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微生物源性抗菌肽在可持续农业中的生物前景

林书华[a,b,#]，陈选[a,b,#]，陈惠敏[b]，蔡茜茜[b]，陈旭[b]，汪少芸[b,*]

[a] College of Chemical Engineering, Fuzhou University, Fuzhou 350108, China
[b] College of Biological Science and Engineering, Fuzhou University, Fuzhou 350108, China

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摘要

旨在定义、发现和开发传统抗生素替代品的策略将成为可持续农业系统发展的基础。在这些策略中，具有广谱抗菌活性和多方面作用机制的抗菌肽（AMP）被认为是后抗生素时代的理想替代品。尤其是源自代谢活跃、能适应各种极端环境的微生物的AMP，长期以来备受追捧。因此，本文总结了有关天然存在的AMP的信息，包括其生物活性、抗菌机制以及微生物源AMP的制备；文中还概述了它们的应用以及它们在农产工业中的使用所带来的挑战。

1. 引言

病原微生物是引起动植物疾病的主要原因，需要使用传统抗生素来控制其蔓延，以满足全球巨大的食物消费需求。然而，过度使用抗生素会造成耐药性(ABR)和多药耐药性(MDR)菌株的出现，对农业的可持续发展构成了严重威胁，如从猪分离的耐多黏菌素大肠杆菌，对现有类别的抗生素均有抗性。此外，这些携带耐药基因的病原体可通过食物链传播给人类，对人类生命健康构成重大威胁[1–3]。综上，人们迫切需要开发一种新型的抗菌药物来应对现今因耐药菌株传播引起的人类健康困境[4]。

抗菌肽（AMPs）具有广谱抗菌活性和多重作用机制，被认为是后抗生素时代极具前景的替代品，可通过发酵或酶水解的方式从植物、动物和微生物的母体蛋白中获取。微生物源AMPs与其他来源AMPs的不同之处在于微生物能够分泌大量的免疫调节分子，使它们能够在火山口、矿井和沙漠等极端环境中生存，从而产生具有新颖结构和优越性能的AMPs，这在一定程度上可以避免现有分子的重新发现，丰富AMPs资源库。此外，微生物源AMPs在转化应用中也取得了一定的成果，例如，黏菌素、万古霉素、达托霉素和ε-聚赖氨酸等抗菌肽已获美国食品药品监督管理局（FDA）批准上市[5–6]。现已上市的微生物源AMPs主要是由非核糖体肽合成酶（NRPSs）产生的非核糖体肽（NRPs），其应用场景广泛，使用范围可从抗生素延伸至免疫抑制剂[7–8]。除少数在其他生物中发现的类似NRPS的酶（如来自果蝇的ebony）[9]，NRPSs主要存在于微生物中。NRPs来源广泛，不仅包括土壤来源的微生物，还包括海洋、动物、植物和人类共生

* Corresponding author.
E-mail address: shywang@fzu.edu.cn (S. Wang).
# These authors contributed equally to this work.

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微生物。此外，存在于极端微生物和内生菌中的NRPs均未被发现，这使其成为人类、动物和植物疾病的新型抗菌药物的潜力巨大。

2. 微生物源抗菌肽

自第一例非核糖体肽——青霉素问世以来，微生物一直是人们用于抑制MDR病原体的新型AMPs的主要来源[10]。主要有三类微生物可以产生AMPs：细菌、真菌和微藻。由于微生物的多样性，极端环境是发现AMPs的重要来源。从远洋 *Streptomyces atratus* 中提取的ilamycins E1/E2就是典型的例子：它们对结核病病原体具有强效抗菌活性，其最低抑制浓度（MIC）值仅为9.8 nmol·L^{-1}[11]。此外，从工业矿泥微生物 *Pedobacter lusitanus* NL19中分离的pedopeptins A-C是脂多糖（LPSs）的新型抑制剂[12]。同时，病原体与生物体内生菌之间的共同进化为抵抗MDR病原体提供了策略，因此生物体内生菌也是结构新颖、活性优越的AMPs的重要来源。Lugdunin是一种由鼻部微生物 *Staphylococcus lugdunensis* 产生的含噻唑烷的肽，对MDR革兰氏阳性（G^+）病原体具有优异的杀菌效果，且不受血清影响[13]。尽管很难从土壤微生物中分离出新的化合物，但来自其他栖息地的微生物可能是具有新颖结构AMPs的重要来源。

2.1. 细菌源抗菌肽

细菌为人类提供了丰富的次生代谢产物[14]。然而，高通量测序表明细菌基因组含有的生物合成基因簇（BGCs）远高于目前分离的AMPs，细菌代谢能力被大大低估[15]。在人工培养环境中，这种潜力要么是未开发的，要么是检测不到的，故推测其可能含有理想的化合物

