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REVIEW ARTICLE

Phytochemicals as Therapeutic Agents for ESKAPE Pathogens

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Abstract:

Background:

The worldwide increase of antimicrobial resistance in ESKAPE pathogens, which includes *Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Enterobacter sp.*, constitutes a substantial public health hazard, constraining treatment alternatives and elevating morbidity and mortality rates. As traditional antibiotics diminish in efficacy, phytochemicals are capturing interest due to their varied antibacterial characteristics and decreased susceptibility to developing antibiotic resistance. Phytochemicals, such as alkaloids, terpenes, phenolics, flavonoids, and organosulfur compounds, have multi-target processes that might provide innovative strategies for addressing infections caused by ESKAPE pathogens.

Objective:

The investigation sought to evaluate the effectiveness and mechanisms *via* which different phytochemicals could hinder and destroy the resistance pathways of ESKAPE bacteria, emphasizing their potential to serve as therapeutic agents in combating antimicrobial resistance.

Results:

Investigation demonstrates that some phytochemicals may disrupt many bacterial functions, such as cell wall production, membrane integrity, quorum sensing, and biofilm development in ESKAPE pathogens. For example, carvacrol from essential oils has shown efficacy against *S. aureus* by reducing staphyloxanthin synthesis and altering regulatory proteins, including SarA. Furthermore, conessine has altered resistance in *A. baumannii* by inhibiting the AdeIJK efflux pump. Flavonoids like resveratrol and curcumin have shown synergistic benefits with conventional antibiotics by improving their effectiveness while minimizing toxicity. These chemicals address several resistance pathways, impairing the ability of infections to build resistance.

Conclusion:

Phytochemicals provide an opportunity to facilitate the development of novel therapies targeting antimicrobial resistance in ESKAPE bacteria. Extensive efficacy and distinctive multi-target mechanisms of phytochemicals provide them promising candidates for combination therapy, possibly reinstating antibiotic effectiveness and decelerating the development of resistance. Additional investigation into the increase of bioavailability and clinical usage is essential to fully exploring the medicinal potential of phytochemicals.

Keywords: ESKAPE, Phytochemicals, Antimicrobial agents, Multidrug resistance, Biofilm formation, Quorum sensing.

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1. INTRODUCTION

Over the past four decades, the pharmaceutical industry has created quite a large number of novel antibiotics, that are work against organisms by preventing their growth or eliminating them either by interfere with the synthesis of bacteria's cell wall [1] or interfere with the synthesis of nucleic acids in microorganisms [2] or inhibits the synthesis of proteins in the organisms [3] or work by blocking these organism's metabolic pathways [4], changing an organism's membrane function [5], and blocking ATP synthase [6]. But the misuse and overuse of these medications has caused a rise in microbial resistance. Antimicrobial drug resistance (AMR) is a condition when an

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antimicrobial drug does not interfere with the growth or survival of microorganisms [7]. Bacteria acquire this AMR through genetic mutations, plasmids, chromosomes, transposons and other mobile genetic elements — a process known as horizontal gene transfer (HGT) [8]. AMR is exhibited by organisms through a variety of means, including disruption of the mechanisms of action of antibiotics, structural modifications of antibiotics, decrease in drug permeability, resistance *via* efflux pumps, inactivation or decrease expression of porin channel, alterations in enzymes, drug target site mutation, target site bypass, and broader cellular adaptations as illustrated in Fig. (**1**) [9, 10]. Antibiotic resistance is among the most significant health issues. Over the past ten years, the issue of nosocomial infections has been accompanied by an increase in the prevalence of antimicrobial-resistant bacteria in hospitals and community settings [11].

A small group of bacterial species that are primarily responsible for the majority of resistance issues in contemporary hospitals called "ESKAPE" pathogens. *Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa,* and *Enterobacter species* come together to form

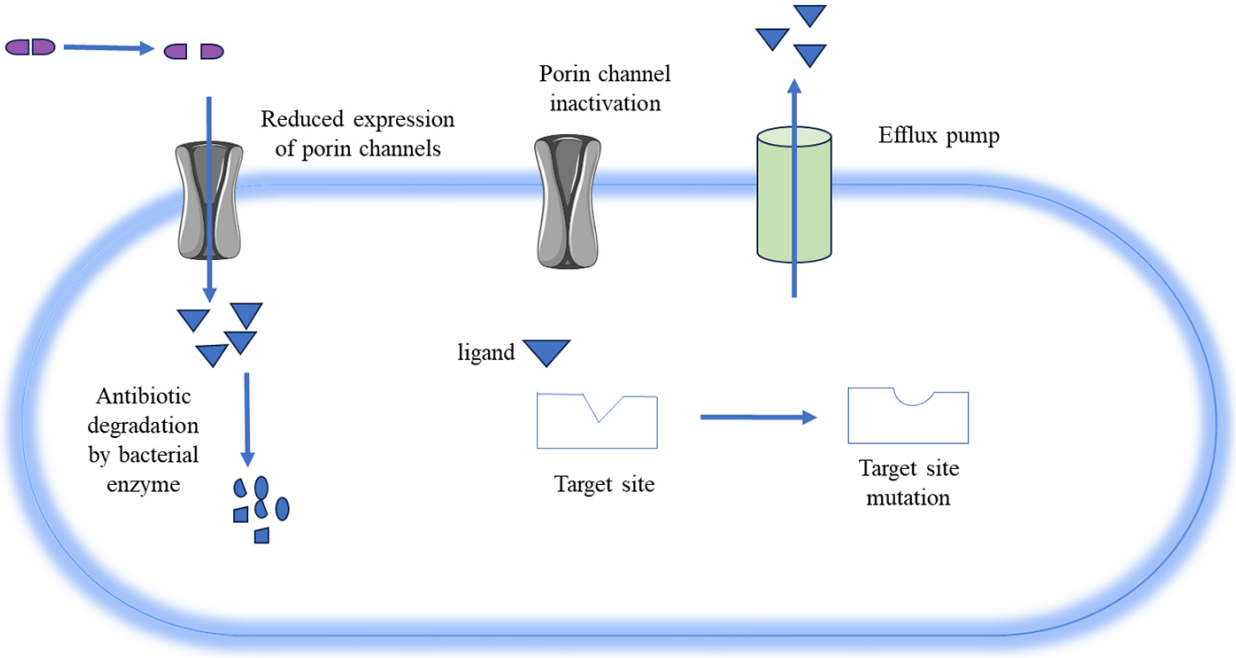

Fig. (1). Mechanism by which antimicrobial resistance can develop by various pathogens.

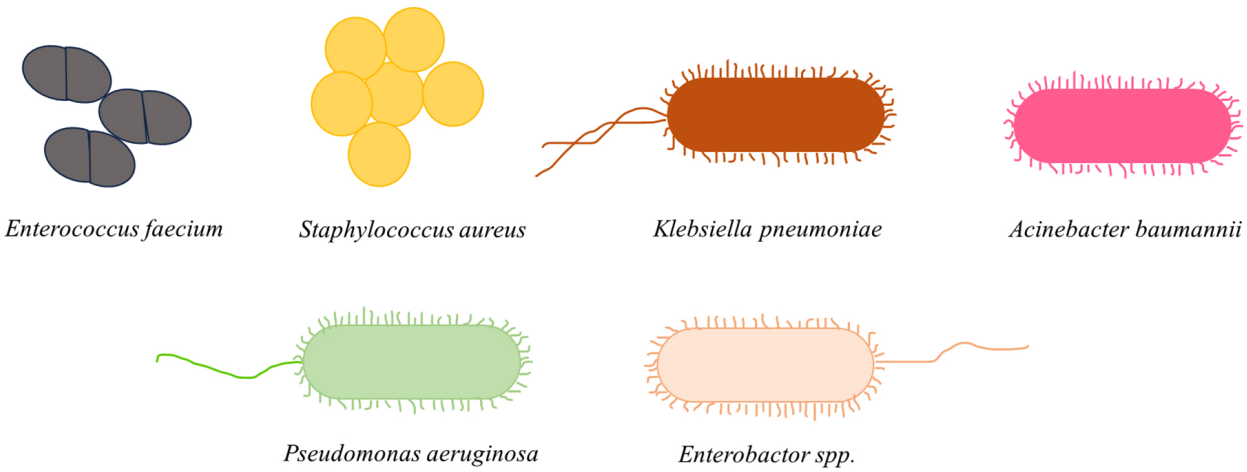

Fig. (2). ESKAPE pathogens.

the abbreviation ESKAPE (Fig. **2**), these are also called opportunistic pathogen because these microorganism causes nosocomial infections in immunocompromised patients. ESKAPE can develop multi drug resistance. According to data from the National Healthcare Safety Network, The ESKAPE pathogens are implicated in just over 40% of infections in patients in intensive care units [12].

