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MICROBIOLOGY

Antarctic organisms as a source of antimicrobial compounds: a patent review

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Abstract: Currently, antimicrobial resistance has become a global public health problem, which has made the need for new antimicrobial compounds to deal with resistant infections an emergency. However, environments that once offered so many innovative molecules, now already exhaustively exploited, do not meet this need. In this context, a geographically isolated, under-explored and extreme environment, such as Antarctica, which holds organisms with unique physiological and biochemical characteristics, assumes great importance as a potential source of new compounds with antimicrobial activity. In this patent review, we investigate the state of technological development in the field of antimicrobial compounds obtained from Antarctic organisms, highlighting the main countries and researchers active in the field, the species utilized, the compounds obtained, and their possible therapeutic applications. As results, few patent documents were found, however they encompass a wide diversity of compounds and species, indicating a great antimicrobial potential present in Antarctic biota, including compounds active against the most important human pathogenic microorganisms, such as including methicillin-resistant *Staphylococcus aureus*, vancomycin-resistant *Enterococcus* spp. and multi-resistant *Mycobacterium tuberculosis*. Furthermore, due to the increasing trend in patent applications, a significant rise in the number of patents in this area is expected in the coming years.

Key words: Antarctica, antimicrobial activity, antimicrobial resistance, natural antimicrobials, secondary metabolites.

INTRODUCTION

Nowadays, there are resistance mechanisms against all classes of antimicrobial drugs available (Genilloud 2014). According to estimates by the World Health Organization (WHO), treatment-resistant infections are a global public health problem that already causes about 700,000 deaths per year and could reach 10 million deaths per year by 2050 (Livermore 2009, Interagency Coordination Group on Antimicrobial Resistance 2019). This scenario makes the need for new antimicrobials an emergency. However, the success in the development of new antimicrobial drugs has become increasingly rare, raising the necessity and the scientific interest for new sources of these molecules (Durand et al. 2018).

The term "antimicrobial" refers to natural, synthetic or semi-synthetic compounds capable of acting against microorganisms (Guimarães 2010, Mariottini & Grice 2016). The concept that chemicals could be used against pathogenic microorganisms in concentrations tolerable by

the infected patient was first conceived by the German researcher Paul Ehrlich, who, in 1910, developed the first synthetic antimicrobial, the Salvarsan, used in the treatment of syphilis (Winau et al. 2004). However, the greatest milestone in the history of antibiotic therapy occurred almost two decades later with the accidental discovery by the English physician Alexander Fleming of the first antimicrobial of natural origin, the penicillin, a substance produced by species of *Penicillium* (Nossa capa: Alexander Fleming e a descoberta da penicilina 2009).

The discovery of penicillin started what is known as the golden age of antibiotic therapy, a period marked by numerous discoveries of natural compounds with distinct mechanisms of antimicrobial activity, whose introduction into clinical practice has widely contributed to the increase in human life expectancy and quality (Brown & Wright 2016, Aminov 2017, Ventola 2015). Notoriously, the main natural sources of these compounds were the microorganisms themselves, which use them as a form of competitive advantage by inhibiting the growth of other surrounding microorganisms (Guimarães et al. 2010, Brown & Wright 2016). However, substances with antimicrobial activity of clinical interest can also be found in multicellular organisms, both in the plant and animal kingdoms, being the result of evolutionary mechanisms to cope with infections (Chandra et al. 2017, Khameneh et al. 2019, Valero et al. 2018, Bulet et al. 1999).

In opposition, microorganisms develop genetic mutations at a high rate that eventually result in defense mechanisms against antimicrobials, thus conferring adaptive advantage and becoming fixed in microbial populations. Furthermore, microorganisms also possess the capacity to transfer these genetic mutations among themselves, sharing the mechanisms of resistance even with other species (Partridge et al. 2018). Simultaneously, the extensive and misdirected use of antimicrobials since their discovery has boosted antimicrobial resistance by serving as an artificial selection mechanism, eliminating sensitive microorganisms and selecting the resistant ones (McEwen & Collignon 2018). This problem is aggravated by the vertiginous decline in the discovery of new antimicrobial drugs over the last decades (Loureiro et al. 2016).

One of the main reasons for the decrease in the discovery of antimicrobial compounds is that several environments, which were previously able to provide numerous innovative molecules, have now been fully explored. In this context, attention is focused on environments that are still under-explored. Because organisms obtained from new ecosystems are frequently associated with new biochemical diversity (Shinde et al. 2019, Donadio et al. 2010), isolated and extreme ecosystems are expected to have a greater probability of harboring organisms with unique and yet unknown physiological characteristics (Katz & Baltz 2016, Danilovich et al. 2018).

Among the main isolated and extreme environments known on Earth, Antarctica is recognized as the coldest, driest, most inaccessible and unexplored continent (NASA Science 2013). However, even with these climatic conditions, it possesses considerable endemic ecological diversity, resulting from millions of years of isolated evolution (Bratchkova & Ivanova 2011). Furthermore, due to the extreme low temperatures, which can reach -92°C, low availability of water in liquid form and the consequent high osmotic stress, well as the constant exposure to high ultraviolet radiation, microorganisms comprise the greatest part of the biomass in Antarctica (Núñez-Montero & Barrientos 2018, Rogers 2007).

Moreover, although it is still an under-explored environment in all its extension, numerous organisms have been obtained from diverse Antarctic habitats, such as microorganisms, fishes, macro- and microalgae, sponges, and plants (Shin et al. 2017, Martins et al. 2018, McClintock & Gauthier 1992). These have yielded compounds with various therapeutic applications, including compounds with antimicrobial activities, which were reported in the academic and patent literature. Some of these are active even against resistant and multi-resistant pathogenic bacteria, such as carbapenemase-producing *Pseudomonas aeruginosa*, lactamase-producing *Klebsiella pneumoniae* β-, and multi-resistant strains of *Serratia marcescens* (Núñez-Montero & Barrientos 2018, Asencio 2014).

In this scenario and considering the importance that the patent evaluation has in identifying technological innovations potentially useful commercially (Pires et al. 2020), a patent review was carried out in the present study in order to identify the trend of patenting in the field of antimicrobial compounds isolated from Antarctic organisms, the world panorama of active countries and researchers in this area, the species of Antarctic organisms used, the nature of the compounds obtained and their possible pharmaceutical applications.