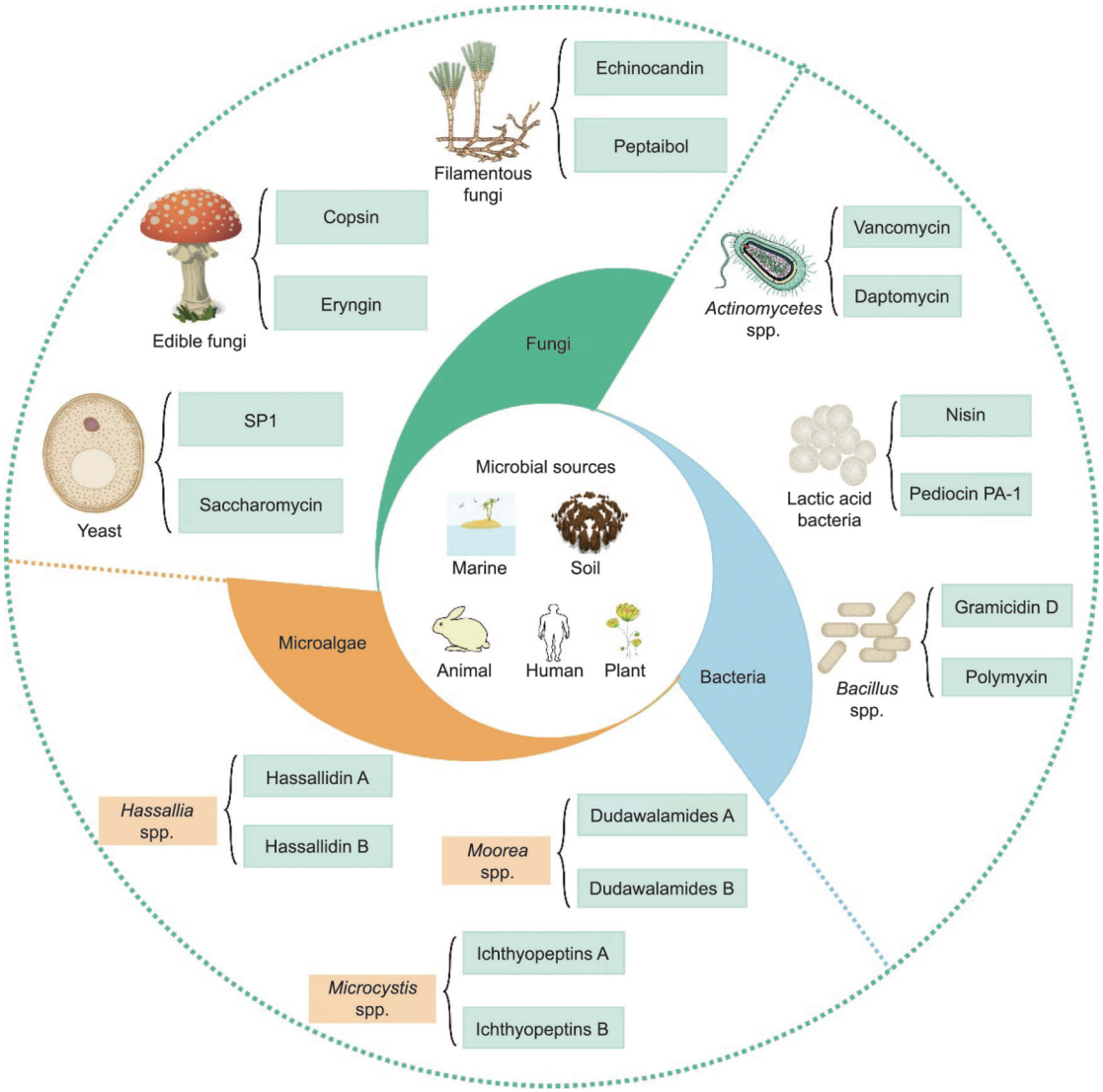

图1. 微生物中天然存在的AMPs。生产者主要来自土壤、海洋、动物、植物和人类微生物，包括细菌、真菌和微藻。

[16]。因此，为了获得更多新颖的AMPs，基因组学驱动的发现策略可用于激活隐藏的BGCs [17]。通过该方法人们从 *Streptomyces* sp. KCB13F003 中分离出六肽 ulleungmycin A–B，其对MDR病原体具有抑制活性[18]。相似地，来源于 *Streptomyces* sp. RK85-270 的环状八肽 octaminomycins A–B，在0~30 μmol·L^{-1}范围内表现出优异的抗疟原虫活性且无细胞毒性[19]。为了开发特定的AMPs，研究人员最近集中研究了与昆虫、真菌和植物具有相互作用的细菌，例如，由雪绒花根际细菌 *Streptomyces* sp. S4.7产生的脂肽viennamycins，显示出对G^+病原体的抑制作用[20]。

除了产生NRPs，细菌还可以合成称为细菌素的核糖体肽，其具有高效、无毒、耐热、无残留等特点[21–22]。通常，根据是否具有翻译后修饰基序将细菌素分为两大类。I类（具有翻译后修饰基序）细菌素可被细分为由G^+细菌产生的lanthipeptides sactipeptides、glycocins和环肽，由G^+和革兰氏阴性（G^-）菌株产生的含线性唑（ine）的肽、套索肽以及由G^-细菌分泌的核苷酸肽和铁载体肽。此外，从放线菌中分离的linaridins和硫肽也属于I类细菌素[23]。对农产品具有良好防腐作用的乳酸菌（LAB）源细菌素是目前细菌素的研究热点，类似地，在病原体控制中具有安全使用历史的芽孢杆菌源细菌素也获得了广泛关注[24]。II类细菌素主要是6~10 kDa的未修饰AMPs，可细分为三类，即含有YGNGV肽片段的pediocin类细菌素，不含该肽片段的细菌素和双肽细菌素。

2.2. 真菌源抗菌肽

近年来，真菌源AMPs因其在促进健康和减少疾病方面的有益作用而备受关注[25]。一个突出的例子是FDA批准的由 *Glarea lozoyensis* 产生的环状非核糖体六肽棘白菌素，其对侵袭性真菌病原体具有活性[26–27]。木霉是一种重要的生防真菌，可以合成具有多种活性（如抗菌、抗肿瘤和抗线虫活性）的线性肽peptaibols [28]。迄今为止，木霉属已被发现超过440个peptaibols，包括tricholongins、longibrachins、trichobrachins和trichovirins [29]。

此外，真菌类防御素肽已成为一类具有良好抗菌性能、低细胞毒性和高稳定性的新型抗感染药物[30]。大量防御素样肽具有优异的抗菌性能，如 *Pseudoplectania nigrella* 产生的plectasin通过抑制肽聚糖合成，在体外和体内均可抑制耐药G^+病原体[31]。由 *Coprinopsis cinerea* 产生的Copsin对李斯特菌具有显著的活性，其MIC仅为0.25~0.5 μg·mL^{-1} [32]。*Eurotium amstelodam* 产生的Eurocin对金黄色葡萄球菌和肺炎链球菌表的MIC值分别为16 μg·mL^{-1}和0.25 μg·mL^{-1} [33]。同时，食用真菌和酵母也是AMPs的重要来源。源自酿酒酵母GAPDH蛋白的抗菌肽SP1，在微摩尔水平上显示出对 *Cryptococcus neoformans* 和 *Cryptococcus gattii* 的抑制作用[34]。另一种典型的酵母源AMPs是saccharomycin，它可以抑制葡萄酒中腐败微生物的定殖[35]。此外，由杏鲍菇产生的eryngin具有高效的抗尖孢镰刀菌作用，半抑制浓度（IC_{50}）仅为1.35 mol·L^{-1} [36]。

