微生物学通报
Microbiology China
http://journals.im.ac.cn/wswxtbcn

Sep. 20, 2024, 51(9): 3372−3383
DOI: 10.13344/j.microbiol.china.231076

专论与综述

昆虫共生菌在医药领域的应用

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王争艳, 叶天伟, 谢琳钰, 李可欣, 郭雨璐. 昆虫共生菌在医药领域的应用[J]. 微生物学通报, 2024, 51(9): 3372-3383.
WANG Zhengyan, YE Tianwei, XIE Linyu, LI Kexin, GUO Yulu. Application of insect symbionts in the medical field[J]. Microbiology China, 2024, 51(9): 3372-3383.

摘　要：昆虫共生菌及其代谢产物复杂多样，具有潜在的医药价值。一些可体外培养的昆虫共生菌活体菌株可用于临床加快伤口愈合和治疗肠易激综合征等。一些昆虫共生菌产生的有机酸、抗菌肽和生物碱能抑制人体病原菌，产生的脂肪酶、酵母毒素 KT 和活性氧能杀死疟原虫，产生的肽类、聚酮和酯类能抑制人体肿瘤。但是，受到功能菌株分离培养困难、临床试验不足和次级代谢产物引起的临床不良反应等方面的限制，共生菌在医药领域的应用仍处于初级阶段。本文对昆虫共生菌及其代谢产物的医药功能进行了综述，并分析了它们在医药领域的应用现状、存在的问题和解决途径，以期推进功能性共生菌的研究和应用。

关键词：昆虫；共生菌；代谢产物；医药功能

Application of insect symbionts in the medical field

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Abstract: Insect symbionts and their metabolites are complex and diverse and have potential medical values. Some culturable symbionts in insects can be used to accelerate wound healing and treat the irritable bowel syndrome. The culturable symbionts in insects can produce a variety of active compounds. Among them, organic acids, antimicrobial peptides, and alkaloids can inhibit the pathogens of humans; lipases, yeast killer toxin (KT), and reactive oxygen species can kill malaria parasites; peptides, polyketides, and esters can inhibit human tumors. However, due to the limitations from immature isolation and culture methods, insufficient

资助项目：国家自然科学基金(32272531)；河南省科技攻关项目(222103810069)
This work was supported by the National Natural Science Foundation of China (32272531), and the Science and Technology Research Project of Henan Province (222103810069).
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Received: 2023-12-26; Accepted: 2024-02-13; Published online: 2024-03-22

clinical trials, and clinical adverse reactions caused by their secondary metabolites, the application of insect symbionts in the medical field is still in its infancy. This paper reviewed the medical functions of insect symbionts and their metabolites and summarized the status, problems, and solutions in the application of insect symbionts and their metabolites in the medical field, aiming to give insights into the study and application of functional symbionts.
Keywords: insect; symbionts; metabolites; medical function

昆虫作为动物界节肢动物门中最大的群体，也是自然界陆地生态系统中数量最多、种类最丰富、分布最广泛的动物之一[1]。昆虫体内有丰富的共生菌，在长期的进化过程中，共生菌和宿主逐渐形成稳定的共生关系[2]。昆虫为共生菌提供定殖的部位，而共生菌可以影响宿主的生理生化过程和行为，包括营养、生长发育、毒素代谢、抗药性、繁殖能力、化学通信等[2-3]。共生菌可以为宿主提供营养素及其前体物质，产生水解酶帮助宿主消化食物，调控肠道环境、肠道组织形成和宿主的营养代谢[4]，还可通过产生抗菌物质、调控宿主免疫相关基因和微生物种间竞争作用等方式保护昆虫宿主免受病原体的侵染[5]，这为筛选具有营养、免疫等医药价值的功能性菌株提供了思路。

目前昆虫共生菌的医药功能已经逐步得到验证。一些共生菌产生的次级代谢产物，如多肽和聚酮类化合物能增强人体抗病原菌、疟原虫和肿瘤的能力[6]。此外，一些昆虫共生菌作为益生菌进入人体后，发挥免疫调节作用，能够改善免疫紊乱引发的疾病[7]，如从西方蜜蜂(*Apis mellifera*)肠道中分离的昆基氏蜜蜂乳杆菌(*Apilactobacillus kunkeei*)分解果糖产生乙醇和甘露醇以再生 NAD^+，促进有氧代谢的顺利进行，并且可以改善由果糖介导的肠易激综合征[8-9]；从家蚕(*Bombyx mori*)肠道中分离的乳酸菌产生的代谢物能抑制胆固醇合成酶和胆汁酸盐(胆固醇的代谢产物)的再循环，还能结合并固定胆固醇，从而抑制胆固醇的生成并降低血液中胆固醇的含量，降低人体心脑血管疾病的发病几率[7]。

