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Review articles

Environmental bacterial species with antimicrobial potential against ESKAPEE pathogens: a scoping review

Andreia Bueno da Silva[a], Eduardo Santos Biasi[b], Bruno Paulo Rodrigues Lustosa[c], Mariana Vieira Porsani[a], Guilherme Fonseca Reis[c], Géssica Slompo de Deus[c], Juliana Thaler[c], Lorena Carolina Peña[a], Arandi Ginane Bezerra Jr[d], Luciano Aparecido Panagio[e], Marconi Rodrigues de Farias[f], Ida Chapaval Pimentel[a,b], Keite da Silva Nogueira[a], Vânia Aparecida Vicente[a,b,c,*]

[a]*Microbiology, Parasitology and Pathology Graduate Program, Basic Pathology Department, Federal University of Paraná - UFPR, Rua Cel. Francisco H. dos Santos, 210, Jardim das Américas, CEP 81530-000, Curitiba, PR, Brazil*
[b]*Laboratory of Microbiology and Molecular Biology, Department of Basic Pathology, Federal University of Paraná - UFPR, Rua Cel. Francisco H. dos Santos, 210, Jardim das Américas, CEP 81530-000, Curitiba, PR, Brazil*
[c]*Engineering Bioprocess and Biotechnology Graduate Program, Department of Bioprocess Engineering and Biotechnology, Federal University of Paraná - UFPR, Rua Cel. Francisco H. dos Santos, 210, Jardim das Américas, CEP 81530-000, Curitiba, PR, Brazil*
[d]*Graduate Program in Physics and Astronomy - PPGFA, Federal Technological University of Paraná - UTFPR, Av. Sete de Setembro, 3165, Rebouças, CEP 80230-901, Curitiba, PR, Brazil*
[e]*Department of Microbiology, State University of Londrina - UEL, Campus Universitário, Rodovia Celso Garcia Cid, PR-445, Km 380, CEP 86057-970, Londrina, PR, Brazil*
[f]*Department of Veterinary Medicine, School of Life and Sciences, Pontifical Catholic University of Paraná - PUCPR, R. Imac. Conceição, 1155, Prado Velho, CEP 80215-901, Curitiba, PR, Brazil*

Highlights

- Bacterial extracts from environmental strains represents an alternative for the development of drugs against ESKAPEE group multidrug-resistant bacteria
- The marine environment represents an expressive source of antimicrobial potential bacteria
- *Streptomyces* species demonstrated potential production of antimicrobial against ESKAPEE group multidrug-resistant bacteria
- The combination of two or more analytical techniques can provide a more comprehensive understanding of the biocompounds characterized in bacterial extracts

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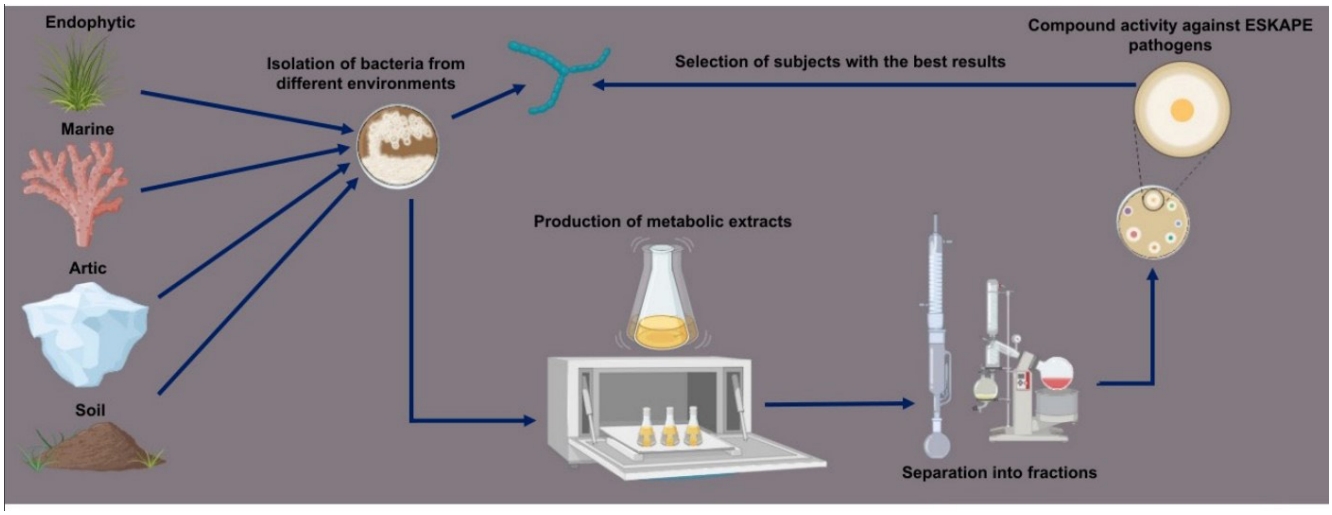
KEYWORDS
Multidrug resistance;
Bioactive compounds;
Streptomyces;
Marine sediment.

Abstract: Antimicrobial resistance poses a serious threat to global health, complicating the treatment of infectious diseases and increasing mortality rates and healthcare expenditures. Although antibiotic use in some areas has decreased, multidrug-resistant bacteria, especially those among significant pathogens such as ESKAPEE, are a major global challenge. The aim of this review was to gather data on bacterial genera from various environmental sources that synthesize compounds with antimicrobial activity against pathogens belonging to the ESKAPEE group. The

*Corresponding author.
E-mail: vaniava63@gmail.com, vicente@ufpr.br (V. A. Vicente).

MEDLINE/PubMed, Scopus, and Science Direct databases were searched for articles published from 2001 to 2023. The included publications were carefully selected based on their relevance to the topic and methodologies used. In total, 50 articles were reviewed and 20 bacterial genera with significant antimicrobial activity were identified, with *Streptomyces* spp. being the most prevalent. The bacteria were isolated from different environments, including marine sediments, endophytes, and extreme environments. The evaluation of bacterial extracts against ESKAPEE pathogens revealed considerable inhibition capacities, particularly for *Streptomyces* spp., *Bacillus* spp. and *Pseudomonas* spp. However, no single extract was effective in inhibiting all target pathogens. Furthermore, 33(33/64) bacterial extracts from the 50 studies included in the review characterized, at least partially, the secondary metabolites responsible for the observed antibacterial potential. Twenty patents filed for compounds characterized with antibacterial activity against ESKAPEE bacteria were found. And in the search for marketed products, a total of 22 compounds were found. The discussion highlights the marine environment as a rich source of antimicrobial-producing bacteria due to its unique ecological conditions. *Streptomyces* spp. remains promising candidates for antibiotic discovery, due to a diverse range of antimicrobial compounds. In conclusion, this review highlights the strong ability of bacteria from a wide range of environments to combat antimicrobial resistance. By elucidating antimicrobial activity and compound characterization, this review provides valuable insights into antibiotic research, crucial to managing the growing threat of multidrug-resistant pathogens.