E. faecium is nearly always resistant to β-lactam medicines, in the UK and Ireland, the frequency of total resistance to ampicillin and imipenem reached 98.8% in 2006 [13]. Vancomycin-resistant Enterococcus (VRE) emerged in North America in the late 1980s, with 61% of *E. faecium* isolates resistant by 2002. European incidence rose from 20% to over 30% between 2001 and 2006 [14]. Francey *et al*., reported nineteen instances of *A. baumannii* infection in dogs and cats Over a two-and-a-half-year period from an intensive care unit (ICU) (urinary, wound, respiratory and bloodstream infections). They showed that *A. baumannii* can impair the effectiveness of both routine treatments and intensive care, and that it can lead small animals to contract potentially fatal hospital-acquired illnesses. It also affected treatment results, with a 100% fatality rate in patients with systemic infection [15]. *S. aureus* has developed resistance to commonly used antibiotics, with MRSA showing higher resistance. Significant multidrug resistance (71.8%) was observed, raising serious public health concerns in infection management [16]. According to Antoniadou *et al*., studied from November 2003 to August 2005, 18 *K. pneumoniae* isolates resistant to colistin were identified in 13 patients. Most isolates produced extended-spectrum beta-lactamase (ESBL) or metallo-beta-lactamase (MBL). Thirteen cases involved colonization, while five were infections which highlights the importance of understanding this organism [17]. Because of *P. aeruginosa*'s complex methods of antibiotic resistance, ability to build biofilms, and propensity to cause persistent infections in both human and animal hosts, *P. aeruginosa* presents a significant problem in therapeutic settings. It may spread zoonotically across animals, the environment, and human populations, according to recent research, which emphasizes the need for awareness of this organism [18]. *Enterobacter aerogenes* and *Enterobacter cloacae* are opportunistic, multi-resistant pathogens in hospitals, adapting efficiently to antibiotics through regulatory cascades, mobile genetic elements, and environmental adaptability, complicating infection control [19]. Since ESKAPE pathogens are difficult to treat with antibiotics due to high levels of resistance, phytochemicals are being explored as alternative treatments for infections caused by these pathogens.

Nature offers a rich repository of therapeutic substances, many of which have been harnessed in contemporary medicine. In developing nations, conventional medicine is one of the most accessible forms of treatment. In some areas, it is estimated that around 80% of humanity relies on traditional medicine for their basic healthcare requirements [20]. Many pharmacologically active substances and new drug developments originate from plants, as evidenced by the fact that many popular drugs are in some way derived from them. As of the beginning of the twenty-first century, the World Health Organization (WHO) lists 11% of 252 medications as fundamental and necessary, these medications are the only ones that came from flowering plants [21]. Conventional medicinal plants comprise a diverse array of physiologically active substances, making them a valuable source of medicinal substances and most of them are act against ESKAPE pathogens [22]. This review emphasizes on the usage of these phytochemicals which can be employed as efficient anti-ESKAPE medications.

2. ESKAPE PATHOGENS: A WORLDWIDE CONCERN

ESKAPE pathogens causing AMR, poses a worldwide risk to public health. AMR can be caused by both Gram-negative and Gram-positive bacteria. *E. faecium, S. aureus* is Gram positive bacteria and *K. pneumoniae, A. baumannii, P. aeruginosa, Enterobacter sp*. are Gram-negative bacteria. A concerted global response is needed for microbial resistance awareness because the ESKAPE pathogens' acquisition of antibiotic resistance genes has decreased therapeutic option for major infections, raised the load of illness, and raised the mortality rates from unmet treatment.

2.1. *Enterococcus Faecium*

E. faecium is a Gram-positive spherical bacterium *i.e*. coccus that grows in pairs or chains, live in intestine of both humans and animals. It is typically the cause of nosocomial septicaemia in patients with compromised immune systems. Enterococci-caused nosocomial infections have spread widely around the world. The main cause of enterococci's long-term persistence in hospitals is their innate resistance to several commonly used antibiotics as well as their resistance to newly developed antibiotics caused by gene mutation or plasmid and transposon transmission [11]. High level resistance (HLR) enterococci have been found in meat and dairy products, and additionally in strains that include vancomycin and have numerous antibiotic resistances [23,24]. By producing low-affinity PBPs, enterococci exhibit resistance to cephalosporins. Glycopeptide antibiotics (*e.g*. Vancomycin) target the bacterial D-Ala-D-Ala site. Transposon-mediated vancomycin resistance in *E. faecium*, *via* the *vanA* and *vanB* operons on Tn1546 and Tn5382, remains prevalent in clinical isolates, informing new approaches required to treat vancomycin-resistant strains [12]. Bacteria's resistance to glycopeptides originates from operons encoding enzymes that replace the final D-Ala with D-Ser or D-Lac that have low affinity, as well as enzymes that eliminate or inhibit the synthesis of the high-affinity native precursors (Carboxypeptidases and D, D-dipeptidases). Among eight characterized operons (van A, B, D, E, G, L, M, N), only van A, B, D, M, and N are found in *E. faecium* [25]. Vancomycin-resistant Enterococci (VRE) have a genetic material that may encode a protein that helps the bacteria to develop thicker biofilms [26]. As a result, infections like intra-abdominal infections, urinary tract infections (UTI), endocarditis and bacteraemia arise [27]. The primary method by which *E. faecium* resists aminoglycoside is through the synthesis of aminoglycoside-modifying enzymes (AMEs) like aminoglycoside nucleotidyltransferases, aminoglycoside phosphotransferases and aminoglycoside acetyltransferases (AAC(6′)-Ii). Two chromosomal enzymes produced by *E. faecium* are AAC (6′)-Ii and EfmM, both are responsible for

developing resistance against aminoglycoside specially to kanamycin and tobramycin. EfmM is a 16S rRNA methyltransferase that methylates the 16S rRNA, hindering the binding of aminoglycosides to the bacterial ribosome [28]. Point mutations in the gyrA and parC genes, which encode the subunits A of DNA gyrase and topoisomerase IV, cause acquired resistance in *E. faecium*. Mutations in these genes alter the target sites of fluoroquinolone antibiotics, reducing their binding affinity and thereby conferring resistance to these drugs [29].

2.2. *Staphylococcus Aureus*

The Gram-positive Staphylococcaceae family bacteria is *S. aureus* [30]. Groups of cells which look like grapes make up the *S. aureus* cluster. Skin flora contains this naturally occurring component. This is usually segregated from area beneath arm and from outside of the nose because of its easy growing needs [13]. The most common bacteria found in pus specimens is *S. aureus* (64.4%) [31]. *S. aureus* is known to induce pyogenic lesions and tissue infection that affect several organs [32]. By limiting drug uptake *S. aureus* can develop AMR against glycopeptide (Vancomycin) and this AMR is called Vancomycin resistant *S. aureus*, By drugs inactivation develop AMR against Chloramphenicol, by producing β-lactamase which hydrolyse β-lactam ring develop resistance against β-lactams, by altered penicillin binding protein (PBP) develop resistance against methicillin, by active drug efflux develop AMR against Fluroquinolones and tetracyclines (by tetA), by drug target modification develop AMR against β-lactams, lipopeptides, lincosamide, tetracyclines, streptogramins, macrolides, oxazolidinone, fluroquinolones, glycopeptides, aminoglycosides [33]. In *S. aureus*, various erm genes provide resistance to macrolides, lincosamides, and streptogramin B (MLSB antibiotics) through two patterns: constitutive expression (MLSBc phenotype), with constant resistance, and inducible expression (MLSBi phenotype), activated by specific antibiotics. Additionally, the msrA gene encodes an efflux pump (MS phenotype), expelling macrolides and enhancing resistance [11]. Methicillin and oxacillin resistance in *S. aureus* arises from acquiring a gene encoding PBP2a. The production of PBP2a is controlled by two regulatory systems *i.e*. the mecR1/mecI operon and the blaR1/blaI β-lactamase regulon [34]. The transpeptidase active site serine of PBP2a is deeply embedded, preventing β-lactam antibiotics from binding effectively, allowing the bacteria to continue building its cell wall even in the presence of these antibiotics [35]. Cytoplasmic modifying enzymes are the source of *S. aureus* resistance to aminoglycosides. Bifunctional acetyltransferase A-phosphotransferase D is involved in gentamicin and neomycin resistance, whereas phosphotransferase A or adenyltransferase D enzymes are involved in neomycin resistance [36]. In healthcare settings, *S. aureus* frequently causes bloodstream infections, surgical site infections, and pneumonia. It is a major contributor to nosocomial infections. It spreads *via* direct contact, particularly in susceptible patients, and is frequently resistant to several medications, including methicillin (MRSA), making infection treatment more difficult [37]. Gurung *et al*. found that *S. aureus* was more common in inpatients (55.7%) compared to outpatients (44.3%). This suggests a higher risk of hospital-acquired infections, including MRSA, among hospitalized patients [16].

2.3. *Klebsiella Pneumoniae*

A Gram-negative rod-shaped bacterium *i.e*. bacillus is *K. pneumoniae*. This microorganism is responsible for one-third of all Gram-negative bacterial illnesses [38]. One of the main causes of nosocomial infections, especially in individuals with weakened immune systems, is *K. pneumoniae*. It presents significant treatment and infection control issues, particularly in intensive care units and among patients with invasive devices, due to its propensity to acquire resistance to several medications, including carbapenems [39]. They are accountable for the development of endocarditis, pneumonia, septicaemia, urinary tract infections, and cystitis. It can also cause necrotizing pneumonia, endogenous endophthalmitis, and pyogenic liver abscess. *K. pneumoniae* infections result in increased mortality rates, extended hospital stays, and extremely expensive treatment. It is known that strains of *K. pneumoniae* resistant to carbapenem (CRKP) acquire β-lactamases, which renders them resistant to common antibiotics like carbapenem [38]. By altering penicillin-binding proteins (PBPs) *K. pneumoniae* resists β-lactam antibiotics. Thereby PBP reduce their affinity for the drugs. The reason behind *K. pneumoniae*'s resistance to fluoroquinolones is point mutations in particular regions of topoisomerase IV (parE genes and parC genes) and DNA gyrase (gyrA genes and gyrB genes) [40]. The porins (OmpK36 and OmpK35) that the antibiotic molecules must employ are altered or reduced in number, which lowers the membrane's permeability. Quinolone resistance can also be developed by active ejection pumps such as OqxAB and AcrAB pumps are another frequently occurring mechanism in *K. pneumoniae* strains [41, 42].

