Potential Antibacterial Activity of Plant Compounds against Carbapenem-Resistant Bacteria

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Abstract

Antimicrobial resistance, especially in carbapenem-resistant Gram-negative bacteria, is a global and urgent threat to public health. Carbapenems, the last line of defense, are now being challenged by the spread of resistance mechanisms among bacteria, especially the production of carbapenemases. Infections caused by carbapenem-resistant Gram-negative bacilli are associated with higher mortality rates and much more severe outcomes than drug-susceptible infections due to the failure of conventional therapies. This growing crisis has led researchers to urgently search for alternative therapeutic strategies. In the meantime, plant compounds have shown significant potential in combating these bacteria due to their unique chemical diversity and multiple mechanisms of action. These compounds exert their antibacterial effects through mechanisms such as the induction of oxidative stress and cell membrane damage, direct inhibition of carbapenemase enzymes, inhibition of efflux pumps, and inhibition of biofilm formation. In addition, many of these plant metabolites have shown a synergistic effect in combination with carbapenem antibiotics, leading to a significant reduction in the minimum inhibitory concentration (MIC) of these antibiotics. Plant compounds are promising candidates for the development of new antimicrobial agents or therapeutic adjuvants against carbapenem-resistant bacteria because of their multi-target arsenal, favorable safety profile, and ability to create synergy with conventional antibiotics. However, a large proportion of the world's plant species remain unknown. Extensive research and the use of *in silico* techniques can be effective in the discovery and development of plant compounds with antimicrobial activity. Although there are challenges in the path to the clinical development of these compounds, research in this area opens a promising path to overcoming antimicrobial resistance.

Keywords: Antimicrobial resistance, Carbapenem, Carbapenemase, Herbal compounds, Synergy

Introduction

Antimicrobial resistance (AMR), often described as a "silent pandemic," is widely recognized as one of the most serious chal-

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lenges to global health. This crisis has extensive consequences, reaching beyond clinical medicine to affect other critical sectors such as agriculture, economics, and food security (Read and Woods, 2014, Tang et al., 2023, Rafeeq et al., 2025). The proliferation of multidrug-resistant (MDR) bacteria represents a central aspect of this global challenge. Leading health authorities, including the Centers for Disease Control and Prevention (CDC) and the World Health Organization (WHO), have classified AMR among the most critical threats to human health (Salam et al., 2023, Rafeeq et al., 2025). According to estimates in 2021, AMR directly caused 1.5 million deaths and was associated with 4.71 million other deaths (Collaborators, 2024). Projections show that this figure will increase by 2050, with direct deaths reaching 1.91 million and related deaths reaching 8.22 million (Collaborators, 2024, Cesaro et al., 2025). The main drivers of this multifaceted crisis include the overuse and misuse of antibiotics in human medicine and agriculture, their environmental release, inadequate infection control, and a weak pipeline for new antibiotics. These elements have collectively accelerated the spread of MDR bacteria, posing a serious global challenge (Mancuso et al., 2023, Rafeeq et al., 2025).

Among these, carbapenem-resistant bacteria, particularly Gram-negative ones, represent the most challenging cases to treat. This is very important because carbapenems have long been considered the "last line of defense" and the most reliable weapon against the most dangerous pathogens (Aurilio et al., 2022). Infections caused by carbapenemase-producing Gram-negative bacilli, due to the failure of conventional treatments, are associated with an alarming mortality rate and have far more severe outcomes than drug-sensitive infections (Hu et al., 2020, Shariati et al., 2024). Given the critical importance of this type of resistance, the WHO has placed carbapenem-resistant Gram-negative bacteria, including *Acinetobacter baumannii*, Enterobacterales and *Pseudomonas aeruginosa* on its priority list of pathogens requiring urgent research and development of new antimicrobial treatments (Sati et al., 2025). This growing crisis has led researchers to urgently search for alternative therapeutic strategies. In this regard, approaches such as the use of natural compounds, bacteriophages, probiotics, monoclonal antibodies, and antimicrobial peptides have received attention (Dhanarani et al., 2017, Shariati et al., 2024). Among these options, plant compounds have emerged as very promising candidates. These compounds show tremendous potential due to their unique chemical diversity, multi-target mechanisms, and historical safety record in human consumption (Abdallah et al., 2023). The exploitation of plants is not only a leading scientific opportunity but also a socio-economic necessity in the global fight against antimicrobial resistance (Rafeeq et al., 2025). Accordingly, this review aimed to investigate the potential of plant-derived compounds as alternative solutions for the control of carbapenem-resistant bacteria.

Carbapenems and their importance in clinical settings

Carbapenems, along with *penicillins, cephalosporins* and monobactams, belong to the diverse and widely used family of β-Lactam

antibiotics (Figure 1). However, what distinguishes carbapenems is their unique chemical structure, which includes an unsaturated, sulfur-free beta-lactam ring. This structural feature gives them two major advantages: higher stability against β-lactamase enzymes and a much broader spectrum of activity (Tooke et al., 2019).

Well-known examples of this group include imipenem, meropenem, and ertapenem, and newer generations such as doripenem, biapenem, panipenem, razupenem, and tomopenem have also been developed (El-Gamal et al., 2017).