Graphical Abstract



Introduction

Antimicrobial resistance (AMR) greatly threatens global health (Jee et al., 2018; Murray et al., 2022) which has made it difficult to treat infectious diseases and, consequently, increased mortality rates (Murugaiyan et al., 2022). The increase in AMR, particularly among clinically important ESKAPEE pathogens (*Enterococcus* species, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, *Enterobacter* spp., and *Escherichia coli*), has greatly burdened the healthcare system and the veterinary and agricultural industries (Ruekit et al., 2022). By 2050, 10 million deaths are estimated to occur per year due to AMR caused by ESKAPEE pathogens, resulting in a cumulative cost of $100 trillion to the global economy if no preventive action is taken (O'Neill, 2016; Poudel et al., 2023). According to the World Health Organization (WHO), 30 new antibiotics were approved for treating bacterial infection; however, only two were new compounds (Efimenko et al., 2018). Thus, new antibiotics with new compounds need to be developed to reduce the effect of AMR, as multidrug-resistant (MDR) strains can be resistant to most antibiotic classes (World Health Organization, 2021, 2024).

Microorganisms inhabiting a variety of environments, especially extreme and unexplored environments, are a promising source of novel antimicrobial compounds (Quinn & Dyson, 2024). Among the microorganisms that produce bioactive compounds, bacteria are prominent for their ability to produce various secondary metabolites with antimicrobial activity (Srinivasan et al., 2021; Barzkar et al., 2024). In this scenario, this review addresses relevant publications on bioprospecting of bacterial strains isolated from diverse environmental sources as a promising strategy to identify compounds with bioactivities against the ESKAPEE group. Additionally, the characterized chemical compounds, the applied analytical methods and an analysis of registered patent data were discussed.

Materials and methods

This scoping review was conducted following the guidelines of the Transparent Reporting of Systematic Reviews and Meta-Analyses for Scoping Reviews (PRISMA-ScR) extension (Tricco et al., 2018) to address the following question, according to the context, concept, and population (CCP) criteria/guidelines: "*What is the antimicrobial potential of bacteria of environmental origin against multidrug-resistant bacteria*?" Three online databases were searched for suitable articles published from 2001 to 2023 that met the aim of this review: MEDLINE (via PubMed), Scopus (Elsevier: Amsterdam, Netherlands), and Science Direct (Elsevier: Anglo-Dutch).

Peer-reviewed studies describing the production of bacterial extracts with antibiotic activity against MDR ESKAPEE pathogens were included in the review. Articles were searched using the following keywords: "antibacterial activity"; "secondary metabolites*"; "bioactive compounds" and "multidrug-resistant bacteria". The keywords were combined with the Boolean operators "AND" or "OR" with the proximity operators ["" and ()] and the truncation operator (*) when required. The search strategy was modified according to the databases (Figure 1). The electronic database search was supplemented by a manual search using references from all included articles. As search criteria included information on the country of isolation, the environmental source of strain, the taxonomic status from at least the genus level, the deposit code for the culture collection, the ESKAPEE pathogens inhibition capacity, the compound characterization (if available), and the extract fraction used for inhibition. The studies that did not include the information described above and those that did not evaluate antimicrobial activity against AMR pathogens were excluded. The type of article included was also restricted; reviews, short communications, conference abstracts, preprints, and book chapters were excluded.

Patent databases were searched to identify emerging biotechnological trends in the field of chemical compounds with antibacterial activity. The patent numbers were collated using the advanced search option (title or abstract) from the following databases: the Espacenet patent search (worldwide.espacenet.com), the INPI (National Institute of Intellectual Property) Intellectual Patent (https://www.gov.br/inpi/en-br), and the PubChem (National Center for Biotechnology Information, 2024a) databases. The analysis of patents was limited to those published between 2010 and 2023. In the search bar of the respective websites, the terms "antibacterial" or "antibiotic" were entered along with the name of the compound described in the article.

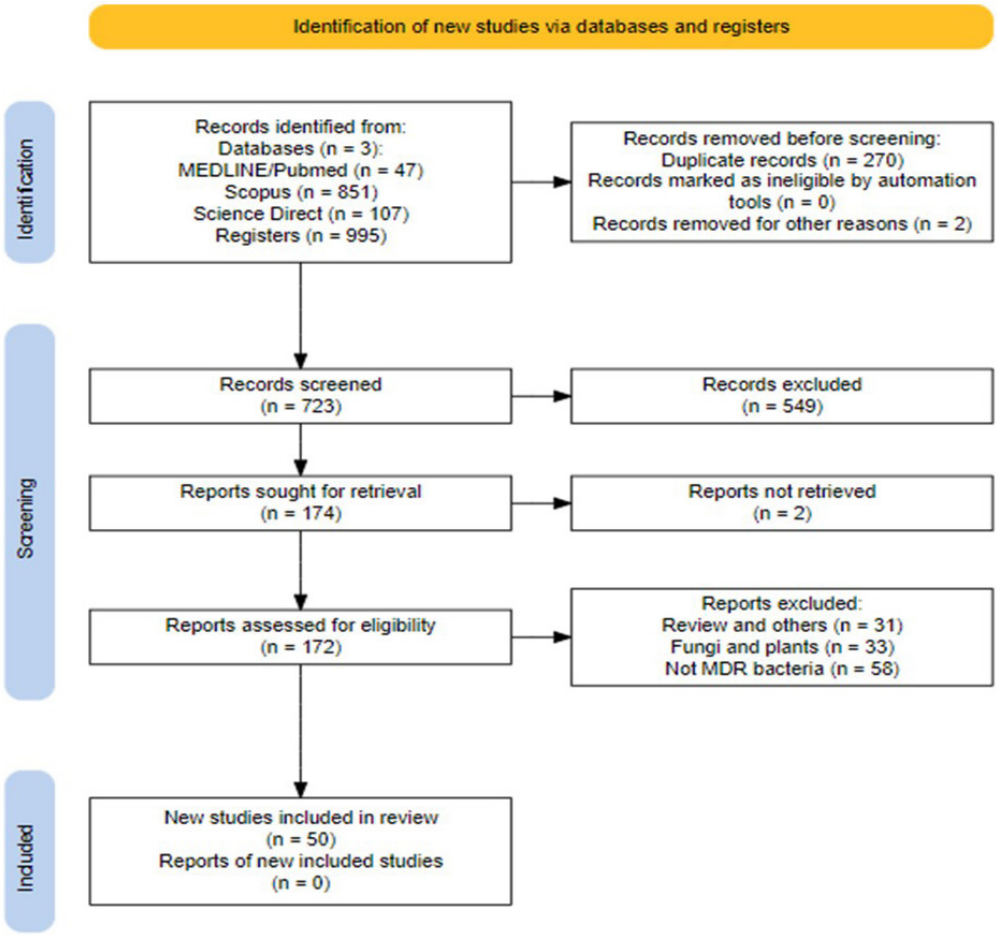


Figure 1. Prisma Flowchart for search strategies. Flowchart structured using R Program (Haddaway et al., 2022).

Results

The initial search resulted in 995 studies, of which 47 were in MEDLINE/PubMed, 841 in Scopus, and 107 in Science Direct. After removing 270 duplicate studies, 549 studies were rejected after screening the articles by their titles and abstracts. The remaining 174 studies were retrieved and analyzed. Overall, 50 articles published from 2001 to 2023 met the inclusion criteria. The flowchart of the search strategy is shown in Figure 1.

Taxonomic and isolation sources of environmental bacteria with antimicrobial potential

From the studies selected, 20 bacterial genera capable of producing bioactive compounds were identified (Figure 2). The most frequent genus with antimicrobial production potential was *Streptomyces* spp. (n = 27), followed by *Bacillus* spp. (n = 8), *Pseudomonas* spp. (n = 5), and *Salinispora* sp. (n = 3) (Figure 2).