鉴于昆虫共生菌及其代谢产物的医药功能，昆虫共生菌在医药领域有较好的应用前景。目前，被国内外广泛研究的昆虫功能性共生菌主要是肠道共生菌，但是被临床应用的共生菌很少，有很大的开发利用空间[10]。此外，昆虫共生菌及其代谢产物也存在培养困难、分离成本高和难以大规模应用等局限性[11]。因此，昆虫共生菌及其产物在医药领域的应用仍处于初级阶段[11]。基于这种现状，本文对昆虫共生菌及其代谢产物的医药功能进行了综述，并分析了它们在医药领域的应用现状、存在的问题及其解决途径，以期推进功能性共生菌的研究和应用。由于已有共生菌与昆虫营养互作的相关综述[4]，本文不再涉及具有营养功能的共生菌。

1 昆虫共生菌的医药功能

1.1 抑制人体病原菌

昆虫共生菌可以产生有机酸，通过降低宿主消化道的 pH 值来抑制人体病原菌(表 1)。西方蜜蜂肠道中的干酪乳杆菌(*Lactobacillus casei*)产生乳酸、草酸、戊二酸和乙酸，抑制大肠埃希氏菌(*Escherichia coli*)、鼠伤寒沙门氏菌(*Salmonella typhimurium*)和金黄色葡萄球菌(*Staphylococcus aureus*)[12]。西方蜜蜂胃中的乳酸菌 PAM 3 和 PAM 4 会产生大量有机酸，抑制金黄色葡萄球菌和鼠伤寒沙门氏菌[13]。西方蜜蜂蜂蜜的共生乳酸菌会产生乙酸和乳酸，抑制单核增生李斯特氏菌(*Listeria monocytogenes*)和大肠埃希氏菌[14]。

昆虫共生菌还能产生抗菌肽、大环内酯类、

生物碱、玫瑰黄色素等物质抑制人体病原菌(表1)。抗菌肽可以与质膜结合，破坏质膜结构的完整性，改变膜内外的渗透压，引起细胞死亡[31]。一些多烯大环内酯类化合物具有抗真菌活性，会与真菌细胞膜上的麦角甾醇结合，破坏膜的完整性并抑制膜蛋白的功能[15]。生物碱通过多种机制抑制细菌生长，包括抑制细菌核酸和蛋白质合成，改变细菌细胞膜通透性，破坏细胞膜和细胞壁，抑制细菌代谢，抑制外排泵等[32]。玫瑰黄色素是黄素单核苷酸(flavin mononucleotide, FMN)和核黄素的类似物，可以结合 FMN 核糖开关 ribD 适配体，下调 ribD 操纵子基因的表达，抑制 FMN 的合成，从而抑制病原菌生长所必需的核黄素的合成[24]。