2.4. *Acinetobacter Baumannii*

A. baumannii is an aerobic, non-motile, pleomorphic Gram-negative bacterium, responsible for about 2% of nosocomial infections. It has been discovered that 45 percent of the strains of this deadly opportunistic infection are multidrug-resistant (MDR). Pneumonia related to ventilation and bloodstream infections connected to central lines are most common infections caused by it. Because of their capacity to form biofilms, and possession of key pathogenic characteristics like surface adhesions, secretion system and glycoconjugates, *A. baumannii* can undergo extremely harsh environments [43, 44]. *A. baumannii* has been considered one of the most efficient nosocomial pathogens because of its capacity to endure in hospital settings. *A. baumannii*, prevalent in clinical settings, colonizes skin, hair, and various surfaces, adhering to devices like catheters and respiratory [45]. Contaminated objects such as mattresses, computers, gloves, and even pets may spread the pathogen [46]. Resilient to disinfectants like chlorhexidine, A. baumannii survives on dry surfaces, enduring nutrient starvation by forming biofilms, complicating infection control [47]. *A. baumannii* uses β-lactamases as a primary method for resisting β-lactam antibiotics. *A. baumannii* has the AdeABC efflux pump and is resistant to aminoglycosides [48]. CraA and CmlA efflux pump are associated with

chloramphenicol resistance [49]. Resistance towards tetracycline is linked to TetA [50]. In *A. baumannii*, reduced expression of a few porins—Omp37, Omp44, Omp47 is linked to carbapenem resistance [51]. OXA-51-like carbapenemases in *A*. baumannii Omp29 deletion causes increased imipenem resistance [52]. OmpA is linked to resistance to nalidixic acid, chloramphenicol, and aztreonam [53]. In *A. baumannii*, loss or alteration of lipopolysaccharide (LPS) results in a reduction in the integrity of the membrane and a spike in colistin resistance [54]. Acetyltransferases, phosphotransferases and adenyl transferases are examples of AMEs. They are the primary way by which aminoglycoside resistance is imparted by *A. baumannii* [55]. Imipenem resistance can only be brought on by the upregulation of mutant PBPs having minimal imipenem affinity [56].

2.5. *Pseudomonas Aeruginosa*

A gamma-proteobacterium that is Gram-negative is *P. aeruginosa*, has an inherent resistance to a number of antibiotics because of its multi-transport system and very minimally permeable outer membrane. It can use a variety of strategies, including β-lactamases, efflux pumps, porin channel modification, point mutations in DNA gyrase or topoisomerase IV and target alterations, to build resistance to antimicrobial agents. Because this infection can cause blood clots and leave behind persistent cells in the lungs, patients with cystic fibrosis (CF) are more likely to contract it [57]. *P. aeruginosa* exhibits resistance against several antibiotics, such as β-lactams, quinolones, and aminoglycosides. *P. aeruginosa* enhanced resilience to gentamicin and polymyxin B due to stability of the outer membrane caused by LPS modification. *P. aeruginosa* produce β-lactamases enzyme which can hydrolyse β-lactam ring of β-lactam antibiotics [58]. Absence of OprD porin channel in *P. aeruginosa* increases resistance to carbapenems, which are β-lactam antibiotics [59]. MexCD-OprJ efflux pump has the capacity to expel β-lactams, MexXY-OprM push out aminoglycosides, whereas MexEF-OprN can extrude quinolones [60]. *P. aeruginosa* is less susceptible to quinolones due to mutations in genome encoding topoisomerase IV (parE and parC) and DNA gyrase (gyrA and gyrB) and which lower the binding affinity of the encoded proteins to quinolones [61]. In many hospitals, ciprofloxacin's effectiveness against *P. aeruginosa* has diminished due to the emergence of several multidrug efflux pumps and the ensuing topoisomerase mutations that generate a high degree resistance [12]. *P. aeruginosa* is a common cause of nosocomial infections, including pneumonia, surgical site infections, UTIs, and bacteraemia. In ICUs, it causes 23% of infections, predominantly respiratory-related, with rising prevalence. Second only to *S. aureus, P. aeruginosa* was predicted to be the source of 11% of all HAP (Healthcare-associated pneumonia) and VAP (Ventilator-associated pneumonia) among ICU patients considered to be at risk of developing nosocomial pneumonia in prospective observational research of 28 ICUs in the USA [62].

2.6. *Enterobacter sp.*

Enterobacter sp. is a member of the Enterobacteriaceae family of Gram-negative anaerobes. This pathogen primarily causes urinary tract infections or respiratory infections in patients who are immunocompromised [63, 64]. The National Nosocomial Infections Surveillance System estimates that between 1976 and 1989, *Enterobactersp*. caused 5-7% of hospital-acquired bacteremias in the US. *Enterobacter* was the fourth most prevalent pathogen in surgical wounds, the fifth most common pathogen in the bloodstream and urinary tract and the third most common pathogen in the respiratory tract among isolates in the ICU [65]. *E. cloacae* and *E. aerogenes* exhibit nearly universal resistance to a vast range of antibiotics including ampicillin, cefoxitin, cephalothin and other β-lactam antibiotics [63]. *Enterobacter sp.* resists β-lactam antibiotics by altering penicillin-binding proteins (PBPs), reducing their affinity for the drugs [66]. *Enterobacter sp*. develop resistance by reducing porin production and occasionally complete cessation of partial porin production. Collectively, Enterobacteriaceae family bacteria develop resistance against carbapenems by lowering the number of porins [67].

3. PHYTOCHEMICALS FOR ESKAPE

Plant-sourced substances are predominantly secondary metabolites, often formed through oxygen replacement or derived from phenols. Such secondary compounds have a variety of advantageous properties, such as antibacterial, antifungal, antioxidant, anti-inflammatory properties. The main groups of plant-derived chemicals with antibacterial properties include quinones, tannins, terpenoids, saponins, phenolics, flavonoids and alkaloids [68]. Plant extracts limit bacterial growth by a synergistic impact of their active components. The synergistic effect arises from various factors, such as the activation of multi-target mechanisms the presence of compounds that can inhibit bacterial resistance pathways, and improvements in pharmacokinetic or physicochemical properties, which lead to increased bioavailability, dissolution and absorption rates and mitigation of side effects [69].

Phytochemicals have the potential to serve as alternative or complementary treatments to antibiotics for several key reasons: Antimicrobial compounds derived from phytochemical can suppress the bacterial growth, fungus, protozoa and viruses through mechanisms that differ from those of current antimicrobial agents. This unique mode of action may offer substantial clinical benefits in treating infections caused by resistant microbial strains [70]. They possess diverse chemical structures and modes of action, making it harder for microbes to develop resistance. Many phytochemicals from various groups have effectively demonstrated their inhibitory potential against AMR pathogens by targeting bacterial membrane proteins, biofilms, efflux pumps, and bacterial cell-to-cell communication. But with prolonged use of antibiotics, bacteria can develop resistance through a variety of methods, including target change, decreased drug absorption, biofilm formation, and the development of destructive enzymes [71,72]. Subsequently, chemically complicated plant products offer significant therapeutic potential since they have fewer adverse effects and are less likely to develop resistance than synthesized medications. Phytochemicals hold great promise for discovering new bioactive compounds that can combat resistant microorganisms. They have the ability to enhance the

effectiveness of older antibiotics, potentially revitalizing their clinical use and helping to mitigate the issue of resistance. Certain active compounds exhibit intrinsic antibacterial properties along with the ability to modify antibiotic resistance. While some of these compounds may not act effectively as antibiotics on their own, they can enhance the effectiveness of antibiotics when used in combination, aiding in the fight against antibiotic resistance in bacteria [73]. Alongside their benefits, phytochemicals also have some limitations, phytochemicals cannot be used as monotherapy because their MIC (minimum inhibitory concentrations) range from 100 to 5000 µg/ml, which is significantly higher than that of antibiotics [74]. Similar to antibiotics, bacteria may acquire resistance to single phytochemical targeting a particular bacterial site [75]. The antimicrobial properties and mode of action utilized by phytochemicals, specifically secondary metabolite compounds, are explored in the following sections. Table **1** provides an overview of the medicinal plants that work against ESKAPE pathogens. A summarized depiction is provided in Fig. (**3**).

Table 1. A concise summary of active components, their sources and mode of action of secondary metabolites against ESKAPE.