MATERIALS AND METHODS

The present study was based on a bibliographic search by patent documents (patent applications and granted patents) that refer to compounds with antimicrobial activity isolated from Antarctic organisms. To this end, a patent review was conducted between June and July 2020, covering the main international patent databases: Patenscope, database of the World Intellectual Property Organization (WIPO), Espacenet, database of the European Patent Office (EPO), The Lens, Patent Inspiration and Derwent Innovations Index.

The search was based on the key terms: (Antimicrobial OR Antibiotic OR Antibacterial OR Antiviral OR Antifung* OR Antimycotic OR Antiprotozo*) AND (Antarcti* OR Antarti* OR "South pole"). The terms were reorganized and arranged according to the respective search tools of the utilized databases. For greater efficiency in the selection of patents related to the present object of study, when allowed by the search tools of each database, the appearance of key terms was considered only in the fields: title, abstract, and claims of the patent documents, reducing, in this way, the recovery of documents that contained the key terms by causality, without presenting any relation to the scope of this review.

The patent search in the five databases returned 860 results, then an accurate reading of the documents was done in order to discard the patents not related to the scope of this review, duplicated patents, and the patents belonging to the same family. Twenty-two documents belonging to 22 different patent families were obtained at the end, as shown in Table I. However, it is important to note that, due to the confidentiality period to which some patents may be submitted, which can last up to 18 months (USPTO 2020), the number of patent documents filed in the 18 months preceding this review (January 2019 to June 2020) may be incompletely represented.

The selected patent documents were organized in electronic spreadsheets using the Microsoft Office Excel 2019® software, where descriptive analyses and preparation of tables and graphs were performed. For patent analysis, the following fields were considered: priority date, place of application (country or international office), assignees,

Table I. Patent search results.

Patent databases	Search Results	Selected documents*	Removal of duplicates and documents from the same family	Search terms
Derwent Innovations Index	112	8	22	(Antimicrobial OR Antibiotic OR Antiseptic OR Antibacterial OR Antiviral OR Antifung* OR Antimycotic OR Antiprotozo*) AND (Antarcti* OR Antarti* OR "south pole")
Espacenet	91	9		
Patent Inspiration	60	8		
Patentscope	533	11		
The Lens	64	6		
Total	860	42		

***The selection criterion included only patent documents (patents applications and granted patents) containing antimicrobial compounds obtained from Antarctic organisms.**

inventors, country of origin, International Patent Classification (IPC) codes, the Antarctic organisms used as antimicrobial sources, the chemical characterization of these antimicrobial compounds, the type of antimicrobial activity and the possible applications.

RESULTS AND DISCUSSION

Temporal distribution of the patent applications

As shown in Figure 1, the 22 patent families claiming Antarctic compounds with antimicrobial activity were filed over 29 years, from 1991 to 2019, in a discontinuous time arrangement, with the longest interval without new patent applications being between 1994 and 2002. On the other hand, 2012 and 2015 were the years with the highest number of applications (3 per year). Moreover, it is possible to observe throughout the historical series an increase in the number of patent applications involving Antarctic antimicrobials, better evidenced by sectioning the application period into decades, with only three applications in the first decade, the double in the second decade and 13 new applications in the last decade, which alone corresponds to more than half (59%) of patent applications made in the entire period.

This growing trend in patenting is in line with the growth observed in Antarctic research, especially in the research for industrial and pharmacological applications of Antarctic organisms, which have recently begun, in the late 20th century (Danilovich et al. 2018, Núñez-Montero & Barrientos 2018), and has experienced a rapid growth reflected in the number of patent applications involving Antarctic biological material (Tvedt 2011). These facts confirm that the growing interest of the scientific community in the biotechnological potential of Antarctica extends to the field of antimicrobial compounds.

Geographical distribution of the patents

The 22 patent documents selected in this review have inventors from 13 different countries, according to the distribution shown in Figure 2a. Among them, China leads as the country of

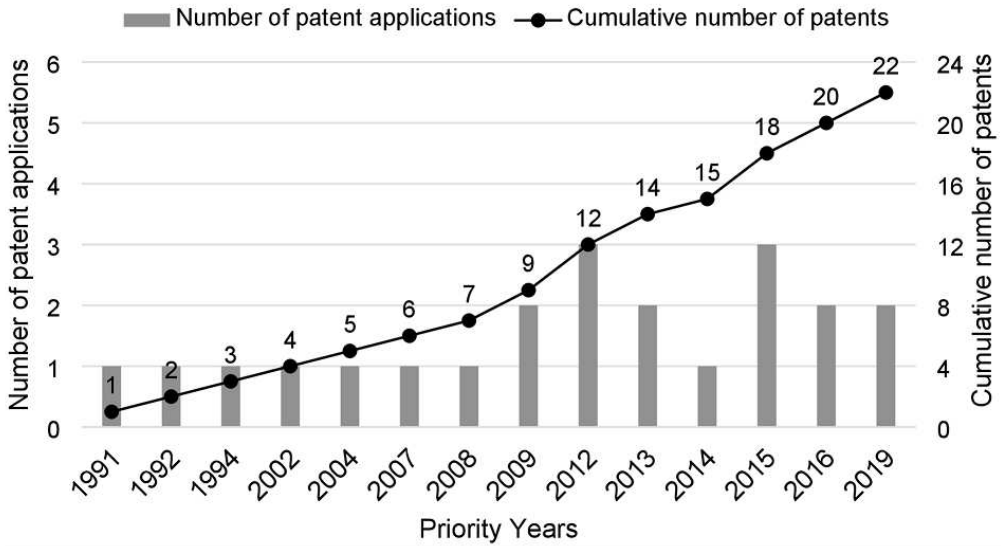

Figure 1. Distribution of the patents on antimicrobial compounds of Antarctic origin according to their respective priority years (year of the first application in the respective patent family).

origin of the inventors of six patent documents, followed by the United States with five, South Korea and Sweden, both origin countries of the inventors of three patent documents each. Likewise, when the documents are distributed according to the country of origin of their assignees, as shown in the Figure 2b, the leading countries are China, with six, United States, with four, and South Korea, with three. These data confirm these three countries where most of the research and technology development involving antimicrobials obtained from Antarctic organisms are done.

However, it is worth mentioning that, while the United States has been a marked presence in Antarctica since the beginning of explorations after the Antarctic Treaty, which in itself justifies its number of patents (Cool Antarctica 2020), China and South Korea have a relatively more recent history of research development on the continent (Brady 2013). Of particular note is China, which since 2005 has expanded its economic and political influence on several continents, including a sudden increase in investment in exploration and research in the Antarctic continent (Brady 2010). Consequently, all six patent documents in this review that have Chinese inventors and assignees are recent, being deposited over the last decade.