表 1 能产生次级代谢产物抑制人体病原细菌的昆虫共生菌

Table 1 Insect symbionts that produce antibacterial secondary metabolites

昆虫宿主 Insect host	寄生部位 Parasitized site	共生菌 Symbiont	抑菌活性 Antibacterial activity	参考文献 Reference
西方蜜蜂 *Apis mellifera*	肠道 Gut	干酪乳杆菌 *Lactobacillus casei*	产生乳酸、草酸、戊二酸和乙酸，抑制大肠埃希氏菌、鼠伤寒沙门氏菌和金黄色葡萄球菌 *Lactobacillus casei* inhibits the growth of *Escherichia coli*, *Salmonella typhimurium*, and *Staphylococcus aureus* by producing lactic, oxalic, glutaric and acetic acids	[12]
	胃 Stomach	乳酸菌 PAM 3 和 PAM 4 Lactic acid bacteria PAM 3 and PAM 4	产生有机酸，抑制金黄色葡萄球菌和鼠伤寒沙门氏菌 Lactic acid bacteria inhibit the growth of *Staphylococcus aureus* and *Salmonella typhimurium* by producing organic acids	[13]
	蜂蜜 Honey	乳酸菌 *Lactobacillus* sp.	产生乙酸和乳酸，抑制单核增生李斯特氏菌和大肠埃希氏菌 *Lactobacillus* inhibits the growth of *Listeria monocytogenes* and *Escherichia coli* by producing acetic and lactic acids	[14]
翼切叶蚁属 *Apterostigma*	蚁巢 Ant nests	假单胞菌 *Pseudomonas* sp.	产生的多烯大环内酯类化合物 selvamicin 会与白色念珠菌细胞膜上的麦角甾醇相互作用，破坏膜的完整性并抑制膜蛋白的功能 Selvamicin produced by *Pseudomonas* interacts with ergosterol on the cell membrane of *Candida albicans*, thus compromising the integrity of the membrane and inhibiting the function of membrane proteins	[15]
黑水虻 *Hermetia illucens*	肠道 Gut	芽孢杆菌 *Bacillus* spp.	产生脂肽，抑制金黄色葡萄球菌 *Bacillus* spp. inhibit the growth of *Staphylococcus aureus* by producing lipopeptides	[16]
无刺蜂 *Heterotrigona itama*	蜂蜜 Honey	乳酸菌 Sy-1、Sy-2、Sy-3 和 Sy-4 Lactic acid bacteria Sy-1, Sy-2, Sy-3 and Sy-4	产生细菌素干扰病原菌生物被膜的形成，抑制铜绿假单胞菌、大肠埃希氏菌、枯草芽孢杆菌、金黄色葡萄球菌和肺炎克雷伯氏菌 Bacteriocins produced by lactic acid bacteria inhibit the growth of *Pseudomonas aeruginosa*, *Escherichia coli*, *Bacillus subtilis*, *Staphylococcus aureus,* and *Klebsiella pneumoniae* by interfering with the formation of biofilms of pathogenic bacteria	[17]

(待续)

(续表 1)

昆虫宿主 Insect host	寄生部位 Parasitized site	共生菌 Symbiont	抑菌活性 Antibacterial activity	参考文献 Reference
亚洲飞蝗 *Locusta migratoria*	肠道 Gut	拟无枝酸菌 HCa4 *Amycolatopsis* sp. HCa4	产生 2 个新型的内酰胺类化合物，抑制耐受甲氧西林的金黄色葡萄球菌 *Amycolatopsis* sp. inhibits the growth of methicillin-resistant *Staphylococcus aureus* by producing two new macrolactams	[18]
撒哈拉大白蚁 *Macrotermes natalensis*	肠道 Gut	拟无枝酸菌 M39 *Amycolatopsis* sp. M39	产生 4 种新型的糖基化内酰胺类化合物 macrotermycins A–D，抑制金黄色葡萄球菌 *Amycolatopsis* sp. inhibits the growth of *Staphylococcus aureus* by producing macrotermycins A–D	[19]
白蚁 *Microtermes* sp.	肠道 Gut	真菌 X802 *Pseudoxylaria* sp. X802	产生 4 种新型的环状四肽类化合物 pseudoxylallemycins A–D，抑制铜绿假单胞菌 *Pseudoxylaria* sp. inhibits the growth of *Pseudomonas aeruginosa* by producing pseudoxylallemycins A–D	[20]
大黑埋葬虫 *Nicrophorus concolor*	肠道 Gut	分枝杆菌 *Mycobacterium*	产生抗菌肽 nicrophorusamides A，抑制金黄色葡萄球菌和粪肠球菌 *Mycobacterium* inhibits the growth of *Staphylococcus aureus* and *Enterococcus faecalis* by producing nicrophorusamides A	[21-22]
红斑尼葬甲 *Nicrophorus vespilloides*	肠道 Gut	褪色沙雷氏菌 *Serratia marcescens*	产生抗菌环脂肽 serrawettin W2，抑制耐受甲氧西林的金黄色葡萄球菌和单核增生李斯特氏菌 *Serratia marcescens* inhibits the growth of methicillin-resistant *Staphylococcus aureus* and *Listeria monocytogenes* by producing serrawettin W2	[22-23]
黑翅土白蚁 *Odontotermes formosanus*	体表 Body surface	达沃链霉菌 *Streptomyces davaonensis*	产生玫瑰黄色素，抑制 FMN 的合成，从而抑制细菌核黄素的合成 Roseoflavin produced by *Streptomyces davaonensis* inhibits the synthesis of bacterial FMN and thus inhibits the synthesis of bacterial riboflavin	[24-25]
	肠道 Gut	高阳链霉菌 *Streptomyces koyangensis*	产生生物碱类化合物吲哚嗪，抑制金黄色葡萄球菌和白色念珠菌的二氢叶酸还原酶，干扰细胞的四氢叶酸代谢 Indolizine produced by *Streptomyces koyangensis* inhibits the dihydrofolate reductase and thus interferes with tetrahydrofolate metabolism in cells of *Staphylococcus aureus* and *Candida albicans*	[26-27]
点蜂缘蝽 *Riptortus pedestris*	肠道 Gut	多节孢 *Nodulisporium* sp. IFB-A163	产生新型的环缩酚酸肽 nodupetide，抑制铜绿假单胞菌 *Nodulisporium* sp. inhibits the growth of *Pseudomonas aeruginosa* by producing nodupetide	[28]
泥蜂 *Sceliphron caementarium*	肠道 Gut	链霉菌 *Streptomyces* sp.	产生多烯烃大环内酰胺类化合物 sceliphrolactam，抑制白色念珠菌 *Streptomyces* sp. inhibits the growth of *Candida albicans* by producing sceliphrolactam	[29]
灰翅夜蛾 *Spodoptera littoralis*	肠道 Gut	蒙氏肠球菌 *Enterococcus mundtii*	产生细菌素 mundticin KS，抑制铅黄肠球菌 *Enterococcus mundtii* inhibits the growth of *Enterococcus casseliflavus* by producing mundticin KS	[30]