The mechanism of action of these drugs, similar to other beta-lactams, is through the inhibition of penicillin-binding proteins (PBPs) and the disruption of bacterial cell wall synthesis. Among these molecular targets, PBPs 1a, 1b, 2, and 3 serve as the primary sites of inhibition, with PBPs 2 and 3 being particularly specific to Gram-negative bacteria (Aurilio et al., 2022). Over the past decade, the use of carbapenems in clinical settings has increased dramatically, by 45%. This trend has been a response to the spread of strains producing extended-spectrum β-lactamases (ESBLs), as carbapenems serve as the last line of defense in the treatment of serious infections caused by resistant pathogens(Blair et al., 2015, Patrier and Timsit, 2020).

These drugs are used to treat several infections, including those of the lower respiratory tract, skin and soft tissue, urinary tract, central nervous system, abdomen, and pelvis. They are also used in managing complex conditions such as febrile neutropenia and complications arising from cystic fibrosis (Lo et al., 2008, Nguyen and Joshi, 2021).

Carbapenems possess a broad antibacterial spectrum and are primarily employed to treat infections caused by highly resistant Gram-negative bacteria, including members of the *Enterobacteriaceae* family and non-fermentative bacteria. They also demonstrated efficacy against certain drug-resistant Gram-positive bacteria (Au-

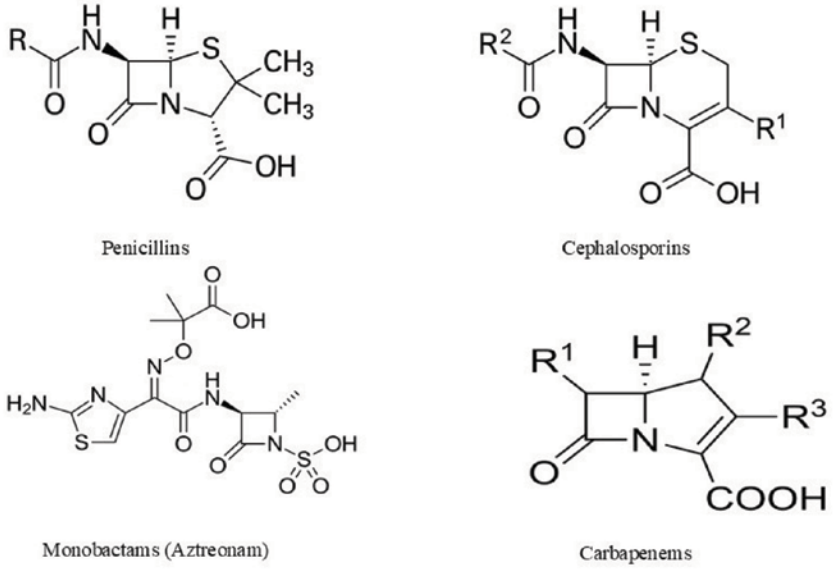

Fig. 1. Chemical structure of the main classes of β-lactam antibiotics (Terico and Gallagher, 2014, Lee et al., 2016)

rilio et al., 2022).

Furthermore, due to their more favorable safety profile and fewer side effects compared with other last-line agents such as polymyxins, carbapenems are regarded as one of the safest and most reliable classes of antibiotics in modern medicine (Meletis, 2016). However, their excessive and irrational use has led to resistance to carbapenems.

Carbapenem resistance and its underlying mechanisms

Carbapenem resistance has emerged as a critical and growing threat to global public health. Over the past decade, the global dissemination of carbapenem-resistant pathogens has reached alarming levels, particularly in certain European and Asian nations where the resistance rates have surpassed 50% (Hansen, 2021).

The magnitude of this threat is clearly illustrated by data from the United States, where an estimated 13,100 infections and 1,100 deaths were attributed to carbapenem-resistant pathogens in 2017 alone (Livorsi et al., 2018, Dong et al., 2020).

Patients with compromised immune systems, complex underlying diseases, or those using invasive medical devices such as indwelling catheters are among the groups at the highest risk for these infections (Martin et al., 2018).

This resistance is mediated through diverse molecular mechanisms, broadly categorized into enzymatic and non-enzymatic pathways. Non-enzymatic mechanisms include reduced permeability of the bacterial outer membrane (primarily through the loss or decreased expression of porins) and the activation of efflux pumps that expel the antibiotic from the cell (Tompkins and van Duin, 2021).

In contrast, the primary enzymatic mechanism involves the production of hydrolyzing enzymes called carbapenemases. These enzymes, which belong to a diverse family of β-lactamases, are capable of inactivating a wide range of antibiotics, including carbapenems, cephalosporins, penicillins, and monobactams, and are recognized as the key factor in the global spread of this resistance in Gram-negative bacteria (Suay-García and Pérez-Gracia, 2019, Tompkins and van Duin, 2021).

Currently, the link between specific resistance mechanisms and particular geographic regions is constantly evolving with extensive international travel and widespread exposure to healthcare systems (Bonomo et al., 2018).

Molecular classification of carbapenemases

Based on the Ambler classification system (Table 1), which relies on conserved and variable amino acid motifs in the protein structure, carbapenemases are categorized into three main classes: A, B, and D (Hammoudi Halat and Ayoub Moubareck, 2020, Sawa et al., 2020).

Class A carbapenemases are characterized by a serine residue at their active catalytic site. The genes encoding these enzymes can be chromosomal, plasmid-borne, or both (Aurilio et al., 2022). These carbapenemases hydrolyze a broad spectrum of β-lactam antibiotics, including carbapenems. The most clinically significant member, *Klebsiella pneumoniae* carbapenemase (KPC), has been identified worldwide, while Imipenem-hydrolyzing β-lactamase (IMI) and Guy-

ana extended-spectrum β-lactamase (GES) represent less common variants (Hammoudi Halat and Ayoub Moubareck, 2020, Mancuso et al., 2023). A key therapeutic feature is their susceptibility to conventional β-lactamase inhibitors such as clavulanate, sulbactam, tazobactam, and avibactam (Tehrani and Martin, 2018).