The studies reported species isolated from various extreme environments, such as hot springs (n = 1), ice deserts (n = 3), deserts (n = 5), saline lagoons (n = 1), and soil from high-altitude mountains (n = 2), as described in Figure 3. The isolates were also found in marine sediments (n = 4) associated or not associated with animals such as sea sponges (n = 6) and sea slugs (n = 2) and associated with plants as endophytes (n = 6). The most diverse sources were endophytes and deserts (both n = 6). Some species were isolated from a single source; for example, *Thermomonas* sp. was the only species isolated from hot springs, whereas the genus *Streptomyces* was the most diverse and was found in seven different environments; it was also the only genus isolated from saline lagoons (Figure 3).

Streptomyces spp. was the most common genus isolated from endophytic, industrial wastewater, and marine environments that might represent an important source of antimicrobial compounds (Table 1). This genus was isolated

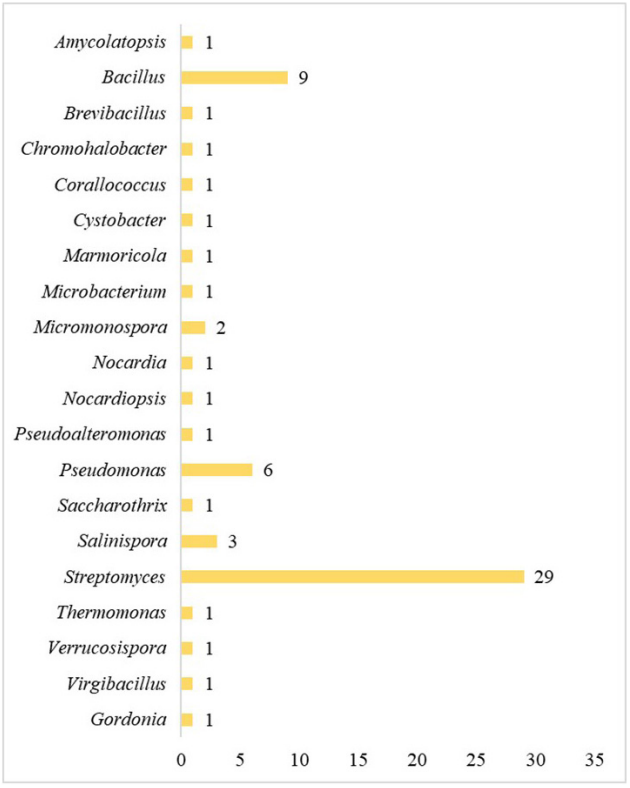


Figure 2. Number of isolates by genera (n=64) based on the fifty publications gathered.
Notes: Some publications have more than one isolate; therefore, it is computed according to the total of isolates tested in the study.

Table 1. Main environmental sources are indicated in the boxes as specified by the genera from the strains isolated.

Number*	Environmental sources	Bacterial genera
1	Industrial Wastewater	*Streptomyces* spp.
		Bacillus spp.
2	Endophytic	*Bacillus* spp.
		Brevibacillus spp.
		Marmoricola spp.
		Pseudomonas spp.
		Streptomyces spp.
		Verrucosispora spp
3	Mountain High altitude	*Amycolatopsis* spp.
		Streptomyces spp.
4	Hot spring	*Thermomonas* spp.
5	Soil	*Serratia* spp.
		Streptomyces spp.
6	Hot desert	*Corallococcus* spp.
		Cystobacter spp.
		Microbacterium spp.
		Nocardia spp.
		Saccharothrix spp.
7	Saline Lagoon	*Streptomyces* spp.
8	Artic desert	*Bacillus* spp.
		Gordonia spp.
		Pseudomonas spp.
9	Marine (symbiote Marine algae)	*Bacillus* spp.
9	Marine	*Micromonospora* spp.
		Nocardiopsis spp.
		Salinispora spp.
		Streptomyces spp.
9	Marine /] (symbiote Sea Slug)	*Pseudoalteromonas* spp.
		Virgibacillus spp.
9	Marine (symbiote Sea Sponge)	*Bacillus* spp.
		Chromohalobacter spp.
		Micromonospora spp.
		Pseudomonas spp.
		Salinispora spp.
		Streptomyces spp.

Notes: *Number is according to the diagram in Figure 3.

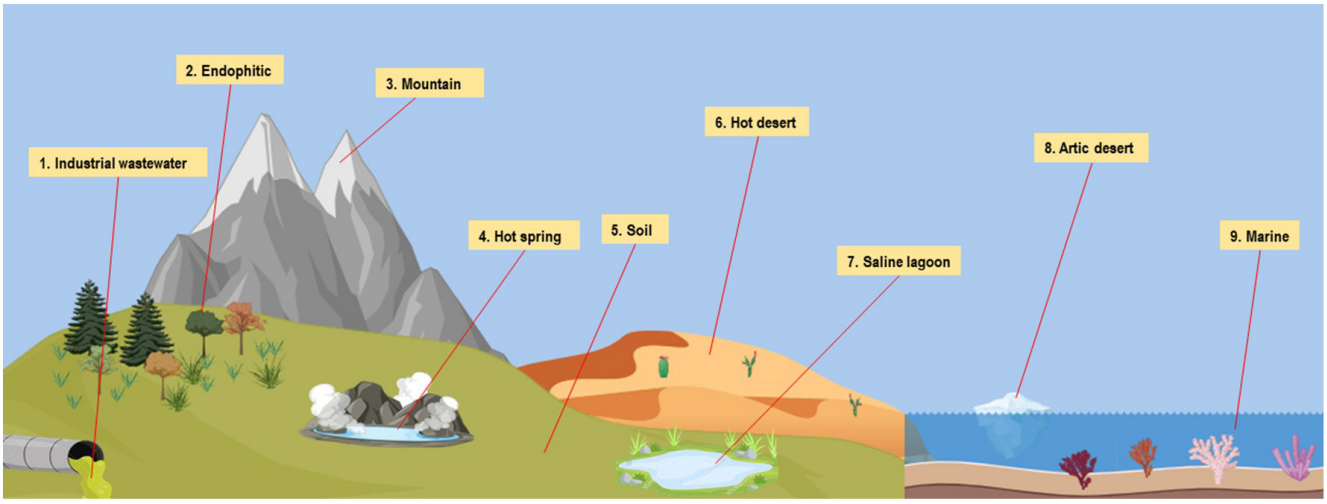


Figure 3. Schematic picture of the main sources of isolation of bacteria with the potential to produce antibiotics compounds to treat ESKAPEE pathogens.

from endophytic plants in Brazil, China, India, Indonesia, and Malaysia, industrial wastewater from India, marine sediments from Argelia, Costa Rica, India, Morocco, Peru, Philippines, and Saudi Arabia, mountains from China, saline lagoons from Peru, sea sponges from India, and soils from Iran, Ireland, Nigeria, and Thailand. Moreover, it was observed other genera able to produce bioactive compounds such as *Bacillus* spp. isolated from plants in Indonesia, marine algae and sea sponges in India, and extreme environments such as ice deserts in Antarctica. Likewise, *Pseudomonas* spp. isolated as endophytes from the medicinal plant Phragmites *australis* in Italy, from sea sponges in Brazil, India, and Malaysia and from ice deserts in the Canadian tundra (Table 1).

