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Medicinal applications and environmental fate of antimicrobial peptides: a review

Owen Daniel¹ · Thomas Thiebault¹ · Elodie Guigon¹

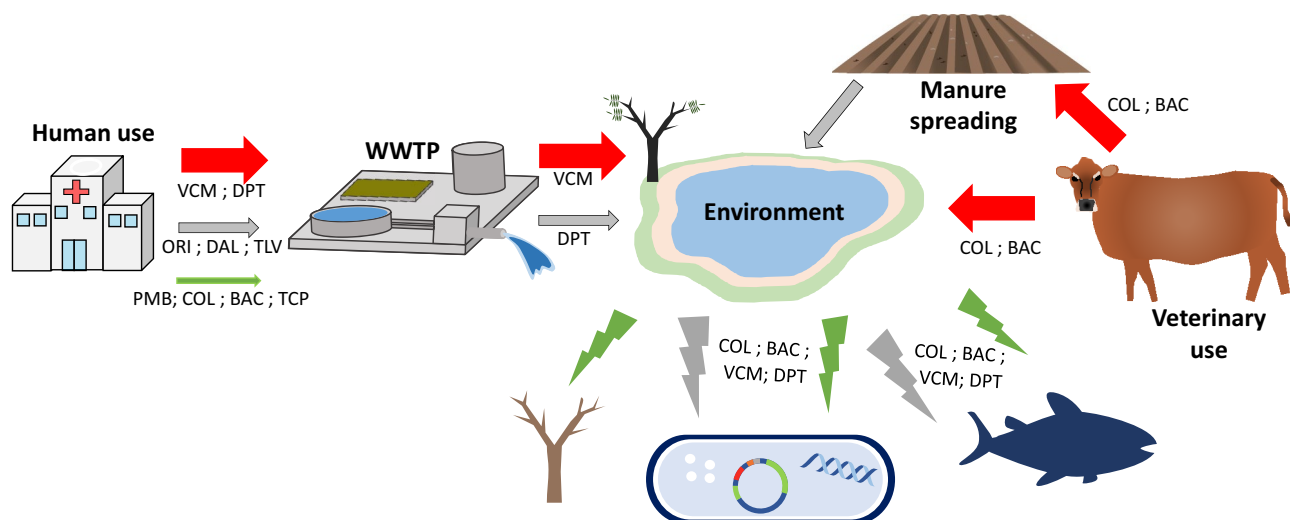
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Abstract

Antimicrobial resistance is a major global issue endangering human, animal, and environmental health, calling for alternative antibiotics. Here, we review antimicrobial peptides with focus on their history, properties, medicinal use, clinical applications, and environmental fate. Antimicrobial peptides include glycopeptides, daptomycin, polymyxins, gramicidin, tyrocidine, and bacitracin. We present their environmental degradation pathways such as hydrolysis, photolysis, biodegradation, and adsorption, and their potential toxicity. Although antimicrobial peptides are increasingly used, their environmental occurrence and transformation products remain poorly known. In particular, emission sources such as wastewater treatment plants are poorly documented, and the influence of antimicrobial peptides on environmental antimicrobial resistance is still largely unknown.

Graphical abstract



Keywords Antimicrobial peptide · Vancomycin · Environmental fate · Photolysis · Adsorption · Biodegradation

Introduction

Before the widespread use of antibiotics, bacterial infections were responsible of the majority of the deaths [1]. The discovery of penicillin in 1928, prontosil in 1937, and the systematic screening of antibiotics produced by microbes [2, 3] enabled rapid advancements in human medicine and significantly increased the human life expectancy throughout

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the twentieth century [1]. Many classes of antibiotics were discovered during the “Golden Age” of antibiotic discovery (1940–1960). However, the extensive use of these drugs in both human and veterinary medicine has led to the emergence and spread of antimicrobial resistance. While antimicrobial resistance primarily originates within the healthcare system, the presence of antibiotics in the environment contributes to its development and dissemination, exacerbating the global antimicrobial resistance crisis. Antibiotics and their transformation products are now widely detected across ecosystems impacted by human activity [4–6]. This contamination may promote the development of resistance in natural microbial communities, potentially impacting ecosystems and human health if resistance genes are transferred to human pathogens. Although this environmental dimension of antimicrobial resistance is still poorly understood, it could have significant consequences [7–9]. By 2050, antimicrobial resistance could be associated with 8.3–10 million deaths worldwide and cost 4.6 billion in the USA alone [10–12]. To tackle antimicrobial resistance, various proposals have been made, including the development of new antibiotics that are less prone to resistance. However, there remains a shortage of new, effective antibiotics [1, 3].

Antimicrobial peptides are natural molecules synthesized by most living organisms, from bacteria to plants and animals, and play important roles in their innate immune systems [13]. Due to their ability to neutralize a wide range of pathogens, including bacteria, yeasts, fungi, and certain viruses, these peptides are gaining increasing attention as promising alternatives to conventional antibiotics in the context of antimicrobial resistance crisis [14]. Their mechanisms of action are diverse and include both membrane-targeting and non-membrane-targeting mechanisms, which are often non-specific, thereby reducing the likelihood of resistance development [15, 16]. However, antimicrobial peptides have several limitations including toxicity, low stability and high production costs [17], necessitating the use of technologies such as cyclization or halogenation to improve their clinical properties [16]. Currently, ten antimicrobial peptides are approved for use in human and veterinary medicine, spanning several classes such as glycopeptides, lipopeptides, and polymyxins [14].

Like conventional antimicrobials, antimicrobial peptides can enter the environment through wastewater effluent, agricultural runoff, and pharmaceutical manufacturing discharge [5, 18, 19]. Once released, their persistence depends on attenuation processes such as hydrolysis, photolysis, biodegradation and adsorption, and they may degrade into transformation products [20]. Although antimicrobial peptides are generally considered less likely than traditional antibiotics to promote resistance, studies have shown that bacteria can develop resistance mechanisms [21–23]. This raises concerns about the long-term environmental and

clinical consequences of antimicrobial peptides use. Their presence in the environment could contribute to the development and spread of antimicrobial resistance, thereby reducing their clinical effectiveness, and impact natural microbial communities, which could lead to ecological disruptions [7, 24]. Notably, the role of antibiotic contamination in the antimicrobial resistance crisis remains poorly understood and requires further investigation [8, 25]. Antimicrobial resistance is a global threat to human, animal, and environmental health, underscoring the “One health” Concept [26]. Only a balanced approach, maximizing the beneficial use of antimicrobial peptides while minimizing ecological risks, will allow to fully realize their clinical potential while preserving ecosystem health. Therefore, understanding the environmental fate and impacts of antimicrobial peptides is essential. This review aims to assess the current state of knowledge on the environmental fate and risks of approved antimicrobial peptides, identify current gaps in the scientific literature, and guide future research efforts (Fig. 1).

Methodology

This review synthesizes the current knowledge on the environmental fate processes and environmental impacts of commercialized antimicrobial peptides (Sects. “Antimicrobial peptide environmental fate and impacts on the environment” and “Antimicrobial peptides”). The reviewing method is presented in Fig. 2. Prior to conducting this review, a systematic literature search was performed on May 2024 on several databases, such as Web of Science, Scopus, and Google Scholar. Carefully selected keywords, such as environmental fate, hydrolysis, photolysis, biodegradation, adsorption, phototransformation, surface water, and river water were used to guide the search. The complete list of keywords is provided in Text S1. Citation searches were also used. Based on titles and abstracts, all the scientific articles addressing the fate processes, environmental occurrence, and impacts of antimicrobial peptides were considered relevant and included, resulting in a total of 114 publications.

Only peer-reviewed articles were selected, and no geographical sorting was performed. The selected articles were then thoroughly reviewed. Sixteen articles were excluded because of outdated methodology or data considered out of the scope of the review, i.e., not representative of environmental conditions, no antimicrobial peptide quantification. The final dataset comprised 98 scientific publications providing valuable information. Depending on the objectives, either raw data or general conclusions were extracted from the articles for standardization and comparison purposes. Additionally, data on the history, use, and properties of antimicrobial peptides (Sect. “Antimicrobial peptides used in medicine, history, clinical positioning, and properties”)

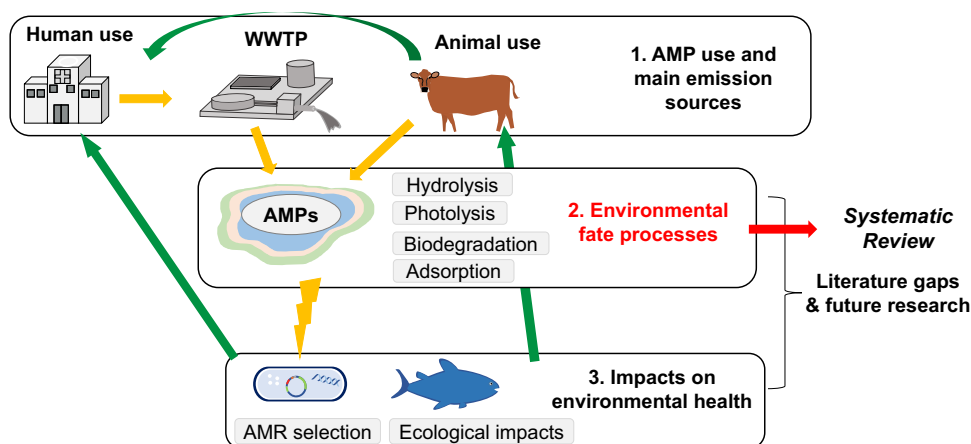
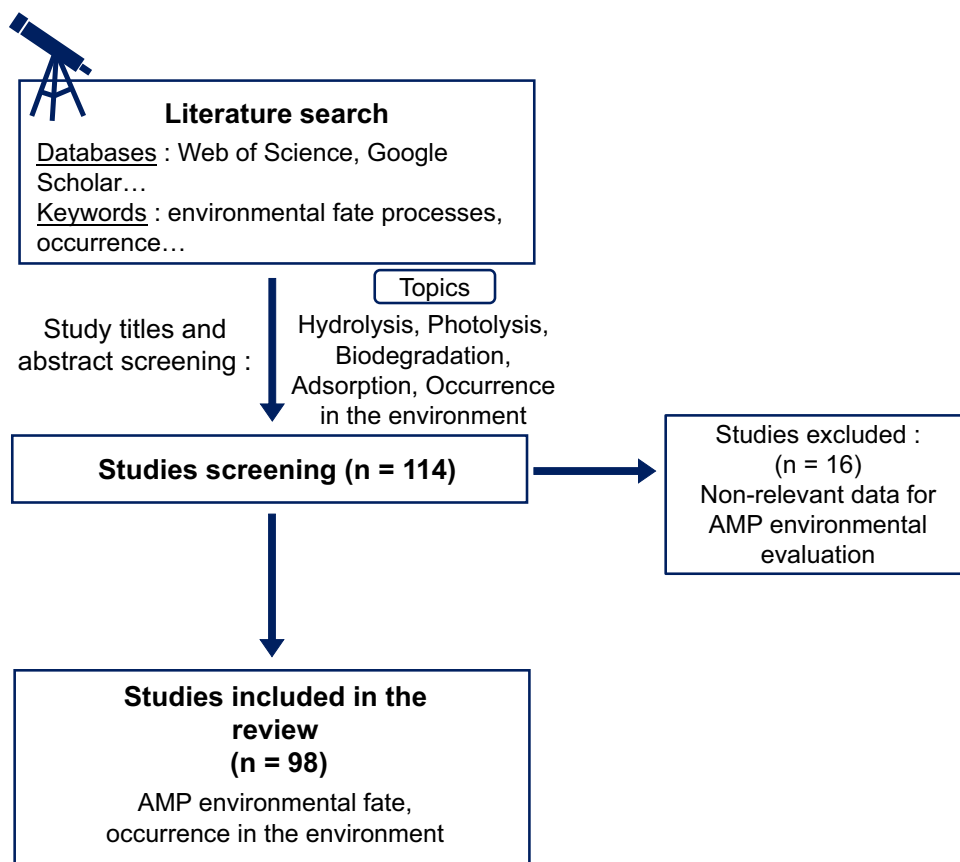


Fig. 1 Topics of this article. This article reviews antimicrobial peptides (AMPs) fate and impacts on the environment, with the initial hypothesis that they behave like conventional antibiotics. Antimicrobial peptides could be emitted into the environment from two main sources, human use (via wastewater treatment plants) and animal use. A fraction of used antimicrobial peptides in excreted unchanged is transferred to the environment. In the environment, the fate of the antimicrobial peptides should be driven by environmental fate processes, i.e., hydrolysis, photolysis, biodegradation, adsorption that control their mobility and persistence. Antimicrobial peptides could

impact natural microbial communities, nontarget organisms, and therefore the ecosystems. Antimicrobial peptides could also select antimicrobial-resistant bacteria. Environmental antimicrobial resistance (AMR) factors can be transferred to human and animals. If these factors are integrated into human pathogens, it creates antimicrobial-resistant pathogens and worsen the antimicrobial resistance crisis. Black frames represent the three main axis of this work. Yellow arrows represent antimicrobial peptide transfer; green arrows represent antimicrobial resistance transfer; yellow lighting represent antimicrobial peptide impact

Fig. 2 Flowchart of the review strategy. A literature search was performed on the environmental fate processes and occurrence of antimicrobial peptides (AMPs) in the environment. Databases such as Web of Science, Google Scholar, and Scopus were used, and keywords like environmental fate processes, occurrence, hydrolysis, photolysis, or adsorption were combined with the names of the studied antimicrobial peptides using the query “AND”. The titles and abstracts of studies were then screened to identify studies containing relevant data. One hundred and fourteen publications were selected this way. Sixteen studies were then excluded because of the lack of relevant information environmental fate of antimicrobial peptides. The 98 remaining publications were included in the review



and on the environmental impacts of antimicrobial peptides (Sect. "Impact of antimicrobial peptides on the environment") were aggregated from recent and relevant literature selected in the same databases. The aim of this research was to provide valuable and recent information to contextualize the fate of antimicrobial peptides, rather than exhaustively reviewing all the existing literature on the topic. Only peer-reviewed articles were selected, with the exception of governmental reports and World Health Organization reports.