S.No.	Plant Secondary Metabolites	Active Components	Biological Source	Target Pathogens	Mode of Actions	References
1.	Alkaloids	Tetrahydrosecamine and Streptanol	*Rhazya stricta*	MRSA, *P. aeruginosa*	Rupturing the bacteria's cell wall	[166]
		Caffeine	*Coffea arabica*	*P. aeruginosa*	interactions with QS proteins	[167]
		8-Epidiosbulbin-E-acetate	*Dioscorea bulbifera*	*P. aeruginosa*	effectively cure the antibiotic-resistant R-plasmids	[168]
2.	Polyphenols	Haloemodins	Rheum species	MRSA, vancomycin-resistant *E. faecium*	block DNA gyrase	[169]
		Malvidin	*Syzgium cumini*	*K. pneumoniae*	Inhibits violacein production, biofilm formation, exopolysaccharide generation	[170]
		Proanthocyanidins and Hydrolysable tannins	*Commiphora leptophloeos*, *Anadenanthera colubrina*, *Myracrodruon urundeuva*	*P. aeruginosa*	Stop biofilm formation	[171]
		Biochanin A	*Brassica oleracea*	MRSA	lowering the expression of the NorA protein	[84]
		Pinostrobin	*Pinus strobus*	*P. aeruginosa*	Inhibits the activity of NorA efflux pumps	[172]
		Myricetin, Phloretin, Hesperetin	*Vitis vinifera, Citrus limon*	MRSA, *Staphylococcus* strains	inhibit biofilm formation, disruption of norA efflux mechanism	[173]
		Quercetin	*Capparis spinosa, Polymnia fruticose, Ginkgo biloba*	*P. aeruginosa*	lowering the generation of virulence factors and the expression of genes linked to QS	[174]
		Sophoraflavanone B	*Desmodium caudatum*	MRSA	rupturing the cell membrane and causing internal leaking	[175]
		Vitexin	Vitex species plants	*P. aeruginosa*	suppresses the QS mechanism by blocking a number of genes	[176]
		Wogonin	*Agrimonia pilosa*	*P. aeruginosa*	suppresses the generation of virulence agents as well as the expression of genes linked to QS	[177]
		Morusin	*Morus alba*	*S. aureus*	disruption to the bacterial membrane	[178]
		Norwogonin, Chebulinic acid, Chelagic acid and Terchebulin	*Scutellaria baicalensis, Terminalia chebula*	*A. baumannii*	_	[179]

(Table 1) contd.....

S.No.	Plant Secondary Metabolites	Active Components	Biological Source	Target Pathogens	Mode of Actions	References
3.	Terpenes	Cryptotanshinone	*Salvia miltiorrhiza*	vancomycin- and methicillin-resistant *S. aureus*	inhibits the respiratory chain by attacking type II NADH:quinone dehydrogenase	[180]
		Oridonin	*Rabdosia rubescens*	MRSA	Disruption in the metabolism of protein and DNA, as well as permeation of the cell wall.	[181]
		Andrographolide	*Andrographis paniculata*	*P. aeruginosa*	Suppress the QS-controller LasR and RhlR	[182]
		Thymoquinone	*Nigella sativa*	*S. aureus* *P. aeruginosa*	generation of reactive oxygen species	[183]
		Cinnamonaldehyde	*Cinnamomum zeylanicum*	*A. baumannii* *P. aeruginosa*	inhibits the action of amino acid decarboxylase inhibits the formation of AHLs and QS- regulated pyocyanin.	[118, 184]
		(4R)- (-)-Carvone	*Mentha viridis*	*E. faecium*	_	[185]
		α-terpinene	*Chenopodium ambrosioides*	*S. aureus*	Inhibits the efflux pump	[186]
		6-gingerol	*Zingiber officinale*	*P. aeruginosa*	inhibit biofilm development and pathogenicity	[187]
4.	Organosulfur compounds	Diallium sulfide and Diallium disulfide	*Allium sativum*, *Allium cepa*	MRSA	_	[188]
		Diallium disulfide		*P. aeruginosa*	suppressed the three QS systems (rhl, pqs, and las)	[189]
		Allyl isothiocyanate, Benzyl isothiocyanate and Phenethyl isothiocyanate		*Enterobacter sp.* *S. aureus*	Antibacterial activity	[190]
		Hirsutine	*Cocullus hirsutus*	*Enterobacter sp.* *S. aureus* *P. aeruginosa* *K. pneumoniae*	anti-microbial activity	[191]

3.1. Alkaloids

Alkaloids are secondary metabolites, found abundantly in various medicinal plants, containing nitrogen in their chemical ring. Alkaloids can be grouped into semi-synthetic and natural categories [76]. Additionally, they can be classified by heterocyclic ring and a non- heterocyclic ring [7]. Alkaloids are distinctive in their bioactivity because they include nitrogen, which may receive protons, and one or more hydrogen atoms that donate to amines. These hydrogen atoms are typically accompanied by functional [77]. Some significant Alkaloids and their structure shown in Fig. (**4**). *Sanguinaria canadensis* roots are the source of the benzophenanthridine alkaloid known as sanguinarine. Sanguinarine has demonstrated antibacterial action against methicillin-resistant *S. aureus* (MRSA), and the mechanism behind this involves the induction of cell lysis, which is facilitated by the discharge of autolytic enzymes [78]. Sanguinarine can cause oxidative stress in pathogenic bacteria by creating reactive oxygen species. The buildup of ROS (reactive oxygen species) disrupts essential biological components, resulting in bacterial death. This oxidative attack is specifically efficient against MRSA [79]. Sanguinarine's structure comprises a planar, polycyclic benzophenanthridine system that enables it to easily intercalate with bacterial DNA. This intercalation can interfere with the activity of bacterial DNA, especially MRSA [80]. Sanguinarine also revealed antibacterial efficacy against *S. aureus*. Its work by interacting with FtsZ, suppressing its GTPase activity, preventing the formation of the Z-ring and promoting cell extension [81]. The alkaloid component conessine, which was extracted from *Holarrhena antidysenterica*, inhibits the bacteria's efflux pump, exhibiting strong inhibitory effect against *P. aeruginosa*. Conessine enhances antibiotic action by blocking the MexAB-OprM efflux pump system in *P. aeruginosa* [82]. By blocking the AdeIJK efflux pump, it has demonstrated the ability to modify resistance in *A. baumannii* [83]. Tomatidine, a naturally occurring steroidal alkaloid, is present in plants of the Solanaceae family like potatoes, tomatoes, has demonstrated significant antibacterial activity toward *S. aureus* either on its own or in conjunction with aminoglycosides. Furthermore, it has been demonstrated that tomatidine and aminoglycosides work synergistically to combat antibiotic-resistant forms of *S. aureus*. Consequently, tomatidine is considered a potential enhancer for the effectiveness of several antibiotics, such as gentamicin, ciprofloxacin, cefepime and ampicillin. Its potential extends to treating infections caused by *S. aureus*, *P. aeruginosa* [84]. Tomatidine prevents *S. aureus* by acting on the bacterial ATP synthase subunit c, which results in decreased ATP generation [85]. Combining ciprofloxacin with piperine, an alkaloid of the piperidine type that originates from *Piper longum* and *Piper nigrum*, prevents a mutant *S. aureus* from developing. Moreover, the *S. aureus* MIC levels significantly decline [86]. Piperine inhibits *S. aureus* and MRSA through impeding the NorA efflux pumps [87, 88]. Piperine and gentamicin given together work well to treat MRSA infections [87]. Piperine reduces the hydrophobicity of

the cell membrane in MRSA, an important factor in biofilm generation. It also inhibits microbial movement, indicating that it interacts with QS components. Additionally, exposure to piperine elevates intracellular ROS, improves permeability of cell membranes, and reduces the release of different virulence genes from MRSA [89]. Isoquinoline alkaloid berberine is derived from numerous naturally occurring therapeutic plants including *Hydrastis canadensis*, *Coptis chinensis*, *Berberis aristata*, and *Coptis japonica*. Berberine cleaves bacterial DNA and successfully disrupts the cell wall of drug-resistant *A. baumanii* [90]. All investigated MRSA strains are susceptible to berberine's antimicrobial action, with MIC levels fluctuating between 32 to 128 µg/mL. Berberine has the ability to prevent MRSA adherence and internal penetration in HGFs (Human gingival fibroblasts) and to make beta-lactam drugs more effective against MRSA [91]. Berberine inhibits MRSA biofilm generation by disrupting the self-assembly of PSMs (phenol-soluble modulins) into amyloid fibrils, hence increasing antibiotic bactericidal action [92]. By inhibiting the MexXY-OprM efflux pump system, berberine works synergistically with the carbapenem antibiotic to restore the sensitivity of imipenem resistant *P. aeruginosa* [93]. A dose of 63.5 g/ml of berberine inhibits the formation of biofilms in a large number of pathogenic strains of *K. pneumoniae* [94]. Reserpine, an indole alkaloid extracted from *Rauwolfia serpentina*, exhibits inhibitory efficacy against *K. pneumoniae* biofilms with a MIC level of 15.6 g/ml [95]. Reserpine makes *K. pneumoniae* more susceptible to antibiotics by blocking the efflux pump [96]. Reserpine can inhibit and destroy the biofilm of *S. aureus* at various sub-inhibitory doses. Reserpine interacts with *S. aureus* biofilm- and virulence-controlled proteins, resulting in a reduction in the pathogenicity [97]. Reserpine also supresses the efflux pump mechanism of *S. aureus* [98].