With regards to the places of application for these documents, the 22 families of patents have a total of nine different priority countries, as shown in Figure 2c. From these, the United States is responsible for the largest number, with seven families (31.8%), followed by China, with six (27.3%), and South Korea, with three (13.6%), while the remaining countries have one each. However, the 22 families were applied in a total of 29 different locations, including 26 national offices, two regional offices, and the WIPO international office. Currently, 10 of the 22 documents (45.4%) have not yet been granted, and only 14 of the 29 offices have granted any of these patents in their coverage territory, as illustrated in Figure 2d. China had most of the applications received (n=9) and most of the patents granted (n=6), followed by the United States, with seven applications received and five granted, and South Korea, with seven applications received and four granted.

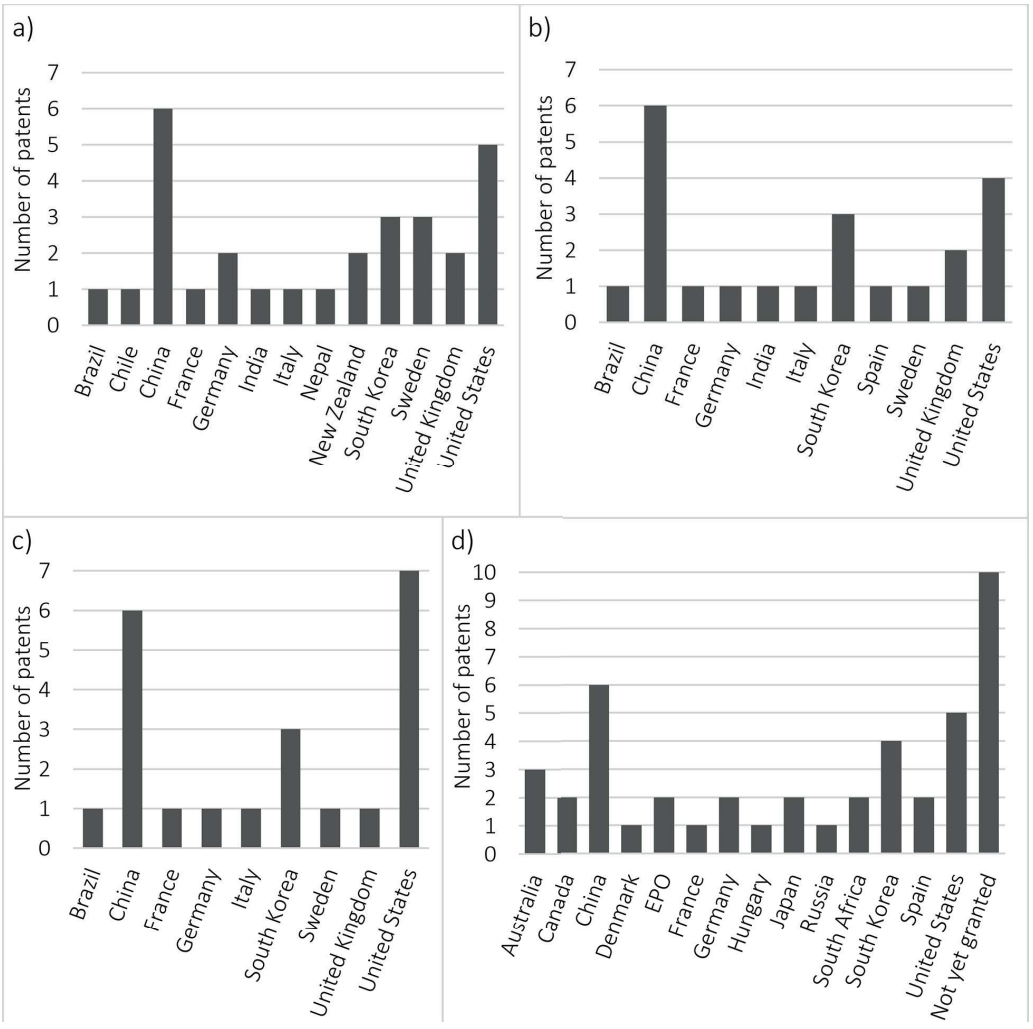

Figure 2. Geographical distribution of the patents with antarctic antimicrobial compounds. a) Distribution of the patents according to the country of origin of their inventors, b) Distribution of the patents according to the country of origin of their assignees, c) Distribution of the patents by priority country and d) Distribution of the patents by the regional/national offices where they were granted.

Analysis of inventors and assignees of the patent documents on Antarctic antimicrobials

The 22 patent documents in this review have 92 different inventors, from 13 different countries, and 20 assignees, from 11 different countries. Among the inventors, the greatest fraction is Chinese (n=25, 27.2%), followed by the American inventors (n=16, 17.4%) and the South Korean (n=13, 14.1%). The principal inventor is Baker BJ, a North American researcher, professor of chemistry at the University of South Florida, who develops studies encompassing the isolation, characterization, and application of secondary metabolites of marine organisms (Chemistry College of Arts and Sciences 2019). He is an inventor in three of the 22 patent documents, while seven other inventors are present in two documents each and the rest of the inventors in one document each (Figure 3a).

Similar to the inventors, most of the assignees are Chinese (n=6, 30%), while the United States, South Korea, and India are the countries of origin of two assignees each (10%). However, the main assignees are the UAB Research Foundation and the University of South Florida, owners of three documents each, as shown in Figure 3b, but they share two of these documents. Meanwhile, the Korean Institute of Ocean Science and Technology and the United Kingdom Company, Phairson