Antimicrobial peptides in medicine, history, clinical positioning, and properties

Antimicrobial peptides history, clinical positioning, and use

Glycopeptides

Glycopeptides are a class of antimicrobial peptides used in many countries to treat Gram-positive pathogens, especially methicillin-resistant *Staphylococcus aureus*. In 1952, the first glycopeptide, vancomycin, was discovered in a soil sample from Borneo [27]. This molecule, which is produced by the bacterium *Streptomyces orientalis*, was subsequently tested and approved in 1958 by the United States Food and Drug Agency (FDA) to treat infections caused by penicillin-resistant *staphylococcus* [28]. However, because of its toxicity and the discovery of safer alternative drugs such as methicillin and cephalosporins, vancomycin use was rare until the development of β -lactam antibiotic resistance in the 1990s [29]. The emergence of methicillin-resistant *S. aureus* highlighted the importance of vancomycin, as 99% of the methicillin-resistant *S. aureus* strains were susceptible to this drug. Vancomycin has become widely used, ultimately leading to the appearance of a methicillin-resistant *S. aureus* strain that is less susceptible to vancomycin [30].

The second discovered glycopeptide, teicoplanin, is produced by *Actinoplanes teichomyceticus* and was discovered in 1978 before its approval by the European Medicine Agency in 1988 [31]. Notably, teicoplanin has never been approved in the USA [30]. Compared with vancomycin, teicoplanin has a hydrophobic side chain and is therefore classified as a lipoglycopeptide. Furthermore, teicoplanin is a mixture of five compounds differentiated by the structure of their side chains [32]. The second generation of glycopeptides retains this hydrophobic constituent, among other modifications, improving their pharmacokinetic and pharmacodynamic properties. Compared with vancomycin, they have longer half-lives and greater potencies [33]. Telavancin, a derivative of vancomycin, was the first second-generation lipoglycopeptide approved in 2009 by the FDA and in 2011 by the European Medicines Agency [34]. Dalbavancin and

oritavancin are derivatives of teicoplanin and the peptide chloroeremomycin, respectively. They have both been approved by the FDA in 2014 and by the European Medicine Agency in 2015 [35, 36].

Glycopeptides have relatively similar structures, but their pharmacokinetics and pharmacodynamics are different, as are their dosages, which are presented in Table 1. Owing to their poor oral absorption, all glycopeptides are administered intravenously [30]. In blood, 10–50% of vancomycin is bound to protein. Its half-life is 6–12 h, and 80–90% of the injected dose is excreted in the urine [37]. Because of its hydrophobic side chain, 90% of teicoplanin is bound to plasma proteins, granting a terminal half-life greater than 40 h. Teicoplanin is mainly excreted via the kidney [38]. The half-life of telavancin (7–9 h) is similar to that of vancomycin despite it being highly bound to plasma proteins (93%) [39]. However, this compound appears to be 16–32 times more potent against methicillin-resistant *S. aureus* than vancomycin is [40]. Oritavancin and dalbavancin both have long half-lives of 393 h and 174 h, respectively [35, 36]. Oritavancin excretion is slow; 5% of the dose is excreted in the urine in 5 days, whereas 25–45% of the dalbavancin load is excreted in the urine [39, 41].

Vancomycin has been used for decades as a first-line antibiotic to treat gram-positive bacterial infections, especially methicillin-resistant *S. aureus*. However, the use of the antimicrobial peptide avoparcin in veterinary medicine has led to the development of vancomycin-resistant bacteria such as vancomycin-resistant *enterococci* [57]. The prevalence of vancomycin-resistant *enterococci* is increasing, resulting in nosocomial infections [58]. Despite a slight decrease in vancomycin consumption since 2016, it is still considered a first-line drug to treat methicillin-resistant *S. aureus* infection. On the other hand, the use of other drugs that are more potent and less toxic are increasing (e.g., daptomycin, linezolid) or are expected to increase, e.g., dalbavancin and oritavancin [59, 60]. Indeed, dalbavancin and oritavancin were originally approved for the treatment of acute bacterial skin and skin structures infection, but evidence shows that they could be used to treat other pathologies, such as bone-joint infections, thus increasing their use [61, 62]. Moreover, pharmacokinetics of these new lipoglycopeptides allows weekly dosing, which can reduce hospital admissions and therefore save money [63]. Telavancin is another marketed lipoglycopeptide and has a shorter half-life than the other two lipoglycopeptides. It was approved for the treatment of complicated skin and skin structure infection in 2009 and for the treatment of nosocomial bacterial pneumonia in 2013. Owing to its nephrotoxicity, telavancin use is rare and is often considered a last-resort option [64]. Teicoplanin has been approved for the treatment of complicated skin and soft tissue infection, pneumonia, and complicated urinary tract infections, but since it is considered an alternative to

Table 1 Approval date and clinical properties of antimicrobial peptides. The table describes approval date, administration route, practiced dosage, excretion, and excretion half-life ($t_{1/2}$) of antimicrobial peptides. These information on the clinical use of antimicrobial peptides allow to contextualize the clinical positioning of these drugs.

Pharmaceutical emissions from healthcare are partly influenced by clinical use, which is key to understanding the environmental fate of antimicrobial peptides. The table indicates whether antimicrobial peptides are used in human, veterinary, or both types of medicine, as their emission sources may vary by usage

Molecule	Human -Veterinary use	First approval (FDA)	Activity spectrum	Administration route (Human)	Practiced dosage (Human)	Excretion (Human)	$t_{1/2}$ (Human)	References
Vancomycin	Human	1958	Gram-positive	Intravenous	15–20 mg kg^{-1} per 8–12 h $^{-1}$	Renal (80–90% urine 24 h)	6–12 h	[28, 37, 42]
Polymyxin B	Human & veterinary	1960s	Gram-negative	Intravenous, Topical	2–2.5 mg kg^{-1} then 1.25–1.5 mg kg^{-1} per 12 h $^{-1}$	Non-renal (< 5% urine)	9–11.5 h	[43–46]
Colistin	Human & veterinary	1950s	Gram-negative	Intravenous, Topical	300 mg then 150 mg per 12 h $^{-1}$	Non-renal	Not available	[43, 45–47]
Bacitracin	Human & veterinary	1948	Gram-positive	Topical	Not available	Not available	Not available	[48]
Teicoplanin	Human	1988 (approved by EMA, not FDA)	Gram-positive	Intravenous	10–15 mg kg^{-1} per 12 h $^{-1}$ (3 doses) then 10–15 mg kg^{-1} per 24 h $^{-1}$	100% urine	> 40–70 h	[31, 38, 49]
Gramicidin S	Human	Not available	Gram-positive & negative	Topical	Not available	Not available	Not available	[50]
Gramicidin D	Human	Not available	Gram-positive & negative	Topical	Not available	Not available	Not available	[50]
Daptomycin	Human	2003	Gram-positive	Intravenous	4–10 mg kg^{-1} per day $^{-1}$	78% urine in 24 h	8–9 h	[51, 52]
Dalbavancin	Human	2014	Gram-positive	Intravenous	1000 mg and 500 mg at 7 d	25–45% urine	174 h	[36, 39, 53]
Telavancin	Human	2009	Gram-positive	Intravenous	10 mg kg^{-1} per 24 h $^{-1}$	78% urine (52% biologically active)	8–9 h	[34, 39, 54]
Oritavancin	Human	2014	Gram-positive	Intravenous	1200 mg once	Non-renal (5% in urine)	393 h	[35, 53, 55, 56]

FDA United States Food and Drug Agency, EMA European Medicines Agency

vancomycin, its use is rare [65, 66]. The use of teicoplanin increased during the COVID-19 crisis because of its potential antiviral effects [31]. These differences between glycopeptides properties are responsible for their different clinical positions.

Daptomycin

Daptomycin is a cyclic lipopeptide isolated in 1980 from a complex peptide synthesized by *Streptomyces roseosporus* [51]. Daptomycin was approved in 2003 by the FDA and

in 2006 by the European Medicine Agency [67, 68]. Daptomycin half-life is 8–9 h (Table 1), and urine is its main excretion route (Table 1). Since its approval in 2003 for the treatment of complicated skin and skin structure infections, the use of daptomycin has increased, including for the treatment of infections caused by vancomycin-resistant *enterococci* [68]. Daptomycin contributed to the decrease of vancomycin consumption because it has fewer adverse effects and fewer treatment failure than vancomycin [60, 69, 70].

Polymyxins

Polymyxins are cyclic lipopeptides discovered in the 1940s and synthesized from *Bacillus polymyxa* strains. Among the five known polymyxins, only colistin (polymyxin E) and polymyxin B are used in human and veterinary medicine [71]. Both colistin and polymyxin B are mixtures of compounds, the difference being their N-terminal fatty acyl groups [72]. They display a narrow antimicrobial spectrum against gram-negative bacteria, including ESKAPE pathogens (*Enterococcus faecium*, *S. aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa* and *Enterobacter* spp.), and were approved for clinical use by the FDA in the 1950s for colistin and in the 1960s for polymyxin B [73]. They are administered topically or parenterally in human medicine and mainly orally in veterinary medicine (Table 1), with regulatory differences from one country to another. For example, in Europe, polymyxin B is only used topically [74, 75]. Polymyxin B is used in its active form, while colistin is administered under its colistin methanesulfonate (also known as colistimethate) form intravenously and under its colistin sulfate form topically [45, 76]. Once in the body, colistin methanesulfonate is hydrolyzed, and active colistin is formed. Because polymyxins are toxic to the kidneys, their use decreased in human medicine in the 1970s [73, 77].

For colistin, international guidelines on polymyxin use recommend a loading dose of 300 mg colistin base activity (equal to 727 mg colistin methanesulfonate) and then 150–180 mg colistin base activity per 12 h, whereas for polymyxin B, these guidelines recommend a loading dose of 2–2.5 mg polymyxin B kg⁻¹ and then 1.25–1.5 mg polymyxin B per 12 h [45]. Because colistin methanesulfonate degradation can produce 32 different compounds, colistin pharmacokinetic is complex [72]. The half-life of colistin methanesulfonate is 2 h, and 60% of the dose is excreted in urine in 24 h, whereas colistin excretion is mostly non-renal [71]. The half-life of polymyxin B is 9–11.5 h, and polymyxin B is excreted via both renal and nonrenal routes. However, the exact processes involved are not known [43]. Colistin and polymyxin B are potent against some ESKAPE pathogens; thus, the World Health Organization placed them on the list of critically important antimicrobials for human medicine in 2016 [78]. However, polymyxins are nephrotoxic and are used as a last resort when less toxic treatments have failed and if the patient's renal condition permits it [45].