3.2. Phenolic Compounds

Plant phenolics have a broad spectrum of pharmacological activity and potent pharmacological impacts making them significant bioactive substances [99]. Phenols generated from plants have an aromatic ring configuration with a number of hydroxyl groups and can exist in simple or polymerized variants [100]. Phenolic substances are classified into different categories depending on their molecular structure [101]. These different groups include simple phenols, flavonoids, phenolic acids, stilbenes, quinones, lignans and tannins [102]. Phenolics generated from plants have shown antibacterial efficacy against

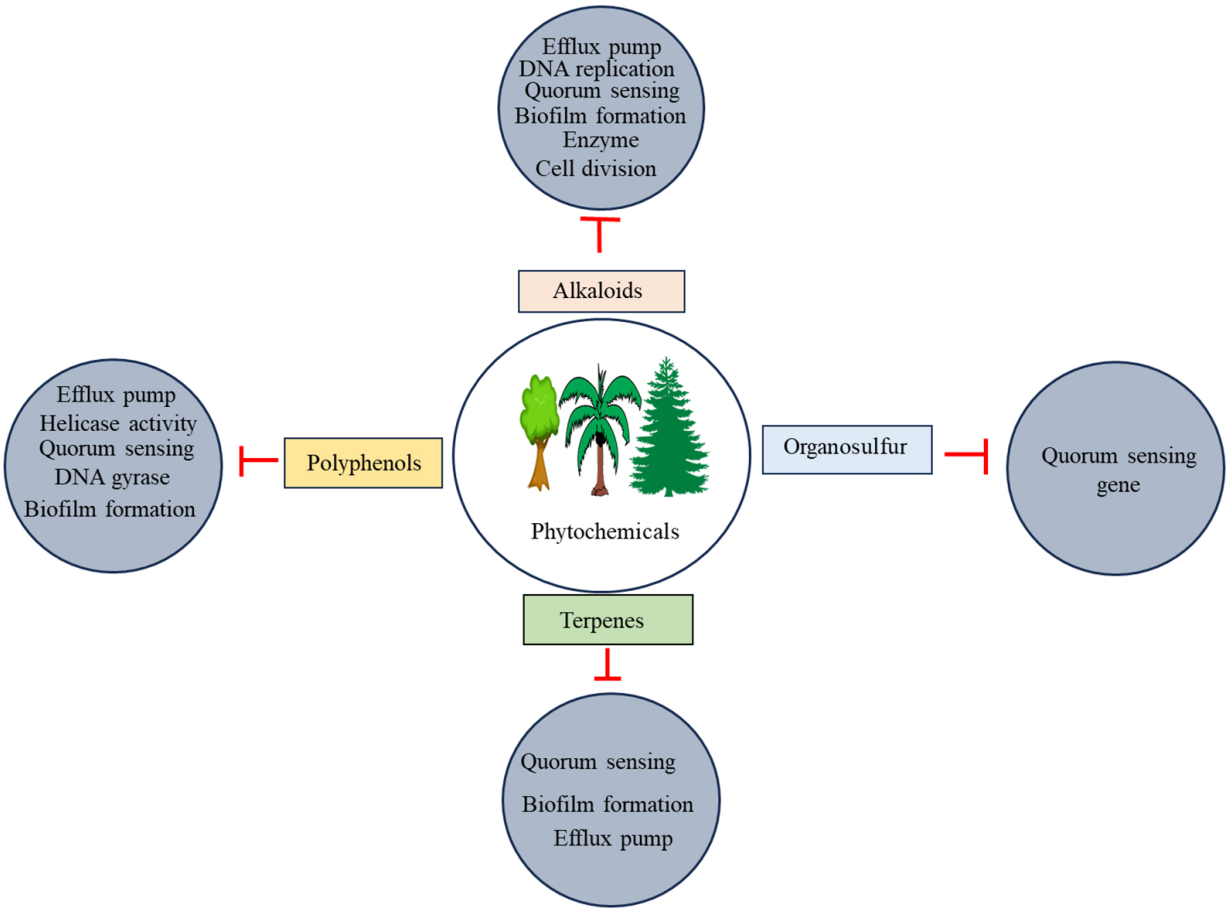

Fig. (3). Phytochemicals generated from plants and their antibacterial mechanisms.

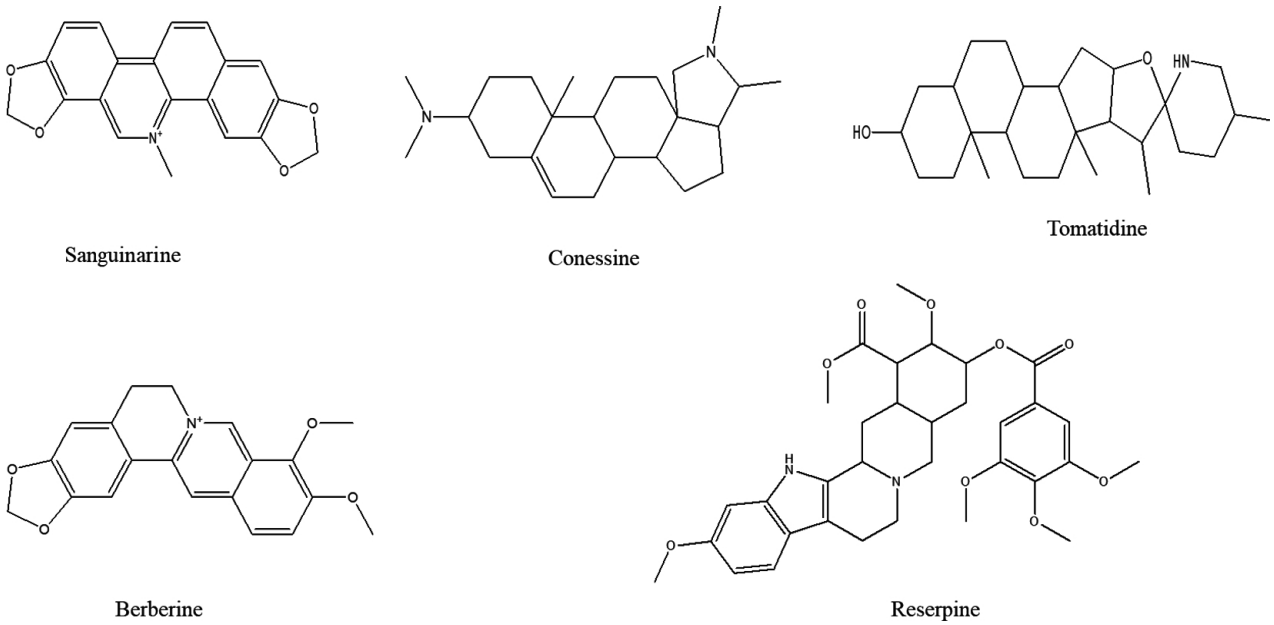

Fig. (4). Some potent Alkaloids that used against ESKAPE pathogens.

a range of microbes by increasing their susceptibility to antibiotics and acting as potent inhibitors of the efflux pump to decrease efflux pump activity [99]. Some significant Phenolic compounds and their structure shown in Fig. (**5**). Due to varying numbers of hydroxyl substituents on their aromatic rings, the flavonols galangin, quercetin, myricetin and kaempferol may prevent the primary replicative DnaB helicase of *K. pneumoniae* (KpDnaB) from binding to deoxyribonucleic acid (dNTP). This helicase is a vital part of the cellular replication machinery that is necessary for the survival of bacteria [103]. The hydroxyl groups of phenolic substances establish hydrogen bonds with the amino acid sequences of DnaB helicase. Phenolic chemicals interact with several bacterial cell locations due to their hydroxyl groups [104]. The helicase *S. aureus* PriA (SaPriA), which is necessary for DNA replication and crucial for bacterial viability, is inhibited by kaempferol [105]. A naturally occurring kaempferol derivative from *Persea lingue* termed kaempferol rhamnoside may up to eight times block the NorA efflux pump of the *S. aureus* strain, hence increasing the antibacterial action of ciprofloxacin [106]. Flavone baicalein is mostly extracted from *Scutellaria baicalensis* Georgi. It works by blocking NorA efflux pumps, which makes antibiotics like β-lactams, ciprofloxacin, and tetracycline more effective against MRSA [107]. Baicalin strengthens the bactericidal properties of several common antibiotics while inhibiting the development of *P. aeruginosa* biofilms. Furthermore, baicalin reduces the quorum sensing (QS)-regulated virulence characteristics in *P. aeruginosa* in a dose-dependent manner [108]. Baicalein inhibits *P. aeruginosa*-induced cytokine release, including IL-8, IL-6, IL-1β and TNFα. It also inhibits the *P. aeruginosa*-induced activation of NFκB and MAPK signalling pathways in macrophages [109]. Another class of phenolic compounds with health advantages is the catechin gallates, which include epigallocatechin gallate. These compounds also show strong antibacterial activity against organisms that are resistant to antibiotics, such MRSA. These substances only slightly impede the NorA efflux pump [110]. The development of MRSA strains is significantly inhibited by tea catechin extracts, with a minimal inhibitory dose of 0.1 g/L. Tea catechin hinder the formation of biofilms by repressing the fnbA and fnbB (fibronectin-binding proteins A and B) [111]. Naringenin is a flavanone commonly present in tomatoes and citrus fruits. Naringenin greatly diminishes the generation of elastase and pyocyanin in *P. aeruginosa*, yet it does not influence bacterial growth. Naringenin inhibits the activity of QS-controlled genes in *P. aeruginosa*, including lasA, lasB, lasI, asR, phzA1, rhlA, rhlI, and rhlR. Additionally, it significantly lowers the levels of the N-butanoyl-L-homoserine lactone (C4-HSL) and acylhomoserine lactones N-(3-oxododecanoyl)-L-homoserine lactone (3-oxo-C12-HSL) [112]. Naringin reduces biofilm development by up to 57%. It significantly decreases biofilm-related features such as EPS (exopolysaccharides) and alginate formation [113]. Both gallic acid and ferulic acid exhibit noteworthy antimicrobial properties against *P. aeruginosa* and *S. aureus*. Their mechanism of action is attributed to the leakage of potassium ions, modification of the hydrophobicity of the cell surface, and loss of cell membrane integrity. Ferulic acid achieves MICs of 500 mg/mL for *P. aeruginosa* and 1750 mg/mL for *S. aureus*, while gallic acid shows antimicrobial efficacy of 1100 mg/mL for *S. aureus* and 100 mg/mL for *P. aeruginosa* against the microorganisms [114]. Curcumin, which is widely distributed in *Curcuma longa* L., has been shown to exhibit antimicrobial properties towards *S. aureus*. This antibacterial activity is ascribed to curcumin's ability to permeate into the bilayer and increase the permeability of the membrane [115]. α-Hemolysin (Hla) is a key virulence factor secreted by *S. aureus*. Curcumin effectively inhibits hemolysis