2.3. 微藻源抗菌肽

微藻是一种光合微生物，具有多种细胞策略、生理能力和适应性，能够在自然界中广泛生存[37]。术语“微藻”是指原核蓝藻和真核光合微生物，主要存在于肺泡类、单倍体、绿藻属、真核菌科、青藻属、红藻和叶绿素类群[38]。来自不同生态系统的微藻（尤其是海洋蓝藻）是多功能生物肽的重要来源[39–41]。因此，已从不同微藻中分离出大量的AMPs，如glycolipopeptides（*hassallidin* sp. 产生的hassallidin A–B）、cyclodepsipeptides（源自 *Moorea* sp. 的dudawalamides A–D）、凝集素（由 *Nostoc* sp. 产生的cyanovirin-N）和microginins（源自 *Microcystis* sp. 的microginin FR3）[42–46]。

微藻因其快速生长、遗传可处理性和可培养性等优势成为AMPs的可持续来源，其非凡的生物活性在药物化学、动物科学和农学等领域备受关注。如 *Moorea producens* 分泌的含β-羟基炔酸环的dudawalamides A–D族AMPs具有广谱抗寄生虫活性和较低的细胞毒性[44]。从 *Lyngbya majuscule* 中分离的氯化脂肽barbamide对无脊椎动物害虫 *Biomphalaria glabrata* 具有强效杀螺活性（LC_{100} = 10 μg·mL^{-1}）[47]。

3. 微生物源抗菌肽的生物活性

微生物可以产生其生存所必需的AMPs，以保护它们免受恶劣环境如缺乏营养等造成的损害。这些AMPs具有丰富多样的生物活性，最典型的是抗微生物活性和免疫调节活性（图2）。除上述活性外，微生物源AMPs还具有多种其他功能，如抗肿瘤、抗氧化、降压和防污活性[48]。以ieodoglucomides为例，其对肺癌和胃癌细胞系的GI50值分别为25.18 g·mL^{-1}和17.78 g·mL^{-1} [49]。Cordymin对大鼠局灶性脑缺血/再灌注损伤具有保护作用[50]。在本节中，我们将对这些功能进行深入的分析。

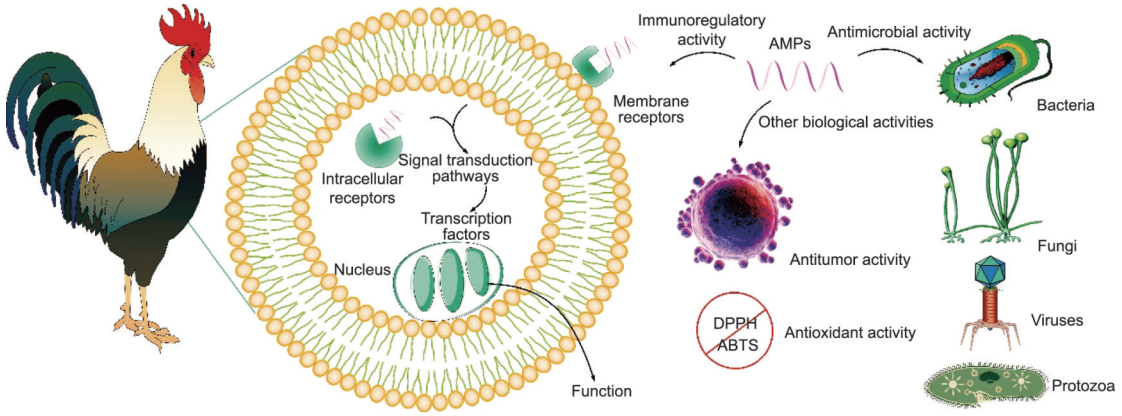

图2. 微生物源抗菌肽的生物活性。DPPH：1,1-二苯基-2-三硝基苯肼；ABTS: 2,2'-Azinobis-(3-ethylbenzthiazoline-6-sulphonate)。

3.1. 抗菌活性

AMPs的抑制病原体活性是迄今为止研究最为深入的功能[51]。对病原微生物具有活性的典型AMPs包括乳链球菌肽（nisin，由乳酸乳球菌产生）、阳离子脂肽黏菌素（由多黏芽孢杆菌分泌）、环寡肽硫链丝菌肽（从蓝色链霉菌中提取）和阳离子聚合物ε-聚赖氨酸（由白色链霉菌产生），这些都是FDA批准上市的化合物[52]。其中，nisin在极低浓度下对多种腐败生物（包括片球菌属、分枝杆菌属和乳球菌属）具有广泛的抗菌作用[53]。黏菌素是针对MDR菌株（如碳青霉烯类耐药肠杆菌科和碳青霉烯类耐药不动杆菌属）的一线药物[54]。ε-聚赖氨酸通常被用作抗菌食品添加剂，因为它对广谱G^+和G^-细菌、病原酵母菌和霉菌及噬菌体具有高效的抑制作用[55–56]。硫链丝菌肽是一种属于硫肽类的强效药物，广泛用于治疗畜牧生产中细菌或寄生虫感染[57]。

3.2. 免疫调节活性

越来越多的研究表明，AMPs还可作为强大的免疫调节因子来改变宿主基因的表达，抑制脂多糖诱导的促炎细胞因子的产生，促进伤口愈合，并调节树突状细胞或T细胞的反应从而间接地发挥保护作用，而不是简单地消灭微生物[58]。通过这种方式，AMPs可以作为先天免疫和获得性免疫之间的枢纽，有助于解决感染和逆转潜在的破坏性炎症，并发挥抗菌作用[59–61]。