Polymyxins are widely used in veterinary medicine on all continents for livestock production (mainly pigs), aquaculture, and pets [21]. Colistin is principally administered orally in a premix form, i.e., colistin sulfate, and trivially via the topical route, via injection or via the intramammary route [21, 74, 79]. Colistin is used to control gastrointestinal tract infections caused by *Enterobacteriaceae* in rabbits, pigs, or beef cattle

[75, 76, 80]. For decades, colistin has been used as a growth promoter, but this usage has been banned in most regions: in 2006 in Europe, in 2016 in South Africa, in 2017 in China, and in 2019 in India [81–83]. Consequently, global colistin consumption has decreased, but is still higher in veterinary medicine than in human medicine [74]. Polymyxin B is also used in veterinary medicine, such as in the USA, Australia or Canada, where colistin is not used as such [21, 74, 84, 85].

Gramicidin and tyrocidine

Two gramicidins exist, namely gramicidin D and gramicidin S. Gramicidin D was isolated from a *Bacillus brevis* strain from American soil in 1941, and gramicidin S was isolated from a *Bacillus brevis* strain from Russian soil [86, 87]. These two compounds are relatively different. Gramicidin D is a component of a peptide mixture named tyrothricin, the other component being tyrocidine. Gramicidin D is composed of a mixture of 3 gramicidins (A, B, C). Gramicidin S is a cyclic peptide [50]. Both types of Gramicidin display antimicrobial activity against Gram-negative bacteria but acute toxicity against blood cells [14, 88]. Therefore, they are only used topically to treat infections of the eyes, nose, throat, or root canal [14, 89–93]. There are no data on the pharmacokinetic of gramicidin, as it is only used topically.

Bacitracin

Bacitracin is a mixture of more than 50 cyclic polypeptide congeners synthesized by *Bacillus subtilis* that was isolated from an infected wound in 1943 [48, 94, 95]. In human medicine, bacitracin is used topically, principally to treat eye infections [96]. It is also used in its zinc bacitracin form in combination with polymyxin B and neomycin [77]. As for gramicidin and tyrocidine, there is no available information about the pharmacokinetic of bacitracin in humans.

Bacitracin is administered orally in its bacitracin zinc form to control enteritis in livestock (mainly poultry) and increase weight gain [97]. Regulations vary greatly from country to country. In Europe, the use of bacitracin as a growth promoter was banned in 1998 to reduce the development of bacitracin resistance, which can reduce bacitracin efficiency in human medicine [98]. However, bacitracin is still used for the treatment of mastitis and skin infections [99]. China banned the use of zinc bacitracin as a growth promoter in 2019, but in Brazil and the USA, bacitracin is still used as such [100–102].

Chemical structure and physicochemical properties of antimicrobial peptides

Little is known about the physicochemical properties of antimicrobial peptides. The physicochemical properties of the

antimicrobial peptides are presented in Table 2. For some of them, there are no measured data available. All antimicrobial peptides display several acid dissociation constants (pKa) values; consequently, their charge state highly depends on the pH value. At environmental pH, some antimicrobial peptides are polycationic, i.e., colistin, polymyxin B, oritavancin, and dalbavancin, whereas others are zwitterionic. According to the available octanol–water partition coefficient values, vancomycin, colistin, and daptomycin are hydrophilic molecules and are considered highly soluble in water. There are no log octanol–water partition coefficient values for oritavancin, dalbavancin, telavancin, or gramicidin, the latter being insoluble. Despite high calculated water solubility values, oritavancin and telavancin are reported to have limited solubility in water in the literature, with the pH value playing a key role in their solubility [54, 103]. This highlights that antimicrobial peptide structures are complex and difficult to model. Their organic carbon–water partition coefficient was modeled via the Estimation Programs

Interface (EPI) Suite™ (Table 2). All antimicrobial peptides molecular masses are outside the model range (greater than 1000 g mol⁻¹); therefore, the results are presented for guidance. According to the EPI Suite™, all antimicrobial peptides display high affinity for organic carbon, which could influence their fate in the environment via adsorption mechanisms.

The quantification of antimicrobial peptides in environmental matrix is often challenging because of their physicochemical properties [110]. Antimicrobial peptides are typically analyzed via high-performance liquid chromatography-ultraviolet spectroscopy (HPLC–UV) or via high-performance liquid chromatography-tandem mass spectrometry (HPLC–MS/MS), the latter being more sensitive and selective but also more expensive. Both these methodologies, however, display satisfying performances. Extraction of antimicrobial peptides from environmental matrix turns out to be more difficult. Extraction from water typically involves solid phase extraction, e.g., hydrophilic lipophilic

Table 2 Physicochemical properties of antimicrobial peptides. The table provides molar mass, acid dissociation constants (pKa), octanol–water partition coefficient (Log K_{ow}), organic carbon–water partition coefficient (Log K_{oc}), and solubility of antimicrobial peptides. These properties are essential information for understanding the environmental fate of pharmaceuticals, in particular environmental

fate processes. Measured properties are displayed if available, otherwise calculated values are given. There are few measured physicochemical properties for antimicrobial peptides. All antimicrobial peptides display several pKa values and high Log K_{oc} values. Therefore, high adsorption of antimicrobial peptides on organic soils and sediments is expected

Molecule	Molar mass (g mol ⁻¹)	pKa (measured)	pKa range ^a (calculated)	Log K _{ow} (measured)	Log K _{ow} ^b (calculated)	Log K _{oc} ^b (calculated)	Solubility (measured)	Solubility ^b (calculated ^d)
Vancomycin	1449.27	2.18/7.75/8.89/ 9.59/10.4/12 ^c	2.99–9.89	–3.1 ^f	–0.84	13.63	0.225 g L ^{-1f}	1.93 × 10 ⁻⁵ mg L ⁻¹ 100 g L ⁻¹
Teicoplanin	1564.3– 1907.7	5/ 7.1/9–12.5 ^g	3.04–7.09	1.3 (pH 7.4) ^g	–3.26	Not available	100 g L ^{-1g}	Not available
Dalbavancin	1816.71	Not available	Not available	Not available	3.70	19.86	Not available	1.38 × 10 ⁻¹⁰ mg L ⁻¹ 1.5 g L ⁻¹
Oritavancin	1793.12	2.93 ^c	2.98–9.96	4.1 ^d	2.25	17.82	10 g L ^{-1c}	3.48 × 10 ⁻⁹ mg L ⁻¹ 68 g L ⁻¹
Telavancin	1755.65	Not available	1.55–9.99	Not available	1.24	15.18	Not available	4.66 × 10 ⁻⁸ mg L ⁻¹ 100 g L ⁻¹
Colistin	1155.4– 1169.5	"around 10" ^h	Not available	Not available	–6.34	12.66	564 g L ^{-1c}	0.29 mg L ⁻¹ 100 g L ⁻¹
Polymyxin B	1301.57	7.99/8.71/9.09/9.43 ⁱ	Not available	Not available	–6.04	Not available	Soluble ^c	Not available
Bacitracin	422.7 (baci- tracin A)	[3.9;4.6]/ 6.9/ [7.4;8.5]/ 10 ^j	3.19–9.63	Not available	–3.26	18.26	Not available	0.01 mg L ⁻¹ 100 g L ⁻¹
Gramicidin	1882.3	Not available	11.56	Not available	–0.75	15.91	Insoluble	Not available
Daptomycin	1620.7	1.3/3.8/4.4/10.7/13.19 ^k	2.98–9.59	–5 ^k	–9.77	18.01	Not available	0.17 g L ⁻¹ 100 g L ⁻¹

^aChemaxon ^bEPI Suite™ ^cDrugbank ^dboth WS Kow and Water NT models from Estimation Programs Interface (EPI) Suite™ were used

^e[51, 104–109]

^f[104], ^g[105], ^h[106], ⁱ[107], ^j[108], ^k[109], ^l[51]

balanced (HLB) or weak cationic exchange (WCX) phases, and extraction from solid matrix is generally achieved via solid–liquid extraction using various organic solvents potentially combined with acids. Vancomycin quantification via classical multi-residue method appears to be efficient. In contrast, sample preparation for polymyxins and for bacitracin analysis is complex. The recovery of the extraction methods of bacitracin is often low [111]. Colistin analytical methods and associated problems have been reviewed elsewhere [110]. For dalbavancin, oritavancin, telavancin, gramicidin, and tyrocidin, there are no sample preparation methodologies available as their occurrence in the environment and their fate have never been addressed.

Antimicrobial peptide environmental fate and impacts on the environment

Antimicrobial peptide environmental fate

In this section, we describe the environmental fate of peptide-based antimicrobials. To provide a comprehensive description of it, the following information is presented for each class of antimicrobial peptides. First the environmental fate processes, second the emission pathways to the environment, and third the environmental concentrations measured in the literature. The environmental fate processes will be described in the following order: hydrolysis, photolysis, biodegradation and adsorption; they will contribute to the accurate discussion of the emission and environmental occurrence of antimicrobial peptides.

Glycopeptides

The environmental fate of five glycopeptides was reviewed, and that of vancomycin has been widely studied, especially via environmental monitoring, which is unique among peptide-based antimicrobials. Several publications have also assessed the contributions of natural attenuation processes to vancomycin degradation in the laboratory. Tables 3, 4, 5 and 6, respectively, present the results of hydrolytic degradation, photolysis, biodegradation, and adsorption of vancomycin.

In ultrapure water at 37 °C and free pH, a 20% decrease in the initial vancomycin concentration was observed after 7 days, whereas in the polybutylene succinate and magnesium chloride (MgCl_2) solutions, a 60% decrease was observed [112]. Conversely, at ambient temperature and pH above 5, phosphate buffer was shown to increase vancomycin degradation (at pH greater than 7, degradation was fast and not studied further) [113]. In the same publication, the degradation kinetics increased with increasing ionic strength of the solution. In a polyethylene infusion syringe at 25 °C at pH 5.1–5.6 and after 24 h, vancomycin degradation was less

than 10% in water and in the two tested saline solutions (50% and 2%) [114], whereas at ambient temperature and pH 3, less than 10% of the vancomycin load was degraded after 48 h [115]. In polyvinyl chloride bags (used for the conservation of vancomycin in hospitals) at 4 °C with noncontrolled pH, vancomycin degradation was also less than 3% within 2 months [116]. As with phosphate buffer, the environmental water matrix could have an impact on the reaction, but to the author's knowledge, this has not been tested. Vancomycin degradation via hydrolytic reactions under environmental conditions in an environmental matrix has never been addressed. The vancomycin-enhanced hydrolysis half-life was found to be 0.3 h at 85 °C, and this method could help remove vancomycin from treated waters [118].

Vancomycin photolysis has been assessed for wastewater treatment purposes. In the presence of titanium dioxide (TiO_2) nanoparticles at pH 5.5 and 20 °C at λ higher than 300 nm, the vancomycin photolytic half-life was 19.5–53 min, depending on the titanium dioxide (TiO_2) concentration [129]. Another publication investigated the photocatalytic degradation of vancomycin with different titanium dioxide (TiO_2) nanostructures [131]. The observed half-lives were in the range of 2 min. Both of these studies detected transformation products, and the authors highlighted the importance of identifying them, notably because some appeared to be toxic to *Daphnia magna* [129]. At 21 °C, direct photolysis of vancomycin was faster at pH 11 than at pH 3 (λ equal to 254 nm) [130]. There is a clear gap in the literature on the photolysis of vancomycin under environmental conditions, which has been assessed in only one publication. In river water, vancomycin photolysis (both direct and indirect) is fast, with half-lives ranging from 15 to 51 min [132].