1.2 抑制疟原虫

疟原虫寄生人体会引发疟疾，治疗疟疾的常规方法是使用青蒿素，而在过去十几年中，耐青蒿素的疟原虫在东南亚湄公河流域广泛传播，因此，需要寻找新的化合物治理疟原虫[33]。疟原虫通过媒介雌蚊的叮咬传播给人类。疟原虫须在蚊子的肠道中完成孢子生殖阶段，而定殖在蚊子肠道的共生菌会产生脂肪酶、酵母毒素 KT 和活性氧直接或间接杀死疟原虫[34-35]。例如，从中华按蚊(*Anopheles sinensis*)肠道中分离出的新型解脲沙雷氏菌(*Serratia ureilytica*) Su_YN1 能分泌脂肪酶 AmLip 直接靶向杀灭疟原虫[34]；从斯氏按蚊(*Anopheles stephensi*)肠道中分离出的异常威克汉姆酵母(*Wickerhamomyces anomalus*)可分泌酵母毒素 KT，KT 与伯氏疟原虫细胞配子表面的特定受体——β-葡聚糖蛋白受体结合，在配子细胞壁上形成跨膜通道，使细胞质渗漏，无法发育成合子[36-37]；从赞比亚按蚊(*Anopheles arabiensis*)体内分离的肠杆菌(*Enterobacter* sp.) Esp_Z 能产生活性氧杀死疟原虫的卵母细胞[38]。但是，多数共生菌影响疟原虫发育的具体分子机制尚不清楚[34]。

1.3 抑制人体肿瘤细胞

正常体细胞的基因突变和染色体变异积累到一定程度后，细胞增殖失控，形成肿瘤细胞。肿瘤细胞的增殖依赖于有丝分裂，细胞分裂周期仍然包括分裂间期 G 和分裂期 M，但肿瘤细胞的细胞分裂周期调控失常，这种异常的细胞分裂周期与细胞分裂周期检查点的突变有关，也可能是上游信号通路突变和编码细胞分裂周期蛋白的基因遗传损伤的结果[39-40]。此外，肿瘤细胞还会下调细胞凋亡通路和失巢性细胞死亡通路，从而避免程序性死亡，这可能与调控线粒体途径的信号通路异常有关[41]。线粒体途径是生存信号通路的主要靶标，生存信号能稳定线粒体功能和完整性，抑制细胞色素 c 的释放，一旦细胞色素 c 从线粒体中释放出来，它就会协调细胞内凋亡复合体的组装，从而诱导细胞凋亡[42]。