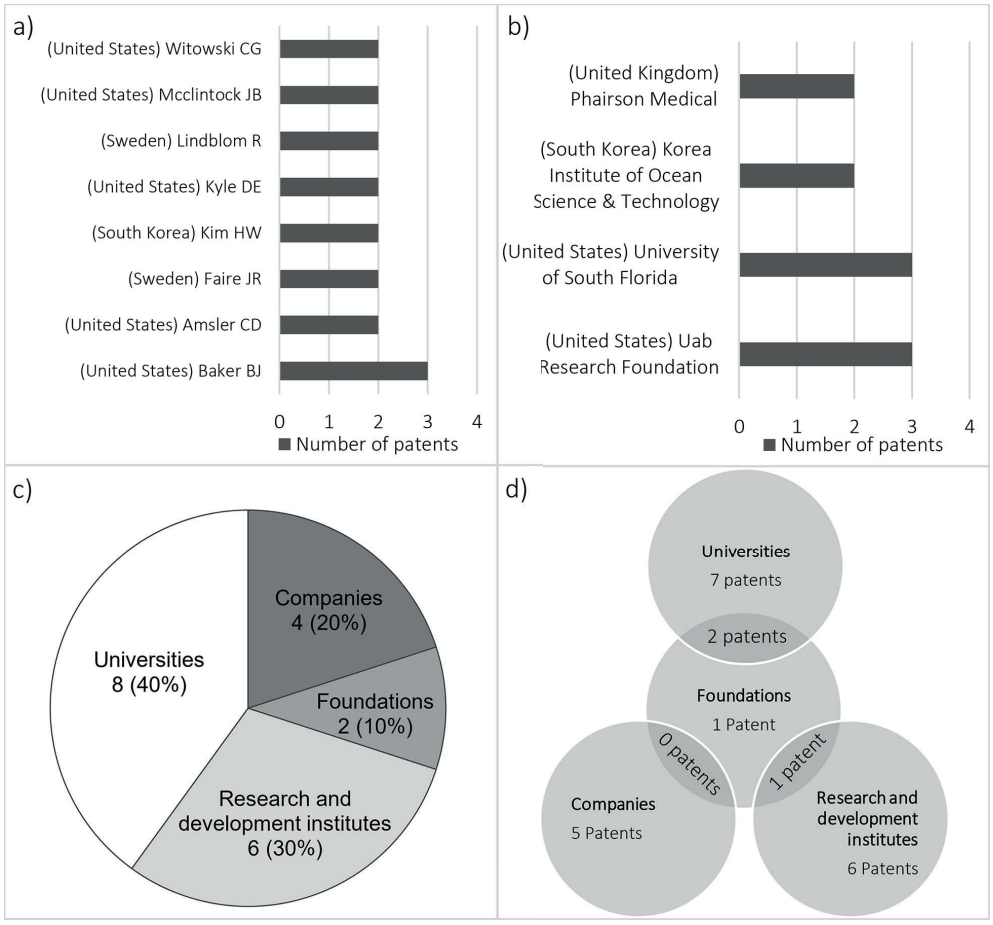

Figure 3. Analysis of inventors and assignees of the patents with antarctic antimicrobial compounds. a) Main* patent inventors, b) Main* patent assignees, c) Number of different assignees in each category and d) Venn diagram illustrating the distribution of the patents according to the categories of their respective assignees. *All other assignees/ inventors, omitted here, are present in only one patent family each.

Medical, which is currently dissolved, owns two documents each, being the main assignees when considering the patent documents with a single owner. As Figure 3c illustrates, most of the assignees are universities (n=8, 40%), while the second largest group comprises research and development institutes (n=6, 30%), the two groups are responsible for nine and seven of the 22 documents, respectively, according to the patent distribution shown in Figure 3d.

Analysis of the International Patent Classification (IPC) codes

Most of the patent documents in this review (n=17, 77.27%) have codes belonging to IPC class A61, which corresponds to patents involving medical or veterinary science. At the same time, another significant group of documents has the class code C12 (n=9, 40%), which corresponds to patents involving biochemistry, microbiology, and enzymology. As expected, when considering the distribution of documents according to IPC group codes, the leading group is A61P31, a group of patents on anti-infectives, whose code is present in nine out of 22 patent documents (40%). Other numerous groups are A61K38, a group of medicinal preparations containing peptides, with seven documents (31.8%), and A61K31, a group of medicinal preparations containing active organic ingredients, with six documents (27.3%). Among the groups outside the A61 class, the main one is C07K14, with four documents (18.2%), which corresponds to a group of patents involving peptides with more than 20 amino acids (World Intellectual Property Organization 2020).

Evaluation of antimicrobial compounds and source organisms

Taxonomy of Antarctic organisms referred to in the patents

As shown in Table II, the 22 patent families selected in this review refer to compounds with antimicrobial activity obtained from a total of 20 different species of Antarctic organisms, including species of bacteria, fungi, lichens, fishes, seaweed, sponges, krill, penguins and springtails. The most recurrent organism in the patent documents was the Antarctic krill, *Euphasia superba*, present in seven out of 22 documents (31.8%), followed by bacteria, present in four documents (18.2%), with five species mentioned, two of them belonging to the genus *Streptomyces*. Sponges were mentioned in three documents (13.6%) with two different species. It is also worth mentioning the diversity of Antarctic seaweed species referred, with a total of five distinct species mentioned in two patent families.

Compounds with antimicrobial activity obtained from Antarctic bacteria

Although data on Antarctic microorganisms are relatively scarce compared to microorganisms from other environments, there are several genera and species of bacteria isolated from Antarctica that produce compounds with different mechanisms of antimicrobial action in the academic literature (Núñez-Montero & Barrientos 2018). Among these studies, several innovative molecules have been reported, with activity against multiple clinically relevant pathogens, such as *Staphylococcus aureus*, *Escherichia coli*, *Candida albicans*, and even resistant and multi-resistant strains of *Pseudomonas aeruginosa* and *Klebsiella pneumoniae* (Lo Giudice et al. 2007, Bratchkova & Ivanova 2011, Rojas et al. 2009, Cheah et al. 2015). However, despite the diversity of studies in the academic literature pointing to the commercial and therapeutic potential of Antarctic bacteria in the field of antimicrobials, only four patent documents were found mentioning Antarctic bacteria, which referred to a total of only five different taxa, identified as *Janthinobacterium* sp., *Flavobacterium* sp., *Streptomyces radiopugnans*, *Streptomyces* sp. and *Bacillus* sp.

