Advances in Clinical Medicine 临床医学进展, 2020, 10(8), 1729-1742
Published Online August 2020 in Hans. http://www.hanspub.org/journal/acm
https://doi.org/10.12677/acm.2020.108260

Hans汉斯

Sources, Mechanism and Clinical Application of Antimicrobial Peptides

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Received: Aug. 3rd, 2020; accepted: Aug. 19th, 2020; published: Aug. 26th, 2020

Abstract

Antimicrobial peptides (AMPs), also known as host defense peptides (HDPs), are usually small peptides composed of 7~100 amino acids, which are an important part of the natural immune defense system. AMPs have many biological activities, such as broad-spectrum anti-infective bacteria (G^+, G^-), antiviral, antifungal, antiparasitic, antitumor and immunomodulatory activities. AMPs can inhibit and kill pathogenic bacteria through membrane acting mechanism and non-membrane acting mechanism. AMPs have been widely concerned in recent years because of their potential therapeutic effects. Compared with traditional antibiotics, AMPs are not easy to produce drug resistance, low toxicity, biodiversity and direct attacking properties. AMPs are considered to be the most promising new generation of antibacterial agents in the post antibiotic era. At present, more than 60 AMPs drugs already reached the market and hundreds of novel therapeutic AMPs are in the clinical trials. This paper reviews the sources, mechanism and recent clinical application of antimicrobial peptides.

Keywords

Antimicrobial Peptides, Antibiotic Resistance, Therapeutic Drugs, Clinical Trials, Immunomodulatory Activity

抗菌肽的来源、作用机制及临床应用研究进展

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收稿日期：2020年8月3日；录用日期：2020年8月19日；发布日期：2020年8月26日

文章引用: 吴阳开, 金明昌. 抗菌肽的来源、作用机制及临床应用研究进展[J]. 临床医学进展, 2020, 10(8): 1729-1742. DOI: 10.12677/acm.2020.108260

摘　要

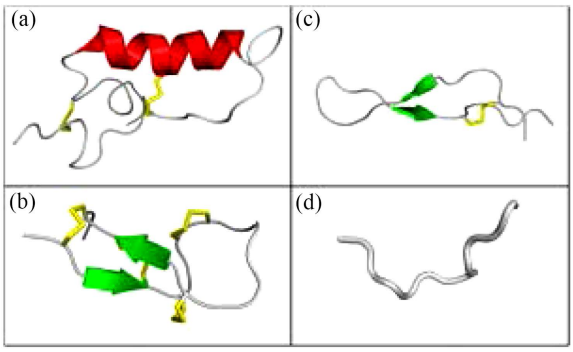
抗菌肽(Antimicrobial peptide, AMPs)又叫宿主防御肽(Host defence peptide, HDPs)，通常是由7~100个氨基酸组成的小分子多肽，是生物体天然免疫防御系统的一个重要组成部分。AMPs具有广谱抗感染性细菌(G^+、G^-)、抗病毒、抗真菌、抗寄生虫、抑杀肿瘤细胞和免疫调节等生物学活性。AMPs通过膜作用和非膜作用两种机制抑杀病原菌。AMPs由于其潜在的治疗作用，近年来受到了人们的广泛关注。与传统的抗生素相比，AMPs具有不易产生耐药性、低毒性、生物多样性和直接攻击性的特点，AMPs被认为是后抗生素时代最有前途的新一代抗菌药物。目前已有60多种AMPs药物进入市场，数百种AMPs药物正处于临床试验阶段。文章综述了抗菌肽的来源、作用机制及在临床上的应用。