表面活性素、多黏菌素、替考拉宁和杆菌肽是典型的免疫调节肽分子[62]。此外，耐甲氧西林金黄色葡萄球菌（MRSA）刺激宿主免疫反应后，达托霉素通过抑制细胞因子表达表现出免疫调节特性[63]。表面活性素可以减弱参与核因子-κB（NF-κB）细胞信号通路的核因子NF-κB的激活，从而减少巨噬细胞中LPS产生的促炎细胞因子[64]。在鼠疫耶尔森菌感染小鼠中，细胞穿透肽YopM抑制了TNF及白细胞介素12、15和18（促炎细胞因子）的转录，而不影响抗炎因子的表达水平[65]。MccJ25通过抑制丝裂原活化蛋白激酶（MAPK）和NF-κB的激活，调节白细胞介素-6、IL-8和肿瘤坏死因子-α水平，缓解炎症反应[66]。在牛乳腺上皮细胞中，nisin A刺激奶牛乳腺炎症和免疫反应激活的指标——抗菌酶*N*-乙酰-*β*-*D*-氨基葡萄糖苷酶（NAGase）和溶菌酶的分泌[67]。此外，一些AMPs通过结合蛋白分子表现出免疫活性。例如，存在于微生物细胞壁中的胞壁酰二肽（MDP）是有效的免疫刺激剂，其通过结合参与先天免疫的多功能转录因子Y-box蛋白1而起作用[68]。

4. 微生物源抗菌肽的作用机制

AMPs是生物体抵御环境危险的第一道防线。其抗菌作用主要为膜损伤机制，即直接对病原体细胞膜结构完整性进行破坏（图3）[69]。许多AMPs还可在膜中自聚集或聚合，形成跨膜通道，使细胞内容物渗出，导致细胞死亡[70]。此外，有研究表明微生物源AMPs还可通过靶向胞内物质从而消除病原体（图3）[71]。

4.1. 膜损伤机制

4.1.1. 环形孔模型

在环形孔模型中，AMPs的两亲性使得亲水和疏水区域分别与病原体磷脂分子的极性头和非极性尾结合[72]。当AMPs与磷脂分子的比例达到一定阈值时，微生物源AMPs会嵌入磷脂双层中。这种位移导致脂质膜向内弯曲，造成膜损伤，细胞内容物外漏，使细胞无法维持正常的生理代谢活动[73]。这一机制已在多种微生物源AMPs中得到证实，如乳酸链球菌素Q [74]、双歧杆菌素A [75]

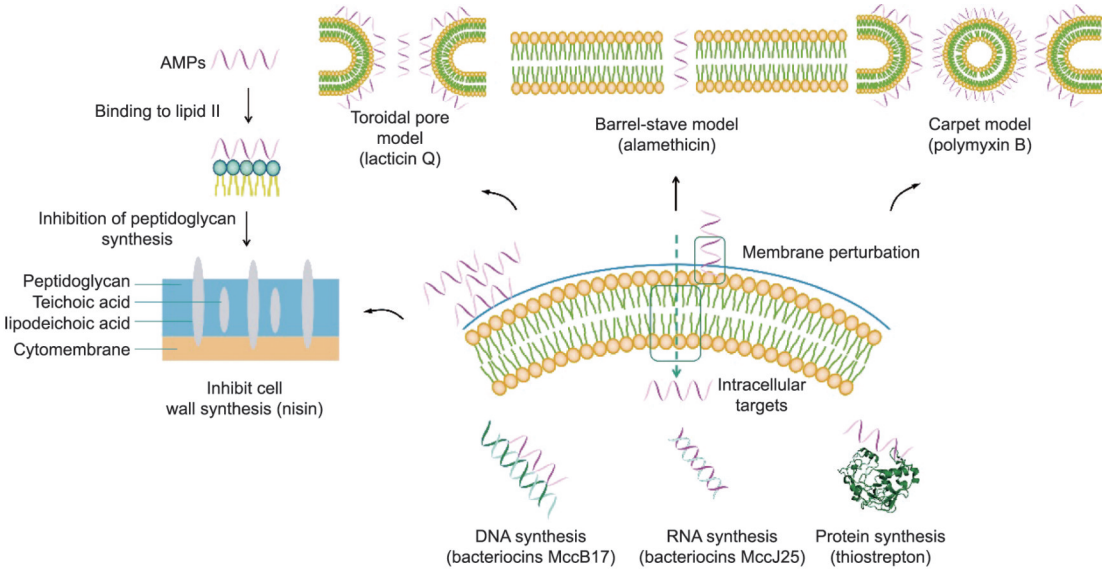

图3. 抗菌肽的抗菌机制。

和大肠杆菌素E1 [76]。

4.1.2. 桶壁模型

虽然桶壁模型的机制与环形孔模型相似，但桶壁模型与环形孔模型的区别在于桶壁模型机制与膜极性无关[77]。桶壁模型是指AMPs与细胞膜结合促使更多的AMPs聚集到细胞膜表面，AMPs像桶板一样垂直嵌入脂质双层，每个肽单体成为桶状簇中的板条[78]。在磷脂双分子层中，形成桶形通道，凸起的肽分子使通道尺寸扩大，通过引起细胞内容物的渗漏而诱导细胞死亡。由绿色木霉产生的Alamethicin是第一个通过桶壁模型作用机制发挥作用的AMPs。在该模型中，Alamethicin的螺旋结构与中腔结合在一起，形成以螺旋肽为桶板的桶[79]。

4.1.3. 地毯模型

在地毯模型中，由于细胞膜与阴离子磷脂头基之间的静电相互作用，AMPs以地毯状的方式覆盖膜表面，并与细胞膜平行地进行相互作用[78]。AMPs在高浓度下生成胶束，从而破坏磷脂双分子层。通过这种机制，裂解肽可以裂解不同微生物细胞以及正常哺乳动物细胞，导致明显的细胞毒性问题。作为耐药G^+微生物感染的最后治疗手段的多黏菌素类药物，是通过这一机制发挥作用的AMPs [80]。