The patent US8956669B2 (Bej 2015) refers to pigments isolated from two Antarctic bacteria phylogenetically associated with the genera *Janthinobacterium* and *Flavobacterium*, respectively. The first one is the producer of a purple-violet pigment (PVP), identified by Nuclear Magnetic Resonance (NMR) as (3-[5-(3-hydroxyl-1H-indol-3yl)-2-R1-1H-pyrrol-3-ylidene]-2-R1-1H-indol), a molecule structurally similar to violacein, another antimicrobial pigment obtained from the bacterium *Chromobacterium violaceum* (Mojib et al. 2010, Rettori & Duran 1998). The second bacterium, *Flavobacterium* sp., produced a yellow/orange pigment (YOP), closely related to other carotenoid pigments of *Flavobacterium* and identified as a probable flexirubin (Mojib et al. 2010). Both pigments have been demonstrated as antimicrobial agents with promising activity against bacteria of the genus *Mycobacterium*, including *Mycobacterium tuberculosis*, the etiologic agent of tuberculosis, a disease considered by the WHO as a global health emergency and frequently associated with multidrug resistance, thus requiring new medications (World Health Organization 2008).

Another document, US10501492B2 (Mishra & Mahajan 2019), reports a new antibacterial compound obtained from the fermented broth of an actinomycete identified as *Streptomyces radiopugnans* MTCC 5447, the first bacterium of the species to be isolated from Antarctica (Bhave et al. 2013). The antimicrobial potential of actinomycetes is already well known in

Table II. Phylogenetic distribution of the antarctic organisms referred to as source of compounds with antimicrobial activity in the patent literature.

Organisms Types	Number of patents	Species	Product category	Antimicrobial activities	Reference
Bacteria	4	*Janthinobacterium* sp.	Pigments	Antibacterial	Bej 2015
		Flavobacterium sp.			
		Streptomyces radiopugnans	NI*	Antibacterial	Mishra & Mahajan 2019
		Streptomyces sp.	Angucyclinone	Antibacterial	Bringmann et al. 2005
		Bacillus sp.	Fermentation supernatant	Antifungal	Chen et al. 2019
Fungus	1	*Penicillium crustosum*	Indole Alkaloid	Antiviral	Li et al. 2019
Lichen	1	*Stereocaulon alpinum*	Depsidone and pseudodepsidone	Antibacterial	Yim et al. 2014
Fishes	2	*Notothenia coriiceps*	Peptides	Antibacterial and Antifungal	Shin et al. 2018
		Parachaenichthys charcoti			
		Chionodraco hamatus	Peptides	Antibacterial	Buonocore & Scapigliati 2012
Seaweeds	2	*Palmaria decipiens*	Solvent Extracts	Antibacterial and antifungal	Lund et al. 2013
		Plocamium cartilagonuem			
		Desmarestia anceps			
		Prasiola crispa			
		Gigartina skottsbergii	Solvent Extracts	Antiviral	Olphen et al. 2014
Sponges	3	*Dendrilla membranosa*	Diterpenes	Anti-Leishmania	Baker et al. 2018
				Antibacterial	Baker et al. 2017
		Kirkpatrickia varialosa	Alkaloid	Antiviral	Blunt et al. 1993
Krill	7	*Euphausia superba* (Antarctic Krill)	Krillases (Enzymes)	Antibiofilm	Kochinke et al. 2013
				Antibacterial, antiviral and antifungal	Lindblom & De Faire 2002
				Antifungal	Faire et al. 2000
			Proteins	Antibacterial	Guo et al. 2019
			Polysaccharide	Antibacterial	Lu et al. 2017, Zhao et al. 2014, Yang et al. 2020
Penguin (Stomach)	1	*Aptenodytes patagonicus* (king penguin)	β-defensins (Peptides)	Antibacterial and antifungal	Bulet et al. 2009
Springtail	1	*Cryptopygus antarcticus*	Enzymes	Antifungal	Lo Giudice et al. 2007

***NI - Not identified.**

the academic literature and is recognized as one of the most biotechnologically useful microorganisms in this area, especially the genus *Streptomyces* (Elbendary et al. 2018, Nedialkova & Naidenova 2005). The compound referred to in this patent has been identified as a broad-spectrum antibacterial, with a molecular formula not yet reported in the literature ($C_{71}H_{83}N_{19}O_{18}S_5$), especially useful in the treatment of infections by methicillin-resistant *S. aureus* (MRSA), vancomycin-resistant *Enterococcus* spp. (VRE), and even strains of *M. tuberculosis* resistant to four of the standard antibiotics (rifampicin, isoniazid, pyrazinamide, and ethambutol), indicating the great potential of this compound for application in the treatment of multidrug-resistant tuberculosis.

Another bacterium of the genus *Streptomyces*, which was identified as *Streptomyces* sp. Strain KC 1030, was reported in the patent document DE102004004906A1 (Bringmann et al. 2005), that claims a novel compound with antibacterial activity. This compound had the structure determined by Nuclear Magnetic Resonance (NMR) and was identified as gephyromycin, a molecule belonging to the class of angucyclinones, a well-known group of antibiotics commonly isolated from *Streptomyces* spp. Gephyromycin was tested against the Gram-positive bacteria *S. aureus* and *Bacillussubtilis*, the gram-negative bacteria *E. coli* and *Vibrio* sp., and the yeast *C. albicans*. However, it showed selective antimicrobial activity against the Gram-positive bacteria, with no effect observed on the other microorganisms (Rohr & Thiericke 1992).

Finally, the patent CN105420164B (Chen et al. 2019) refers to the use of a bacterium isolated from Antarctica, identified as *Bacillus* sp. N311, in the preparation of a fermentation supernatant with strong antifungal inhibitory activity against several phytopathogenic fungi, namely: *Fusarium* sp., *Paecilomyces variabilis*, *Alternaria alternata*, *Trichoderma viride*, *Rhizoctonia solani*, *Botrytis*, and *Agaricusbisporus*, thus showing great potential for application in the biological control of plant diseases in agriculture.

This patenting profile demonstrates a particular discrepancy between what is observed in the academic and patent literature about antimicrobial compounds isolated from Antarctic bacteria. While the scientific papers report numerous studies with positive results for antimicrobial activity, as shown in a literature review of 2018 (Núñez-Montero & Barrientos 2018), few patents are observed in this respect. This may indicate a state of underutilization and immaturity in the field of antimicrobials obtained from Antarctic bacteria, Nichols hypothesis reinforced by the temporal distribution of these patent documents, since the four patent families referring to Antarctic bacteria are recent, with priority years between 2004 and 2015. However, taking into account that bioprospecting in Antarctica has started recently (Nichols et al. 2002), and considering the growth trend in the amount of patent application on antimicrobials of Antarctic origin, mentioned earlier in this paper, more patent fillings involving Antarctic bacteria can be expected in the following years.