关键词

抗菌肽，抗生素耐药性，治疗药物，临床试验，免疫调节活性

1. 引言

抗菌肽(Antimicrobial peptide, AMPs)又叫宿主防御肽(Host defence peptide, HDPs)，通常是由 7~100 个氨基酸组成的小分子多肽[1]，是生物体天然免疫防御系统的一个重要组成部分[2]，也是各种生物抵御入侵病原体的第一道防线[3]。AMPs 具有广谱抗感染性细菌(G^+、G^-) [4]、抗病毒[5]、抗真菌[6]、抗寄生虫[7]、抑杀肿瘤细胞[8]和免疫调节[9]等生物学活性。尽管大多数 AMPs 是阳离子肽，但在脊椎动物、无脊椎动物和植物中已经发现了一些阴离子 AMPs (Malik 等，2016) [10]。根据 AMPs 的二级结构，AMPs 可分为四大类：1) α-螺旋(α-helical)、2) β-折叠(β-Stranded)、3) β-发夹或环(β-hairpin or loop)和 4) 延伸型肽(extended)，其中 α-螺旋肽和 β-折叠肽是最常见的(图 1) [11]。本文就抗菌肽的来源、作用机制及在临床上的应用作一综述。



(a) α-螺旋(α-helix)、(b) β-折叠(β-strand)、(c) β-发夹或环状(β-hairpin or loop)、(d)延伸型(extended)

Figure 1. The secondary structural classes of antimicrobial peptides. Adapted from Ahmed T A E, Hammami R. (2019)
图 1. AMPs 的二级结构。引自 Ahmed T A E, Hammami R. (2019)

2. 抗菌肽的来源

AMPs 的发现可以追溯到 1939 年，当时，Dubos 从土壤样本的芽孢杆菌(*Bacillus*)中分离出一种抗菌剂[12]，这种物质能预防小鼠肺炎球菌(*Pneumococcus*)的感染，后来被命名为 gramicidin (短杆菌肽) [13]。此后，从原核生物和真核生物中相继发现了许多 AMPs [14] [15] [16]，仅蛙皮肤中就发现了 300 多种 AMPs [15]。据 APD 抗菌肽数据库报道(截止 2020 年 5 月)，已经有 3099 种天然抗菌肽被鉴定、分离出来，其中来自于动物 2359 种(76.12%)、植物 352 种(11.36%)、细菌 355 种(11.46%)、真菌 20 种(0.65%)、原虫 8 种(0.26%)、古细菌 5 种(0.16%) [17] (见图 2)。表 1 总结了从各种生物中发现的部分 AMPs。

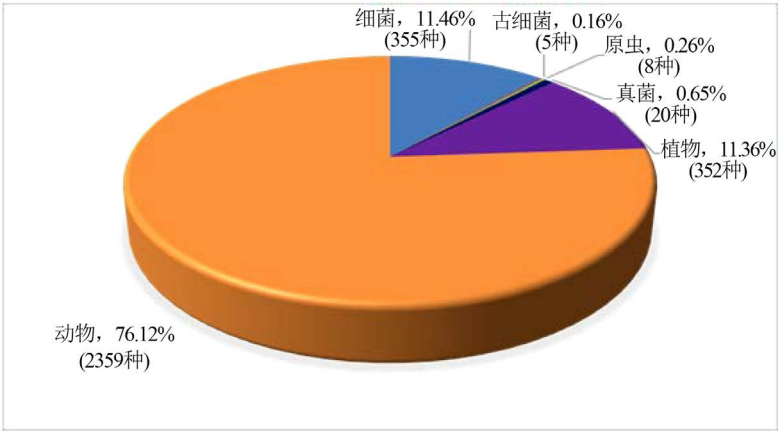


Figure 2. The sources of AMPs. Adapted from http://aps.unmc.edu/ap/main.php (May, 2020)
图 2. AMPs 的来源。引自 http://aps.unmc.edu/ap/main.php (2020 年 5 月)