4.2. 非膜损伤机制

尽管最初报道AMPs的杀菌作用是通过膜靶向机制进行的，但最近的研究表明AMPs还可靶向细胞成分以诱导病原体死亡。这些AMPs在不破坏细胞膜的情况下穿过细胞膜，随后与重要的细胞内靶点相结合，阻碍病原菌关键的生命活动。迄今为止，已经报道了多种胞内机制，如抑制蛋白质、核酸和细胞壁的形成。

4.2.1. 抑制细胞壁的生物合成

细胞壁是微生物抵御各种环境压力的最外层屏障，是微生物生存的关键[81]。Lcn972是一种具有非典型66-氨基酸序列的细菌素，可抑制乳酸乳球菌中隔膜的产生，而不是产生细胞膜孔[82]。进一步的研究表明，Lcn972与脂质II结合，阻断了中隔区细胞壁前体的合成，从而抑制了细胞分裂[83–84]。硫醚抗生素是一个众所周知的影响细胞壁形成的抗菌肽家族；它们是由G^+细菌产生的翻译后修饰的细菌素[85]。1928年，L. A. Rogers发现了最经典的硫醚抗生素——乳链球菌肽[86]。Nisin是由34个氨基酸和5个（甲基）-羊毛硫氨酸环（环A~E）组成的化合物（图4）[87]。其通过N端环A和B与细胞壁前体脂质II的焦磷酸部分结合，抑制细胞壁生物合成[88–89]。通过与脂质II结合，nisin的C端可以插入细胞膜形成由8个nisin和4个脂质II分子组成的孔，从而导致细胞的快速死亡[90–91]。后来发现硫醚抗生素家族中的细菌素haloduracin和乳酸菌素3147可以通过攻击细胞膜和抑制细胞壁合成的双重机制杀灭细菌[92–93]。

4.2.2. 抑制核酸的合成

一些AMPs可通过跨膜作用进入细胞，干扰细胞的正常生命功能[94–95]。Albicidin是一种源自*Xanthomonas albilineans*的多聚寡肽，通过干扰DNA裂解-再结合循环过程，对G^+和G^-病原体发挥强大的抗菌作用[96]。Griselimycin是一种来自灰色链霉菌的环状缩肽，通过作用于

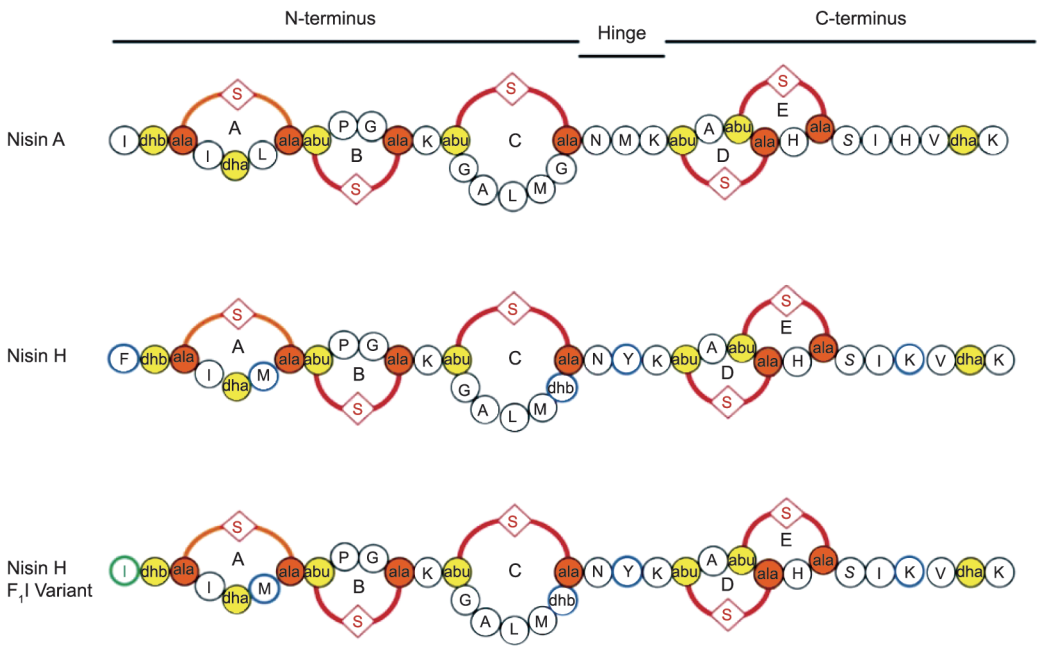

图4. 硫醚抗生素乳链菌肽A，乳链菌肽H和乳链菌肽H F1I的结构示意图。蓝色突出显示乳链菌肽H和乳链菌肽H F1I与乳链菌肽A相比的点突变。黄色和橙色标记用于鉴定有助于（甲基）-羊毛硫氨酸环合成的半胱氨酸残基和脱水氨基酸（环A~E）。乳链菌肽H F1I变体的突变以绿色突出显示[1]。

DNA聚合酶滑动夹而发挥抗分枝杆菌活性[97]。源自大肠杆菌的细菌素大肠杆菌素E系列肽，以Tol系统依赖性方式（即通过BtuB受体）进入敏感病原体的细胞质，然后通过裂解其DNA（大肠杆菌素E2、E7、E8和E9）、16S RNA（大肠杆菌素E3、E4和E6）或转移RNA（tRNA）（大肠杆菌素E5）来抑制病原体[98]。

4.2.3. 抑制蛋白质合成

蛋白质合成始于将DNA转录为信使RNA（mRNA），再通过70S微生物核糖体机制将其翻译成多肽，最后将多肽折叠并在分子伴侣的帮助下组装成功能蛋白[99]。当相关酶或效应分子受到干扰时，蛋白质合成终止。值得注意的是，大多数硫肽，如nocathiacins、thiostrepton和thiazomycin通过扰乱蛋白质翻译显示出对G^+病原体的纳摩尔效力[100]。Bottromycins通过选择性阻碍氨酰基-tRNA与微生物核糖体位点的结合来发挥其抗菌作用[101]。Odilorhabdins是从线虫共生细菌*Xenorhabdus nematophila*中分离出来的NRPs，通过靶向微生物核糖体的小亚基从而抑制MDR病原体[102]。