induced by Hla, potentially reducing infection severity [116]. Curcumin inhibits the production of *S. aureus* PBP2a protein and disrupts protein synthesis by disrupting RNA. It inhibits early biofilm formation genes, affects QS-dependent virulence, interferes with the SOS response, and hampers bacterial DNA damage repair processes [117]. Curcumin shows anti-infective efficacy against *P. aeruginosa* infections by impacting virulence, disrupting QS, and inhibiting the initiation of biofilm formation [115]. Curcumin exhibits minimal antibacterial efficacy against *A. baumannii* strains Its antibacterial effects stem from multiple mechanisms, such as bacterial cell division and interruption of the folic acid biosynthesis pathway [118]. Curcumin decreases pellicle production and surface mobility in *A. baumannii* and exhibits antibiofilm action against *A. baumannii* [119]. Clinical specimens of *A. baumannii* are susceptible to the antibacterial effects of the polyphenol theaflavin found in black tea. Theaflavin's antibacterial effect is believed to be mediated by membrane interaction. The activity of theaflavin against *A. baumannii* can be enhanced by epicatechin. It's likely that epicatechin enhances the antibacterial activity of flavin by blocking its oxidation [120]. The primary phenolic component of *Magnolia officinalis* is magnolol. Antibacterial efficacy of magnolol against *S. aureus*, especially drug-resistant strains with MIC level between 8 and 16 ppm. Magnolol displays a strong affinity for the cell division protein FtsZ [121]. Magnolol inhibits MRSA by upregulating *mecR1* and repressing *mecA* and *mecI* [122]. *Lonicera japonica* contains a flavonoid called lonicerin. At sub-MIC concentrations, Lonicerin considerably decreases alginate production (25 µg/mL) and biofilm generation (12.5 µg/mL) without affecting alginate secretion protein (AlgE) expression or *P. aeruginosa* proliferation. This suggests that licorerin directly inhibits AlgE [123]. One of the primary active ingredients in pomegranate peel, punicalagin, has a wide range of documented benefits, including immunosuppressive, antiviral, antibacterial, and antioxidant effects. Punicalagin significantly inhibits the production of *S. aureus* biofilms. MIC of 0.25 mg/mL for punicalagin indicates strong antistaphylococcal activity. Punicalagin treatment at 2xMIC causes an increase in the release of potassium in the cells. The cell membrane is structurally disrupted by punicalagin [124]. Sortase A (SrtA), an enzyme located on the surface of *S. aureus*, is essential for bacterial virulence while not impacting bacterial viability. Punicalagin effectively inhibits SrtA activity, with a low IC50 value of 4.23 µg/mL. Additionally, punicalagin reduces the virulence-associated function of SrtA by limiting the attachment of *S. aureus* to fibrinogen, limiting the expression of protein A (SpA) and suppressing biofilm generation [125]. *Aloe vera*, *Cassia occidentalis,* and *Polygonum multiflorum* can all be used to extract aloe-emodin, a naturally occurring anthraquinone derivative and active component. Aloe-emodin inhibits MRSA at 16 µg/mL, *P. aeruginosa* at 256 µg/mL, and *S. aureus* at 32 µg/mL. Aloe emodin-treated cells exhibit modifications in the genes responsible for sulfur metabolism, biofilm formation, and the manufacture of L-lysine and peptidoglycan [126]. Natural polyphenolic chemical resveratrol can be found in significant quantities in red wine, peanuts, grapes, and other plant sources. It has strong antibacterial activity, and recent research has shown that it can significantly enhance the effectiveness of aminoglycoside medicines, including tobramycin, amikacin, gentamicin and netilmicin, against *P. aeruginosa* biofilms. Resveratrol has the ability to disable ATP synthase, increasing *S. aureus*'s susceptibility to polymyxin B. Resveratrol has a capacity to make polymyxin B more effective in killing MDR-*K. pneumoniae* by increasing its sensitivity to the antibiotic. Resveratrol may break down the bacterial cell envelope, which would make it possible for polymyxin B to attach to greater targets in the outermost layer of the membrane [127]. Resveratrol can regulate norfloxacin resistance by inhibiting the NorA efflux pump, which increases the antibiotic's efficacy against *S. aureus* [128].

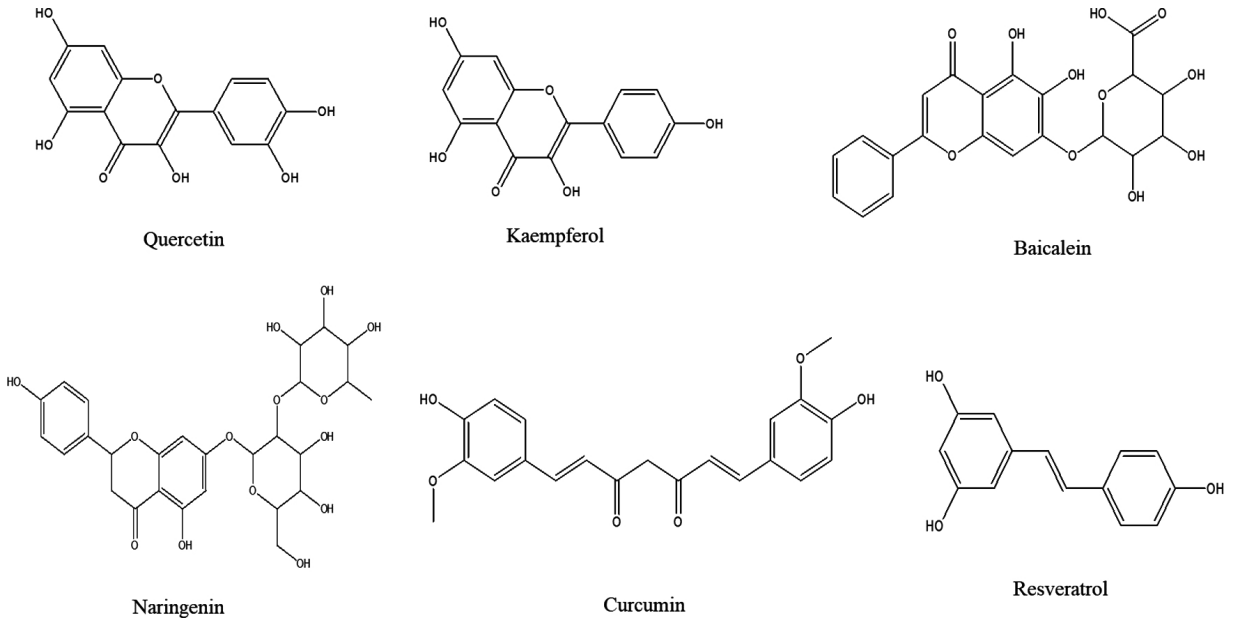

Fig. (5). Some potent phenols that used against ESKAPE pathogens.