Class B carbapenemases, known as metallo-β-lactamases (MBLs), require a metal ion (Zn^{2+}) as a cofactor for nucleophilic attack on the β-lactam ring and demonstrate the highest carbapenem-hydrolyzing activity. A critical distinction from Class A enzymes (serine β-lactamases) is their resistance to conventional β-lactamase inhibitors. MBLs confer resistance to almost all β-lactam drugs, with the major exception being aztreonam (Hammoudi Halat and Ayoub Moubareck, 2020, Sawa et al., 2020, Ortega-Balleza et al., 2024). The most clinically prevalent MBLs include the Verona integron-encoded MBL (VIM), Imipenemase (IMP), and New Delhi MBL (NDM) (Hammoudi Halat and Ayoub Moubareck, 2020). The number of reported alleles for IMP and VIM carbapenemases is increasing at a remarkable rate, with more than 100 variants of IMP-like enzymes now identified in many parts of the world and in many Gram-negative species (Le Terrier et al., 2025). These figures indicate the continuous and dynamic spread of these resistance mechanisms (Sawa et al., 2020).

MBL genes are frequently located on mobile genetic elements, such as class 1 integrons, which facilitates their rapid dissemination among bacterial species (Aurilio et al., 2022, Behboudipour et al., 2025). While MBL enzymatic activity can be inhibited in laboratory settings by metal chelators (*e.g.*, EDTA) or specific compounds such as sodium mercaptoacetate, the toxicity of these agents prevents their clinical application (Doi and Paterson, 2015). There are current-

Table 1. Ambler classification of carbapenemases.

Class	Active site	Common enzymes	Gene Location	Substrate	Organism	Reference
A	Serine	KPC (*Klebsiella pneumoniae* carbapenemase) GES (Guiana extended spectrum)	Plasmid	Carbapenems Penicillins Cephalosporins Aztreonam		(Lee and Doi, 2014, Rabaan et al., 2022, Mó and da Silva, 2024)
B	Metal ion (zinc)	IMP (Imipenemase) VIM (Verona integron-encoded metallo-β-lactamase) NDM (New Delhi metallo-β-lactamase)	Plasmid	Most β-lactam antibiotics, except aztreonam	*Enterobacteriaceae* *P. aeruginosa* *A. baumannii*	
D	Serine	OXA (Oxacillin-hydrolyzing carbapenemases)	Plasmid	Oxacillin Third-generation cephalosporins Carbapenems		

ly no approved inhibitors for therapeutic use against MBLs. Given their importance, the development of new anti-MBL agents is a high priority (Ortega-Balleza et al., 2024).

Class D carbapenemases, known as oxacillinases, include OXA-type enzymes such as OXA-48, OXA-72, and OXA-244 (Mancuso et al., 2023). It should be noted, however, that oxacillin hydrolysis is not a universal characteristic of all class D enzymes, as the hundreds of known OXA variants exhibit substantial diversity in their substrate profiles (Bahr et al., 2021). OXA-48 and its variants are the most clinically significant Class D carbapenemases. These enzymes demonstrate hydrolytic capacity against various β-lactams, including carbapenems and third-generation cephalosporins (Pitout et al., 2019).They are resistant to classical β-lactamase inhibitors (Kyriakidis et al., 2021). These enzymes present significant diagnostic challenges as they often exhibit only low-level *in vitro* resistance to carbapenems. Nevertheless, their clinical impact remains substantial (Boyd et al., 2022).

Plants natural reservoirs of antimicrobial compounds

Plants have been an indispensable source of medicine for thousands of years. This role is so undeniable that today more than a quarter of modern drugs are either directly extracted from or inspired by natural compounds. This long history of use affirms their effectiveness and safety in human health (Khameneh et al., 2015, Rafeeq et al., 2025). Plants are estimated to account for a large proportion of the total biomass on Earth, accounting for ≈450 gigatonnes of carbon (Bar-On et al., 2018). Estimates indicate that there are between 250.000 and 500.000 species of angiosperms in the world. Interestingly, less than 10% of these plants are consumed as a food source by humans and other animals, and many of them also have medicinal uses (Cowan, 1999, Abdallah et al., 2023). Phytochemicals are a broad range of bioactive molecules of natural origin (Harvey et al., 2015). Some of these compounds are secondary metabolites of small organic compounds that, although not essential for the initial growth of the plant, play a vital role in its survival and reproduction (Muthamilarasan and Prasad, 2013). Because plants are stationary organisms and cannot escape threats, they have evolved a complex defense system based on these metabolites. This powerful chemical arsenal has enabled them to resist a variety of pathogens (such as viruses, bacteria, and fungi), predators, and adverse environmental conditions and to survive in diverse ecosystems (Mawalagedera et al., 2019, Álvarez-Martínez et al., 2020b). These valuable metabolites are scattered throughout the plant structure, from the roots and stems to the leaves, flowers, fruits, and seeds (Li et al., 2024). Secondary metabolites are extremely diverse in terms of their chemical structure, composition, solubility and biosynthetic pathways, and this characteristic has led to the creation of an amazing range of these compounds with specific defensive functions (Tiwari and Rana, 2015, Anjali et al., 2023).