5. 微生物源抗菌肽的生产

尽管可持续农业对多肽生产的需求越来越大[103]，但用于农业生产的AMPs产量仍有限。迄今为止，酶法合成、重组表达和化学合成是提高其产量的主要方法（图5）。根据AMPs分子结构，可将这些方法单独使用或组合使用以进行AMPs生产[104]。

5.1. 酶水解

农业生产中使用的微生物源AMPs可以通过酶法水解母体蛋白进行生产。有趣的是，一些肽片段在母体蛋白分子中可能是无活性的，经过蛋白酶酶解后其具有生物活性。这些酶可从植物、微生物和动物中获得[105]。胃蛋白酶、胰蛋白酶、菠萝蛋白酶、无花果蛋白酶等是植物或动物来源的常用酶，可单独使用或与其他酶联合使用[106]。微生物蛋白酶中使用最广泛的是从芽孢杆菌属、双歧杆菌属和LAB获得的蛋白酶[107]。由于以下原因，来自微生物来源的蛋白酶比来自其他来源的蛋白酶更有吸引力：首先，微生物具有低营养需求和短的成熟期，故其培养成本较低；其次，大多数微生物蛋白酶——尤其是来自LAB的蛋白酶均在细胞膜上表达，这使得分离和纯化相对便宜且省力。随着微生物培养和鉴定过程的最新进展，微生物学家可以分析各类天然微生物及其产物。

影响AMPs特性的主要因素（即分子大小、氨基酸序列、疏水性和极性基团）包括蛋白酶对底物的选择性、pH值、温度和水解时间[108]。因此，在可控的条件下，通过酶解可以改善AMPs的功能特性[109]。Agyei和Danquah [107]简要描述了酶解法制备AMPs的过程（图5）。该过程中首先是原料的获取：母体蛋白和蛋白酶或微生物[110]，其中生物能源、食品和酿造工业的副产品，如微

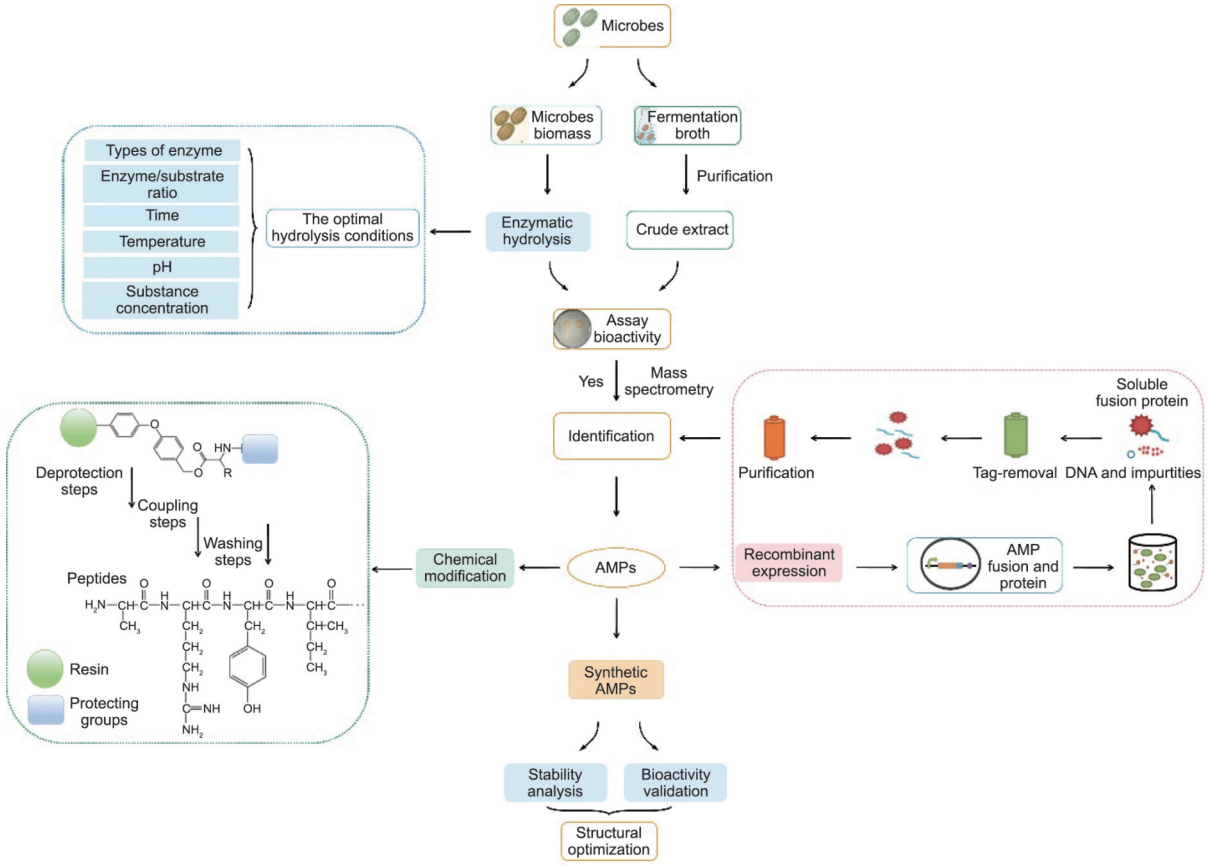

图5. 制备AMPs的流程图。

藻[111]、蘑菇[112]、酵母[113]等是AMPs的合适且廉价的来源；其次是AMPs的酶解、分离和纯化。尽管已有关于超滤、溶剂沉淀和液相色谱技术纯化AMPs的报道，但其目前的高价格限制了其大规模应用。电膜过滤是一种成熟的替代技术，它结合了电泳和传统膜过滤，因此是比上述技术更具成本效益的纯化AMPs的选择。