Among the most cryptic bacteria, *Salinispora* spp. were isolated from marine sediment in Mexico and from sea sponges in Fiji. *Amycolatopsis* sp. was isolated solely from high mountains in China. *Brevibacillus brevis* was isolated from an endophytic environment in India, *Chromohalobacter salixipes* was isolated from a sea sponge in Indonesia, *Corallococcus* sp. and *Cystobacter* sp. were isolated from deserts in Iran), *Gordonia terrae* was isolated from an ice desert in the Antarctic, *Marmoricola* sp. was isolated from plants in China, *Microbacterium* sp. was isolated from a desert in China, *Micromonospora marina* was isolated from marine sediment in India, *Micromonospora robiginosa* was isolated from a sea sponge in the UK), *Nocardia* sp. was isolated from a desert in Iran, *Nocardiopsis* sp. was isolated from marine sediment in Switzerland, *Pseudoalteromonas rubra* and *Virgibacillus salaries* were isolated from sea slugs in Indonesia *Saccharothrix* sp. was isolated from a desert in China, *Serratia marcescens* was isolated from soil in India, *Thermomonas hydrothermalis* was isolated from a hot spring in Jordan, and *Verrucosispora* sp. was isolated from plants in Brazil (Table 1).

Antibacterial activity of the environmental strains against ESKAPEE pathogens

According to the records found (Figure 1), 64 isolates were tested against ESKAPEE pathogens (details in Table 2). The most common genus tested was *Streptomyces*, which can inhibit methicillin-resistant and MDR *Staphylococcus aureus* (MRSA and MDRSA), vancomycin-resistant and MDR *Enterococcus* (VRE and MDRE), MDR *Pseudomonas* (MDRP), MDR *Acinetobacter baumannii* (MDRA), MDR *Klebsiella* (MDRK), and MDR *Escherichia coli* (MDREc). Additionally, the extract from *Bacillus* can inhibit MRSA, MDRSA, VRE, MDRK, and MDREc, whereas the extract from *Pseudomonas* can inhibit MRSA, MDRSA, MDRK, and MDREc. However, no extract tested could inhibit all the ESKAPEE pathogens simultaneously (Table 2).

Only four genera (*Chromohalobacter*, *Micrococcus*, *Saccharothrix*, and *Streptomyces*) showed activity against MDRA, and three genera (*Bacillus*, *Pseudomonas*, and *Streptomyces*) showed activity against MDREc. Moreover, *Streptomyces* exhibited the strongest inhibitory effects on ESKAPEE group, with three isolates demonstrating the ability to inhibit six distinct pathogens, including MDRA, MDRK, and MDRSA (Table 2).

The studies showed that when crossing environments with antibacterial activity, all strains isolated from deserts (Hamedi et al., 2015; Saadatpour & Mohammadipanah, 2020; Liu et al., 2021) and ice deserts (Efimenko et al., 2018; Marcolefas et al., 2019) exhibited activity against MRSA (Table 2). Additionally, the isolation of actinobacteria from marine environments (marine sediment, sea sponges, sea slugs, and marine algae) revealed that this environment had the greatest capacity to inhibit all ESKAPEE pathogens (Table 3). The strains isolated from marine sediments, including *Streptomyces rochei* PM49 (Shanthi et al., 2015) and *Streptomyces* sp. Al-Dhabi-90 (Al-Dhabi et al., 2019), showed the greatest activity against MDR bacteria; their alcoholic extracts can inhibit the growth of six different MDR bacteria (Table 2).

Antibacterial chemical compounds present in the extracts and the analytical methods employed

The 64 bacterial extracts were tested for antimicrobial activity (Table 2), but only 33 of these extracts were characterized (Table 3). Analyzing the activity of individual

Table 2. Antibacterial activity of environmental isolates against ESKAPEE pathogens, according to county of origin, source, and extract.

Specie | Strain	Source	Antibacterial activity								Reference
		MRSA	MDRSA	VRE	MDRE	MDRP	MDRA	MDRK	MDREc	
Amycolatopsis sp. | YNNP 00208	Mountain (High altitude)	-	+	-	-	-	-	-	-	Qian et al. (2022)
Bacillus amyloliquefaciens | MTCC 12713	Marine algae	+	-	+	-	-	-	-	-	Chakraborty et al. (2022)
Bacillus amyloliquefaciens | MTCC 12716	Marine algae	+	-	+	-	-	-	-	-	Chakraborty et al. (2021b)
Bacillus licheniformis | INA 01155	Ice desert (Artic)	+	-	-	-	-	-	-	-	Efimenko et al. (2018)
Bacillus safensis | INA 01154	Ice desert (Artic)	+	-	-	-	+	-	-	-	Efimenko et al. (2018)
Bacillus subtilis| TAAAP010	Industrial wastewater	-	-	-	+	+	-	-	-	Kumar et al. (2021)
Bacillus sp. | DJ4	Endophytic	-	-	-	-	+	-	+	+	Priyanto et al. (2023)
Bacillus sp. | DJ9	Endophytic	-	-	-	-	+	-	+	+	Priyanto et al. (2023)
Bacillus tequilensis | MSI45	Marine Sponge	+	+	-	-	-	-	-	-	Kiran et al. (2018)
Bacillus velezensis | MTCC13048	Marine algae	+	-	-	-	-	-	-	-	Chakraborty et al. (2021a)
Brevibacillus brevis | EGS9	Endophytic	+	+	-	-	-	-	-	-	Arumugam et al. (2017)
Chromohalobacter salixigens | PSP. 39-04	Sea Sponge	+	-	+	+	+	+	-	-	Asagabaldan et al. (2017)
Corallococcus sp. | UTMC 4088	Hot desert	+	-	-	-	-	-	-	-	Saadatpour & Mohammadipanah (2020)
Cystobacter sp. | UTMC 4086	Hot desert	+	-	-	-	-	-	-	-	Saadatpour & Mohammadipanah (2020)
Gordonia terrae | INA 01165	Ice desert (Artic)	+	-	-	-	-	-	-	-	Efimenko et al. (2018)
Marmoricola sp. | 8BTY-J2	Endophytic	+	+	-	-	-	+	-	-	Jiang et al. (2018)
Microbacterium sp. | 16Sb5-9	Hot desert	+	-	-	-	-	-	-	-	Liu et al. (2021)
Micromonospora marina | KPMS1	Marine Sediment	-	-	-	-	-	-	+	-	Raja et al. (2023)
Micromonospora robiginosa | 28ISP2-46	Sea Sponge	+	+	-	-	-	-	-	-	Back et al. (2021)
Nocardia sp. | UTMC 751	Hot desert	+	-	-	-	-	-	-	-	Hamedi et al. (2015)
Nocardiopsis sp. | TFS65-07	Marine Sediment	-	-	+	-	-	-	-	-	Engelhardt et al. (2010)
Pseudoalteromonas rubra	Sea slug	+	-	-	-	-	-	-	-	Kristiana et al. (2020)
Pseudomonas aeruginosa	Sea Sponge	+	-	-	-	-	-	-	-	Ibrahim et al. (2018)
Pseudomonas fluorescens | H40, H1	Sea Sponge	-	+	-	-	+	-	+	-	Nunes et al. (2020)
Pseudomonas sp.	Endophytic	+	+	-	-	-	-	-	-	Delfino et al. (2021)
Pseudomonas sp. | AALPS.10. MNAAK.13	Ice desert (Artic)	+	-	-	-	-	-	-	+	Marcolefas et al. (2019)
Pseudomonas sp. | RHLB12	Sea Sponge	+	-	-	-	-	-	-	-	Skariyachan et al. (2014)
Saccharothrix sp. | 16Sb2-4	Hot desert	+	-	+	-	+	+	+	-	Liu et al. (2021)
Salinispora sp. | 33'5	Marine Sediment	-	+	-	+	+	+	+	-	Contreras-Castro et al. (2020)
Salinispora sp. | 9'4	Marine Sediment	-	+	-	+	+	+	+	-	Contreras-Castro et al. (2020)
Salinispora sp. | FS-0034	Marine Sponge	+	-	+	-	-	-	-	-	Singh et al. (2014)
Serratia marcescens | JSSCPM1	Soil	+	-	-	-	-	-	-	-	Arivuselvam et al. (2023)
Streptomyces agglomeratus | 5-1-3	Mountain (High altitude)	-	+	-	-	-	-	-	-	Jiang et al. (2023)
Streptomyces albidoflavus | CMRP4854	Endophytic	-	-	-	-	-	+	-	-	Assad et al. (2021)
Streptomyces albogriseolus | 6BTZ-4	Endophytic	-	+	-	-	+	-	+	-	Jiang et al. (2018)
Streptomyces anulatus	Soil	+		-	-		-	-	-	Ghashghaei et al. (2018)
Streptomyces bacillaris | RAM25C4	Marine Sediment	+	+	-	-	+	+	-	-	Wahaab & Subramaniam (2018)
Streptomyces bingchenggensis ULS14	Soil	+	-	-	-	-	-	-	-	Flora et al. (2015)