It is estimated that approximately 200.000 plant secondary metabolites (PSM) have been identified and isolated. Any plant species is capable of producing a complex chem-

ical arsenal of 500–800 different secondary metabolites, many of which have antimicrobial properties. These compounds are mainly classified into four main groups: terpenes, phenols, and nitrogen- and sulfur-containing compounds (Figure 2) (Satish et al., 2020, Yadav et al., 2020, Yeshi et al., 2022, Lorca et al., 2024).

Studies have focused primarily on complex plant extracts (which have been studied the most), pure compounds, and essential oils (which rank fifth among the studied agents). Among the pure isolated compounds, terpenes are the most studied antimicrobial compounds, while polyphenols and alkaloids, and other categories, have also accounted for a significant portion of this research (Álvarez-Martínez et al., 2020a, Li et al., 2024). The recent increase in the number of scientific papers on the potentiation of antibiotic effects by plant agents confirms the importance of this area of research in the modern battle against antimicrobial resistance. According to reports, the global herbal medicine market was estimated to be worth $170 billion in 2022 and is expected to grow significantly to $600 billion by 2033 (Sarkar et al., 2024, Zouine et al., 2024). However, most plant species remain unknown, and plants serve as a promising and unexplored frontier for the discovery of new therapeutic agents against drug-resistant bacteria.

Herbal compounds effective against carbapenem-resistant bacteria (CRB)

Terpenes and terpenoids

Terpenes are the key constituents of essential oils. These compounds, which are among the most diverse plant secondary metabolites, are formed by connecting isoprene (C5) units. These compounds include the main classes of monoterpenes, sesquiterpenes, diterpenes, and triterpenes. From a chemical perspective, terpenes have a remarkable structural diversity, with prominent examples including linalool, geraniol, menthol, citral, thymol, carvacrol, carotenoid, cam-

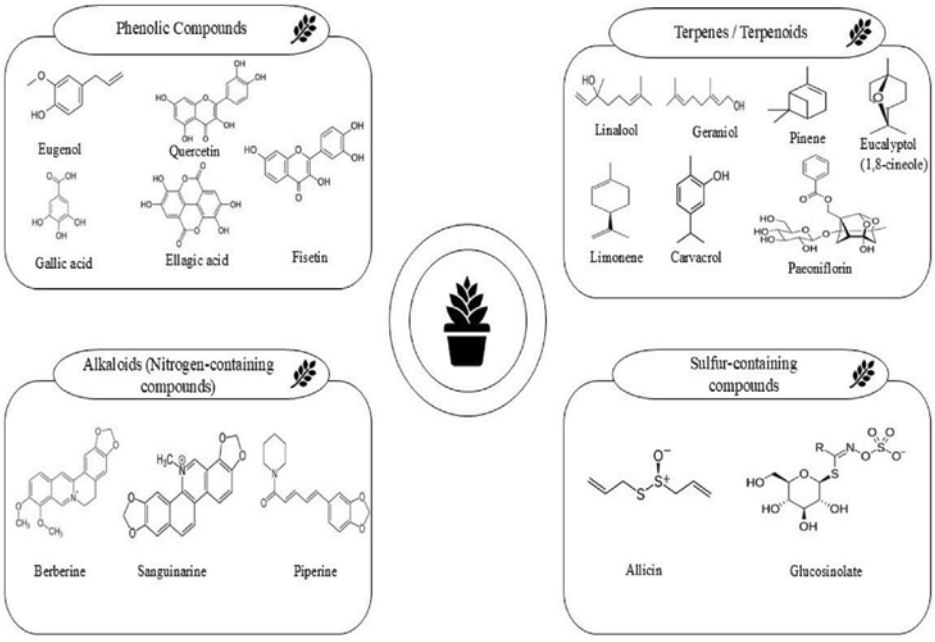

Fig. 2. Structure of plant secondary metabolites (Wang et al., 2019, Al-Khayri et al., 2023, Upadhyay et al., 2024, Sana et al., 2025).

phor, eucalyptol, cymene, pinene, and limonene (Guimarães et al., 2019).

Studies have shown that both the chemical structure and the kinetics of the antibacterial effect of these compounds differ from each other. On the one hand, the presence of polar functional groups such as hydroxyl in phenolic (such as thymol and carvacrol) and alcoholic (such as geraniol and terpineol) compounds is associated with stronger antimicrobial activity (Guimarães et al., 2019). On the other hand, compounds such as terpineol, geraniol, carotenol and citronellol are known as fast-acting agents that are able to inactivate bacteria such as *Escherichia coli* and *Salmonella* Typhimurium in a short time (Friedman et al., 2004, Guimarães et al., 2019).

Accordingly, screening terpenes and terpenoids based on the structure-activity relationship as well as the kinetics of their antibacterial effect can provide a valuable criterion for identifying promising candidates against carbapenem-resistant bacteria. *In vitro* evidence has shown that 1,8-cineole (CN) as a monoterpene exhibits significant bactericidal activity against carbapenemase-producing *Klebsiella pneumoniae* (KPC-KP) (Moo et al., 2021).