Antimicrobial compounds obtained from Antarctic fungi and lichens

Similar to bacteria, fungi are a group of microorganisms frequently associated with pharmacologically useful molecules, including multiple types of antimicrobials (Gonçalves et al. 2015). However, in this review, only one patent family was found referring to an Antarctic fungus as a source of compounds with antimicrobial activity, the family of the Chinese patent CN106892854B (Li et al. 2019). The referred compound was identified as a new indole

alkaloid produced by the fungus *Penicillium crustosum* PRB-2, which belongs to one of the most frequently isolated and biotechnologically active fungal genera in Antarctica (Brunati et al. 2009). The alkaloid has demonstrated significant antiviral activity against the H1N1 virus, the etiologic agent of influenza A and cause of two pandemics, the Spanish flu pandemic, 1918-1920, and, more recently, swine flu pandemic, 2009-2010 (Xu et al. 2010). Theanti-H1N1 activity was determined by observing the inhibitory effect in Madin-Darby Canine Kidney cells (MDCK cells) inoculated with the H1N1 virus. As a result, the compound showed, under the same concentration, a higher inhibitory effect than the positive control-drug, ribavirin, commercially used in the treatment of influenza. Therefore, it has shown to be a potential alternative for the development of antiviral drugs used against influenza caused by the H1N1 virus.

Additionally, a patent was found reporting the use of an Antarctic lichen as a source of compounds with antimicrobial activity, the South Korean patent KR101452324B1 (Yim et al. 2014). Lichens consist of symbiotic associations between fungi and algae and are important components of several ecosystems. They are well known producers of secondary metabolites of several chemical classes, with a variety of biological activities described, such as antimicrobial, antioxidant, analgesic, and antipyretic (Müller 2001, White et al. 2014). However, there are very few reports in the academic literature of bioactive compounds of Antarctic lichens (Paudel et al. 2008, Kumar & Müller 1999). The lichen reported in this patent was *Stereocaulon alpinum*, identified as the producer of two compounds with antimicrobial activity, lobaric acid, belonging to the class of depsidones, and lobarstin, belonging to the class of pseudodepsidones, two classes of secondary metabolites frequently isolated from lichens (Paudel et al. 2008). The two compounds demonstrated antibacterial activity against the Gram-positive bacteria *B. subtilis* and *S. aureus*, but lobarstin proved to be more efficient than lobaric acid.

Compounds with antimicrobial activity obtained from Antarctic fish

Fish have a much slower adaptive immune response than other animals and are relatively ignored organisms as a source of antimicrobials, with very few isolated compounds. Nevertheless, fish have very low infection rates due to the efficiency of their innate immunity, which encompasses a group of compounds of particular importance for these animals, the antimicrobial peptides (AMP's). These molecules are the most frequently isolated among the few antimicrobial compounds obtained from fish (Ravichandran 2010). In this review, two patent documents referring to antimicrobial compounds obtained from Antarctic fish species were identified, named KR101924808B1 (Shin et al. 2018) and ITVT20103A (Buonocore & Scapigliati 2012), both referring to compounds of peptide nature.

The first document, KR101924808B1 (Shin et al. 2018), claims two new AMPs similar to moronecidine, which is an already known AMP isolated from the hybrid bass fish (Shin et al. 2017). The two moronecidine-like peptides, identified from analysis of fish genomes using the BLAST (Basic Local Alignment Search Tool) algorithm, were named moroNC-NH_2 (Amino Acid Sequence: FFWHHIGHALDAAKRVHGMLSG-NH2 – Accession GenBank XP_010768425) and moroPC-NH_2 (Amino Acid Sequence: FFGHLFRGIINVGKHIHGLLSG-NH2 – Accession GenBank AOW44479), respectively, from the Antarctic fish *Notothenia coriiceps* and *Parachaenichthys charcoti*. Both peptides showed strong antimicrobial activity against strains of the Gram-negative bacteria *Shigella sonnei* and *E. coli*, and against the fungus

Candida tropicalis. The peptide from *P. charcoti*, moroPC-NH_2, also showed strong antimicrobial activity against the Gram-positive bacteria *Streptococcus pyogenes*, *Staphylococcus aureus,* and *Listeria monocytogenes*. In addition, both peptides showed low sensitivity to salt concentrations, cold tolerance, and low toxicity, being both potentially applicable to the development of antimicrobial drugs and to the preservation of food without providing risks to human health.

The second patent document, ITVT20103A (Buonocore & Scapigliati 2012), claims a new antimicrobial peptide named chionodracine, isolated from the Antarctic fish *Chionodraco hamatus*. The peptide presented significant antimicrobial activity against the Gram-negative bacterium *Escherichia coli* and the Gram-positive *Bacillus cereus*, especially at low temperatures, which may indicate that this peptide is also specially adapted to cold (Buonocore et al. 2012).

Compounds with antimicrobial activity obtained from Antarctic seaweed

Seaweeds are known to have great potential as sources of bioactive compounds because of the large number of secondary metabolites they produce. However, the state of the research on the pharmacological potential of Antarctic seaweeds is still premature, with few studies published on the topic, even though the Antarctic region is rich in algae clusters (Martins et al. 2018). In the patent literature, however, two patent documents were found referring to five different species of Antarctic seaweeds as a source of antimicrobial compounds, the Brazilian deposit BR1020130047929-A2 (Lund et al. 2013) and the North American US2014274883A1 (Olphen et al. 2014).

The first document, BR1020130047929-A2 (Lund et al. 2013), discusses the use of individual extracts and combinations of four species of Antarctic seaweeds, the red seaweeds *Palmaria decipiens* and *Plocamium cartilagineum*, the brown seaweed *Desmarestia anceps* and the green seaweed *Prasiola crispa*. The document indicates the possible application of the extracts as antibacterial and antifungal agents. For this purpose, different types of seaweed polar solvent extracts were tested: aqueous, hexanic, methanolic, ethanolic, acetonic, etheric and chloroformic extracts, against strains of *Candida albicans*, *C. parapsilosis*, *C.famata*, *C. glabrata*, *C. lipolutica*, *E. coli*, *Enterococcus feacalis*, *P. aeruginosa,* and *S. aureus*. However, in the document, only data of the Minimum Inhibitory Concentration (MIC) of *Prasiola crispa* algae extracts were shown, which exhibited comparatively stronger antimicrobial actions against *E. faecalis* and *P. aeruginosa*.