The biodegradation of vancomycin has been assessed in a few publications. Using a closed bottle test, according to Organization for Economic Cooperation and Development guideline No. 301, and microbial communities from a wastewater treatment plant, a 4% decrease in the theoretical oxygen demand was observed at 28 days; according to the test threshold, vancomycin was not considered biodegradable [135]. In contrast, a 50% decrease in vancomycin concentration, possibly due to sorption and anaerobic degradation mechanisms, was detected via UV–Vis analysis. Another study used the closed bottle test to assess vancomycin biodegradation by wastewater treatment plant microbial communities over 28 days [136]. According to CO_2 and O_2 monitoring, vancomycin was not biodegraded. Vancomycin biodegradation by microbial communities and enzyme pools has also been investigated [137]. Sorption to microbial cells and poor ionization induced bias in the results, but vancomycin biodegradation was found to be low. In soil, vancomycin was completely inactive after 15 days, but the respective importance of sorption and biodegradation was

Table 3 Hydrolytic degradation of antimicrobial peptides. The table describes existing literature on the hydrolytic degradation of antimicrobial peptides. Antimicrobial peptides concentration, experimental pH and T the temperature are provided to contextualize the results. Hydrolysis half-life ($t_{1/2}$) and kinetic constant (k) are displayed when available. The hydrolysis of antimicrobial peptides seems to depend on experimental pH; this parameter could influence their persistence in the environment. The degradation half-life also depends on temperature. For most antimicrobial peptides, no hydrolytic degradation was carried out using environmental conditions

Molecule	pH range	T (°C)	Concentration (g L ⁻¹)	Others	$t_{1/2}$	k	Results	References
Vancomycin	Not available	37	0.06	10-d phosphate buffer and MgCl ₂	6–10 d	Not available	Not available	[112]
Vancomycin	1.3–6.85	Room	0.08	Phosphate buffer	8.63–74.53 d	k_{obs} : 0.0803–0.0093 d ⁻¹	Phosphate buffer increases kinetic at pH ≥ 5.5	[113]
Vancomycin	5.1–5.61	25	25–80	24-h in injection syringes	Not available	Not available	Degradation < 10% in 24 h	[114]
Vancomycin	≈ 3	Room	41.7	2-d in injection syringes	Not available	Not available	Degradation < 10% in 48 h	[115]
Vancomycin	Not available	4	5–10	60 d in PVC bags	Not available	Not available	Degradation < 3% in 58 d at 4 °C	[116]
Vancomycin	Not available	4–25	5	56 d at 4 °C then 418 h at 25 °C	Not available	Not available	Degradation < 10% in 182 d at 4 °C Degradation > 10% in 14 d at 25 °C	[117]
Vancomycin	3–11	85	0.1	2-h antimicrobial activity assay	0.31 h at pH = 11	2.2073 h ⁻¹	Not available	[118]
Telavancin	pH ₀ = 4.4 pH ₁₉₂ = 5.7	2–8	0.6–0.8	24–192 h in elastomeric pump	Not available	Not available	< 10% degradation	[119]
Dalbavancin	Not available	20–110	Not available	28 d 112.8 °C	Not available	Not available	No diminution of antimicrobial activity	[120]
Daptomycin	11.7	Room	0.05	0–180 min 0.005 M NaOH	130.81 min	0.0047 µg mL min ⁻¹	Not available	[121]
Daptomycin	2.97–7.77	60	0.5	7–12 d	1.82–3.15 d (depending on pH)	0.22–0.38 d ⁻¹ (depending on pH)	Reaction pathway depends on pH	[122]
Daptomycin	9–10.5	20–50	0.8–16	5 d n borate, citrate, and carbonate buffers	0.11–1.65 d (depending on buffer)	k_{obs} = 0.42–6.3 d ⁻¹ (depending on buffer, pH, T)	Not available	[123]
Colistin	3–11	85	0.1	24-h antimicrobial activity assay	3.41 h at pH = 11	0.2031 h ⁻¹ at pH = 11	optimal degradation pH = 11	[118]
Colistin A	5–7	4–25	0.01	24 h Water and wastewater	1.6 h at 25 °C at pH = 7 in wastewater	Not available	Not available	[124]
Colistin	5.63–7.4	4–37	0.1	120 h to 60 d in water and phosphate buffer	Not available	Not available	No degradation in water Around 45% degradation in 120 h in buffer	[125]
Colistin A	1.4–7.4	37–60	0.5	60 d	69–6300 h (at 37 °C depending on pH)	0.11–10.00 h ⁻¹ (at 37 °C depending on pH)	Degradation kinetic: basic and neutral > acid T increases kinetic	[126]

Table 3 (continued)

Molecule	pH range	T (°C)	Concentration (g L ⁻¹)	Others	t _{1/2}	k	Results	References
Bacitracin	3–9	25	0.050	14 d	Not available	Not available	50% hydrolysis at pH = 9 No degradation at other pH	[95]
Bacitracin	3–11	85	0.1	2-h antimicrobial activity assay	0.41 h at pH = 11	1.6904 h ⁻¹ at pH = 11	Optimal degradation pH: pH = 11	[118]
Polymyxin B	5.6	4–25	0.056–0.078	7-d antimicrobial activity assay	9.2–29 d at 25 °C	0.024–0.075 d ⁻¹ at 25 °C	No difference between 4 and 25 °C	[127]
Polymyxin B	1.4–7.4	37–60	0.5	60 d	6300–84 h (depending on pH at 37 °C)	0.11–8.26 h ⁻¹ (depending on pH at 37 °C)	Degradation kinetic: basic and neutral > acid T increases kinetic	[126]
Polymyxin B	2–10	32–52	0.26	30 d	t90 ≈ 130 d (pH = 6 at 4 °C)	5.3–90.1 h ⁻¹ × 10 ⁴ (depending on pH)	Degradation kinetic: basic > neutral and acidic T° increases kinetic	[128]

not investigated [145]. There has been little research into vancomycin biodegradation; hence, there is a need for an adapted methodology to assess this mechanism under environmental conditions and in wastewater treatment plants. However, it can be assumed that vancomycin biodegradation is not the main attenuation process for this molecule in the environment. Only two publications have investigated vancomycin adsorption onto environmental solids. The determined solid-water partition coefficients were close to 3 [145, 146]. Overall, information on the attenuation processes of vancomycin in the environment is rare. Assessing the partition and degradation of vancomycin would improve sampling methodologies for its monitoring and deepen the understanding of its environmental occurrence and environmental risks. Toxic transformations product effects of vancomycin have been reported [129]. It is therefore necessary to characterize these transformation products and their toxicity.

Vancomycin discharge can occur via industrial wastewater, as might be the case for many drugs and some other antimicrobial peptides [18, 118]. A scientific publication reported a vancomycin concentration close to 50 mg L⁻¹ in industrial wastewater [148], and despite a removal efficiency of 99% during wastewater treatment, the effluent concentrations remain as high as 200 µg L⁻¹. Industrial wastewater therefore appears to contribute to vancomycin discharge into the environment. In 2008, a study highlighted the lack of data on environmental contamination by vancomycin despite its routine use in hospitals [149]. Figure 3 shows the number of scientific publications assessing the presence of vancomycin in wastewater, during wastewater treatment and in environmental compartments. The number of publications increased from 2010 to 2017 and then declined until 2023. This underlines the scientific community's interest in vancomycin, which has been added to contaminant monitoring lists in a number of publications. Although vancomycin is the most studied antimicrobial peptide, this molecule has been monitored without previous data on its degradation or partition in the environment. As a result, knowledge of the environmental fate of vancomycin is still incomplete.

In France, vancomycin consumption decreased by 20.7% from 2012 to 2021, partly because of the increased use of alternative drugs, e.g., daptomycin. However, 604 kg of vancomycin was used in France in 2022, according to the National Public Health Agency [150]. In Belgium, on the other hand, the use of vancomycin and telavancin has increased from 233 kg in 2005 to 316 kg in 2022 [151]. This highlights the differences in vancomycin use between countries. Approximately 80–90% of the injected vancomycin is excreted unchanged in the urine [37]. Therefore, excreted vancomycin is expected to reach sewage and wastewater treatment plants.

Several scientific publications have monitored vancomycin occurrence in hospital wastewater. Vancomycin appears

Table 4 Photolysis of antimicrobial peptides. The table presents available data on the photolysis of antimicrobial peptides. Antimicrobial peptides concentration, pH range, T the temperature, irradiation mode and others experimental parameters are provided to contextualize the synthesized results. Photolysis half-life ($t_{1/2}$) and kinetic constant (k) and quantum yield are displayed when available. Antimicrobial peptides are not or little degraded via direct photolysis. On the contrary, indirect photolysis appears to be fast with $t_{1/2} < 24$ h for most of antimicrobial peptides. This degradation process could be significant in driving the environmental fate of antimicrobial peptides

Molecule	pH range	T(°C)	Concentration (g.L ⁻¹)	Irradiation	Others	$t_{1/2}$	k	Results	Quantum yield	References
Vancomycin	5.5	20	0.05	Xenon lamp (<300)	Ferrioxalate actinometry [TiO ₂] = 0.1–0.2 g L ⁻¹	53 and 19.5 min (at 0.1 and 0.2 g L ⁻¹ TiO ₂)	0.013 and 0.036 min ⁻¹ (at 0.1 and 0.2 g L ⁻¹ TiO ₂)	Irradiated solution is toxic to <i>D. magna</i>	Not available	[129]
Vancomycin	Free & 3–11	21	0.02	Mercury Lamp (254 nm)	2-h irradiation Ferrioxalate actinometry	Not available	Not available	photolysis kinetic: pH = 11 > free pH > pH = 3 Degradation faster in presence of oxidants	0.5–0.7 mol mol photons ⁻¹	[130]
Vancomycin	Free	32–33	0.0005	Xenon Lamp; UV-Vis et Vis (> 400 nm)	20-min irradiation	1.5 min	0.46 min ⁻¹	TiO ₂ catalysis	Not available	[131]
Vancomycin	6.10–6.98	25	0.0005	Suntest CPS (300–800 nm)	300–120-min irradiation	ultrapure: 36 min spring water: 15–51 min wastewater: 30–32 min	ultrapure water: 0.0083–0.0082 min ⁻¹ spring water: 0.0059–0.0195 min ⁻¹ wastewater: 0.0094–0.0099 min ⁻¹	Not available	Not available	[132]
Daptomycin	7.5	21	0.016	Heraeus model Suntest CPS+ (290–400 nm)	10 mgC L ⁻¹ dissolved organic carbon: indirect photolysis	direct: 13.7 h	k_{obs} direct: 1.4×10^{-5} s ⁻¹ k_{obs} indirect: 1.5×10^{-5} s ⁻¹	Not available	0.0003 mol mol photons ⁻¹	[133]
Daptomycin	Not available	Not available	0.1	352-nm light chamber	12-h irradiation	Not available	Not available	54% degradation in 12 h	Not available	[121]
Colistin	7.5	21	0.011	Heraeus model Suntest CPS+ (290–400 nm)	10 mgC L ⁻¹ dissolved organic carbon: indirect photolysis	indirect: 1.15 h	k_{obs} direct: n.d k_{obs} indirect: 16.6×10^{-5} s ⁻¹	Not available	Not available	[133]
Polymyxin B	7.5	21	0.013	Heraeus model Suntest CPS+ (290–400 nm)	10 mgC L ⁻¹ dissolved organic carbon: indirect photolysis	indirect: 1.6 h	k_{obs} direct: n.d k_{obs} indirect: 12.2×10^{-5} s ⁻¹	Not available	Not available	[133]

Table 4 (continued)

Molecule	pH range	T(°C)	Concentration (g.L ⁻¹)	Irradiation	Others	t _{1/2}	k	Results	Quantum yield	References
Bacitracin	7.5	21	0.014	Heraeus model Suntest CPS+ (290–400 nm)	10 mgC L ⁻¹ dissolved organic carbon: indirect photolysis	indirect: 7.4–8.3 h	k _{obs} direct: n.d indirect: 2.3–2.6 × 10 ⁻⁵ s ⁻¹	Not available	Not available	[133]
Bacitracin	5–8	Not available	0.085	Xenon Lamp (<455 nm) Photochemical reactor (365 nm)	DOM and Quenchers	no DOM: 21 h DOM: 0.27–21 h pH (5–8); 0.34–2.3 d	no DOM: 0.088 × 10 ⁻⁴ s ⁻¹ k _{obs} with DOM: 0.088–7 × 10 ⁻⁴ s ⁻¹ k _{obs} pH (5–8): 0.84–5.51 × 10 ⁻⁴ s ⁻¹	No direct photolysis ¹ O ₂ is a major contributor to degradation Sorption on MO increases kinetic	Not available	[134]
Bacitracin	6.5	25	0.05	Mercury vapor lamp (254 nm)	Ultraviolet C and ultraviolet C/H ₂ O ₂ photolysis 120-min irradiation	0.1–0.5 h	3.8 × 10 ⁻⁴ –1.9 × 10 ⁻³ s ⁻¹ depending on quantum yield	No direct photolysis Irradiated solution not toxic to <i>V. fischeri</i> ; no antimicrobial activity on <i>S. aureus</i>	0.0141 mol mol photons ⁻¹	[95]

DOM dissolved organic matter

Table 5 Biodegradation of antimicrobial peptides. The table synthesizes existing literature on the biodegradation of antimicrobial peptides. AMP concentration, pH range, T the temperature, *inoculum* type and others experimental parameters are provided to contextualize the synthesized results. Biodegradation half-life ($t_{1/2}$) and kinetic constant (k) are displayed when available. Biodegradation experimental setup are various, which makes comparison between studies less reliable. Most tested microorganisms were able to degrade AMPs at variable reaction speed. Extrapolating these results to environmental kinetics is, however, not reliable