Similarly, paeoniflorin ($C_{23}H_{28}O_{11}$), a monoterpene bicyclic glycoside derived primarily from the roots of the peony plant (*Paeonia lactiflora*), has shown promising activity against carbapenem-resistant *K. pneumoniae* (CRKP) with a reported MIC of 1.2 mg/mL (Qian et al., 2020). Although paeoniflorin is traditionally known for its anti-inflammatory and neuroprotective properties in traditional medicine, recent research has revealed significant antimicrobial potential, indicating its effective antibacterial activity (Hou et al., 2025).

Phenolic compounds

Phenolic compounds (PCs) are key secondary metabolites in horticultural plants that contain one or more hydroxyl groups attached to aromatic rings. Structurally, they are classified into major groups such as simple phenols, flavonoids, stilbenes, and tannins. These compounds are not only responsible for the attractive colors and unique flavors of fruits and flowers but also play vital ecological roles (Rafeeq et al., 2025, Xu and Wang, 2025).

Notably, their biological significance also extends to good antimicrobial activity, showing promising potential against carbapenem-resistant bacteria. For example, tannic acid, epigallocatechin gallate, quercetin, and epicatechin have shown significant inhibitory effects on β-lactamases in both *in vitro* and *in silico* analyses (Mandal et al., 2017).

A prominent example is eugenol, a major phenolic compound found in the extracts of cloves (*Syzygium aromaticum*) and cinnamon, which exhibits broad-spectrum efficacy, including against carbapenem-resistant bacteria (Liu et al., 2023a).

According to Liu et al. (2023), eugenol exerted significant and dose-dependent inhibitory effects on planktonic CRKP bacteria. At a concentration of 0.5 mg/mL, the compound killed more than 85% of the bacterial population, and when the concentration was increased to 1.0 mg/mL, almost complete (100%) eradication of bacteria was observed (Liu et al., 2023a).

Quercetin is a common flavonoid of the fla-

vonol type in nature, which is of plant origin and is widely found in fruits (such as berries, apples and grapes), vegetables (especially the cabbage family), seeds, nuts and various flowers (Yang et al., 2020a). This compound has been studied as an effective agent in inhibiting carbapenem-resistant Gram-negative bacteria (Blair et al., 2014, Pal and Tripathi, 2020). Quercetin has also shown significant synergistic interactions with antibiotics such as colistin and amikacin against the resistant bacterium *A. baumannii in vitro* (Pal and Tripathi, 2020, Odabaş Köse et al., 2023).

Fisetin, which belongs to the flavonoid group, is a naturally occurring chemical compound in several fruits and vegetables, including strawberries, apples, and grapes. Its amount in plant foods varies from 2 to 160 μg/g. This compound is known as a health-promoting agent because of its antioxidant, anti-inflammatory, and anticancer properties and is even found in some dietary supplements (Kubina et al., 2021, Cordaro et al., 2022, Dong et al., 2025).

Interestingly, in one study, fisetin, with the lowest MIC (0.0625 mg/mL) among the compounds tested, showed significant antibacterial activity against CRKP (ATCC BAA-1705) (Adeosun et al., 2022).

A study on the bark extract of *Matayba opositifolia* showed specific efficacy against CRKP (MIC = 31.25–500 μg/mL) and *A. baumannii* (MIC = 125–250 μg/mL). GC-MS analysis identified several bioactive compounds in the extract, with palmitic acid, friedelan-3-one and 7-dehydrodiosgenin as the main components (de Jesús Dzul-Beh et al., 2023).

A study by Uc-Cachón et al. showed that *Schoepfia schreberi* extracts containing gallic acid (GA) and ellagic acid (EA) derivatives showed significant growth inhibition against carbapenem-resistant *A. baumannii* (CRAB). Furthermore, *S. schreberi* exhibits broad anti-infective properties against different *A. baumannii* strains by simultaneously targeting multiple pathogenic mechanisms, including biofilm formation, efflux pump activity, motility, and resistance to catalase-mediated oxidative stress(Uc-Cachón et al., 2024).

The pentagalloyl glucose (PGG) compound obtained from the *Schinus terebinthifolia* extract showed broad-spectrum antimicrobial activity against CRAB (MIC 64-256 μg/mL) and *P. aeruginosa* (MIC 16 μg/mL). Mechanistic studies showed that PGG acts through iron chelation and, remarkably, no resistant mutants emerged after 21 days of passage (Dettweiler et al., 2020).

Nowadays, molecular docking studies provide valuable insights into the mechanism of action of phenolic compounds. For example, a study on mangiferin revealed that this compound interacts with the NDM-1 enzyme through the formation of hydrogen bonds and hydrophobic interactions. Interestingly, the Glide docking score of mangiferin (-9.12 kcal/mol) was even negative than that of the antibiotic meropenem (-8.77 kcal/mol), indicating a more stable binding and higher potential for this plant compound to inhibit the NDM-1 enzyme. This finding makes mangiferin a promising candidate for inhibiting carbapenemases (Vasudevan et al., 2022).

Alkaloids compounds

Alkaloids are a large class of natural secondary metabolites characterized by a basic nitrogen atom in their structure. More than 18.000 distinct alkaloids have been identified from diverse sources(Gutiérrez-Grijalva et al., 2020, Heinrich et al., 2021, Thawabteh et al., 2021).

These compounds have attracted much attention due to their broad spectrum of pharmacological activities, including antibacterial, anticancer, antiviral, and central nervous system depressant effects. In particular, the antimicrobial potential of alkaloids has been promising in combating infections caused by multidrug-resistant (MDR) pathogens. Well-known alkaloids such as berberine, sanguinarine, and piperine have shown potent antibacterial activity against several microorganisms (Horani et al., 2015, Thawabteh et al., 2021, Plazas et al., 2022).