5.2. 重组表达

近年来，AMPs的重组表达以其较低的生产成本和生态负荷而备受关注，如防御素Pvd1在大肠杆菌中的表达，plectasin在枯草芽孢杆菌中的表达，protegrin在毕赤酵母中的表达[114]。基因工程菌株不仅有助于所需生物活性化合物的产生和功能表达，且可生产其他方法无法合成的生物工程肽和加密肽[115]。目前，大多数微生物源AMPs仍隐藏在其基因组中，因为仅有一部分微生物是在人工环境中培养的，且在理想的发酵试验中分离出相对较小比例的微生物基因组编码的肽[116]。因此，现代测序技术可用于挖掘微生物群和开发AMPs [116–117]。Hover等[118]创建了一个不依赖于培养物的开发平台，该平台整合了样本的BGCs测序、生物信息学分析和重组表达。此外，序列引导宏基因组开发过程还提供了一种方法，即通过追踪未知的BGCs来解析宏基因组，以开发这些未知物质。利用该技术提取了一种新型钙依赖性肽malacidins，其通过靶向MDR病原菌的脂质II发挥抑菌活性[118]。

然而，由于一系列的选择性因素的影响，异源表达的成功概率可能存在一定的差异。宿主和表达系统的选择和设计受所需AMPs的组成和理化特性的影响。宿主的选择、密码子偏好性、蛋白表达载体、质粒拷贝数和融合蛋白都会影响重组AMPs的合成、折叠和分泌。大肠杆菌作为AMP最受欢迎的表达宿主，也存在产量较低的局限，这是由于AMPs对大肠杆菌具有一定的毒害作用[119]。此外，大多数抗菌肽具有正电荷，因此易被蛋白酶降解[120]。因此，已经开发了几种生产融合蛋白的方法来解决这些问题，因为融合蛋白可以掩盖AMPs的毒性，同时提供保护其免受蛋白水解[121–122]。但这些方法存在蛋白表达水平较低的不足，仅有约10～30 mg·L^{-1}的融合蛋白和1~5 mg·L^{-1}的AMPs产生[123]。作为重组生产AMPs的宿主，真菌是细菌的潜在替代品，因为此类微生物具有耐受肽介导杀伤的优势。此外，真菌物种可以有效地向培养液中分泌AMPs，以具有高成本效益的方式实现生产规模扩大[124–125]。

5.3. 化学合成

AMPs的早期发现依赖于将其从生产菌株中直接分离提取，这通常需要大量的发酵液，从而分离出少量的纯化合物[126]。现在可以通过化学合成来收获大量的纯肽——尤其是残基少于50个的肽链。化学肽合成主要有两种类型：液相肽合成（LPSS）和固相肽合成（SPPS）。LPPS适用于多肽的大规模生产。在LPPS，酰基受体的α-羧基通常被酯化或酰胺化修饰，导致序列更长[127]。LPPS的主要不足之处在于合成周期长，工作量大。SPPS常用于小规模生产AMPs，需要将目标化合物的C端氨基酸连接到聚合物固体支持物上，通常是通过一种可裂解的化学接头。随后进行连续的脱保护和氨基酸构建模块的偶联以延长肽链[126,128]。一旦形成所需的片段，就可以将其与树脂分离，以高产率和高纯度生产目标产物。

值得注意的是，LPPS和SPPS也可以结合，由SPPS合成特定的肽片段，然后通过LPPS连接。然而，合成工艺的高成本限制了其应用，特别是对于氨基酸长度较长或结构复杂的肽段[129]。以lactocin S为例，其生物合成仅需两个酶促步骤（修饰和裂解）[130]。而利用SPSS，lactocin S的生产需要71个步骤（包括所有脱保护和偶联）[131]，这是由于SPPS固有的工艺复杂性，需要对每个引入的残留物进行多种化学保护脱保护工艺。

6. 抗菌肽在可持续农业系统中的应用

在过去的几十年里，抗生素在可持续农业系统中的广泛使用导致了MDR菌株的出现以及耐药基因在病原体中的传播。探索替代药物以控制传染病暴发、降低抗生素选择压力的紧迫性已成为AMPs发展的主要推动力。有趣的是，除了直接的抗菌作用外，AMPs是多功能分子，具有多种治疗特性，如抗氧化、免疫调节和抗癌活性，是可持续农业系统的良好候选者。到目前为止，nisin、ε-聚赖氨酸和片球菌素PA-1已经成为商业化防腐剂[114]。人们还尝试了将其他微生物源AMPs用于农业生产。基于此，在接下来的章节中，我们将讨论一些已经过农业应用测试的微生物源抗菌肽，并列举了一些在农产品保鲜方面有潜力的微生物源抗菌肽。

6.1. 抗菌肽作为动物抗生素替代品

由于抗生素耐药基因具有从微生物传递给人类的潜在风险，故抗生素耐药感染日益成为公共健康和食品安全的重大威胁[132]。基于此，微生物源AMPs被提出作为抗生素饲料添加剂的替代品，以提高生产性能、免疫力和促进肠道健康（表1）[133–137]。添加nisin的家兔生长性能更好，吞噬活性更高，粪便凝固酶阴性假单胞菌显著减少[138]。Gassericin A是一种细菌素，可与肠上皮细胞上的角蛋白19相互作用以增强液体吸收，因此可以作为抗生素替代品来避免牲畜腹泻[139]。多项研究表明，在动物饲粮中添加AMPs可以通过增强宿主的免疫功能和减少肠道病原体对宿主产生有益影响，如gassericin A [140]、colisin E1 [141]和albusin B [142]。源自苏云金芽孢杆菌的5种细菌素（即morricin 269、kurstacin 287、kenyacin 404、entomocin 420和tolworthcin 524）对引起乳腺炎的病原体金黄色葡萄球菌表现出杀菌活性[143]。此外，来自芽孢杆菌属物种的脂肽对感染动物的病毒如猪细小病毒、新城疫病毒和法氏囊病毒表现出直接的灭活作用[144]。