Molecule	pH range	T (°C)	Incubation	Concentration	Inoculum	Other	$t_{1/2}$	k	Results	References
Vancomycin	free	20	28 d	$2.88 \times 10^{-6} \text{ g L}^{-1}$ and $3.55 \times 10^{-3} \text{ g L}^{-1}$	Microbial communities from communal WWTP	Closed bottle test	Not available	Not available	28 d: No degradation (ThOD measurement) 28 d: 50% degradation (HPLC measurement)	[135]
Vancomycin	Not available	Not available	28 d	100 mg TOC L ⁻¹ and 367 g ThCO ₂ L ⁻¹	WWTP sludge	CO ₂ evolution test + DOC elimination test 1.5 L 200 mg d.s. L ⁻¹ activated sludge	Not available	Not available	28 d: No degradation (–4% ThOC and –14% TOC)	[136]
Vancomycin	Not available	Room	42 h	$100 \times 10^{-6} \text{ g L}^{-1}$	Wastewater microbial communities from New York State	Pools intra and/or extracellular enzymes 180 rpm	<6.9 h	<0.1 h ⁻¹	High vancomycin sorption Vancomycin “slightly degraded”	[137]
Daptomycin	Not available	30	2 d	$20 \times 10^{-3} \text{ g L}^{-1}$	Actinomyces Iso-late WAC4713	Not available	Not available	Not available	Complete degradation in 12 h by isolate WAC4713	[138]
Daptomycin	Not available	Room	42 h	$100 \times 10^{-6} \text{ g L}^{-1}$	Wastewater microbial communities from New York State	Pools intra and/or extracellular enzymes 180 rpm	<1.7 h	>0.4 h ⁻¹	Degradation faster by total enzymes pool	[137]
Daptomycin	7.7–8.1	19.6	7 d	$3.24 \times 10^{-3} \text{ g L}^{-1}$	Periphyton from a local stream in flow channels	40 mL 12-h/12-h light/dark	Not available	Not available	95% degradation at 4 d	[133]
Colistin	“basic”	25	56 d	$10\text{--}40 \times 10^{-3} \text{ g kg}^{-1}$	Soil microbial communities	Sandy loam	13.2–29.3 d	Not available	97–67% degradation at 56 d	[139]
Colistin	“basic”	25	14 d	$147.7 \times 10^{-6} \text{ g kg}^{-1}$ in feces	Soil microbial communities	Manure from chicken feed with colistin + sandy loam	Not available	Not available	72–75% degradation in 14 d Transfer from manure to soil	[139]
Colistin	Not available	38	44 d	0.5 g kg^{-1}	Natural microbial communities	Reactors 20 L 5 kg liquid substrate + 7.5 g colistin sulfate	Not available	Not available	Degradation almost complete at 44 d	[140]
Colistin	7.1	37	72 d	10 g L^{-1}	Proteolytic enzymes	Not available	Not available	Not available	Colistin degraded by proteolytic enzymes	[141]
Colistin	7.6	27	2–12 h	1 g L^{-1}	<i>Sphingosinicella</i> sp. B9 strain	Not available	Not available	Not available	Complete degradation in 12 h	[142]

Table 5 (continued)

Molecule	pH range	T (°C)	Incubation	Concentration	Inoculum	Other	t _{1/2}	k	Results	References
Colistin	8.5	50	4 h	500 × 10 ⁻³ g L ⁻¹	<i>S. maltophilia</i> Col1 strain	Not available	Not available	Not available	80% degradation at 4 h	[143]
Colistin	7.7–8.1	19.6	7 d	23.1 × 10 ⁻³ g L ⁻¹	Periphyton	40 mL 12-h light–12-h dark	Not available	Not available	Colistin not detected at 24 h	[133]
Polymyxin B	7.6	27	2–12 h	1 g L ⁻¹	<i>Sphingosinicella</i> sp. B9 strain	Not available	Not available	Not available	Complete degradation in 12 h	[142]
Polymyxin B	7.7–8.1	19.6	7 d	26.0 × 10 ⁻³ g L ⁻¹	Periphyton	40 mL 12-h light–12-h dark	Not available	Not available	Polymyxin B not detected at 24 h; 86% due to sorption	[133]
Bacitracin	7.6	27	2–12 h	1 g L ⁻¹	<i>Sphingosinicella</i> sp. B9 strain	Not available	Not available	Not available	Complete degradation in 12 h	[142]
Bacitracin	7.7–8.1	19.6	7 d	28.4 × 10 ⁻³ g L ⁻¹	Periphyton from	40 mL 12 h light–12 h dark	Not available	Not available	80–90% degradation at 4 d	[133]
Bacitracin	6	4–30	Soil + feces microbial activity	0.05–0.8 × 10 ⁻³ g L ⁻¹	Not available	12–22 d	Not available	Not available	66% degradation at 30 d at 30 °C	[144]

DOC dissolved organic carbon, TOC total organic carbon, ThOD Theoretical Oxygen Demand, ThCO₂ Theoretical CO₂ amount, WWTP wastewater treatment plant, rpm rotation per minute

to be detected in all these studies. The measured concentrations were as high as 4.7–13 µg L⁻¹ and below the limit of quantification to 13.98 µg L⁻¹ in Romania, 1.31 µg L⁻¹ in South Korea and 3.6 µg L⁻¹ in France [152–155]. Vancomycin was also measured in all influents of wastewater treatment plant receiving hospital wastewater in Italy, France, Poland, Hong Kong SAR, the USA, Germany, and Singapore. Because vancomycin is only used in hospitals, it could be considered a proxy for hospital wastewater in wastewater treatment plants in regions where it is used. In fact, vancomycin was detected at a concentration of 20.6 ng L⁻¹ in untreated water from a wastewater treatment plant receiving 2% hospital wastewater [156]. In contrast, wastewater from regions without hospitals does not contain vancomycin [155, 157]. These results indicate that hospitals are a major source of vancomycin wastewater.

Vancomycin discharge in the environment is controlled by the removal efficiency in wastewater treatment plants. Eleven scientific publications reported vancomycin removal efficiencies, which appeared to be highly variable from one wastewater treatment plant to another (Table S1). Removal rates were greater than 94% in five publications [148, 153, 158–160] and ranged from 0 to 52% in five publications [155, 157, 161–163]. It was not possible to precisely understand which wastewater treatment plant parameters control the removal of vancomycin. However, according to laboratory experiments, residence time should be an important parameter because of the slow biodegradation of vancomycin [137]. Additionally, adsorption onto sludge should contribute to vancomycin removal.

There are little information from laboratory experiments on vancomycin adsorption, and only three publications have assessed its adsorption in wastewater treatment plants. One study measured 840 ng L⁻¹ vancomycin in sludge leachate, another measured 266 µg kg⁻¹ vancomycin on particles in wastewater treatment plant influents, and the last study did not detect this compound in wastewater treatment plant sludge [158, 163, 164]. In the first study, 24% of the vancomycin load was adsorbed onto the sludge of the two monitored wastewater treatment plants, and the removal rates of vancomycin were 67% and 94%, respectively. These results demonstrate that adsorption is not the only removal mechanism for vancomycin in wastewater treatment plants. In the second study, the removal rate was 29%; these differences may indicate that vancomycin adsorption depends on the sludge properties.

The use of sewage sludge in agriculture could promote the discharge of vancomycin into the environment. A study conducted in Poland measured a concentration of vancomycin to 0.55 µg kg⁻¹ in amended soil [158]. In several wastewater treatment plants, the removal rate was insufficient, and significant concentrations of vancomycin were measured in wastewater treatment plant effluents. A scientific publication

Table 6 Adsorption of antimicrobial peptides. The table describes data on the adsorption of antimicrobial peptides onto soils and sediments. Antimicrobial peptides concentration, pH range, T the temperature and others experimental information are provided to contextualize the synthesized results. Solid-water partition coefficients (Log K_d) are displayed when available. Antimicrobial peptides adsorption to the different soils and sediments is high and fast, as are the associated Log K_d values. These results suggests that adsorption may be a key driving factor of the environmental fate of antimicrobial peptides of which adsorption experiments have been conducted

Molecule	pH	T (°C)	Other	Concentration (g.L ⁻¹)	Log K_d	Results	References
Vancomycin	6.8	Not available	Soil at 70% water-holding capacity 0–70 d	2–200 u mL ⁻¹	Sand = 3.22 Sandy loam = 3.16 Loam = 2.95	High sorption in the top 5cm	[145]
Vancomycin	7.4	27 °C	30 mL solution / 300 mg clay	19	Bentonite = 2.95	Not available	[146]
Daptomycin	4.87–6.88	Not available	50 mg soil; 1 mL 10 mM CaCl ₂ 30 h kinetic–6h isotherm	0.016 (kinetic) 0.0016–0.16 (isotherm)	Acidic soil = 1.3 Neutral soil = 1.6	Not available	[133]
Daptomycin	4	25 °C	50 mL solution, 25 mg adsorbent	0.025	Biochar = 3.47	Not available	[147]
Colistin	"basic"	25 °C	5 g sorbent; 25 mL colistin solution 10 min	1 × 10 ⁻³	Sand = 2.26 Sandy loam = 2.31 Loam = 2.43	Instantaneous colistin / soil interaction Adsorption equilibrium at 12 h	[139]
Colistin	"basic"	25 °C	Adsorption/desorption 5 g soil; 25 mL colistin solution 12 h	0.1–1.5 × 10 ⁻³ (isotherm)	Not available	Moderate adsorption affinity Low desorption	[139]
Colistin	4.87–6.88	Not available	50 mg soil; 1 mL 10 mM CaCl ₂ 30 h kinetic and 6 h isotherm	0.011 (kinetic) 0.0011–0.11 (isotherm)	Acidic soil = 2.04 and 2.41	Few points quantified	[133]
Polymyxin B	4.87–6.88	Not available	50 mg soil; 1 mL 10 mM CaCl ₂ 30 h kinetic and 6 h isotherm	0.013 (kinetic) 0.0013–0.13 (isotherm)	Not available	Complete sorption and no desorption	[133]
Bacitracin	4.87–6.88	Not available	50 mg soil; 1 mL 10 mM CaCl ₂ 30 h kinetic; 6 h isotherm	0.014 (kinetic) 0.0014–0.14 (isotherm)	Acidic soil = 0.76 and 0.90 Neutral soil = 2.23 and 2.40	Not available	[133]
Bacitracin	6.8	Not available	Soil 70% water-holding capacity 0–70 d	10 × 10 ⁻⁶ g g ⁻¹ soil	Not available	High sorption in the top 5 cm	[145]

analyzed effluents from 52 European wastewater treatment plants, and vancomycin was detected in 17 out of 56 samples (method detection limit of 80 ng L⁻¹) at concentrations ranging from 89.9 to 1,288 ng L⁻¹ [165]. The results from this study show that the transfer of vancomycin into the environment is highly variable and depends on the presence of hospitals in the wastewater treatment plant area, the use of vancomycin in these hospitals and the removal efficiency of vancomycin in the wastewater treatment plant. Wastewater treatment plant effluents can therefore be considered sources of vancomycin in the environment through effluent discharge and possibly through the use of sludge as an amendment. The results from several publications support this conclusion. Vancomycin was measured before wastewater treatment plant discharge in one study out of 5 in a Polish

river at a concentration of 27 ng L⁻¹ [158]. After wastewater treatment plant discharge, the mean measured vancomycin concentration in surface water was 258 ng L⁻¹ [157, 158, 164, 166, 167]. Details of the reported concentrations are given in Table S2.

Vancomycin emissions might indicate that this compound is present in the environment next to wastewater treatment plants. Many scientific publications have investigated the occurrence of vancomycin in the environment. In most cases, vancomycin was included in monitoring lists. Seventeen publications analyzed surface water, one analyzed ground water, two analyzed sea water, and two analyzed sediments. Figure 4 shows that the vancomycin concentration in the environment depends on the impact of hospital sewage in several countries. As expected, vancomycin occurrence in

to vancomycin; consequently, its use is rare. For example, 27 kg of teicoplanin was used in France in 2022 [150]. During the COVID-19 crisis, teicoplanin consumption increased due to its potential antiviral effects [31]. Once excreted, teicoplanin can be transferred to the environment via wastewater treatment plants. The EPI Suite™ has been used to model teicoplanin fate in wastewater treatment plants [188]. Owing to the complexity of the teicoplanin structure, no removal efficiency for teicoplanin could be modeled; consequently, the value was set to 0%. Then, using the daily drug dose for COVID-19 treatment, the authors predicted an environmental concentration of 165 ng L⁻¹ in surface water. Two publications evaluated teicoplanin concentrations in surface waters [152, 189]. Both methods detect teicoplanin in only one sample at concentrations of below the limit of quantification and 8 ng L⁻¹ in surface waters. The environmental emission and fate of teicoplanin have not been addressed in the literature, so it is not possible to draw conclusions on these issues. However, teicoplanin has been measured in the environment, indicating possible environmental contamination despite the small quantities used.