近年来，肿瘤发病率不断上升，极大地危害了人类的健康，抗肿瘤物质的探索和开发迫在眉睫[43]。昆虫共生真菌和共生放线菌是产生抗肿瘤次级代谢产物的重要来源，这些抗肿瘤活性物质主要是肽类、聚酮类化合物，以及一些烷烃、酯、蒽醌、苯乙烯类等化合物[44]。

1.3.1 肽类化合物对肿瘤的抑制作用

肽类通过控制细胞分裂周期和细胞 DNA 转录等途径抑制肿瘤，为开发新型的抗肿瘤策略提供了思路。一种昆虫体表共生的层生镰刀菌(*Fusarium proliferatum*)产生的一种环六肽 enniatin S 使人慢性髓系白血病细胞 K-562 的细胞分裂周期阻滞在 G_0/G_1 期[45-46]。铗蠓(*Forcipomyia marksae*)肠道致病真菌 *Culicinomyces clavisporus* LL-12I252 产生的一种十肽 culicinins D 能抑制细胞分裂周期进程的正调节因子 cyclin D3，增加细胞分裂周期抑制剂 p27 Kip1 的水平，并抑制调节细胞生长的 mTOR 信号通路，从而抑制人乳腺癌细胞 MDA468 的增殖[47]。切叶蚁(*Apterostigma octospinosus*)菌圃中的链霉菌(*Streptomyces* sp.) Av25_2 产生的放线菌素能在转录起始位置与 DNA 形成复合体，抑制肿瘤细胞 RNA 的合成[48-49]。

1.3.2 聚酮类化合物对肿瘤的抑制作用

聚酮化合物通过控制细胞分裂周期、诱导细胞凋亡和增强 T 细胞功能等机制而发挥抗肿瘤活性。蚂蚁肠道中的链霉菌(*Streptomyces* sp.) 1H-GS5 会产生一种聚酮类化合物 spectinabilin，通过两种途径抑制肝癌细胞 HepG2：(1) 通过降低 HepG2 细胞分裂周期蛋白 B1 和 cdc2 的蛋白水平，增加 p21 的蛋白水平，导致 HepG2 细胞在 G_2/M 期阻滞；(2) 通过在 HepG2 细胞中下调 Bcl-2 蛋白表达，上调 Bax 蛋白表达，激活 caspase-9 和 caspase-3，诱导 HepG2 细胞凋亡[50-51]。

中华剑角蝗(*Acrida cinerea*)肠道共生草酸青霉(*Penicillium oxalicum*)产生的一种苯并吡喃酮二聚体类化合物 secalonic acid A 能有效破坏 HepG2 细胞的线粒体膜电位，导致线粒体通透性转变孔持续开放和内膜通透性增加，从而抑制肿瘤细胞[52-53]。美洲大蠊(*Periplaneta americana*)内生曲霉(*Aspergillus taichungensis*) SMU01 产生的具有新型骨架结构的聚酮化合物 aspertaichunol A，能增强 Th9 细胞中白细胞介素 IL-9、γ 干扰素(IFN-γ)和肿瘤坏死因子(TNF-α)的表达和分泌水平，而 TNF-α 协同 IFN-γ 激活巨噬细胞以增强 Th9 的抗肿瘤能力[54]。

1.3.3 其他化合物对肿瘤的抑制作用

昆虫共生菌还能产生其他的化合物，通过诱导细胞凋亡和抑制磷脂酰肌醇-3-激酶/蛋白激酶 B (phosphoinositide 3-kinase/protein kinase B, Pl3K/Akt)途径来发挥抗肿瘤活性。中华稻蝗(*Oxya chinensis*)体内球毛壳菌(*Chaetomium globosum*)产生的烷烃和脂肪酸可诱导 HepG2 细胞的凋亡[55]。西方蜜蜂(*Apis mellifera yemintica*)肠道链霉菌产生的烯类、烷烃和酯类物质会增强乳腺癌细胞系 MCF7 和 HepG2 的细胞凋亡信号通路，诱导肿瘤细胞凋亡[56]。蝗虫肠道共生曲霉(*Aspergillus* sp.) HCf2 产生的一种蒽醌类化合物 bostrycin，通过下调 Pl3K/Akt 途径蛋白抑制人肺癌细胞 A549 细胞增殖[57-58]。昆虫共生致病杆菌(*Xenorhabdus* sp.)能产生一种苯乙烯衍生物 WBI-1001，通过降低抗凋亡基因 Bcl-2 mRNA 的表达，同时增加促凋亡基因 Bax、Bad 和 mRNA 的表达，能将 A549 细胞系阻滞在 G_1 期[59-60]。