Note: (+) the extract or cell-free was tested against bacteria with a known resistance profile; (-) negative result against resistant bacterial pathogens or bacterial extract has not been tested; MRSA = Methicillin Resistance *Staphylococcus aureus*; MDRSA = Multi-Drug Resistance *Staphylococcus aureus*; VRE = Vancomycin Resistance *Enterococcus*; MDRE = Multi-Drug Resistance *Enterococcus*; MDRP = Multi-Drug Resistance *Pseudomonas*; MDRA = Multi-Drug Resistance *Acinetobacter baumannii*; MDRK = Multi-Drug Resistance *Klebsiella*; MDREc = Multi-Drug Resistance *Escherichia coli*.

Table 2. Continued...

Specie | Strain	Source	Antibacterial activity								Reference
		MRSA	MDRSA	VRE	MDRE	MDRP	MDRA	MDRK	MDREc	
Streptomyces chryseus	Soil	+	-	-	-	-	-	-		Ghashghaei et al. (2018)
Streptomyces coelicoflavus | EMM112	Marine Sediment	+	-	-	-	-	-	-	+	Ibrahimi et al. (2020)
Streptomyces erythrogriseus | M10-77	Marine Sediment	+	+	+	-	-	-	-	-	León et al. (2011)
Streptomyces fulvissimus | ULK2	Soil	+	-	-	-	-	-	-	-	Flora et al. (2015)
Streptomyces gandocaensis | DHS287	Marine Sediment	-	-	-	-	-	+	-	-	Park et al. (2016)
Streptomyces griseus | TAAAP033	Industrial wastewater	-	-	-	+	+	-	-	-	Kumar et al. (2021)
Streptomyces longispororuber | SBRK2	Sea Sponge	+	-	-	-	-	-	-	-	Mary et al. (2021)
Streptomyces omiyaensis | SUK 25	Endophytic	+	-	-	-	-	-	-	-	Alshaibani et al. (2016)
Streptomyces parvulus | Av-R5	Endophytic	-	+	-	-	+	-	+	+	Chandrakar & Gupta (2019)
Streptomyces phaeoluteichromatogenes | 7BMP -1	Endophytic	-	+	+	+	-	-	-	-	Jiang et al. (2018)
Streptomyces rochei | PM49	Marine Sediment	-	+	-	-	-	-	-	-	Shanthi et al. (2015)
Streptomyces smyrnaeus | UKAQ 23	Marine Sediment	+	-	-	-	-		-	-	Qureshi et al. (2021)
Streptomyces sp. | Al-Dhabi-90	Marine Sediment	+	-	-	-	+	+	-	+	Al-Dhabi et al. (2019)
Streptomyces sp. | CJ13	Soil	+	-	-	-	-	-	-	-	Quinn et al. (2020)
Streptomyces sp. | DSD011	Marine Sediment	+	+	-	-	-	-	-	-	Sabido et al. (2020)
Streptomyces sp. | MW562807	Saline Lagoon	-	-	-	-	-	+	-	-	Flores Clavo et al. (2021)
Streptomyces sp. | PS95	Soil	+	-	-	-	-	-	-	-	Chanthasena & Nantapong (2016)
Streptomyces sp. | RO-S4	Marine Sediment	+	-	-	-	-	-	-	-	Ouchene et al. (2022b)
Streptomyces sp. | S3	Marine Sediment	+	-	-	-	-	-	-	-	Ouchene et al. (2022a)
Streptomyces sp. | SA 11	Marine Sediment	+	-	-	-	-	-	-	-	Al-Ansari et al. (2020)
Streptomyces sp. | SA32	Endophytic	+	+	+	+	-	-	+	+	Ryandini et al. (2021)
Streptomyces sp | TAAAP012	Industrial wastewater	-	-	-	+	+	-	-	-	Kumar et al. (2021)
Streptomyces sundarbansensis | 3BXP - 1	Endophytic	-	-	-	-	+	-	-	+	Jiang et al. (2018)
Thermomonas hydrothermalis | H1	Hot spring	-	+	+	-	-	-	-	-	Al-Daghistani et al. (2021)
Verrucosispora sp. | CMRP4860	Endophytic	+	-	+	-	-	-	-	-	Assad et al. (2021)
Virgibacillus salarius	Sea slug	+	-	-	-	-	-	-	-	Kristiana et al. (2020)

Note: (+) the extract or cell-free was tested against bacteria with a known resistance profile; (-) negative result against resistant bacterial pathogens or bacterial extract has not been tested; MRSA = Methicillin Resistance *Staphylococcus aureus*; MDRSA = Multi-Drug Resistance *Staphylococcus aureus*; VRE = Vancomycin Resistance *Enterococcus*; MDRE = Multi-Drug Resistance *Enterococcus*; MDRP = Multi-Drug Resistance *Pseudomonas*; MDRA = Multi-Drug Resistance *Acinetobacter baumannii*; MDRK = Multi-Drug Resistance *Klebsiella*; MDREc = Multi-Drug Resistance *Escherichia coli*.

Table 3. Description of the chemical compounds detected in the secondary metabolites of extracts of environmental bacteria with antibiotic activity against ESKAPEE pathogens and the analytical method used.