New synthetic glycopeptides are recent drugs, and their environmental fate has not been studied considerably yet. Telavancin stability was tested at several temperatures in the dark in buffers and in different containers. In intravenous injection bags, telavancin was shown to be stable for 32 days at -20 °C in dextrose (5%) and sodium chloride (0.9%) solutions [190]. In elastomeric pumps, telavancin is not degraded after 8 days at 2 and 8 °C in dextrose (5%), sodium chloride (0.9%) or water [119]. There is no information on the hydrolytic degradation, photolysis, biodegradation, and sorption of telavancin under environmental conditions. Telavancin is considered a last-resort drug when treatments with vancomycin and linezolid have failed or when these treatments are not suitable for the patient [34]. Telavancin use is scarce and is unlikely to be environmentally relevant. However, if the use of telavancin increased, it would be necessary to deepen the knowledge of the environmental fate of telavancin and to survey its occurrence.

To the author's knowledge, dalbavancin hydrolytic degradation, photolysis, biodegradation, or sorption have not been assessed under environmental conditions. Its antimicrobial activity did not decrease after a polymerase chain reaction cycle up to 112 °C and after 28 days at 37 °C in pure water [120]. Dalbavancin was shown to sorb on plastic surfaces in laboratory tests [191]. These findings might indicate that dalbavancin sorption could be significant in the environment. In human medicine, dalbavancin use is rare. In France in 2022, no dalbavancin was used among the monitored healthcare facilities [150]. However, several studies in Spain, Germany, and Italy reported that dalbavancin use could reduce the length of hospital stay and save hundreds of euros for patients who are not hospitalized [192–195]. These

studies also highlight that the use of dalbavancin could be extended to infections other than acute bacterial skin and skin structure infection, such as endocarditis. Because of these advantages, the use of dalbavancin should increase in the future. It is therefore necessary to study its environmental fate and to develop analytical methodologies for wastewater treatment plant and environmental monitoring.

Environmental fate processes have never been addressed for oritavancin. Like dalbavancin, oritavancin was shown to bind to plastic surfaces [196]. This might mean that oritavancin sorption could be high in the environment. Oritavancin use in human medicine is increasing. In 2016, the treatment of acute bacterial skin and skin structure infections in the USA included 92% vancomycin, 6% vancomycin, and 2% other antibiotics [63]. However, this study reported that the optimal cost-efficient treatment would be 66% vancomycin, 6% daptomycin, and 26% oritavancin [63]. A study that took place in Spain, Greece, and Italy also reported potential reductions in costs due to early discharge from hospitals [197]. Moreover, because of its advantages, oritavancin could be used to treat infections such as bone or joint infections or bacteremia [59, 198]. As the use of oritavancin is expected to increase and its environmental fate is unknown, more knowledge is needed to understand the occurrence of oritavancin in the environment.

Daptomycin

The environmental fate of daptomycin has been studied in a number of publications, particularly at the laboratory scale. Daptomycin hydrolytic degradation was assessed under different conditions. At acidic pH, no degradation was observed within 24 h, whereas at alkaline pH, 26% of the daptomycin was hydrolyzed in 30 min [121]. In the same study, at alkaline pH, the half-life of daptomycin was 130 min. These results are consistent with those of the two other studies. Daptomycin degradation was faster at pH 7.77 than at pH 2.97 for both monitored reactions at 60 °C for 12 days in different buffers [122]. According to the authors, the buffer concentration had no effect on daptomycin degradation. In another publication, the effects of alkaline pH on daptomycin hydrolysis were addressed [123] and degradation was faster at pH 10 than at pH 9 and was overall faster than that reported by Kirsch (1989).

Daptomycin photolysis has also been investigated (Table 4). After 12 h under UVA radiation (λ equal to 352 nm), 54% of daptomycin was degraded in ultrapure water, whereas under simulated solar light (λ = 290–400 nm) at 21 °C at pH 7.5 in phosphate buffer, daptomycin degradation resulted in a low quantum yield associated with a half-life of 13.75 h [121, 133]. In the presence of organic matter, daptomycin was degraded by indirect photolysis, with ¹O₂ being responsible for 15% of the degradation. Overall, in the photic

zone of surface waters, direct and indirect photolysis could contribute to the degradation of daptomycin and reduce its persistence. Daptomycin adsorption was assessed in only one publication [133]. The adsorption of this compound was greater in the neutral soil than in the acidic soil. Daptomycin is anionic at the pH of the two soils; therefore, this difference can be explained by differences in the organic carbon content. According to the calculated organic carbon–water partition coefficient, the main sorption mechanism of daptomycin is hydrophobic interactions, which depend on the organic carbon content of the soil [133]. The organic carbon content of the tested soils was moderate (less than 2%); therefore, daptomycin sorption might be more important in the aquatic environment than in this study.

Daptomycin biodegradation was assessed under various experimental conditions. One study tested the ability of actinomycete strains to inactivate daptomycin [199]. Of the 80 strains tested, 80% were able to inactivate daptomycin. A *Streptomyces* sp. strain also completely degraded daptomycin in 12 h [138]. A 100 $\mu\text{g L}^{-1}$ daptomycin solution was also degraded in less than 5 h by microbial communities from 3 wastewater treatment plants of the New York State [137]. At 19.6 °C, biofilm degraded 95% of the daptomycin load (initial concentration of 238 $\mu\text{g L}^{-1}$) in four days in another study (Table 5). Daptomycin biodegradation by various microorganisms has been shown to be fast and could prevent daptomycin from persisting in the environment. Overall, the fate of daptomycin in the environment could be mediated by photolysis in the photic zone, while rapid biodegradation can be expected in the aphotic zone. However, there is no available information on the biodegradation and photolysis of adsorbed daptomycin. Adsorption is often considered capable of preventing degradation and could therefore slow daptomycin attenuation in the environment. There is also a data gap about transformation products in the scientific literature that has to be addressed. One study provided evidence of the production of phototransformation products but did not characterize them [133].

Daptomycin production could provoke its discharge in the environment via the spread of pharmaceutical sludge in agriculture. Daptomycin concentrations were measured in three types of pharmaceutical waste: pharmaceutical sludge, anaerobic digestate, and compost [200]. Daptomycin concentration in the anaerobic digestate was 4.5 mg kg^{-1} but was below the limit of quantification (0.10 mg kg^{-1}) in the other wastes. However, in a soil amended for 17 years with pharmaceutical sludge, daptomycin was not detected [201]. Daptomycin appears to be biodegraded by aerobic microorganisms; therefore, aerobic treatment of pharmaceutical waste could reduce the risk of daptomycin discharge via sludge use in agriculture.

Daptomycin is used mainly in human medicine to treat methicillin-resistant *S. aureus* infections. Its use

has increased since its approval, and this drug has partly replaced vancomycin. In France, daptomycin consumption in healthcare facilities increased by 1090% from 2012 to 2021 [202]. In Spain, a publication reported that 12.4 in 1000 patients received daptomycin among the 98 monitored Spanish hospitals [203]. Daptomycin was used as first-line therapy in 44.5% of the patients. This study highlights that the clinical position of daptomycin is evolving toward first-line therapy. In France in 2022, the national mission on antibiotic resistance surveillance in healthcare establishments reported that daptomycin consumption was 201 kg among the responding healthcare facilities [150].

Daptomycin is excreted from the human body in a partly unchanged manner (Table 1) and is expected to reach wastewater treatment plants. One publication addressed daptomycin adsorption on biochars as a treatment solution [147]. Adsorption on biochars was greater at acidic pH values than at neutral and alkaline pH values and was dependent on contact time. The biochar displayed an adsorption capacity of 55.56–217.39 g kg^{-1} depending on the treatment. There is a lack of information on daptomycin treatment efficiency in real wastewater treatment plants. Because daptomycin is biodegraded by wastewater treatment plants communities, the contact time in conventional activated sludge system might be the critical point for daptomycin removal [137]. However, adsorbed daptomycin might be emitted into the environment via the spread of sewage sludge without adequate aerobic treatment [200] or via wastewater treatment plants with limited residence times. Daptomycin occurrence in wastewater treatment plants and in the environment has never been assessed. Daptomycin susceptibility to natural attenuation processes has been studied in the laboratory, and the results suggest that daptomycin should not persist in ecosystems. Nonetheless, this type of experiment often underestimates the environmental persistence of pharmaceuticals [204]. As daptomycin consumption is close to vancomycin consumption and vancomycin monitoring has unveiled its presence in wastewater treatment plants and in the environment, it is necessary to address daptomycin fate in wastewater treatment plants and its presence in the environment.

Polymyxins

The environmental fate of polymyxin B and polymyxin E is described thereafter. The stability of colistin in solution has notably been assessed under various conditions. At 85 °C in buffer solutions, colistin antimicrobial activity decreased by 35% in 1 h at pH 11 due to hydrolytic reactions and decreased less at pH values of 3, 5, and 7 (Table 3). Two studies were conducted at 37 °C; in one of them, no degradation of colistin was observed within 120 h at 37 °C in water or within 60 days at 4 °C [125]. In addition, colistin degradation in water after 60 days was faster at pH 5.4

and 7.4 than at pH 1.4–3.4. This second publication also revealed that degradation is faster at higher temperatures [126]. According to the authors, racemization was the main degradation mechanism of colistin. Interestingly, in another study, loss of colistin was shown to be more rapid in a complex matrix, wastewater, than in Milli-Q water at 4 °C and 25 °C and at pH 5 and 7 [124]. Conversely, colistin degradation via hydrolysis was enhanced in a buffer solution in another study [125]. Colistin hydrolysis appears to be dependent on environmental conditions such as pH, temperature, and the matrix. Under certain conditions, namely in wastewater at pH 7 and 25 °C, colistin hydrolysis is fast, with a half-life of 1.6 h, and can significantly contribute to its degradation [124].

Only one publication characterized colistin photolysis [133]. After 5 h at pH 7.5 and 21 °C in water, colistin was not degraded by direct photolysis (λ between 290 and 400 nm). However, in the presence of dissolved organic carbon, colistin was rapidly degraded by indirect photolysis (half-life of 1.15 h), with 29–40% of the degradation due to singlet oxygen. Colistin sorption onto soils and sediments has been shown to be spontaneous in two publications [133, 139]. The solid-water partition coefficient values derived from these publications range from 2.04 to 2.43, which depict the significant sorption of colistin onto solids. Colistin desorption was also limited, with 0.04–5.66% of the sorbed amount being desorbed [139]. In the environment, sorption may be the main mechanism driving the fate of colistin. Sorbed colistin could be refractory to hydrolysis and photolysis and therefore more persistent than dissolved colistin.

Colistin can be biodegraded by various bacterial strains or enzymes intentionally chosen for its ability to degrade organic molecules, and colistin-degrading enzymes have been identified [141–143]. However, these publications might poorly represent colistin biodegradation in the environment. Importantly, the sorption of colistin appears to be a limitation in biodegradation studies [133]. It was, however, found that colistin was biodegraded in by periphyton. One publication presented colistin biodegradation results in soils [139]. In soils, the colistin biodegradation half-life was 13–29 days, depending on the initial load. The adsorbed colistin appears to be biodegraded by natural communities in soil. As this attenuation mechanism occurs while colistin is adsorbed, it could be the main degradation process of colistin in the environment.

Like other drugs [18], colistin production could lead to its emission into the environment. Wastewater from colistin production via microbial fermentation processes contains large amounts of this molecule. Therefore, without adequate wastewater treatment, colistin is emitted into the environment in this way. The minimal half-life of colistin hydrolysis at 85 °C is 3.41 h at pH 11 [118]. Therefore, other treatment

methods are necessary. Anaerobic digestion of colistin was characterized in anaerobic digesters [205]. After 55 days at 37 °C, the colistin concentration decreased from 2.3 g L⁻¹ to below the limit of quantification. Anaerobic digestion of colistin production wastewater could prevent the release of this compound into the environment. To the author's knowledge, there is no available information on the relevance of this emission pathway in reality.

As mentioned previously, colistin is considered a last-resort treatment in human medicine. Consequently, its use is very limited. In France in 2022, a national mission reported that in 1,573 healthcare facilities representing 78% of hospitalizations, 2456 g of injectable colistin was used [150]. Between 2018 and 2019, 354,442 polymyxin doses were used in hospitals in China [206]. It represents 5,310 g of colistin. Little is known about colistin degradation in wastewater treatment plants. However, it can be assumed that human medicine is not a major source of colistin contamination since the quantities used are small.