2 昆虫共生菌在医药领域的应用现状

2.1 功能性菌株的应用

昆虫共生菌可治疗多种人类疾病，在医药领域有较好的应用前景。例如，从蜜蜂蜂蜜中可以分离出副干酪乳杆菌(*Lactobacillus paracasei*)、鼠李糖乳杆菌(*Lactobacillus rhamnosus*)和植物乳杆菌(*Lactobacillus plantarum*)，将其制成鼻喷雾剂和口服混悬液用于治疗感染耐受甲氧西林的金黄色葡萄球菌的患者，可以根除耐受甲氧西林的金黄色葡萄球菌[61-62]；从蜜蜂肠道分离的乳酸菌和双歧杆菌能有效治疗耐甲氧西林金黄色葡萄球菌、铜绿假单胞菌和耐万古霉素肠球菌感染的伤口，这些菌能够产生乳酸和甲酸，降低伤口环境的 pH 值，抑制伤口的恶化，乳酸菌还能产生过氧化氢促进伤口的愈合[63]。

尽管许多研究已明确昆虫共生菌的医药功能，但其在医药领域的应用仍然面临着诸多挑战：(1) 由于昆虫共生菌基因组小(基因组越大，内共生体越有可能被培养)和分离培养方法的不成熟，仅有少数共生菌能在常用培养基和昆虫细胞培养基(活的宿主细胞会通过释放共生菌生长所需的生长因子来调节培养基)中培养[64]；(2) 靶向部位的活菌数量不足，一些活菌难以或无法到达肠道的某些部位[65]；(3) 理论上，共生菌具有引起菌血症、真菌血症，耐药基因的转移，敏感个体免疫刺激，产生有害代谢产物等风险[66]；(4) 仅有少数共生菌的安全性和临床效果明确，如乳酸杆菌和双歧杆菌，大多数共生菌安全性有待评估，并且临床试验不足；(5) 虽然多数研究显示共生菌有效，但也有一部分试验结果显示其无效，研究结果存在不一致性和不稳定性[67]。因此，需要开展更多完整的、严谨的随机对照试验及临床研究[68]。

昆虫共生菌在医药领域的应用处于初级阶段，需要筛选更多的共生菌菌株，明确其功能和作用机制，提高共生菌的功效[2]。现代生物技术的发展有助于筛选出更多共生菌，如利用宏基因组测序技术从家蚕肠道中筛选出了具有医药功

能的植物乳杆菌、鼠李糖乳杆菌、副干酪乳杆菌、嗜酸乳杆菌(*Lactobacillus acidophilus*)和芽孢杆菌[61]。还可以对临床使用的益生菌进行全基因组测序，以此确定其在人体的定殖能力相关基因，如抗生素抗性基因，然后通过分子标记辅助选择技术将功效基因筛选出来，加速共生菌筛选的进程，并把多个功效基因集合到同一个共生菌，使其具有多种功效[69-70]。联用多种共生菌，如使用含有鼠李糖乳杆菌、嗜酸乳杆菌和双歧杆菌(*Lactobacillus bifidus*)的多菌株制剂，以及含有双歧杆菌和嗜酸乳杆菌的多菌株制剂治疗头孢曲松引起的儿童不良反应比使用单菌种共生菌更有效[71]。共生菌与协同作用成分相结合，如将水果中的酚类化合物与鼠李糖乳杆菌和嗜酸乳杆菌共用，可以选择性地抑制大肠埃希氏菌和鼠伤寒沙门氏菌的生长，而不影响共生菌的活力[72]。