The document US2014274883A1 (Olphen et al. 2014), in turn, claims the antiviral activity of extracts from the Antarctic seaweed *Gigartina skottsbergii*, but indicates that other species of the same genus can be equally useful. In addition, this patent claims the individual use of any of the active compounds contained in the extracts, of which the study identified 18 sequences of amino acids. In the document, Gigartine extracts have been shown to possess antiviral activity capable of inhibiting, controlling, and destroying viruses, especially useful against various strains of influenza viruses.

Compounds with antimicrobial activity obtained from Antarctic sponges

Marine sponges host a wide range of biologically active molecules, including antimicrobial compounds that are potentially clinically useful. It is believed that sponge antimicrobial molecules have the role of preventing predation, excessive growth, and incrustations of microorganisms (McClintock & Gauthier 1992).

In this review, three patent documents involving sponges as a source of antimicrobials were found. Two of them, named US9872849B2 (Baker et al. 2018) and WO2017177142A1 (Baker et al. 2017), belong to the University of South Florida and refer to the same species, *Dendrilla membranosa*, whose antimicrobial activities were identified in a screening program.

The first document, US9872849B2 (Baker et al. 2018), claims novel diterpenoid secondary metabolites active against *Leishmania donovani*, the protozoan that causes leishmaniasis, as well as other species of the same genus. The compounds were identified as Aplysulphurin, Tetrahydroaplysulphurin and eight other semi-synthetic derivatives, named membranolides A to F. Of these, the molecules with the most potent anti-leishmanial activity were Aplysulphurin and the membranolides G and H. The second document about the *Dendrilla membranosa* sponge, WO2017177142A1 (Baker et al. 2017), claims antibacterial activity of a new compound, also from the diterpenoid classes, identified as darwinolide. The antimicrobial action of darwinolide has shown to be useful in the elimination of infections and prevention of biofilm formation by methicillin-resistant *Staphylococcus aureus*, being indicated by the authors for application on surfaces, whether living tissues or inanimate surfaces, suggesting a potential use in the prevention of biofilm in medical devices as well.

A third document, GB9301952D0 (Blunt et al. 1993), refers to the application of compounds isolated from extracts of the Antarctic sponge *Kirkpatrick variolosa*, of which an alkaloid, identified as variolin-B, showed considerable antiviral activity against the Herpes simplex type I DNA virus.

Compounds with antimicrobial activity obtained from Antarctic Krill

According to the Antarctic Biological Prospecting Database, until the beginning of the last decade, most biotechnological innovation patents for Antarctic organisms were related to the use of Antarctic krill, *Euphausia superb* (Yarzábal 2016, XXXV Antarctic Treaty Consultative Meating 2012, XXXVI Antarctic Treaty Consultative Meating 2013). This organism is a species of crustacean of fundamental ecological role in the Antarctic oceans, it is rich in nutrients and has a high protein content, being referred to as a source of several types of active principles, such as peptides with antihypertensive activity, photoprotective compounds efficient against ultraviolet light, carotenoids, and chitins (Sun & Yan 2001, Hatanaka et al. 2009, Zhao et al. 2013). Notoriously, it is the most economically important Antarctic organism, with hundreds of tons being fished annually and increasingly related to patents applied for over the years (Nicol 2011).

In accordance with this scenario, almost one-third of the patent families selected in this review involves applications of Antarctic Krill compounds, mainly enzymes. The document WO2013149809A1 (Kochinke et al. 2013), for example, refers to a mixture of enzymes obtained from Antarctic Krill useful for the removal of bacterial plaque and biofilms in soft tissues and mucous membranes, as well as for the prevention of biofilm formation in tissues where they are expected to form. The patent EP0642351B1 (Lindblom & De Faire 2002), in turn, claims the use of an enzyme composition obtained from Antarctic Krill, including proteolytic enzymes, for topical use in the treatment of a wide range of conditions, including bacterial, fungal and even viral infections such as Herpes. Another patent document, US6030612A (Faire et al.

2000), claims a method for the treatment of fungal infections, such as topical, oral, vaginal, urinary, rectal or esophageal infections, through the administration of a sufficient amount of a multifunctional hydrolase enzyme derived from Antarctic Krill. The document also indicates that enzymes with similar structural composition obtained from other crustaceans, or fish, can be employed for the same purpose.

The patent document CN110512304A (Guo et al. 2019), on the other hand, refers to the manufacture of a composition based on chitosan and Kryll-derived proteins for the production of fibers with antimicrobial properties useful in the manufacture of medical dressings, antibacterial clothing and other similar products. Meanwhile, patent CN104630313B (Lu et al. 2017) discusses a method for preparing low molecular weight chitosan with antimicrobial activity against *E. coli* and *S. aureus*, using Antarctic Krill as raw material. Similarly, document CN103690956A (Zhao et al. 2014) refers to the use of chitosan obtained from the Antarctic Krill shell to compose a hemostatic powder with antimicrobial properties, able to stop bleeding while protecting the wound against microorganisms. However, the document indicates the addition of an antimicrobial drug to the composition to maximize the antimicrobial protective effect, while the central role of the chitosan powder is the hemostatic effect. Finally, the patent document CN110724311A (Yang et al. 2020) refers to the use of chitosan extracted from the Antarctic Krill shell to prepare a degradable, antibacterial, inexpensive product with excellent mechanical properties for food packaging.

It is pertinent to note that, despite the higher number of patent documents involving Antarctic Krill, this is not a reflection of an equally large number of new compounds. Most of these documents are correlated, referring to chitosan and proteolytic enzymes, corresponding to new applications/adaptations of an already known group of compounds.

Compounds with antimicrobial activity obtained from Antarctic penguins

Antimicrobial compounds obtained from birds are already well known in the academic literature. Antimicrobial peptides of the β-defensin class have already been identified in the blood and epithelial cells of birds such as chicken, turkey, and ostrich (Cuperus et al. 2013, Sugiarto & Yu 2004). These peptides have been shown to be active against a wide range of microorganisms, including Gram-positive and Gram-negative bacteria, filamentous fungi and yeasts, demonstrating considerable potential for applications in health products (Sugiarto & Yu 2004).