The use of colistin as a growth promoter has been banned in many countries, resulting in a decrease in its consumption. However, in 2012, veterinary use was still 600 times greater than human medicine use [74]. Since then, consumption has continued to decline, with a 76% decrease between 2011 and 2020 [81]. New regulations have also been adopted worldwide to fight colistin resistance, which threatens the efficiency of colistin in treating infections [82]. Despite these efforts, the use of colistin in veterinary medicine is still much greater than its use in human medicine. In 2022, despite the ban of prophylactic colistin use, 126 tons of polymyxins were used for livestock in the European Union, including 8.3 tons in France [99, 207, 208]. There are disparities from country to country both in the European Union and in the world. In fact, the use of colistin for livestock is banned in the Netherlands, whereas the consumption of colistin in France or Poland is still relatively high [209]. In sub-Saharan Africa, a lack of regulation and surveillance of antimicrobial use and antimicrobial resistance has been recently reported [210]. In this study, the use of colistin, including as a growth promoter, was shown to be significant, but no consumption data were presented. Aquaculture could be a determining factor in the veterinary use of colistin. Indeed, this food industry is developing, and its antimicrobial consumption is increasing: a 33% increase to 13,600 tons per year by 2030 has been predicted [19]. Fish farming has recently been suggested as an important source of mobile colistin resistance genes [211]. However, no information is available on the quantities of colistin used in aquaculture.

Therefore, colistin can be emitted into the environment via its use for livestock. Despite the decrease in colistin consumption, large amounts of colistin are still used in veterinary medicine. Then, colistin can be released from the feces into the environment, notably via the spread of

manure. A total of $1,248 \mu\text{g kg}^{-1}$ colistin has been measured in piglet manure fed 20 mg kg^{-1} colistin sulfate [212]. Colistin is poorly absorbed orally, resulting in the excretion of large amounts of this compound (Table 1). In poultry manure, the measured concentrations were lower. In Belgium, colistin A and colistin B were detected in all swine manure from farms using this compound; the measured concentrations ranged from 627 to $48,600 \mu\text{g kg}^{-1}$ [213]. The efficiency of the colistin ban as a growth promoter in China has been studied [214–216]. Fecal samples from 118 farms collected before and after the ban were analyzed. The mean colistin concentration in manure was $191.1 \mu\text{g kg}^{-1}$ in 2017 and decreased to $7.5 \mu\text{g kg}^{-1}$ on the investigated farms [215]. In this study, differences were observed from one farm to another. In another study, samples from five swine collected before and after the ban were analyzed. In 2016, before the ban, concentrations in manure ranged from below the limit of quantification (of $140 \mu\text{g kg}^{-1}$) to $7529 \mu\text{g kg}^{-1}$, whereas after the ban, all colistin concentrations were below the limit of quantification in all samples, including feed [216]. These publications show that reducing the use of colistin allows a reduction in the concentrations measured in manure, except in a study conducted on one broiler farm in which colistin concentrations increased after its ban [214]. After 44 days at 38°C in 20 L reactors, colistin A and colistin B are almost completely degraded [140]. Another study addressed the degradation of antibiotics during manure biological treatment. However, colistin was not used before sampling and was never detected [217].

The use of colistin in veterinary medicine has drastically decreased over the last decade. However, tons of this compounds are still used, and little is known about its emission into the environment via livestock use. A publication predicted that the colistin concentration in soils could reach $100 \mu\text{g kg}^{-1}$ following the spread of manure [218]. One study revealed the transfer of colistin from spread manure to soil, generating colistin concentrations of up to $10 \mu\text{g kg}^{-1}$ in soils [139]. In this study, the colistin concentration in manure was $147 \mu\text{g kg}^{-1}$. It can therefore be assumed that a greater colistin load in feces would increase the amount released into soils. One scientific publication quantified colistin in environmental samples [214]. In this study, colistin residues were detected in soils surrounding the monitored pig farm. The detected concentrations ranged from 0 to $64.4 \mu\text{g kg}^{-1}$, with no clear relationship between the manure and soil concentrations. The observed lack of environmental monitoring studies could be due to the difficulty of colistin analysis, especially in environmental samples [110]. Despite evidence that colistin sorption could drive the environmental fate of this drug, it is not possible, on the basis of the literature, to clearly determine the fate of colistin within environmental compartments. Moreover, further monitoring studies

are necessary to assess the occurrence of colistin in the environment, especially in soils receiving manure.

The environmental fate of polymyxin B has not been widely studied, and either laboratory or field publications are scarce. Three publications investigated polymyxin B degradation in solution [126–128]. After one week at pH 5.6 in sodium chloride (NaCl) solution, 21–25% of polymyxin B was degraded at 4°C and 25°C , respectively [127]. Polymyxin B degradation in disodium phosphate buffer strongly depends on pH and temperature; degradation is much faster at pH greater than 7, and kinetics are 4.6 times faster at 52°C than at 32°C [128]. Overall, at 37°C at pH equal to 7, polymyxin B half-life was 441 h. Similarly, at 25°C in potassium phosphate buffer, polymyxin B degradation was faster at pH 3.4 and 1.4 than at pH 7.4, and temperature increased the kinetics [126]. According to the authors, the main degradation mechanism was racemization. In these studies, polymyxin B degradation was rather slow. It therefore seems unlikely that this attenuation process will play a major role in the environmental fate of polymyxin B.

Only one publication addressed polymyxin B photolysis. Polymyxin B is not degraded by direct photolysis in pure water but is degraded by indirect photolysis in the presence of organic matter (Table 4), with an associated half-life of 1.6 h [133]. This same study is also the unique publication about polymyxin B sorption. Owing to strong sorption and high limit of quantification, no residual polymyxin B was measured in the supernatant, and no polymyxin B could be extracted from the tested soils. This reflects the strong sorption of polymyxin B on the tested soils. Therefore, no partition coefficient could be derived. Sorption could be the main process regulating the fate of polymyxin B in the environment. No data are available on the impact of environmental conditions on polymyxin B sorption, which limits interpretation of this process. Polymyxin B biodegradation by a *Sphingosinicella* sp. strain was close to 90% in 2 h [142]. Since this strain was selected because of its ability to degrade peptides, this study does not represent the environmental biodegradation of polymyxin B. Under environmental conditions, at 19.6°C and pH equal to 7.7–8.1 in the presence of periphyton, polymyxin B was no longer detected 24 h after the start of the experiment; however, it was mostly due to sorption onto suspended particles [133]. The effect of polymyxin B sorption on its biodegradation is not sufficiently known, as this compound could not be analyzed. Colistin can be biodegraded when adsorbed [139]. Sorption is expected to be the driving factor of the environmental fate of polymyxin B, and biodegradation might attenuate this compound. The biodegradability of polymyxin B when it is adsorbed is also a question that needs to be addressed.

Production could be a source of polymyxins in the environment. It has been used for colistin and bacitracin but not for polymyxin B [118]. However, production might be a

way for polymyxin B to be emitted into the environment. Like colistin, polymyxin B is the last-resort antibiotic added in 2018 to the World Health Organization list of “Highest Priority Critically Important Antimicrobial” [78]. Its use is limited; for example, polymyxin B is not listed in the human antimicrobial consumption monitoring program in France [150]. Therefore, human medicine is unlikely to be an important source of polymyxin B in the environment.

In the European Union, for veterinary use, polymyxin B is only approved for topical use in dogs, cats and guinea pigs for the treatment of otitis and skin infections [99]. The use of polymyxin B in veterinary medicine is rare in the European Union. In most monitoring programs, colistin and polymyxin B consumption are not differentiated, but it can be assumed that polymyxin B use is minor. In fact, in Belgium, its consumption was 0.9 kg in 2015 and 0.8 kg in 2022 [151]. In the United States, polymyxin B is approved for topical use in cattle, dogs, cats, sheep and equids for the treatment of local infections. According to the FDA, in 2022, in the US, polymyxin B consumption in food-producing animals was less than 1872 kg [219]. Polymyxin B release into the environment via veterinary use therefore seems negligible. The fate and occurrence of polymyxin B in the environment are essentially unknown. Sorption could control its partition and persistence, but further study is needed.

Gramicidin and tyrocidine

There is no available information on the environmental fate of gramicidin D, gramicidin S, and tyrocidine in the laboratory or in the field. In human medicine, these compounds are used topically to treat bacterial infections, and their uses are limited [89, 91]. Therefore, despite the knowledge gap concerning the fate of gramicidins and tyrocidine, human medicine is unlikely to be a source of emissions into the environment, and their occurrence should be negligible.

Bacitracin

Few studies have investigated the degradation of bacitracin, especially its natural attenuation processes. Tables 3, 4, 5 and 6 present publications reporting experimental data on the sensitivity of bacitracin to natural degradation processes. Among those studies, 3 investigated bacitracin hydrolytic degradation. Major bacitracin congener A is almost not hydrolyzed in buffer solution after 14 days at pH 3 and pH 5 at 25 °C, with 11.9% of the initial amount being degraded [95]. In contrast, at pH values of 7 and 9, 25.7% and 62.5% of the initial bacitracin loads, respectively, were degraded. At 25 °C, a second publication reported 50% degradation in one week at pH 5–7 [220]. At pH 11 and 85 °C, the antibacterial activity of bacitracin congeners decreased by approximately 80% in 1 h due to hydrolysis, corresponding to a

half-life of 0.4 h [118]. At pH greater than 7, less than 60% of bacitracin was hydrolyzed, and at pH 5 and pH 3, less than 20% of bacitracin was hydrolyzed. These publications show that bacitracin hydrolysis is highly pH dependent, with degradation occurring faster at neutral and alkaline pH values and, at environmental pH values, hydrolysis being rather slow. Information on bacitracin photolysis is scarce in the scientific literature.

Bacitracin is not degraded by direct photolysis under simulated sunlight at pH 7.5 [133] or pH 5–8 [134]. In contrast, bacitracin undergoes indirect photolysis in the presence of organic matter. Among the different photochemically produced reactive intermediates, $^1\text{O}_2$ appears to be a major contributor to bacitracin degradation [133, 134]. Ultraviolet C are capable of degrading bacitracin within 2 h, and hydrogen peroxide (H_2O_2) accelerates the reaction [95]. Therefore, indirect photolysis might be an important process for the degradation of bacitracin in the environment, and Ultraviolet C treatment could be effective in removing bacitracin from wastewater. Bacitracin biodegradation in soils has been studied, and its half-life was determined to be 12–20 days [144]. The total disappearance of antimicrobial activity after 16 days in soil was reported [145], whereas according to another publication, bacitracin was completely degraded after 7 days in manure [221]. In water, bacitracin appears to be degraded by periphyton [133], and by a *Sphingosinella* sp. strain [142]. Bacitracin sorption highly depends on soil characteristics (Table 6). The pH value and clay content seem to be important factors in controlling bacitracin sorption, as the charge of a molecule influences its sorption on clay [133]. Bacitracin is produced by microbial fermentation processes, and high antibiotic concentrations can be found in production wastewater [118]. Without appropriate treatment, these residues can disturb the biological treatment of wastewater and eventually be discharged into the environment.

Bacitracin has been used for decades as a growth promoter in Europe [98] and in the USA, where it was the most commonly used antibiotic in livestock production in 1996 [222]. Its use as a growth promoter has been prohibited since 1998 in Europe [223] and since 2019 in China [101], whereas it is still authorized in Brazil and the USA [97, 100]. In the latter, 200 tons were used in 2021 [97]. Since bacitracin was banned in Europe, its consumption has decreased and was less than 7 tons in 2022 [209]. In contrast, bacitracin use is rare in human medicine.

Large amounts of bacitracin are excreted via farms. In feces from growing and finishing pigs, 51 mg kg⁻¹ bacitracin A was measured, and 320 mg kg⁻¹ bacitracin A was measured in feces from pigs fed with 39.7 mg kg⁻¹ bacitracin A [111, 224]. Once excreted, feces are either treated, stored to produce manure or released directly into the environment, determining bacitracin congener fate. In an experiment simulating bacitracin congener fate after manure

incorporation into soil, no bacitracin A was detected, neither was bacitracin F, i.e., the main bacitracin transformation product, in either runoff or soil [111]. The fate of bacitracin in the case of feces storage or treatment has been studied. Bacitracin A appears to be partially degraded in an anaerobic digester, with 3,400 mg kg⁻¹ measured in the digester sludge, and completely degraded in the lagoon following the digester [224]. In contrast, bacitracin A was not detected in an anaerobic degradation experiment, and bacitracin F was completely degraded after 7 days [221]. Notably, bacitracin is a mixture of more than 50 congeners, and one or two congeners are generally analyzed in publications [95]. Moreover, only a few transformation products are known. Bacitracin does not seem to be emitted into the environment via livestock production. Two publications analyzed bacitracin in the environment at different sampling sites. Bacitracin was not detected in the water or sediment of a river receiving treated water from a swine farm, likely because the lagoon was able to degrade it [224]. In urban watershed water samples from 114 sites near Brisbane, including sites receiving hospital wastewater, bacitracin was not detected because there was no bacitracin consumption for human medicine during the sampling [225]. These studies highlight that bacitracin can be degraded before it reaches the environment and that the quantity of bacitracin used in human medicine is small. However, further research on bacitracin contamination in rural zones, including in soils receiving manure and surface water near livestock farms, is needed.