Mechanisms of action of plant compounds against CRB

Induction of oxidative stress and cell membrane damage

The induction of oxidative stress is one of the key mechanisms of plant compounds in combating resistant bacteria. A review by Itri et al. (2014) documented the role of this mechanism in the killing of bacteria. According to this study, oxidative stress leads to bacterial cell death by destroying the integrity of the plasma membrane and causing the leakage of intracellular contents (Itri et al., 2014).

Considerable evidence supports the role of this mechanism in the activity of various plant extracts and compounds. Proteomic analyses have shown that cinnamon bark essential oil (*Cinnamomum verum*) disrupts the membrane of KPC-KP by inducing oxidative stress, which is characterized by an increase in oxidative stress-regulating proteins such as glycyl radical cofactor, catalase peroxidase, and DNA mismatch repair protein. This oxidative attack damages the cell membrane, facilitates the penetration of reactive oxygen species (ROS), and disrupts the DNA and membrane repair systems (Yang et al., 2019).

Similarly, lavender essential oil (LVO) exerts its antibacterial effect against KPC-KP by increasing ROS levels, lipid peroxidation, and increasing membrane permeability, which not only causes content leakage but also enhances the uptake of other antimicrobial agents (Yang et al., 2020b).

In addition, certain phytochemicals have been identified as oxidative stress-inducing agents. Notable examples include eugenol, which significantly increases ROS and decreases glutathione (GSH) in CRKP, leading to membrane disruption and leakage of cytoplasmic components such as DNA, proteins, and β-galactosidase (Liu et al., 2023a).

Other compounds such as acetic acid, geranyl acetate, linalool, and various pyrrolidine derivatives are also capable of inducing oxidative stress, highlighting the broad applicability of this mechanism among diverse plant metabolites (Tafazoli and O'Brien P, 2004, Quintans-Júnior et al., 2013, Riera et al., 2015).

Carbapenemase inhibition

The search for antimicrobial compounds that are safe against carbapenemase-producing bacteria, especially NDM-1 strains, remains an ongoing priority. While some compounds from fungi have been investi-

gated for this purpose, the main source of drugs in the plant kingdom remains largely unexplored (King et al., 2014).

A comprehensive study by Chandar et al. (2017) screened ethanolic leaf extracts of 240 diverse medicinal plant species for antibacterial activity against NDM-1-producing *E. coli*. Extracts of six plants, including *Combretum albidum* and *Hibiscus acetosella Welw. ex Hiern*, showed significant antibacterial activity (MICs ranging from 2.56 to 5.12 mg/mL) and effectively inhibited NDM-1 enzyme activity in vitro. IC50 values ranged from 0.50 to 1.2 ng/μL. Phytochemical analysis of these extracts revealed a diverse profile of secondary metabolites with steroids and saponins being the least abundant. Interestingly, flavonoids and phenolic compounds were identified as the dominant metabolites in several extracts. A notable finding was that *Tamarindus indica* L. extract, despite showing a low MIC of 2.56 mg/ml, contained the lowest overall concentration of secondary metabolites. The inhibitory mechanism against NDM-1 is proposed to involve the direct inactivation of the enzyme or chelation of zinc ions essential for catalytic activity (Chandar et al., 2017).

In the direction of discovering natural adjuvants, quercetin acts as a potent dual inhibitor against carbapenem-resistant Gram-negative bacteria. Evidence suggests that quercetin (at a concentration of 64 μg/mL) significantly inhibits carbapenemase enzyme activity in the resistant strains of *E. coli*, *K. pneumoniae*, *P. aeruginosa*, and *A. baumannii*. The stability of quercetin-carbapenemase complexes was confirmed in molecular docking studies, and it was shown that this compound binds directly to the active site of carbapenem enzymes by a competitive mechanism and prevents the hydrolysis of the carbapenem antibiotic (meropenem) in the periplasmic space (Pal and Tripathi, 2020).

A recent study on coumarin showed that this compound significantly inhibited the activity of carbapenemase enzymes in CRKP. In addition, coumarin reduced the expression of the carbapenemase-encoding genes. Molecular docking revealed significant binding free energies ranging from -7.8757 to -6.2064 kcal/mol for coumarin binding to NDM1, VIM-2, OXA-48 and OXA-9 enzymes. These effects resulted in the restoration of the susceptibility of meropenem-resistant bacteria, with the coumarin-meropenem combination exhibiting a strong synergistic effect (fractional inhibitory concentration index (FICI) ≤ 0.5). These findings suggest that coumarin is a promising candidate for overcoming carbapenem resistance (Abdel-Halim et al., 2024).

In the study by Shi et al. (2019) baicalin was identified as a novel NDM-1 inhibitor, which showed effective inhibition of the enzyme with an IC50 of about 3.8 μM. Docking and molecular dynamics studies showed that the carboxyl group of baicalin directly interacts with the zinc ion (Zn^{2+}) in the active site of the enzyme, and hydrogen bonds with key amino acid residues stabilize the complex (Shi et al., 2019).