表1 动物生产中的抗生素替代品

Name	Source	Reference
Divercin AS7	*Carnobacterium divergens* AS7	[133]
Garvicin A	*Lactococcus garvieae* 21881	[134]
Surfactant	*Pseudomonas* H6	[135]
Sublancin	*Bacillus subtilis* 168	[136]
Albusin B	*Ruminococcus albus* 7	[137]

6.2. 抗菌肽作为农药替代品

每年世界各地都会使用大量的农药和抗生素，尤其是链霉素来减少作物种植过程中害虫和植物病原体造成的产量损失[145]。然而，化学杀虫剂和抗生素在野外的广泛使用是造成环境污染和人类健康问题的根本原因之一。微生物源AMPs是对抗植物病原体和害虫的重要候选药物（表2）[146–150]。研究表明，大量的微生物源AMPs是潜在的植物保护剂；脂肽丰霉素就是典型的例子之一，其通过膜孔的形成对各种植物病原体发挥高效的抗菌活性[151–153]。Mycosubtilin对病原真菌具有微量高效的抑制作用，仅以50 μg·mL^{-1}的mycosubtilin处理禾谷镰刀菌和轮枝镰刀菌24 h，其孢子萌发率分别为17.52%和29.03%[154]。Tailocins对植物病原体*Xanthomonas vesicatoria* Xcv Bv5-4a有较强的抑菌活性，且对哺乳动物细胞无毒副作用[155]。Cycloaspeptide E是由多种丝状真菌产生的五肽，因其对Lepidoptera具有良好的杀虫活性而备受农业界的关注[156]。

6.3. 抗菌肽作为农产品防腐剂

农产品——特别是水产品、蔬菜和水果，以其味道鲜美和丰富的营养价值备受消费者青睐。然而，农产品中的营养物质能够支持病原体的定殖，从而增加消费者的健康

表2 实用植物中的农药替代品

Name	Source	Reference
Bacilysin	*Bacillus velezensis* FZB42	[146]
Orfamide A	*Pseudomonas*	[147]
Bacillomycin D	*Bacillus amyloliquefaciens* FZB42	[148]
Thuricin 17	*Bacillus thuringiensis* NEB17	[149]
Poaeamide	*Pseudomonas poae*	[150]

风险和农业经济损失[157–158]。AMPs是解决这一问题的合理选择（表3）[159–163]。例如，amylolysin具有抗李斯特菌作用，可保护禽肉免受单核增生李斯特菌的侵害[164]。添加pentosin 31-1的猪肉在4 ℃下保存15天，其感官特性仍保持良好[165]。细菌素DY4-2对水产品腐败菌荧光假单胞菌、铜绿假单胞菌、副溶血弧菌、温和气单胞菌等具有良好的抑制活性[166]。鼠李糖乳杆菌产生的细菌素GP1用于石斑鱼鱼片的保藏，能有效抑制多种细菌，且能将TVB-N含量和TMA水平保持在可接受的范围内[167]。从*Bacillus* XT1 CECT 8661中分离的脂肽是果蔬（包括番茄、葡萄和草莓）灰霉病菌的高效拮抗剂[168]。相似地，Jia等[169]报道了新鲜草莓在室温下喷洒细菌素LF-1 6天后，其采后病原菌*Rhizopus*的孢子萌发受到抑制且草莓的整体品质未发生明显变化，货架期得到显著延长。综上所述，AMPs能够以食品防腐剂的形式应用于农产品的储藏和保鲜。

表3 农产品保鲜中的防腐剂替代品

Name	Source	Reference
Plantaricin DL3	*Lactobacillus plantarum* DL3	[159]
Enterocin F4-9	*Enterococcus faecalis* F4-9	[160]
Pentocin JL-1	*Chiloscyllium punctatum*	[161]
Pediocin DT016	*Pediococcus pentosaceus* DT016	[162]
Sonorensin	*Bacillus sonorensis* MT93	[163]

7. 结论和展望

由于耐药病原体不断增加，将AMPs作为传统抗生素替代品的呼声越来越高。与传统抗生素相比，微生物源AMPs在抑制农业生产中的动植物病原体时表现出低耐药性的优势，究其原因是AMPs具有广谱抗菌活性、免疫调节活性和多靶点的作用机制。微生物由于具有非凡的合成可塑性，能够合成核糖体AMPs和NRPs，因而能够分泌多种AMPs。此外，微生物的多样性使其可在有限的空间内生存，仅需微量的营养物质，并在各种生存环境下产生不同结构的生物分子。

AMPs在可持续农业体系应用中面临的挑战包括细胞毒性、生产成本以及肽的生物利用度和稳定性等相关问题。未来研究的重点应是克服上述局限，将AMPs转化为候选药物。首先，通过实施更高效、经济的合成方法或开发更好的重组表达肽生产方法来降低成本。随着可控聚合技术的不断优化和模拟AMPs聚合物的不断开发，聚合物的设计和合成可能成为未来降低成本的替代方案。其次是使用旨在避免蛋白水解破坏的策略来提高AMPs的生物利用度，如通过非自然氨基酸替代改变AMP的主序列、生成肽模拟物、肽环化和杂交构建[170]。此外，为提高AMPs的生物利用度，可对AMPs进行纳米载体的构建从而减少AMPs浪费和脱靶效应，并避免蛋白酶破坏。为实现进入生物肽开发管道的肽剂量更大减少的目标，可以通过计算机辅助选择最新预测工具来筛选更高活性或更低毒性的候选化合物。值得注意的是，交叉创新对于肽基抗菌药物的进一步优化和开发非常重要；需要多学科专家如微生物学家、药物学家和计算机科学家的共同努力来实现这一目标。尽管微生物源AMPs在农业生产的应用方面仍存在许多不足之处，但通过将其与计算机辅助技术相结合可以克服这一局限。

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Compliance with ethics guidelines

Shuhua Lin, Xuan Chen, Huimin Chen, Xixi Cai, Xu Chen, and Shaoyun Wang declare that they have no conflict of interest or financial conflicts to disclose.

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