Impact of antimicrobial peptides on the environment

The impacts of antimicrobial peptides on nontarget organisms and ecosystems have not been studied much. A publication determined the predicted no effects concentrations for the selection of resistant bacteria (PNECr) on the basis

of measured minimum inhibitory concentrations for vancomycin, colistin, teicoplanin, and daptomycin [226]. The lowest PNECr was for teicoplanin (1 µg L⁻¹), and the highest was for vancomycin (8 µg L⁻¹). To date, only colistin and vancomycin have been measured in the environment. For colistin, concentrations of up to 64.4 µg kg⁻¹ have been measured in soils [214], and for vancomycin, most environmental concentrations are lower than the PNECr. In only three publications, vancomycin concentrations greater than PNECr were measured in sediments and surface water [168, 169, 227]. However, a study proposed a PNECr of 0.6 µg L⁻¹ for vancomycin and 0.04 µg L⁻¹ for teicoplanin [228]. Using this PNECr, another publication reported vancomycin concentrations susceptible to select resistance to vancomycin [164]. Therefore, in contamination “hotspots” vancomycin could contribute to the development of resistance and threaten human health.

In the environment, antimicrobial agents can have other ecological effects on microbial communities, thus impacting geochemical cycles, or on other nontarget organisms [24]. This first type of effect is hard to quantify. Few ecotoxicity tests have been performed to assess antimicrobial peptides impacts on nontarget organisms. Table 7 presents the results of these ecotoxicity tests.

The table presents the results of ecotoxicity tests of AMPs available in literature. Only acute toxicity tests have been performed. The EC50 and LC50 of tested AMPs are high, therefore the risk of acute toxicity of these drugs in the environment is expected to be low. Impacts of chronic exposure to AMPs needs to be addressed.

Two studies determined the effective concentration 50% (EC50) for vancomycin [229, 230]. The measured concentrations are high for the tested organisms, namely *Daphnia* and microalgae. Some photocatalytic transformation products have been shown to be toxic to *Daphnia*, thus illustrating the potential toxicity of these products [129]. A publication also

Table 7 Ecotoxicity of antimicrobial peptides (AMPs) expressed as effective concentration 50% (EC50) and lethal concentration 50% (LC50)

Molecule	Organism	Exposure time	EC50	LC50	References
Vancomycin	<i>D. magna</i>	48 h	686.9 mg L ⁻¹	Not available	[229]
Vancomycin	<i>P. subcapitata</i>	72 h	370.8 mg L ⁻¹	Not available	[229]
Vancomycin	<i>F. candida</i>	28 d	546 mg kg ⁻¹	Not available	[229]
Vancomycin	<i>F. candida</i>	28 d	Not available	914 mg kg ⁻¹	[229]
Vancomycin	<i>V. fischeri</i>	No effect	Not available	Not available	[229]
Vancomycin	<i>P. subcapitata</i>	72 h	724 mg L ⁻¹	Not available	[230]
Vancomycin	<i>P. cubensis</i>	4 d	Not available	1 g L ⁻¹	[227]
Colistin	<i>B. amyloliquefaciens</i>	16 h	2.04 mg L ⁻¹	Not available	[231]
Colistin	<i>P. putida</i>	16 h	0.18 mg L ⁻¹	Not available	[231]
Bacitracin	<i>D. magna</i>	24 h	Not available	126.4 mg L ⁻¹	[232]
Bacitracin	<i>D. magna</i>	48 h	Not available	30.5 mg L ⁻¹	[232]
Bacitracin	Artemia	24 h	34.06 mg L ⁻¹	Not available	[233]
Bacitracin	Artemia	48 h	21.82 mg L ⁻¹	Not available	[233]

highlighted that the EC50 of coexposure to vancomycin and gentamicin in *Pseudokirchneriella subcapitata* was 1,500 times lower than that of vancomycin alone [230]. Cocktail effects need to be taken into account for antimicrobial peptides ecotoxicity. Toxicity data on vancomycin are scarce, and several publications evaluating the environmental risks of organic pollutants could not assess vancomycin risks because of the lack of information [157, 158].

Information about colistin ecotoxicity is scarce. Only one study reported EC50 values for two bacterial strains, 2.04 mg L⁻¹ for *Bacillus amyloliquefaciens* and 0.18 mg L⁻¹ for *P. putida* [231]. This study also suggested that colistin sorption could drastically reduce its bioavailability and antimicrobial activity: the EC50 values were 130 and 1,472 times greater in the soil–water test than in the water-only test. Further tests should be conducted to determine the effects of sorption on the acute toxicity of colistin to organisms. Three publications used longer toxicity tests. One study has shown that colistin sulfate alters soil microbial communities at 5 and 50 mg kg⁻¹ after 41 days of exposure [234]. This highlights that acute toxicity tests poorly represent ecosystem complexity and that their use could bias the interpretation of the impacts of colistin and other antimicrobial peptides on the environment. Another study revealed that the inhibitory concentration 50% (IC50) of chronic colistin for *Vibrio fischeri* is lower than the 15 min IC50 by 2 orders of magnitude [235]. Ecotoxicity markers have also been used to study the impact of colistin on *Eisenia fetida* [236]. The expression of two stress proteins was measured in colistin-exposed worms via quantitative-polymerase chain reaction. The expression of HeatShock protein 70 was upregulated under all conditions, which could indicate an impact of colistin on this organism. The experimental concentrations of colistin used were high (10–100 mg kg⁻¹).

Bacitracin ecotoxicity has been assessed via acute toxicity tests [232, 233]. The 24 h EC50 values for artemia and daphnia were 34.06 mg L⁻¹ and 126.4 mg L⁻¹, respectively. Bacitracin was also found to have no impact on antimicrobial communities in soils at any of the tested concentrations (up to 100 mg kg⁻¹), because of its complete removal from soil solution [237]. There is no information on the ecotoxicity of other antimicrobial peptides. It seems unlikely that antimicrobial peptides concentrations in the environment would reach proposed PNECr [226]. However, these concentrations could be exceeded in contamination hotspots such as wastewater treatment plants or manufacturing wastewater, which would create a risk for environmental and human health [7, 24, 238]. Moreover, co-selection for antibiotic resistance to antimicrobial peptides could occur in the environment. Co-selection designates the development bacterial resistance to multiple chemical entities (e.g. metals, biocides, pharmaceuticals) via various mechanism. This phenomenon, which is susceptible to worsen the impacts of antimicrobial peptides

on health through antimicrobial resistance selection, has been reviewed elsewhere [239]. Antimicrobial peptides also appear to have a relatively low toxicity for the organisms tested, although their ecotoxicity needs to be tested. The main ecotoxicological risks associated with antimicrobial peptides are the potential impacts on natural microbial communities, the transformation products toxicity and the cocktail effects; these effects must be addressed.

Antimicrobial peptides

There are substantial gaps in the current scientific literature concerning the environmental fate and risks posed to humans and the environment of marketed antimicrobial peptides. However, the applications and consumption of antimicrobial peptides are highly variable, as is the knowledge on their fate, which justifies the need for further research. This reasoning is presented in Fig. 5.

The use of gramicidin and tyrothricin in human medicine is very limited and is not expected to increase. Given the small quantities consumed, it is unlikely that these compounds will reach the environment in sufficient amounts to create a risk. Therefore, the lack of data on their environmental fate does not seem to require urgent attention. Similarly, the use of polymyxin B is not expected to rise significantly. Other antimicrobial peptides, such as telavancin, dalbavancin, and oritavancin, and, to a lesser extent, teicoplanin,

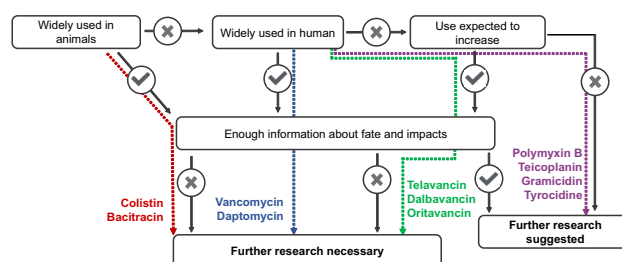


Fig. 5 Decision tree on the need of further research on antimicrobial peptides (AMPs) environmental fate and impacts, based on their use and the state of knowledge on these issues. According to this decision tree, all AMPs except polymyxin B, teicoplanin, gramicidin, and tyrocidine require further research on their environmental fate and impacts. Future research should allow to understand how to use these drugs without promoting antimicrobial resistance (AMR) development in the environment. In the context of the AMR crisis, it is necessary to use the “One health” concept to protect both the environmental health and the efficiency of these drugs. Black frames represent statements, black arrow with gray cross represent negative answer to the statement, black arrows with gray check represent positive answer to the question. Red dotted arrow represents decision tree for colistin and bacitracin. Blue dotted arrow represents decision tree for vancomycin and daptomycin. Green dotted arrow represents decision tree for telavancin, dalbavancin, and oritavancin. Purple dotted arrow represents decision tree for polymyxin B, teicoplanin, gramicidin, and tyrocidine

are receiving increasing interest, with their use expected to rise in the coming years [34, 59, 61, 198]. However, their environmental fate and toxicity have yet to be thoroughly addressed (Tables 3, 4, 5 and 6). If their usage expands as predicted, significant quantities of these compounds could be released into the environment, potentially exacerbating environmental health and human health issues. To assess these risks, research is urgently needed to assess on their environmental fate, both in laboratory and in field settings, and to evaluate their toxicity, including that of active ingredients and metabolites. Although the use of bacitracin and colistin in human medicine is limited, these compounds are widely employed in veterinary medicine. While their environmental fate has been partially studied, substantial gaps remain in the literature regarding their occurrence in the environment and their toxicity. Despite stricter regulations, large amounts of colistin are still used in veterinary medicine, raising significant concerns for both environmental and human health. Thus, an urgent environmental assessment of colistin is warranted.

Vancomycin is the most widely consumed antimicrobial peptide in human medicine [150]. Many studies have monitored its presence in the environment, providing a comprehensive overview of the European situation. However, further research is needed in rest of the world (Fig. 4). Moreover, key knowledge gaps remain, such as monitoring vancomycin in specific environmental compartments like groundwater, where it has been detected [161]. A more detailed understanding of vancomycin attenuation processes could enhance insights into its environmental fate. Furthermore, photolytic transformation products have been shown to exhibit toxicity to *D. magna* [129]. Therefore, it also seems necessary to study the fate and toxicity of vancomycin metabolites. Daptomycin is the second most widely consumed antimicrobial peptide in human medicine, and its use is increasing in certain countries [150]. While several studies have examined its attenuation in laboratory settings (Tables 3, 4, 5 and 6), its transfer to the environment via wastewater treatment plants, its presence in ecosystems, and its toxicity have not been investigated. Given that daptomycin consumption is close to that of vancomycin, it is critical to improve our understanding of its environmental fate, its potential to promote resistance selection in the environment and its toxicity.

Conclusion

This review is the first to synthesize existing scientific literature on the environmental fate, occurrence, and toxicity of antimicrobial peptides. Four key findings emerged from the analysis. First, the quantities used and the predicted environmental concentrations vary significantly between

antimicrobial peptides. Second, the current understanding of their environmental fate and impacts is highly inconsistent. Third, the state of knowledge regarding these issues is insufficient for any of the antimicrobial peptides. Fourth, a prioritization framework has been developed to identify research needs based on the use and existing knowledge for each antimicrobial peptide. Antimicrobial peptides are increasingly considered as essential tools in combating antimicrobial-resistant bacteria. It is therefore crucial to determine whether these compounds and their transformation products may contribute to antimicrobial resistance development or other ecological impacts, particularly in natural environments and wastewater treatment plants. The conclusions drawn here aim to provide guidance for future research on antimicrobial peptides, to ensure the safe and sustainable use of antimicrobial peptides in both human and veterinary medicine.

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Declarations

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