aureus* (MIC = 200 µg/mL) *P. aeruginosa* (MIC = 100 µg/mL) *A. baumannii* (MIC = 25 µg/mL)	Steffy et al. (2018)

MIC_{90} is the lowest concentration of the plant extract at which 90% of the microorganism were inhibited

et al. 2005; Akter et al. 2018). However, compared to the Gram-negative bacteria, *P. aeruginosa*, a higher concentration of silver nanoparticles was needed for the growth inhibition of the Gram-positive bacteria, *S. aureus* (Table 4). The cell wall, including the thicker peptidoglycan of the Gram-positive bacteria, prevented the penetration of silver ions in the cytoplasm (Malanovic and Lohner 2016).

The antimicrobial properties of various other green synthesised nanoparticles such as copper indium disulfide, copper oxide, magnesium oxide and zinc oxide have also been reported. Similarly to the silver nanoparticles, the large surface area of the other nanoparticles allows better interaction between the nanoparticles with microorganisms, resulting in good antibacterial activity (Naseer et al. 2021). Additionally, a cellular disruption that could be attributed to oxidative stress also contributed to the antibacterial activity of nanoparticles (Ohira et al. 2008; Sirelkhatim et al. 2015; Denluck et al. 2018). The direct contact of nanoparticles with the bacterial surface will alter the microenvironment within the vicinity of the contact, which generates reactive oxygen species that damage the bacterial cell. The damage occurred through the cleavage of peptide bond or protein–protein crosslinked derivative through a reaction between carbon-centred radicals (Wang et al. 2012; Bondarenko et al. 2012).

A protein leakage analysis conducted by Steffy et al. (2018) revealed a significant release of protein from bacteria on contact with zinc oxide nanoparticles. This indicates the antibacterial mechanism of the green synthesised zinc oxide nanoparticles by damaging the cell membranes, resulting in leakage of genetic materials, proteins and minerals, which ultimately leads to cell death. Furthermore, the zinc oxide nanostructure can generate more potentially lethal H_2O_2 that cause increased oxidative stress within bacterial cells, involving the cellular component's destruction (Ohira et al. 2008; Sirelkhatim et al. 2015). Table 4 lists the nanoparticles obtained using green synthesis that has been shown to have antimicrobial activities against the ESKAPE pathogen.

Conclusion

Nosocomial ESKAPE bacteria are typical examples of pathogens that cause the diseases to develop, transmit, resist, and pose a significant threat to public health systems worldwide. Their prevalence is expected to rise as more resistance profiles may be altered. This leads to a shortage of antibiotics for ESKAPE treatment, which is cause for concern; hence should spur on new treatment agents or techniques to treat the infections. Antivirulence techniques, probiotics, antibodies and bacteriophage therapy, synthetic inhibitors specified to resistance enzymes, and biofilm inhibition are among the current research efforts aimed at circumventing these pathogens. These cutting-edge techniques offer hope for preventing and treating infections by the ESKAPE bacteria. Unfortunately, despite the fact that various medicines and treatments have been presented, no effective prophylactic measures have yet been discovered. As a result, novel alternative medicines must be developed to overcome MDR-ESKAPE resistance. This condition can be solved by utilising plant extracts in which they are not only have been found

to have an inhibitory effect against the ESKAPE infection but also possess very minimal side effects.

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Declarations

Conflict of interest The authors have no relevant financial or non-financial interests to disclose.

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