3.3. Terpenes

Terpenes, or isoprenoids, represent the most diverse class of natural products [129]. They are intriguing because they are found in nearly all forms of life and serve a broad array of functions, from fundamental to functional [130]. These substances are made from isopentenyl pyrophosphate, a five-carbon precursor unit, and its functional isomer, dimethylallyl pyrophosphate [131]. They are also widely present in flowers, vegetables, and fruits. In general, they are concentrated in large amounts in the leaf and reproductive systems of plants during and right after flowering. Many plants have distinctive scents, which are caused by terpenes, that are the main constituents of resins. Terpenes have a greater effect on Gram-positive bacteria than on Gram-negative ones. The lipophilic characteristics of terpenes are intimately linked to their antimicrobial action. The frameworks of the cell membrane are mostly affected by monoterpenes, which change the topology of its proteins, increase fluidity and permeability, and disrupt the respiration chain [132]. Some significant Terpenes and their structure shown in **Fig.6**. Carvacrol is frequently present in *Thymus vulgaris* and *Origanum vulgare* essential oils. Carvacrol is considered a broad-spectrum antibiotic that works well against fungi, yeasts, and bacteria. Additionally, it exhibits antibiofilm activity against *S. aureus*. Carvacrol has the ability to break bacterial membranes, resulting in the leaking of internal K^+ ions as well as ATP, consequently leading to cell death [133]. Carvacrol decreases the production of the antioxidant molecule staphyloxanthin and its derivatives in MRSA by attacking the key regulatory protein SarA (staphylococcal accessory regulator A) and the new antivirulence substrate CrtM (4,4′-diapophytoene synthase) [134]. By blocking LasI activity and concurrently lowering the levels of lasR, biofilm, and swarming movement, carvacrol decreases *P. aeruginosa*'s pathogenicity [135]. Biofilm inhibition may disrupt QS by reducing the synthesis of pyocyanin and violacein in *P. aeruginosa* [136]. Carvacrol inhibits *A. baumannii* by compromising the integrity of the cell membrane, hindering DNA synthesis, and decreasing enzyme activity. Carvacrol is effective at suppressing twitching motility, which is a critical step in biofilm generation [137]. Thymol, a volatile monoterpenoid phenol found naturally, is the primary active ingredient of oil derived from the *Thymus* v*ulgaris* L. species. Antibiotics and thymol together demonstrate a potent synergistic effect that inhibits the production of *K. pneumoniae* biofilms and destroys preexisting ones [138]. Thymol increases the penetration of lytic agents across the outer membrane of *K. pneumoniae*, especially for SDS (sodium dodecyl sulfate) and Triton X-100. At a concentration of 300 µg ml^{-1}, thymol makes bacterial cells more susceptible to lysis by SDS and Triton X-100 [139]. Moreover, thymol inhibits *S. aureus* by reversing the efflux pump's function [140]. Thymol disturbs the intracellular balance of *S. aureus* by altering ATP and NADPH levels and inducing lipid peroxidation [141]. Thymol suppresses MRSA by limiting biofilm development and eliminating mature biofilms by inhibiting PIA (polysaccharide intercellular adhesin) production and releasing eDNA (extracellular DNA). Nonetheless, the combination of thymol and vancomycin is more effective in eradicating MRSA biofilms [142]. *O*cimum *tenuiflorum* is the source of linalool and eugenol. The generation of QS proteins including lasA and lasB, along with virulence elements such as rhamnolipids and pyocyanin, may be impacted by eugenol and linalool, which significantly impair *P. aeruginosa*'s ability to build biofilms [143]. Eugenol demonstrates effectiveness in suppressing and eliminating biofilms generated by *S. aureus*. Eugenol prevents the phosphorylation of enzyme I in the bacterial PTS (phosphotransferase system), as well as critical carbon metabolism enzymes such as succinyl-CoA synthetase and glucose-6-phosphate isomerase. Moreover, eugenol suppresses AgrA phosphorylation, which reduces the production of agr transcriptional units and virulent genes [144]. Furthermore, it is also discovered that eugenol's ability to downregulate the expression of genes involved in *A. baumannii* biofilm creation significantly contributes to inhibiting biofilm formation and damaging biofilm framework [145]. Ursolic acid (UA), which exhibits antibacterial effect against some pathogens. At a MIC of 0.8 mg ml^{-1}, UA is efficient against CRKP. UA inactivates CRKP cells encased in biofilms, disturbs the integrity of the CRKP cell membrane, and shows potent inhibitory effects against the formation of biofilms and biofilm-related gene expression. For treating MDR-*K. pneumoniae* infections, UA therefore shows potential when used in conjunction with other antibiotics [146]. Fruits contain betulinic acid, a lupane-type triterpenoids that have been shown to have a number of pharmacological properties, such as antibacterial. The MIC of betulinic acid for *P. aeruginosa* and *S. aureus* is 256 µg/mL. Bacterial cells exposed to betulinic acid produce a considerable increase in superoxide anion radical generation and the ratio of NAD+/ NADH increases dramatically in bacteria. After betulinic acid treatments, *P. aeruginosa* and *S. aureus* show a significant drop in reduced glutathione levels along with an increase in malondialdehyde, glutathione disulphide and fragmented DNA [147]. Sesquiterpene alcohols having an aliphatic carbon chain, such as nerolidol and farnesol, exhibit antibacterial action against a range of *S. aureus* strains, including MRSA. These terpene alcohols affect the bacterial cell membrane by measuring intracellular K+ ion leakage. The antibacterial effectiveness of the substances that perturb the membrane is reflected in the release of K+ into the cells. The overall amount of K+ leakage is assessed for antibacterial activity, but the initial pace of leakage is recognized as causing harm to the cell membranes [148]. The leaves and distal branches of *Melaleuca alternifolia* are steam-distilled to make tea tree oil (TTO), which is currently used in conventional medicine. TTO possesses antibacterial properties against MRSA, *K. pneumoniae*, *A. baumannii*, and *P. aeruginosa*, both when used alone and in conjunction with other antimicrobials. The antibacterial activities of TTO are demonstrated by its capacity to suppress bacterial respiration, break microbial membrane structures' permeability barrier, and induce potassium ion leakage into Gram-positive as well as Gram-negative bacteria [149]. A number of plants, including marjoram, lavender, Mexican giant hyssop and thyme, contain the terpene linalyl anthranilate (LNA). By creating ROS and oxidative stress, which rupture the bacterial membrane through lipid peroxidation, LNA destroys *K. pneumoniae* cells that produce carbapenemase [150]. The essential oil of *Rosmarinus officinalis* and one of its main constituents, eucalyptol (1,8-

cineole), show excellent antibacterial efficacy against MDR strains of *P. aeruginosa* and *A. baumannii*, as well as a synergistic effect with ciprofloxacin. The investigation using flow cytometry shows that the natural chemicals work by causing permeabilization of the cell wall and inhibiting the activity of the efflux pumps [151]. The MDR-*K. pneumoniae* is effectively inhibited by 1,8-cineole, which is also able to break up the biofilms that these bacteria generate [152].

3.4. Organosulfur Compounds

Organosulfur compounds are those that have sulfur atoms bound to carbon. Two principal plant groups with organosulfur properties are Allium species Alliaceae family (garlic, onion, *etc*.) containing S-alk(en)yl-l-cysteine sulfoxides and cruciferous plants of Brassicaceae family (cabbage, kale, broccoli, cauliflower, Brussels sprouts *etc*.) including Eruca (rocket salad), containing S-methyl cysteine-l-sulfoxide [153]. Organosulfur compounds are categorized based on the functional group bonded to sulfur [154]. Crucial organosulfur compounds include sulfide, thiol, disulfide, thiosulfates, sulfones, isothiocyanate and sulfoxide. Antibacterial properties of these organosulfur compounds have been found against both Gram-positive and -negative microorganisms [155]. Some significant Organosulfur compounds and their structure shown in Fig. (**7**). An organosulfur compound is allicin (diallyl thiosulfinates) found in plants of the allium genus mostly in garlic (*Allium sativum*). When garlic is chopped, smashed, or chewed, it releases allicin, which is not present in fresh, undamaged cloves of garlic [156]. Allicin is created by the autocondensation of the appropriate sulfenic acid intermediate in the aqueous phase, which is obtained by the enzymatic catalysis of alliinase [157]. Allicin is effective against *S. aureus*, including MRSA strains, even those that have developed resistance to mupirocin [158]. Allicin penetrates Gram-positive cell walls, reacting with conserved proteins and causing thiol specific oxidative and sulfur stress in *S. aureus*. According to Loi *et al*., allicin treatment results in S-thioallylation of 57 proteins, which bacteria are unable to resist *via* adaptation or mutation [159]. Crushed garlic means allicin as active constituent effective against normal strains of *E. faecium* species and MDR enterococci [160]. Ajoene (4,5,9-trithiadodeca-1,6,11-triene-9-oxide) is produced through the process of allicin S-thiolation and the addition of 2-propenesulfenic acid [161]. It was extracted from an ether fraction of garlic extract. Ajoene (disulfide) inhibit QS thereby effective in infection caused by *P. aeruginosa* and MRSA [162, 163]. Sulforaphane and erucin are obtained from glucosinolate glucoraphanin, which is present in cruciferous vegetables like kale, broccoli and Brussels sprouts. The enzyme myrosinase changes glucoraphanin in these veggies into sulforaphane and when it is chopped or chewed and erucin is the thioether analogue of sulforaphane. Sulforaphane and erucin both are isothiocyanate compound [164]. Sulforaphane and erucin (deoxy precursor of sulforaphane) both are efficiently binds LasR (LuxR autoinducer binding site receptor, transcriptional regulator) to block QS activation in *P. aeruginosa* [165].