Table 1. Some antimicrobial peptides from various organisms
表 1. 各种生物来源的部分抗菌肽

序号	抗菌肽名称	来源	氨基酸数量	抗菌活性	参考文献
		昆虫抗菌肽			
1	Acaloleptin	*Acalolepta luxuriosa*	71	G^+, G^-	[18]
2	Andropin	*Drosophila melanogaster*	34	G^+	[19]
3	Apidaecin IA	*Apis mellifera*	18	G^-	[20]
4	Cecropin	*Hyalophora cecropia*	37	G^-	[21]
5	Defensin-*α*	*Aedes aegypti*	40	G^+, G^-	[22]
6	Drosomycin	*Drosophila melanogaster*	44	F	[23]
7	Holotricin	*Holotrichia diomphalia*	43	G^+, G^-	[24]
8	Sapecin-*α*	*Sarcophaga peregrine*	40	G^+, G^-	[25]
9	Tenicin 1	*Tenebrio molitor*	43	G^+, G^-	[26]
10	Thanatin	*Podisus maculiventris*	21	G^+, G^-	[27]
		人体			
1	Cathelicidins	Human neutrophils	30	F, G^+, G^-	[28]
2	*A* Defensins	Human neutrophils	12~80	F, G^+, G^-	[29]
3	Human Histatin 8	*Homo sapiens*	12	F, G^+, G^-	[30]
4	LL37	*Neutrophils* (*Homo sapiens*)	37	F, G^+, G^-	[31]

Continued

		动物			
1	Androctonin	*Androctonus australis*	25	F, G^+, G^-	[32]
2	Bactenecin	Bovine Neutrophils	12	G^+, G^-	[33]
3	Brevinin	*Rana brevipora porsa*	24	F, G^+, G^-	[34]
4	Buforin II	Bufo bufo gargarizans	21	F, G^+, G^-	[35]
5	Cupiennin	*Cupiennius salei*	35	G^+, G^-	[36]
6	Dermaseptin S1	*Phyllomedusa sauvagii*	34	G^+, G^-	[37]
7	Lycotoxin	*Lycosa carolinensis*	27	G^+, G^-	[38]
8	Tachyplesins	*Tachypleus tridentatus* (horseshoe crab)	17	G^-	[39]
		植物			
1	Hevein	Latex of rubber trees	43	F	[40]
2	Purothionins	Wheat endosperm	45	G^+, G^-	[41]
		微生物			
1	Nisin	*Lactococcus lactis*	34	G^+	[42]
2	Alamethicin	*Trichoderma viride*	20	G^+	[43]
3	Enterocin	*Enterococcus*	70	G^+, G^-	[44]
4	Hominicin	*Staphylococcus hominis* MBBL 2-9	21	G^+, G^-	[45]
5	Ericin S	*Bacillus subtilis*	32	G^+	[46]
6	Plantaricin A	*Lactobacillus plantarum*	26	G^+, G^-	[42]
7	Carnobacteriocin B2	*Carnobacterium piscicola*	48	G^+, G^-	[47]
8	Leucocin A	*Leuconostoc pseudomesenteroides*	37	G^+, G^-	[48]
9	Subtilin	*Bacillus subtilis*	32	G^+	[49]
10	Pyrularia thionin	*Pyrularia pubera*	47	G^+, G^-	[50]
11	Microcin J25	*Escherichia coli* AY25	21	G^-	[51]
12	Gramicidin A	*Bacillus brevis*	15	G^+, G^-	[52]
13	Pediocin PA-1/AcH	*Pediococcus acidilactici* PAC-1.0	44	G^+	[53]
14	Mesentericin Y105	*Leuconostoc mesenteroides*	37	G^+	[54]
15	Carnobacteriocin BM1	*Carnobacterium piscicola* LV17B	43	G^+, G^-	[55]
16	Streptin 1	*Bacillus subtilis* A1/3	23	G^+	[56]
17	Planosporicin	*Planomonospora alba*	24	G^+, G^-	[57]
18	Gassericin A	*Lactobacillus gasseri* LA39	58	G^+, G^-	[58]
19	Circularin A	*Clostridium beijerinckii* ATCC 25752	69	G^+, G^-	[59]
20	Divercin V41	*Carnobacterium divergens* V41	43	G^+	[60]
21	Listeriocin 743A	*Listeria innocua* 743	43	G^+	[61]
22	Plantaricin C19	*Lactobacillus plantarum* C19	37	G^+	[62]
23	Enterocin P	*Enterococcus faecium* P13	44	G^+	[63]
24	Subtilosin A	*Bacillus subtilis*	35	G^+, G^-	[64]
25	Plantaricin ASM1	*Lactobacillus plantarum* A-1	43	G^+	[62]
26	Lichenin	*Bacillus licheniformis*	12	G^+, G^-	[65]