One of the patents of this review, EP1517916B1 (Bulet et al. 2009), reported a new group of antimicrobial compounds of the β-defensin category, obtained from an Antarctic penguin species, the king penguin, *Aptenodytes patagonicus*. The peptides were found in the stomach contents of male king penguins, with the function of conserving the food content against degradation by microorganisms of its own microbiota during the incubation period, in which the penguin fasts for up to 2 weeks. The new compounds were called spheniscins, in reference to the name of the family Spheniscidae, to which the king penguin belongs. The sphenicins showed considerable antimicrobial activity against the Gram-positive bacteria *Micrococcusluteus*, *Bacillus* spp., *S. aureus*, *S. haemolyticus*, and *Nocardia asteroids*, the Gram-negative bacteria *E. coli* 1106 and *Vibrio metshnikovii* NCTC 8483, and the fungi *C. albicans* and *C. tropicalis*. Results evidenced great potential for applications in antimicrobial drugs, as well as applications in the food industry to protect food against microorganisms.

Antimicrobial compounds obtained from Antarctic springtails

Springtails belong to the Collembola order, which is constituted by small, numerous and diverse aptero and hexapod arthropods, usually smaller than 6mm, found throughout the world (Fountain & Hopkin 2005, Lee et al. 2009). They form one of the largest groups of invertebrates living on or near the ground. The most common Antarctic representative is *Cryptopygus antarcticus*, or Antarctic Springtail, until now very poorly associated with some biotechnological potential, being more used for ecological monitoring and serving as an indicator for the presence of microplastic in the environment (Bergami et al. 2020). However, the inventors of patent KR100913233B1 (Lee et al. 2009) identified and isolated an enzyme with β-1.3 glucanase activity from the Antarctic springtail. These enzymes are already well known and widely applied, they break glycosidic linkages of the β-1,3 type and may show several biotechnological applications (Mauch et al. 1988), including the control of fungi and yeasts by lysing the cells of the species that have β-1,3-glucan in the cell wall. The inventors of the patent report considerable antifungal activity against *Debaryomyces hansenii*, *C. albicans,* and the phytopathogen *Magnaporthe grisea*.

Main therapeutically applicable findings

As shown, there is a wide diversity of compounds obtained from Antarctic organisms with therapeutically promising antimicrobial activity, most of them being secondary metabolites of peptide/protein nature, since 11 of 22 patents are characterizing the activity of peptides/proteins, as can be seen in Table II. In particular, it is worth mentioning the compounds active against antibiotic-resistant infections, which have caused increasing mortality in recent years and become more and more challenging to treat. Among these infections, this review found possible therapeutic alternatives to the main etiological agents in infections and biofilms, such as methicillin-resistant *S. aureus*, vancomycin-resistant *Enterococcus* spp. (VRE) and strains of *M. tuberculosis*, including a strain resistant to the four standard antimicrobial drugs used in tuberculosis treatment (rifampicin, isoniazid, pyrazinamide, and ethambutol) (Bej 2015, Mishra & Mahajan 2019).

In the field of antifungals, the main target pathogens reported were of members of the genus *Candida*, but without notable activity. Meanwhile, in the field of antivirals, the main targets were strains of influenza virus, mainly H1N1, for which a compound was found with an in vivo efficacy superior to the commercially used drug, ribavirin (Li et al. 2019, Olphen et al. 2014). Additionally, antiprotozoal compounds were found against species of the genus *Leishmania*, including *Leishmania donovani*, which causes leishmaniasis, a severe and geographically widespread disease (Baker et al. 2018, Lukes et al. 2007). This scenario is promising regarding the potential to obtain antimicrobial drugs from active principles isolated from Antarctic organisms, particularly considering that the diversity of compounds described herein is present in a small number of patent documents, with a tendency to grow.

Bioprospecting definition and politics in the Antarctic Treaty Consultative Meeting (ATCM) forum and Scientific Committee on Antarctic Research (SCAR)

The exploration of natural resources in Antarctica is a complex subject. The overwhelming richness of Antarctic natural resources includes many different life forms. However, bioprospecting and the potential biotechnological use of Antarctica organisms have been raised as an issue of

concern by some countries such as Argentine, Australia, Belgium, Brazil, Chile, France, Netherlands, New Zealand, Sweden, United Kingdom and others in various ATCM meetings. According to Working Paper 36 proposed by Netherlands, Belgium and France, presented at the XXX ATCM, biological prospecting was first discussed at ATCM XXV based on a working paper submitted by the United Kingdom (ATCM XXV WP 43 entitled 'Biological Prospecting in Antarctica (XXX Antarctic Treaty Consultative Meating 2009). After that, other Working Papers on Antarctic bioprospecting were proposed in further ATCM meetings. Despite ATCM Parties recognized that Antarctic bioprospecting represents a research area and deserves action, until now there is not an official definition and regulation for biotechnological use of Antarctic organisms. There is a consensus among the ATCM Parties that Antarctic bioprospecting represents a complex issue, which will probably undergo a long and slow process until the final regulation. Recently, in the SCAR Open Science 2020 (organized by Scientific Committee on Antarctic Research), researchers of several countries presented results of their Antarctic bioprospecting studies, showing that diverse organisms are able to produce different compounds with potential biotechnological applications (Rosa et al. 2020). The increase of bioprospecting studies in Antarctica indicates that ATCM Parties should regulate this area urgently.

CONCLUSIONS

This patent review has revealed relatively few patent documents on Antarctic organisms as a source of compounds with antimicrobial activity. However, there has been an increasing trend in the number of applications over the decades, which is the reason why a considerable increase in the number of patents is expected in the coming years. Of particular note is the participation of the United States, South Korea and, more recently, China, as the most involved countries in research and patenting of antimicrobials of Antarctic origin.

Furthermore, although few in number, patent documents have reported high diversity of biological species as sources of the compounds, which confirms the antimicrobial biotechnological potential harbored by the Antarctic biota. It is worth highlighting the versatility of the Antarctic krill, the most recurrent organism among the patent documents, and the potential of the Antarctic bacteria, especially the genus *Streptomyces*, producers of the compounds of highest therapeutic relevance.

In general, most of the antimicrobials isolated from Antarctic organisms were of protein/peptide nature, and the majority had a novel molecular structure. The most common antimicrobial activity was antibacterial. However, antifungals, antivirals, and even anti-leishmanial were also obtained. In conclusion, the main findings of this review include active ingredient options for the treatment of the most relevant treatment-resistant infections, such as methicillin-resistant *S.aureus*, vancomycin-resistant *Enterococcus* spp. and multidrug-resistant *M. tuberculosis*. Further studies are required to elucidate the mechanisms of action of these compounds and to evaluate their therapeutic viability with regard to in vivo efficiency and human toxicity, in order to determine whether they are indeed viable drugs.

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