Specie | Strain	Compound	Analytical Method	Patent code / Commercialized product	Reference
Amycolatopsis sp. | YNNP 00208	Baoshanmycin ($C_{17}H_{19}NO_7$)	$^1H/^{13}C$ NMR HRESIMS	- / -	Qian et al. (2022)
Bacillus amyloliquefaciens | MTCC 12713	Hexahydro-41-hydroxy-macrobrevin-31-acetate	NMR FT-IR LC-MS GC-MS	- / -	Qian et al. (2022)
Bacillus amyloliquefaciens | MTCC 12716	Amylomacin B (amicoumacin compound encompassing 4′-hydroxy-11′-methoxyethyl carboxylate functionality)	$^1H/^{13}C$ NMR GC-MS HRESIMS FT-IR	- / -	Chakraborty et al. (2021b)
Bacillus sp. | DJ4 **	Baptifoline, Dehydromorroniaglycone, Isoleucinopine, Sophoramine, Melazolide A, Rengyoside C, Iedoglucomide A, Paenilamicin A1*, Aeruginopeptin	LC-MS/MS Xevo G2-XS QTof; ESI	- / -	Priyanto et al. (2023)
Bacillus sp. | DJ9 **	Baptifoline, Dehydromorroniaglycone, Isoleucinopine, Sophoramine, Aspersecosteroid A, Rengyoside C, Iedoglucomide A, Paenilamicin A1*, Aeruginopeptin	LC-MS/MS Xevo G2-XS QTof; ESI	- / -	Priyanto et al. (2023)
Bacillus subtilis| TAAAP010	Carbenicillin ($C_{17}H_{18}N_2O_6S$)	RP-HPLC	- / Yes	Kumar et al. (2021)
	Cephalexin ($C_{16}H_{17}N_3O_4S$)		- / Yes	
	Cephalothin ($C_{16}H_{16}N_2O_6S_2$)		- / Yes	
	Tetracycline ($C_{22}H_{24}N_2O_8$)		- / Yes	
Bacillus tequilensis | MSI45	Pyrrolo[1,2-a]pyrazine-1,4-dione, hexahydro ($C_7H_{10}N_2O_{2)}$	FT-IR NMR GC-MS	- / Yes	Kiran et al. (2018)
Bacillus velezensis | MTCC13048	Amido-type 12-membered macrocyclic polyketide, 8-(pent-2-enyl)-1-oxo-5a, 8a-dioxacyclododecanyl-3-oxy-ethyl-5b′-methyl-5′-(7′(9′(methoxyethyl)-dihydrofuranyl) propanmido) succinate ($C_{32}H_{47}NO_{12)}$	$^1H/^{13}C$ NMR	- / -	Chakraborty et al. (2021a)
Micromonospora marina | *KPMS1*	(2E) -3-(2H-1,3-benzodioxol-5-yl) -N- phenyl prop-2-enamide ($C_{16}H_{13}NO_3$)	FT-IR $^1H/^{13}C$ NMR	- / -	Raja et al. (2023)
Micromonospora robiginosa | 28ISP2-46	Isoquinocycline B ($C_{33}H_{32}N_2O_{10}$)	LC-MS	- / Yes	Back et al. (2021)
Nocardia sp. | UTMC 751	Unknown compounds (molecular weights of 274.2, 390.3, 415.3, 598.4 and 772.5 D)	HPLC-MS	- / -	Hamedi et al. (2015)
Nocardiopsis sp. | TFS65-07	Thiopeptide antibiotic TP-1161	HPLC-DAD-TOF $^1H/^{13}C$ NMR HRMS	- / -	Engelhardt et al. (2010)
Pseudoalteromonas rubra	Stearidonic acid ($C_{18}H_{28}O_{2)}$	HPLC-MS	US2020352980A(USA) / Yes	Kristiana et al. (2020)
	Prodigiosin, ($C_{20}H_{25}N_3O$)		US2017058314A1 (USA) / Yes	
			US2021123086A1(USA) / Yes	
			CN105603737A(China) / Yes	
			BR102021023262 5 (Brazil) / Yes	
Pseudomonas sp. | RHLB12	Chromophoric substance	FT-IR	- / -	Skariyachan et al. (2014)

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Table 3. Continued...

Specie | Strain	Compound	Analytical Method	Patent code / Commercialized product	Reference
Saccharothrix sp. | 16Sb2-4	Aldgamycin H	UPLC-QToF-MS/MS; $^{1}H/^{13}C$ NMR	- / -	Liu et al. (2021)
	Aldgamycin K		- / -	
	Aldgamycin G ($C_{37}H_{56}O_{15}$)		EP2202293A2 (France) / Yes	
			US2010120896A1(USA) / Yes	
			US2022021922(USA) / Yes	
			US2019067914(USA) / Yes	
	Swalpamycin B		- / -	
Salinispora sp. | FS-0034	Rifamycin W ($C_{35}H_{45}NO_{11}$)	HRESIMS ^{1}H NMR	IB2010051183 (Italy) / Yes	Singh et al. (2014)
			US2022168384A1(USA) / Yes	
			US2020263224A1(USA) / Yes	
			KR102342719B1 (South Korea) / Yes	
Streptomyces agglomeratus | 05/01/2003	Echinomycin ($C_{51}H_{64}N_{12}O_{12}S_2$)	HPLC; NMR	WO2024002385A1 (China) / Yes	Jiang et al. (2023)
Streptomyces bacillaris | RAM25C4 **	2,6-di-tert-butylphenol; 1H, 5H, Pyrrolo (1′ 2′:3, 4) imidazole; 1,4-Benzenediol, 2,5-bis(1,1-dimethylethyl)	HPTLC GC-MS	- / -	Wahaab & Subramaniam (2018)
Streptomyces fulvissimus | ULK2	Amythiamicins*	GS	- / -	Flora et al. (2015)
Streptomyces bingchenggensis ULS14	Amythiamicins*	GS	- / -	Flora et al. (2015)
Streptomyces gandocaensis | DHS287	Cahuitamycins A ($C_{27}H_{37}N_7O_{11}$) and C ($C_{28}H_{39}N_7O_{11}$)	NMR HPLC-MS	US10239918B2 (USA) / -	Park et al. (2016)
Streptomyces griseus | TAAAP033	Carbenicillin ($C_{17}H_{18}N_2O_6S$)	RP-HPLC	- / Yes	Kumar et al. (2021)
	Cephalexin ($C_{16}H_{17}N_3O_4S$)		- / Yes	
	Cephalothin ($C_{16}H_{16}N_2O_6S_2$)		- / Yes	
	Tetracycline ($C_{22}H_{24}N_2O_8$)		CN20120010019 (China) / Yes	
Streptomyces longispororuber | SBRK2	8-O-metyltetrangomycin ($C_{20}H_{16}O_5$)	HR-LC-MS	EP3303340 (Netherlands) / Yes	Mary et al. (2021)
Streptomyces omiyaensis | SUK 25	Cyclo(L-Pro-L-Trp) ($C_{16}H_{17}N_3O_{2)}$	GC-MS	- / Yes	Alshaibani et al. (2016)
	Chloramphenicol ($C_{11}H_{12}Cl_2N_2O_5$)		KR20230001082A (South Korea) / Yes	
Streptomyces parvulus | Av-R5	Actinomycin D ($C_{62}H_{86}N_{12}O_{16}$)	$^{1}H/^{13}C$ NMR FT-IR HESI-MS	CN104450580A (China) / Yes	Chandrakar & Gupta (2019)
			CN111778178B (China) / Yes	
	Actinomycin X0β ($C_{62}H_{86}N_{12}O_{17}$)		- / Yes	
Streptomyces rochei | PM49	sulfanyl cyslabdan-like compound ($C_{25}H_{41}NO_5S$)	FT-IR HESI-MS $^{1}H/^{13}C$ NMR	- / Yes	Shanthi et al. (2015)
Streptomyces smyrnaeus | UKAQ 23	Actinomycin X2	LC-MS NMR	- / -	Qureshi et al. (2021)
	Actinomycin D ($C_{62}H_{86}N_{12}O_{16}$)		CN104450580A (China) / Yes	
			CN111778178B (China) / Yes	
Streptomyces sp. | Al-Dhabi-90	3-methylpyridazine ($C_5H_6N_2$)	GC-MS	- / Yes	Al-Dhabi et al. (2019)
	n-hexadecanoic acid ($C_{16}H_{32}O_2$)		- / Yes	

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Table 3. Continued...