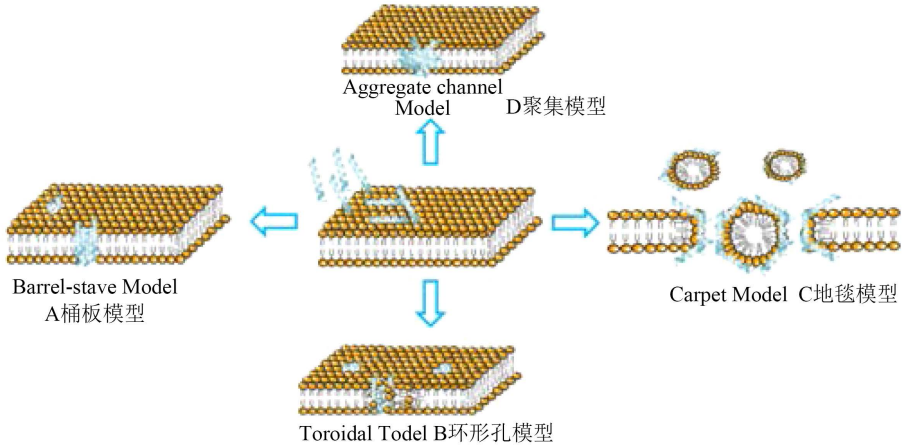
注：F——真菌；G^+——革兰氏阳性菌；G^-——革兰氏阴性菌。

3. 抗菌肽的作用机制

一般来说，AMPs 首先通过静电作用与细菌细胞膜相互吸引[66]。根据其作用方式，AMPs 的作用机制可分为膜作用和非膜作用两种类型。

3.1. 膜作用机制

阳离子 AMPs 通过选择性相互作用与带负电的微生物外膜作用(Zhao 等，2001 [67]；Sani 等，2016 [68])，导致细胞膜破裂而引起细胞内物质的渗漏而杀死细胞(Da Costa 等，2015 [69])。这些 AMPs 在与微生物细胞膜相互作用的过程中显示出结构和拓扑的动态性变化(Mingeot-Leclercq 等，2016 [70]；Haney 等，2017 [71])。目前，解释 AMPs 作用于细菌膜的机制，有桶板模型(barrel-stave model)、环形孔模型(toroidal-pore model)、地毯模型(carpet-like model) 聚合模型(aggregate model)。如图 3 所示(Nguyen 等，2011 [72])。



A 桶板模型(barrel-stave model)、B 环形孔模型(toroidal-pore model)、C 地毯模型(carpet-like model)、D 聚集模型(aggregate model)

Figure 3. The membrane acting mechanisms following initial adsorption of AMPs. Adapted from Nguyen, *et al.* (2011) and Da Costa, *et al.* (2015)
图 3. AMPs 初始吸附后作用于细胞膜的机制。引自 Nguyen 等(2011)和 Da Costa 等(2015)

3.1.1. 桶板模型(Barrel-Stave Model)

在该模型中，α-螺旋结构的 AMPs 与细胞膜结合后，促使更多的 AMPs 结合在细胞膜表面，AMPs 由与细胞膜平行方向逐渐转为垂直方向，通过螺旋结构中的疏水区域，插入至磷脂双分子层中，形成“桶样”的穿膜通道(Yang 等，2001 [73]；Reddy 等，2005 [74])。更多 AMPs 分子的聚集增大了孔径，导致细胞内容物的外溢，最终导致细胞死亡(Brogden，2005 [75])。