In the context of the discovery of natural carbapenem inhibitors, embelin has also been identified as a potent and selective inhibitor of the NDM-1 enzyme. A screening study

showed that embelin has a significant ability to inhibit the activity of the NDM-1 enzyme compared to other natural compounds, inhibiting it by more than 50%. Analyses confirmed its outstanding inhibitory potency with an IC50 value of 2.1 ± 0.2 μM and a Ki value of 0.19 ± 0.02 μM (using meropenem as a substrate). Interestingly, embelin had a weak effect on other carbapenemases such as VIM-1 and IMP-1, which makes its selectivity for NDM-1 outstanding. Molecular modeling studies indicate that this stability and selectivity are most likely due to an extensive van der Waals contact between NDM-1 and the embelin (Ning et al., 2018).

Efflux pump inhibition

Given that the active efflux of antibacterial agents plays an important role in the development of drug resistance in carbapenem-resistant bacteria, inhibition of the efflux pump has emerged as a promising strategy to restore antibacterial efficacy (Liu et al., 2023b). Plant-derived compounds can combat carbapenem-resistant bacteria through this mechanism. Studies have shown that some plant compounds such as α-terpinene, α-pinene, catechol and eugenol acetate fight antibiotic resistance by inhibiting the efflux pump (Prasch and Bucar, 2015, Limaverde et al., 2017).

Similarly, quercetin inhibited the activity of the AcrB efflux pump in enterobacterial strains overexpressing this pump (Pal and Tripathi, 2020).

Consistent with these findings, molecular docking studies have identified α-bisabolol as an inhibitor of the MexB efflux pump in *P. aeruginosa*. α-bisabolol showed a higher affinity for MexB than meropenem. The results of the determination of the MIC showed that the simultaneous application of α-bisabolol and meropenem significantly reduced the MIC by 6.24 μg/mL compared with the application of meropenem alone (12.5 μg/mL) in the resistant strains. These observations indicate the high potential of α-bisabolol in restoring the efficacy of antibiotics through efflux inhibition and providing an adjunct strategy for treating multidrug-resistant infections (Nanjan and Bose, 2025).

Furthermore, several studies have confirmed that ellagic acid (EA) functions as an efflux pump inhibitor, enhancing the in vitro efficacy of various antibiotics against resistant pathogens including *A. baumannii* and *E. coli* (Chusri et al., 2009, Jenic et al., 2021, Uc-Cachón et al., 2024).

Alkaloids can increase the effectiveness of common antibiotics through mechanisms such as the inhibition of efflux pumps and can thus be used as valuable supplements in antimicrobial treatment regimens (Sireesha et al., 2019, Faisal et al., 2023). A notable example of this mechanism is the synergistic effect between imipenem (IMP) and the herbal compound berberine against imipenem-resistant *P. aeruginosa*. Although berberine alone had relatively weak anti-pseudomonal activity (MIC = 512 μg/mL), it showed a strong synergistic effect when combined with IMP. Evidence suggests that the restoration of IMP susceptibility by berberine is likely due to the inhibition of the MexXY-OprM efflux pump. The results confirmed that the combination of berberine with IMP resulted in a significant reduction in the expression levels of the genes encoding MexZ, MexX, MexY, and OprM. Impor-

tantly, no significant change was observed in OprD mRNA expression in clinical isolates after treatment with berberine and/or imipenem (Su and Wang, 2018).

Another example involves piperine (PIP), which shows antibacterial activity against CRPA and targets the MexAB-OprM efflux pump. Molecular docking studies revealed a strong affinity of piperine for efflux pump proteins with a binding affinity of -9.1 kcal/mol. A synergistic effect between PIP and imipenem (IPM) against CRPA was observed. Importantly, PIP effectively inhibited IPM efflux by upregulating *mexR* gene expression and downregulating *mexA*, *mexB*, and *oprM*. In conclusion, PIP enhances the antibacterial activity of IPM by inhibiting the MexAB-OprM efflux pump (Liu et al., 2023b).

However, not all bioactive plant compounds act through this mechanism. Lavender essential oil, despite its strong antimicrobial effect, lacks efflux pump inhibitory activity, and analysis of its composition has not confirmed the presence of any known efflux pump inhibitors (Yang et al., 2020b).

Inhibition of biofilm formation

Plant-derived compounds have shown significant efficacy in disrupting biofilm formation and inactivating cells in the biofilms of carbapenem-resistant bacteria.

The importance of these findings is highlighted by the critical role of biofilms in the pathogenesis of CRKP, where biofilms act as a key factor that protects bacteria from antimicrobial agents and promotes microbial persistence and proliferation (Ernst et al., 2020).

Given that achieving effective antibiotic concentrations to eradicate biofilms in vivo is often impossible due to drug toxicity, the search for alternative therapeutic strategies is increasingly urgent. In this regard, the antibiofilm activity of plant compounds is considered a promising therapeutic alternative (Ciofu et al., 2015, Di Domenico et al., 2020).

For example, Adeosan et al. (2022) showed that phytol significantly altered the biofilm structure in CRKP strains and exhibited significant antibiofilm potential. Their findings showed that phytol and glycitein inhibited the pre-formed biofilm by 43.81% and 39.61%, respectively, against *K. pneumoniae* ATCC BAA-1705 (Adeosun et al., 2022). In a similar vein, another study reported that phytol at concentrations ranging from 5 to 640 μg/mL exhibited significant antibiofilm activity with a maximum of 60% biofilm inhibition against another biofilm-forming pathogen, *A. baumannii* (Ramanathan et al., 2018).

Taken together, these findings position phytol as a promising lead compound for managing carbapenem-resistant bacterial infections. Consequently, targeting biofilm formation with such natural compounds is a critical strategy for developing optimal therapeutic interventions in the future (Adeosun et al., 2022).