2.2 功能性代谢产物的应用

昆虫共生菌产生的新型抗菌活性化合物能抑制人体病原菌或肿瘤，其中一些有望用于治疗耐多药人体病原菌，因此在医药领域具有广阔的应用前景[5]。然而，很多抗菌物质在人体内引起不同程度的不良反应。褐飞虱(*Nilaparavata lugens*)卵中的芽孢杆菌(*Bacillus* sp.)能产生多黏菌素[73]。在临床中，通过脑室和静脉注射多黏菌素，可以治疗革兰氏阴性病原菌引起的耐多药感染和脑膜炎，并被用作气雾剂治疗支气管炎引起的肺部感染[74]。但是病原菌对多黏菌素可产生耐药性，而且多黏菌素会产生不良反应，如肾毒性(急性肾损伤)和神经毒性[75]。昆虫共生致病杆菌能产生具有抗生素功能的化合物WBI-1001，使用含有 WBI-1001 的乳膏可以有效抑制牛皮癣，但是试验组的患者较对照组的患者表现出一些药物不良反应[59,76]。

昆虫共生菌产生的次级代谢产物种类和功能复杂多样，具有极大的开发潜力，但这些产物大多处于初步研究状态，在医药领域的应用还存在一些问题。昆虫共生菌产生的少数抗生素已用于临床，尽管仍然存在抗生素耐药性问题，但是共生菌产生的抑菌物质具有多样的抑菌机制，这为筛选新型抗菌物质、解决抗生素耐药性的问题提供了方向。一些共生菌仅在昆虫内产生次级代谢产物，在无菌培养基中不能产生次级代谢产物，还有些共生菌的次级代谢产物基因处于沉默状态，通过常规方法仅能得到一小部分活性次级代谢产物[77]。利用基因组学工具可以拓宽共生菌次级代谢产物的筛选范围，如通过基因组挖掘出 *Attini* 族蚂蚁体表上的链霉菌中 warkmycins 家族的 sipanmycin A 和 B 两个新化合物[78]。对于昆虫共生菌产生的次级代谢产物在临床中引起的不良反应，应在治疗过程中开展治疗药物浓度监测，进行药物剂量优化，提高靶值达标率，以减轻甚至避免不良反应的发生[79]。

3 总结和展望

目前，多重抗生素耐药菌频繁出现，肿瘤和疟疾较多，昆虫共生菌及其次级代谢产物的医药功能显得尤为珍贵。一些昆虫共生菌作为益生菌被用于临床研究，虽然取得了一定的成果，但仍存在昆虫共生菌难以培养、难以或无法到达肠道的某些部位、安全性和临床功效不明确、共生菌临床研究结果存在不一致性和不稳定性等困难，可以利用现代生物技术、联用多种共生菌、将共生菌与协同作用成分相结合等方法筛选更多共生菌和提高共生菌的功效。一些昆虫共生菌产生的有机酸、抗菌肽和生物碱能抑制人体病原菌，产生的脂肪酶、酵母毒素 KT 和活性氧能杀死疟原虫，产生的肽类、聚酮和酯类能抑制人体肿瘤。但是，在医药领域应用这些活性化合物时，存在着抗生素耐药性、次级代谢产物基因沉默和产生不良反应等问题，可以通过研究次级代谢产物抑

菌机制、利用基因组学工具和开展治疗药物浓度监测等方法解决这些问题。

在工业领域中，高通量筛选技术已被广泛用于筛选功能菌及其次级代谢产物，诱变、定向进化、代谢工程等技术被用来改造功能菌和提高次级代谢产物的活性，并且取得了显著的成效[80]。例如，基于生物传感器的荧光光谱筛选技术的传感器可以识别特定的细胞内代谢产物，而报告基因可以将基因信号转化为定量信号，与显色反应二级筛选技术联用成功筛选出了高产 L-赖氨酸的大肠埃希氏菌突变菌株[80-81]；定向进化技术可以在微生物的功能基因中引入随机突变，从而改善基因所表达酶的催化特性，利用它显著提高了毕赤酵母(*Pichia pastoris*)的 β-葡萄糖苷酶的产率和酶活[82]；代谢工程是采用重组 DNA 技术，操纵细胞的酶、运输及调节功能，以提高或改善微生物的代谢特征，利用它对大肠埃希氏菌进行基因重组，提高了鼠李糖脂的产率[83-84]。这些研究技术为共生菌及其次级代谢产物在医药领域的深入研究提供了方向。

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