Specie | Strain	Compound	Analytical Method	Patent code / Commercialized product	Reference
Streptomyces sp. | DSD011	Fridamycin A ($C_{25}H_{26}O_{10}$)	LCMS-TOF MS/MS	- / Yes	Sabido et al. (2020)
	Fridamycin D ($C_{31}H_{32}O_{12}$)		- / Yes	
Streptomyces sp. | MW562807 **	Cholic Acid; Lobophorin A, B, E, and K; in addition to a Sixth Compound	UHPLC-MS	- / -	Flores Clavo et al. (2021)
Streptomyces sp. | RO-S4	Aquayamycin, *	UHPLC-HRMS/MS	- / -	Ouchene et al. (2022b)
Streptomyces sp. | TAAAP012	Carbenicillin ($C_{17}H_{18}N_2O_6S$)	RP-HPLC	- / Yes	Kumar et al. (2021)
	Cephalexin ($C_{16}H_{17}N_3O_4S$)		- / Yes	
	Cephalothin ($C_{16}H_{16}N_2O_6S_2$)		- / Yes	
	Tetracycline ($C_{22}H_{24}N_2O_8$)		CN20120010019 (China) / Yes	
Thermomonas hydrothermalis | H1 **	l-ornithine, 5-aminocarbonyl-α-amino-ureidovaleric acid (citrulline), tetramethyl-2-hexadecene, 2-hexyl-1,4-trimethylcyclobutane, glycyl-L-proline, pyrrole 1,2 pyrazine-1,4 dione, 2-hydroxy-trimethyl cyclohexanone, pyrolopyrazine-1,2-pyrazine-1,4-dion, 5-nitroso-2,4,6-triamino pyrimidine, pyrimidinone, octadecanoic acid, actinomycin D (cyclic peptide), 2-ethoxy-4,7-dimethylpyrido pyrimidin, octahydro-1H-pyridopyrimidin, ergotaman, octa-decanoic acid, tropyl propanal tosyl hydrazone, and dihydroxy-1,5-naphthyridine	GC-MS	- / -	Al-Daghistani et al. (2021)

Note: (-) The search criteria yielded no patents and no commercially available products containing the specified compounds. (*) Antibacterial compound suggested by the author; (**) Compounds characterized but not proven to have antibacterial activity. GC = Gas chromatography; HRESIMS = High-resolution electrospray ionization mass spectrometry; NMR = nuclear magnetic resonance; FT-IR = Fourier transform infrared spectroscopy; GC-MS = gas chromatography-mass spectrometry; RP-HPLC = Reverse Phase High Performance Liquid Chromatography; UHPLC-HRMS/MS = ultra-high-performance liquid chromatography with high-resolution mass spectrometry; TOF MS/MS = Quadrupole time-of-flight mass spectrometry; DAD = Diode Array Detector.

substances revealed new and old compounds with activity against MDR bacteria. For example, echinomycin produced by *Streptomyces agglomeratus* inhibited MDRS (Jiang et al., 2023), rifamycin W produced by *Salinispora* spp. inhibited MRSA and VRE (Singh et al., 2014), actinomycin X2 and actinomycin D produced by *Streptomyces* inhibited MDRSA, MDRP, MDRK, and MDREc (Chandrakar & Gupta, 2019; Qureshi et al., 2021) (Table 3).

Some strains were also associated with the production of new compounds. These compounds showed inhibitory activity against MDR pathogens. For example, fridamycin A and fridamycin D produced by *Streptomyces* can inhibit MRSA and MDRS (Sabido et al., 2020; Ouchene et al., 2022b). Baoshanmycin, produced by *Amycolatopsis*, can inhibit MDRS strains of *S. aureus* (Qian et al., 2022); pyrrolo [1,2-a] pyrazine-1,4-dione, hexahydro, produced by *Bacillus tequilensis* MSI45, has activity against MRSA and VRE (Kiran et al., 2018). Engelhardt et al. (2010) described a new thiopeptide antibiotic produced by *Nocardiopsis* that can inhibit VRE.

Among the 25 bacterial extracts whose identified compounds exhibited antibacterial activity (Table 3), 12 extracts were subjected to HPLC-MS (high-performance liquid chromatography coupled with mass spectrometry) with or without methodological variations such as high-resolution (HR), electrospray ionization (ESI), and time-of-flight (TOF) mass spectrometry (Qian et al., 2022; Chakraborty et al., 2021a, b; Back et al., 2021; Hamedi et al., 2015; Engelhardt et al., 2010; Kristiana et al., 2020; Liu et al., 2021; Singh et al., 2014; Park et al., 2016; Kumar et al., 2021; Mary et al., 2021; Chandrakar & Gupta, 2019; Shanthi et al., 2015; Qureshi et al., 2021; Sabido et al., 2020). The remaining 10 of the 12 samples were analyzed using alternative spectroscopic techniques, including nuclear magnetic resonance (NMR), Fourier transform infrared (FT-IR), and gas chromatography coupled with mass spectrometry (GC-MS). The remaining bacterial extracts were characterized using the following methods: HPLC (Kumar et al., 2021); NMR (Chakraborty et al., 2021a); GC-MS (Alshaibani et al., 2016; Al-Dhabi et al., 2019); FT-IR (Skariyachan et al., 2014); HPLC and NMR (Jiang et al., 2023); NMR, FT-IR, and GC-MS (Kiran et al., 2018; Raja et al., 2023).

Intellectual properties of chemical compounds with antibacterial activity

In total, 19 patents were found for 9 of the 25 bacterial extracts with characterized compounds (Table 3); the patents originated from six countries (USA, China, South Korea, Brazil, Italy, and France). Moreover, among the 25 bacterial extracts used to characterize the compound(s) responsible for the observed antibacterial activity, 21 biocompounds are commercially available and are widely used in the pharmaceutical and biotechnology industries (Table 3). A total of 7 of these commercially available biocompounds can be used in different forms (tablets, sprays, creams and liquids), such as carbenicillin, cephalexin, cephalothin, tetracycline, chloramphenicol, actinomycin D and 8-O-methyltetrangomycin. In contrast, 14 compounds are used exclusively for research, namely: 3-methylpyridazine, n-hexadecanoic acid, fridamycin A and D, cislabdan sulfanil-type compounds, cyclo(L-Pro-L-Trp), actinomycin X0ß, pyrrolo[1,2-a] pyrazine-1,4-dione, hexahydro, isoquinocycline B, stearidonic acid, prodigiosin, aldgamycin G, rifamycin W, and echinomycin (National Center for Biotechnology Information, 2024b).