3.1.2. 环形孔模型(Toroidal-Pore Model)

在环形孔模型中，AMPs 的亲水段与细胞膜中磷脂的极性部分相互作用，并持续诱导脂质单层弯曲以获得稳定的曲率并形成环形孔(Melo 等，2009 [76])。当插入的 AMPs 的极性面与膜脂的极性头结合时，形成跨膜环形孔，孔内同时排列着肽和脂头基团(Brogden, 2005 [75])。

3.1.3. 地毯式模型(Carpet Model)

在该模型中，AMPs 与靶膜表面结合，并以地毯状的形式覆盖。在 AMPs 达到特定阈值后，肽分子与磷脂头基结合，形成含有碎片的胶束而穿透膜(Melo 等，2009 [76])，最终导致细胞膜崩解和随后的细

胞死亡(Gaspar 等，2013 [77])。

3.1.4. 聚合模型(Aggregate Channel Model)

在该模型中，AMPs 无特定取向地聚集在细胞膜表面，达到一定浓度后与膜磷脂分子形成类似胶状的肽－脂复合物，以类似洗涤剂的方式破坏脂质双层，形成跨膜的动态孔道(Wu 等，1999 [78])。

3.2. 非膜作用机制

一些 AMPs 即使在低浓度下，也不改变膜完整性，穿过膜脂质双层，靶向细胞内成分(Hancock 等，2002 [79])，通过影响细胞内代谢活动，如结合 DNA，阻断酶活性，抑制 DNA、RNA 或蛋白质的合成等而杀死细菌(Cudic 等，2002 [80]；Krizsan 等，2014 [81]；Mansour 等，2014 [82]；Yeaman 等，2003 [83]。见图 4 (Da Costa 等，2015 [69])。表 2 列出了部分作用于细胞内活性的抗菌肽。

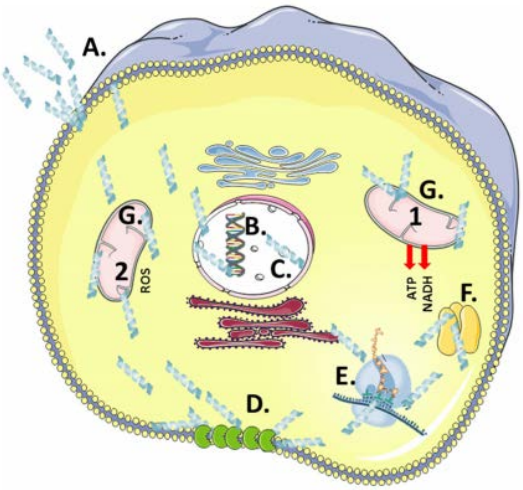


Figure 4. The non-membrane acting mechanisms of AMPs. Adapted from Da Costa, *et al*. (2015). A. Disruption of cell membrane integrity); B. Blocking of RNA synthesis); C. Inhibition of enzymes necessary for linking of cell wall structural proteins; D. Inhibition of ribosomal function and protein synthesis; E. Blocking of chaperone proteins necessary for proper folding; F. Targeting of mitochondria: 1) inhibition of cellular respiration and induction of ROS formation, 2) disruption of mitochondrial cell membrane integrity and efflux of ATP and NADH

图 4. AMPs 非膜作用机制。引自 Da Costa 等(2015)。A. 破坏细胞膜完整性；B. 阻断 RNA 合成；C. 抑制细胞壁结构蛋白连接所需酶的活性；D. 核糖体功能与蛋白质合成的抑制；E. 适当折叠所必需的伴侣蛋白的阻断；F. 靶向线粒体：1) 抑制细胞呼吸和诱导活性氧(ROS)的形成，2) 破坏线粒体膜完整性以及 ATP 和 NADH 的外排