Similarly, paeoniflorin showed significant inhibitory effects on CRKP biofilm formation and effectively inactivated CRKP cells in the established biofilms (Qian et al., 2020).

Synergistic Strategies: Plant Compounds and Carbapenems

A promising strategy to restore the efficacy

of carbapenem antibiotics is to use them in combination with herbal adjuvants. There is a growing body of scientific evidence that combining herbal extracts with conventional antibiotics not only reduces the effective dose of antibiotics required but also significantly reduces the associated side effects. Such synergistic interactions are now considered a promising strategy to address the growing challenge of antimicrobial resistance (Stefanovic, 2018).

In support of this approach, Chandar et al. (2017) showed that the plant extracts studied by them, when combined with meropenem, reduced the MIC of this antibiotic by 4- to 16-fold against NDM-1-producing *E. coli*, producing a strong synergistic effect (ΣFIC = 0.313-0.09). The restoration of bacterial sensitivity to this antibiotic was attributed to the dual ability of the extracts to inhibit the NDM-1 enzyme and disrupt the bacterial cell membrane. This dramatic reduction in MIC highlights the great potential for reducing antibiotic doses in combination treatment regimens. However, it is worth noting that the antimicrobial activity in the crude extracts is usually the result of the combined effect of several substances, and the potency of individual components after isolation may be less than the overall effect of the extract (Chandar et al., 2017).

In this regard, another study also showed that the combination of LVO with meropenem has a strong synergistic effect, reducing the effective concentration of LVO and meropenem by 15-fold and 4-fold, respectively. This synergistic effect was confirmed by a FICI of 0.3125. Notably, the rapid killing kinetics of this combination resulted in the complete killing of KPC-KP bacteria in only 1.5 h. However, the use of each of these agents separately at similar concentrations did not affect the viability of KPC-KP cells. This strategy is a practical strategy to overcome bacterial resistance and reduce the dosage of last-line antibiotics (Yang et al., 2020b).

Research data also show that quercetin, fisetin, luteolin, and 3′,4′,7-trihydroxyflavone, by exerting a synergistic effect, restore the antibacterial activity of piperacillin and imipenem against OXA-48-producing *E. coli* and cause a 2- to 8-fold reduction in their MIC. Compared with previously reported inhibitors, quercetin and its analogs have significant advantages: they are inexpensive, readily available, and can be extracted and purified in large quantities from plant sources. Furthermore, they do not exhibit any cytotoxicity, increasing their potential as safe therapeutic adjuvants (Hytti et al., 2015, Hatahet et al., 2018, Zhang et al., 2022).

Similarly, the combination of embelin, a plant benzoquinone found in the fruits of *Embelia ribes* Burm (*E. ribes*) (Ali et al., 2024), with carbapenems also showed a potent synergistic effect against NDM-1-producing pathogens. Studies have shown that embelin effectively inhibits the activity of the NDM-1 enzyme, thereby restoring bacterial susceptibility to β-Lactam antibiotics. When embelin (at a concentration of 32 μg/mL) was combined with meropenem, a 512-fold reduction in the MIC of this antibiotic was observed against an NDM-1-producing strain (ATCC BAA-2146). This synergistic effect was confirmed with FIC values between 0.05 and 0.15 on various clinical iso-

lates (including *E. coli*, *K. pneumoniae* and *A. baumannii*), indicating a strong synergy. It is noteworthy that embelin alone lacked significant antibacterial activity, emphasizing its role as an "adjuvant" focused on inhibiting resistance, rather than as a standalone antimicrobial agent. Therefore, embelin can be considered a promising lead compound for the development of safer and more efficient adjuvants alongside carbapenems to combat these superbugs (Ning et al., 2018).

Conclusion

The growing crisis of antimicrobial resistance in the present era, especially with the emergence of carbapenem-resistant bacteria, has assumed alarming dimensions. This situation makes the urgent attention to finding inhibitors of resistance not only a priority but also an inevitable action. However, the pharmaceutical industry has gradually reduced its investment in this field due to economic challenges such as low financial returns, short antibiotic use periods and high R&D costs. This gap has made the focus on cost-effective strategies such as the use of natural plant compounds as pristine reservoirs of bioactive compounds more prominent than ever. With several advantages such as broad chemical diversity, multi-targeting of resistance mechanisms (including inhibition of carbapenemase enzymes), and favorable safety profile, these compounds have become promising candidates for the development of antimicrobial agents or adjuvants. Furthermore, their potential for synergy with antibiotics, including carbapenems, could lead to the restoration of the efficacy of these drugs, which in turn reduces the need for alternative antibiotics with more side effects, such as colistin.

Although there is a wealth of *in vitro* data on the efficacy of plant metabolites, translating these findings into commercial products faces obstacles, including the lack of large-scale clinical studies, bioavailability challenges, and the absence of clear regulatory frameworks. However, continued investigation of these compounds paves a promising path toward the discovery of new therapeutic agents against carbapenem-resistant bacteria

Finally, the present study only examined a small subset of the thousands of plant metabolites identified and their potential to combat carbapenem resistance. The potential effects of these compounds on other mechanisms involved in carbapenem resistance, such as porin proteins (*e.g*., OprD in *P. aeruginosa*) or additional efflux pumps, were not investigated. Future studies should therefore more broadly address these limitations, as well as research into clinical validation and formulation of plant metabolites to bridge the gap between laboratory discovery and therapeutic application.

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