Discussion

In this review, the data indicated that the marine environment represents the most extensively investigated niche where bacteria with MDR antimicrobial potential have been isolated (Asagabaldan et al., 2017; Al-Dhabi et al., 2019; Contreras-Castro et al., 2020). Microorganisms that can survive extremely hostile conditions may produce secondary metabolites to suppress their ecological competitors (Schultz et al., 2023). This phenomenon was found in marine sponges, sea slugs, and algae with their microbial symbiosis, which represents a unique ecological phenomenon and acts as a reservoir of new bioactive molecules (Singh et al., 2014; Skariyachan et al., 2014; Asagabaldan et al., 2017; Ibrahim et al., 2018; Kiran et al., 2018; Back et al. 2021; Chakraborty et al., 2021a,b, 2022; Mary et al., 2021).

Over the past two decades, the discovery of previously characterized bioactive compounds and the redundancy of strains have significantly reduced interest in soil-dwelling bacteria as a source of new bioactive compounds. Consequently, microorganisms that inhabit other niches, such as marine environments, have gained popularity due to their chemical diversity (De La Hoz-Romo et al., 2022). Several environmental fluctuations affect marine microorganisms, including temperature, pressure, light, and salinity, all of which facilitate the biosynthesis of distinctive metabolites (Stincone & Brandelli, 2020).

In other extreme environments, such as those with water deficiency (hot and ice deserts), high osmotic pressure (saline lagoons), or high temperatures (hot springs), various microorganisms can also produce unknown secondary metabolites (Hamedi et al., 2015; Efimenko et al., 2018; Marcolefas et al., 2019; Saadatpour & Mohammadipanah, 2020; Al-Daghistani et al., 2021; Flores Clavo et al., 2021; Liu et al., 2021). For example, *Streptomyces* is a gram-positive bacterial genus that can produce various compounds with antimicrobial activity, including streptomycin, chloramphenicol, and tetracycline (Schlimpert & Elliot, 2023; Meenakshi et al., 2024). In this context, the reviewed studies showed a high diversity of *Streptomyces*, presented from all clades of this genus that were not closely related, according to the phylogenetic analysis (Labeda et al., 2017), which revealed that all species from the genus can produce antimicrobial substances. Other highly expressed species associated with these extreme environments are those belonging to the genera *Bacillus*, *Chromohalobacter*, *Nocardia*, *Nocardiopsis*, *Pseudomonas*, *Saccharothrix*, and *Salinispora*, which also produce various antimicrobial substances, including polypeptides and lipopeptides (Engelhardt et al., 2010; Hamedi et al., 2015; Asagabaldan et al., 2017; Efimenko et al., 2018; Marcolefas et al., 2019; Liu et al., 2021).

This review highlighted that some compounds previously identified currently have been related to antimicrobial

activity and so, can be further emerged as new strategies for treating ESKAPEE pathogen infections. For example, the thiopeptide antibiotic produced by *Nocardiopsis* sp. is remarkably like the substance A10255, which is used as an animal growth promoter and has high activity against VRE (Engelhardt et al., 2010). Paenilamycin A1, present in *Bacillus* sp. DJ4 and DJ9 extracts, has antibacterial activity against four multidrug-resistant strains (Priyanto et al., 2023), and was previously described as a secondary metabolite antibiotic produced by the bee pathogenic bacterium *Paenibacillus larvae* and showed cytotoxic activity against insect cells (Garcia-Gonzalez et al., 2014). Fridamycin A, isolated from *Streptomyces* sp. (Sabido et al., 2020; Ouchene et al., 2022b), showed activity against MRSA and VRE. However, it has already been reported as having anantidiabetic effect due to its inhibition of the uptake of glucose into cells by activating AMP-activated protein kinase (AMPK) (Yoon et al., 2019).

Another previously uncharacterized substance has shown an abundance of new compounds with antimicrobial potential, such as the compound pyrrolo [1,2-a] pyrazine-1,4-dione, hexahydro produced by *B. tequilensis*, which exhibits activity against MRSA and VRE (Kiran et al., 2018) and has low cytotoxicity (Kannabiran, 2016). Cahuitamycins A-C produced by *Streptomyces gandocaensis* DHS287 were recently described and shown to have antibiofilm activity against *Acinetobacter* (Park et al., 2016), and a compound called cyclo (L-Trp L-Pro), produced by *Streptomyces omiyaensis* SUK 25, possesses activity against MRSA and *Micrococcus luteus* (Mehdi et al., 2009; Alshaibani et al., 2016). This review also described the production of previously known substances, with only some chemical alterations, which can lead to new activities against previously resistant bacteria. For example, rifamycin W produced by *Salinispora* sp. FS-0034 (Singh et al., 2014), which is an analog of rifamycin SV has high activity against MDRB (Adams et al., 2021) Actinomycin D and actinomycin X produced by *Streptomyces* sp. (Chandrakar & Gupta, 2019; Qureshi et al., 2021) are well-known antibiotics that exhibit high antibacterial and antitumor activity (Finocchiaro, 2020).

The analytical techniques used to characterize bioactive compounds in bacterial extracts were discussed. Among the 25 extracts studied, 12 were analyzed mainly via high-performance liquid chromatography-mass spectrometry (HPLC-MS), with two extracts being analyzed exclusively using this method (Back et al., 2021; Kristiana et al., 2020) (Table 3). LC-MS is a popular technique in metabolomic studies because of its versatility and simplicity (Canuto et al., 2018; Alseekh et al., 2021). Moreover, LC-MS, other techniques, such as NMR, GC-MS, and FT-IR, were used to confirm the structural characteristics of the bioactive compounds. NMR is a reliable technique that requires minimal sample handling but has lower sensitivity and selectivity. GC-MS is widely used in metabolomic studies, but metabolites generally need to be volatilized for analysis at lower temperatures (Schrimpe-Rutledge et al., 2016; Alseekh et al., 2021). Finally, FT-IR was used occasionally in some studies (Neto et al., 2022). Overall, the combination of these analytical techniques provides a comprehensive understanding of the bioactive compounds found in bacterial extracts. Moreover, the cytotoxicity of the compounds was evaluated in only 5 reports (Al-Ansari et al., 2020; Kristiana et al., 2020; Saadatpour & Mohammadipanah, 2020; Al-Daghistani et al., 2021; Back et al., 2021).

Considering the antibacterial activity observed in the characterized compounds, this study also identified the primary patent holders and their geographical distribution by analyzing patent publications without considering the commercial status of patents. As determined by the patent survey of bioactive compounds, the United States holds the greatest number of patents (9/20) for five antibacterial compounds (stearidonic acid, prodigiosin, aldgamycin G, rifamycin W, and cahuitamycins A–C (Table 3), followed by China and South Korea. However, some authors have indicated that China is the predominant patent holder for commercial and non-commercial antibacterial agents. Besides China, the United States, Japan, South Korea, India, the United Kingdom, and Italy have prominent commercial patents (Jiménez et al, 2022; Ralhan et al, 2024).

In this context, the data gathered from the articles under review indicate that bioprospecting bacteria of environmental origin may represent a promising strategy to address the challenge of MDR bacteria. The potential discovery of novel bioactive compounds could offer valuable tools to enhance the efficacy of existing treatments for bacterial infections, which have contributed to significant mortality rates. Furthermore, to enhance the development of new antibacterial agents and expedite the process, it is essential to refine and advance the experimental protocols employed in these studies. In particular, the characterization of compounds present in bacterial extracts requires more comprehensive and rigorous methodology.

Conflict of interests

The authors declare no competing interest.

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