Table 2. Some antimicrobial peptides acting on intracellular activity

表 2. 部分作用于细胞内活性的抗菌肽

序号	抗菌肽名称	细胞内靶点	参考文献
1	Buforin II, tachyplesin	与 DNA 结合	Carrera, 2017 [84]
2	Pleurocidin,dermaseptin,PR-39, HNP-1, HNP-2,Indolicidin	抑制 DNA、RNA 和蛋白质的合成	Nagarajan, 2018 [85]
3	Histatins, pyrrhocoricin, Drosocin, Apidaecin	抑制酶的活性	Le, 2017 [86]
4	N-acetylmuramoyl-L-alanine Amidase	自溶素的活化	Gordon, 2005 [87]
5	PR-39, PR-26, indolicidin, microcin 25	改变细胞质膜(抑制隔膜形成)	Mirski, 2017 [88]
6	Mersacidin	抑制细胞壁的合成	Wuerth, 2017 [89]

4. AMPS 在临床上的应用

4.1. AMPS 作为治疗局部感染的药物

目前，一些抗菌肽已用于治疗人的局部感染药物，如抗菌肽 NEUPREX 为 rBPI21 的注射制剂，用于治疗接受心脏直视手术的儿科患者和严重烧伤患者(Conlon, 2011) [90]；重组肽 HBD-2 用于治疗在使用假体植入过程中获得的感染(Shin, 2013) [91]；来源于两栖动物皮肤的肽，如白细胞介素(alyteserin)、灯盏花素(brevinin)、蛔虫毒素(ascaphin)、假丝酵素(pseudin)、卡氏菌素(kassinatuerin)和颞叶蛋白(temporin),已被有效地用于治疗由鲍曼不动杆菌(*Acinetobacter baumannii*)、肺炎克雷伯菌(*Klebsiella pneumoniae*)、大肠杆菌(*Escherichia coli*)、金黄色葡萄球菌(*Staphylococcus aureus*)、铜绿假单胞菌(*Pseudomonas*)，念珠菌(*Candida spp.*)等多重耐药菌株引起的局部感染(Migoń, 2018) [92]；P113 是另一种天然存在于唾液中的抗菌肽(Haney, 2018) [93]，它以漱口液的形式用于治疗艾滋病毒(HIV)患者的口腔念珠菌病(*Candidiasis*)感染。Pexiganan 用于治疗糖尿病足溃疡中的局部感染(Greber, 2017) [94]；吲哚基肽的变体 MX-226 和 MX-594AN (omiganan pentahcolitan，1%凝胶)分别用于治疗与使用导管相关的感染和治疗寻常痤疮(Sachdeva, 2017) [95]。

4.2. 临床试验中的 AMPs

目前，超过 60 种 AMPs 药物投入市场，数百种新的治疗用 AMPs 正处于临床试验中(Lau, 2018) [96] (见表 3)。新出现的多肽技术，包括多功能肽、细胞穿透肽和肽－药物结合物，将拓宽 AMPs 在医学中的应用(Raucher, 2015) [97]。