4. ASSESSMENT OF THE ANTIMICROBIAL EFFECTIVENESS OF PHYTOCHEMICAL EXTRACTS

A variety of assessment techniques are now being used to determine the potential antibacterial activity of new therapeutic plant extracts [192]. The different antimicrobial susceptibility tests (ASTs) may result in variations in the obtained outcomes [73]. The results achieved will be impacted by the scientific standards utilized in selecting the plant material, the choice of solvent and extraction method, the methodology applied, growth medium composition, and the microorganisms chosen

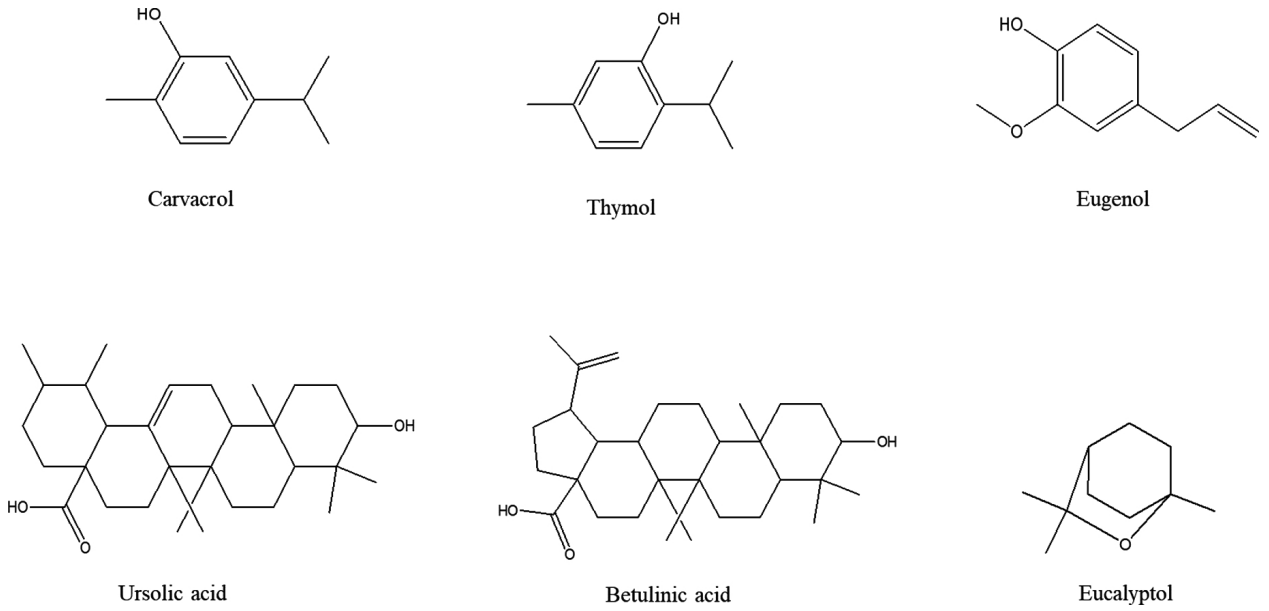

Fig. (6). Some potent Terpenes that used against ESKAPE pathogens.

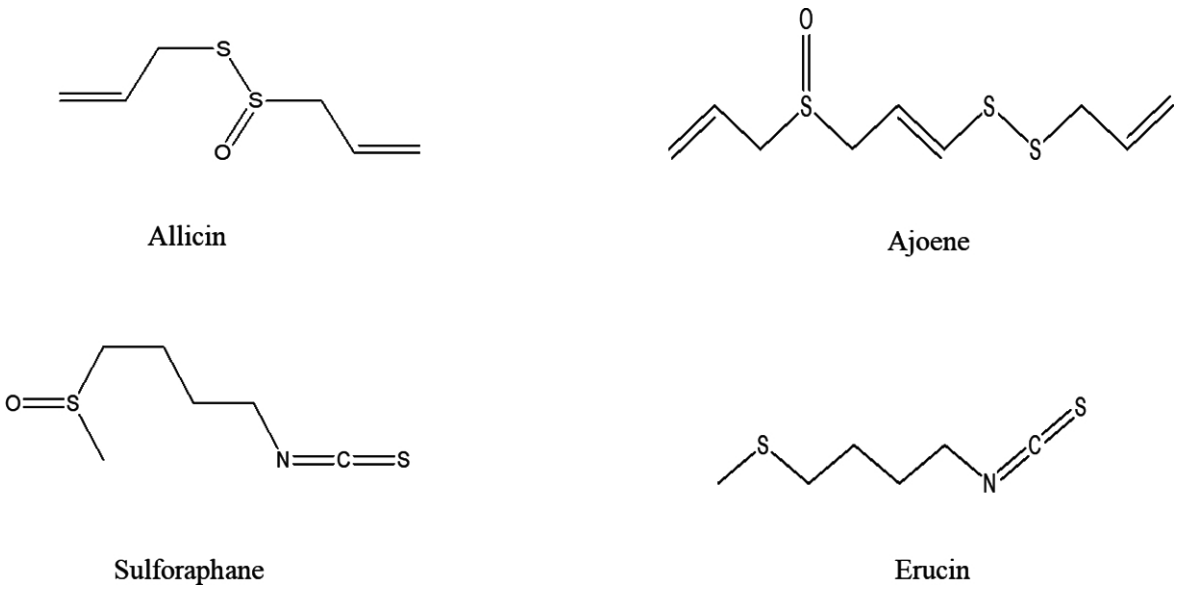

Fig. (7). Some potent organosulfur compounds that used against ESKAPE pathogens.

for the study [193,194]. Recent standard methods for antimicrobial susceptibility testing, generally classified into diffusion and dilution techniques, may not be suitable for plant extracts and require specific modifications [195,196]. A significant issue with diffusion and dilution-based AST involves the accessibility of active principles, which can be affected by the test compound's solubility [197]. Diffusion methods provide qualitative information on the existence or nonexistence of antimicrobial agents. Diffusion tests were commonly used in investigations due to their simplicity and convenience of use, however lack of standardization led to inaccurate as well as non-reproducible outcomes [195]. Dilution procedures are quantitative techniques utilized to determine the MBC (minimum bactericidal concentration) or MIC of antimicrobial substances [198,199]. These approaches have benefits over diffusion methods, such as increased sensitivity for lower extract amounts, quantitative analysis, and differentiation between bactericidal and bacteriostatic effects [200]. In the broth microdilution technique, assays are conducted using small amounts of the test antibiotic, facilitating rapid assessment of bacterial susceptibility. The method's main drawback is the need for human manipulation of antimicrobial solutions, which might lead to errors during preparation. Agar dilution provides several benefits, including the ability to test multiple biological isolates at once, observation of diverse populations or multiple cultures, and versatility in choosing samples and concentration ranges for testing. Etest, a commercial AST that combines agar dilution and disc diffusion methods, exhibits minimal variation, good reproducibility, and is comparable to established MIC approaches [201].

CONCLUSION

Phytochemicals are now recognized as prospective therapeutic options in the fight against AMR, notably ESKAPE infections, which pose substantial threats to world health. This study focuses on a wide range of phytochemicals with antimicrobial properties, including alkaloids, phenolic, terpenoids and organosulfur compounds, proving their ability to limit the growth of these tenacious pathogens. The findings imply that phytochemicals can be useful replacements or adjuncts to traditional antimicrobial agents, potentially circumventing the restrictions given by increasing resistance rates.Integrating scientifically verified phytochemicals into healthcare facilities could make treatment alternatives more accessible, especially in low-resource areas where access to antibiotics may be limited. Through the provision of alternative treatments for mild infections, phytochemicals contribute to antibiotic stewardship by reducing unnecessary application of antibiotics. The effectiveness of present antibiotics should be maintained by public health programs that support research into phytochemical-based formulations as complements to existing medications.

Particularly in low-income communities where access to medications is limited, phytochemicals made from readily available plants provide affordable substitutes. Their accessibility is essential for tackling AMR since it offers feasible treatment options for infections. Incorporating phytochemical knowledge into public health education could encourage communities to adopt more secure and sustainable antimicrobial methods, reducing reliance on conventional antibiotics. public health policies may foster research into the antimicrobial properties of traditional medicinal plants, ensuring that phytochemicals are potent, thoroughly examined for efficacy and safety, and integrated into healthcare strategies to improve the management of resistant infections.

Despite these promising findings, some gaps in current understanding require more exploration. To begin, the mechanisms behind the antibacterial effect of different phytochemicals against ESKAPE infections are not well

characterized. Future research should focus on elucidating these pathways using molecular and cellular investigations, which will lead to the creation of tailored phytochemical-based medicines. Furthermore, thorough *invivo* investigations are required to examine the therapeutic value of these molecules within complex biological systems, as well as their safety profiles, to ensure that they do not cause side effects or interact unfavourably with existing drugs. Furthermore, investigating the combined effects of phytochemicals and traditional antibiotics is an intriguing area of research. Identifying combinations that improve antibiotic efficacy could help develop novel techniques for combating resistant illnesses. While the therapeutic value of phytochemicals in combating AMR is clear, specific research initiatives are necessary to fully exploit their advantages.

AUTHORS' CONTRIBUTION

T.B.: Study conception and design; A.K.H.: Data collection; R.C.: Analysis and interpretation of results; R.C.: Methodology; N.G: Investigation; I.G., M.K., S.S.: Draft manuscript. All authors reviewed the results and approved the final version of the manuscript.

LIST OF ABBREVIATIONS

ICU	=	intensive care unit
ESBL	=	Extended-spectrum Beta-lactamase
WHO	=	World Health Organization

CONSENT FOR PUBLICATION

Not applicable.

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None.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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