Table 3. Partial AMPs in clinical trials
表 3. 临床试验中的部分 AMPs

抗菌肽	公司名称	临床试验阶段	抗菌谱/作用模式	参考文献
CZEN-002	Zengen	临床 I/II 期	GPB，GNP，念珠菌(*Candida*)/酵母调节机制，cAMP 诱导的干扰，抗炎	Ghosh 等，2015 [98]
Daptomycin	Cubicin	已上市	GPB/膜电位去极化，蛋白质、DNA 和 RNA 合成的抑制	Cortes-Penfield 等，2018 [99]
EA-230	Exponential biotherapies	临床 I/II 期	抗炎药/败血症与肾功能衰竭的保护	Gagliardini 等，2017 [100]
Pexiganan (MSI-78)	Genaera Corporation	临床 III 期	感染性糖尿病足溃疡	Jepson 等，2016 [101]
Omiganan	MIGENIX	临床 II/III 期	导管感染与酒渣鼻	Ng 等，2017 [102]
Lytixar (LTX-109)	Lytix Biopharma	临床 I/II 期	革兰氏阳性皮肤感染、脓疱病和金黄色葡萄球菌(*S. aureus*)鼻腔感染	Mohammad 等，2015 [103]
hlF1-11	AM-Pharma	临床 I/II 期	免疫复合造血干细胞移植受者的菌血症和真菌感染	Morici 等，2016 [104]
Novexatin (NP-213)	NovaBiotics	临床 II 期	真菌性指甲感染	Javia 等，2018 [105]
LL-37	Karolinska Institute	临床 I/II 期	下肢静脉溃疡难治症	De Lorenzi 等，2017 [106]
PAC-113	Demegen	临床 II 期	HIV 血清阳性患者的口腔念珠菌病	Mohammad 等，2015 [103]
RDP-58	Genzyme	后临床 II 期	炎症性肠病	Menko 等，2015 [107]
MX-594AN	MIgenix	临床 II 期	寻常痤疮的局部治疗	Moorthy 等，2018 [108]

Continued

MX-226	Migenix	临床 IIIb 期	皮肤病相关感染	Deslouches, 2017 [109]
HB-1345	BioMedix	临床 I 前期	痤疮	Döşler, 2017 [110]
HB-107	Biopharmaceuticals	临床前期	伤口愈合	Mangoni, 2016 [111]
Glutoxim	Pharma BAM	临床 II 期	肺结核	Krutetskaya, 2017 [112]
IMX942	Inimex	临床 IA 前期	免疫调节与化疗患者发热的治疗	Gagliardini 等，2017 [100]
DPK-060	Promore Pharma	临床 II 期	特应性皮炎的治疗	Harvey, 2015 [113]
POL7080	Polyphor Ltd	临床 II 期	非囊性纤维化支气管扩张症的治疗	Butler, 2017 [114]
SB006	SpiderBiotech	临床前期	抗内毒素活性	Giuliani, 2007 [115]
PL-5	江苏普莱医药生物技术有限公司	临床 II 期	皮肤感染	Feng, 2015 [116]
金环蛇毒抗菌肽 BF-30	苏州康尔生物医药有限公司	临床 I~III 期	细菌性阴道病	李惠钰，2019 [117]

5. 总结

抗生素耐药性是世界第二大死亡原因，导致每年约 70 万人死亡，预计到 2050 年每年死于抗生素耐药性的人数将达到 1000 万，造成的经济损失约 10 万亿美元。抗生素耐药性是多方面、多层面的，革兰氏阳性菌和革兰氏阴性菌都对现有的抗菌药物产生了难以治愈的耐药性，如耐万古霉素的粪肠球菌(*Enterococcus faecium*)、阴沟肠杆菌(*Enterobacter cloacae*, MRSA)，耐碳青霉烯类的鲍曼不动杆菌(*Acinetobacter baumannii*)和耐第三代头孢菌素大肠杆菌(*E. coli*)、β-内酰胺酶的 MDR 菌株，耐碳青霉烯类铜绿假单胞菌(*Pseudomonas aeruginosa*)和分枝杆菌(*Mycobacterium*)。对碳青霉烯类抗生素耐药的肺炎克雷伯菌(*Klebsiella pneumoniae*)对美国批准用于治疗的 26 种抗生素均产生耐药性。抗生素耐药性在全球范围内的扩展和蔓延速度远远高于发现并最终批准用于临床的新抗生素的速度。目前已有相当部分的 AMPs 在临床应用或处于临床试验中。AMPs 被认为是后抗生素时代最有前途的新一代抗菌药物。人们对 AMPs 的结构、理化性质以及对其活性的影响已有充分的了解，但对 AMPs 的作用机制以及其对细菌和宿主细胞的反应仍缺乏深入了解。这是未来 AMPs 在临床上普遍应用的主要瓶颈。

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