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专论与综述

畜禽金黄色葡萄球菌流行现状和中草药防控进展

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ZHANG Wenjing, LÜ Ruoyi, XIU Demian, CAI Ziwen, WANG Jing, SUN Zhigang, SI Xiaohui, SUN Yingjian, LIU Xiaoye. Current situation of *Staphylococcus aureus* infection in livestock and poultry and progress in the prevention and control with Chinese herbal medicines[J]. Microbiology China, 2024, 51(8): 2753-2770.

摘 要：金黄色葡萄球菌(*Staphylococcus aureus*)是常见的重要人畜共患条件致病菌，在社区和畜禽环境之间广泛传播，引发严重的兽医公共卫生问题。耐药金黄色葡萄球菌的频繁出现导致以抗生素为主的抗菌策略停滞不前，为响应我国减抗替抗政策，大批减抗替抗中草药抗菌药物已经投入临床前研究。本文通过归纳畜禽金黄色葡萄球感染情况、菌株耐药现状与耐药菌株流行特点，总结了畜禽金黄色葡萄球菌感染防控策略，并分析了中草药防控机制和靶点，为临床研究中草药抗菌策略提供研究内容。

关键词：金黄色葡萄球菌；感染情况；耐药现状；中草药

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Current situation of *Staphylococcus aureus* infection in livestock and poultry and progress in the prevention and control with Chinese herbal medicines

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Abstract: *Staphylococcus aureus*, a common major zoonotic opportunistic pathogen, spreads widely in the community and the livestock and poultry environment, seriously threatening veterinary public health. The frequent occurrence of drug-resistant strains of *S. aureus* has posed a challenge to the antimicrobial strategies based on antibiotics. In response to the Chinese policy of reducing and substituting antibiotics, a large number of Chinese herbal medicines as the alternatives of antibiotics have been put into clinical research. This paper summarized the *S. aureus* infection situation, current status of drug resistance, and epidemic characteristics of *drug-resistant strains* in livestock and poultry, summarized the prevention and control strategies. Furthermore, this paper analyzed the mechanisms and targets of Chinese herbal medicines in the prevention and control of this pathogen, providing research contents for clinical research on the antibacterial strategies of Chinese herbal medicines.
Keywords: *Staphylococcus aureus*; infection situation; current status of drug resistance; Chinese herbal medicine

金黄色葡萄球菌(*Staphylococcus aureus*)引起的传染性疾病日趋严重，根据 2023 年我国 CHINET 网(http://www.chinets.com/)数据显示，临床致病菌中金黄色葡萄球菌占比率为 9.2%，排名第三，是主要的临床致病菌。金黄色葡萄球菌常定殖于皮肤与黏膜，引起如猪子宫内膜炎[1]、奶牛乳腺炎[2]、肺炎[3]等畜禽疾病，并且金黄色葡萄球菌传播范围广泛，可以在动物、人类、环境三者之间传播，对社会公共卫生安全造成威胁。对于金黄色葡萄球菌感染，通常使用抗生素进行治疗，但随着长期大规模不合理使用抗生素，细菌逐渐产生耐药性[4]。研究表明，金黄色葡萄球菌耐药性的产生与耐药基因密切相关，并且耐药基因的出现推动了耐药菌株的不断发展，现已产生耐青霉素金黄色葡萄球菌(penicillin-resistant *Staphylococcus aureus*, PRSA)、耐甲氧西林金黄色葡萄球菌(methicillin-resistant *Staphylococcus aureus*, MRSA)和耐万古霉素金黄色葡萄球菌(vancomycin-resistant *Staphylococcus aureus*, VRSA)，并且在不同时间、地区流行分型也不相同，这极大地增加了金黄色葡萄球菌防控难度[5]。

为了更好地防控金黄色葡萄球菌感染并解决耐药菌临床用药，除了继续研发新型抗生素外，寻找其他用药策略也极为关键。近年来，在我国中草药扶持政策的大力支持下，大量中

草药抗菌生物活性被发现[6-8]，且中草药具有残留量低、耐药性低等优点，符合当下绿色防护理念。大量研究证明，中草药在耐药菌防控方面发挥了重要的作用，是很好的减抗替抗新型药物[9]。

本文汇总我国畜禽金黄色葡萄球菌的感染情况和耐药现状，对其耐药菌株的流行特点进行归纳，为进一步防控金黄色葡萄球菌感染提供数据支撑。最后，本文对中草药针对耐药金黄色葡萄球菌的作用靶点进行分析，以期为研发中草药防控耐药菌提供理论基础。

1 畜禽金黄色葡萄球菌感染情况

金黄色葡萄球菌是畜牧业中常见的病原菌，可引起许多传染性疾病，其中奶牛乳腺炎是最常见的由金黄色葡萄球菌感染引起的疾病。据统计35%[10]的奶牛都患有奶牛乳腺炎，本文将我国河南、河北、上海等12个省、自治区、直辖市奶牛乳腺炎中金黄色葡萄球菌分离率进行汇总(图1)[11-22]。由图1可知，我国金黄色葡萄球菌分离率在10.00%−48.55%，各地金黄色葡萄球菌分离率均不一致，其中吉林省采集样本分离率最高，江苏省分离率最低，具有区域差异，这可能受养殖环境、奶牛自身因素、营养不良等因素影响[23-24]。

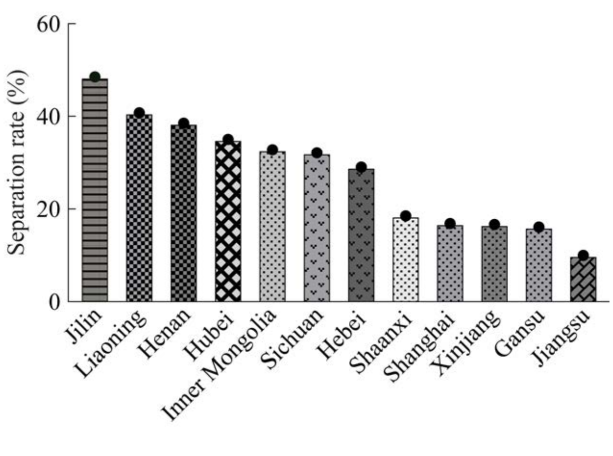

图 1 我国不同地区奶牛乳腺炎金黄色葡萄球菌的分离率[11-22]

Figure 1 Isolation rate of *Staphylococcus aureus* in mastitis of dairy cows in different regions of China[11-22].

除了奶牛感染金黄色葡萄球菌外，近年来，其他养殖动物感染金黄色葡萄球菌的病例也多有报道(表1)。2018年内蒙古自治区呼和浩特市发现一例由金黄色葡萄球菌引起的猪上呼吸道感染病例[25]。2020年北京市某猪场发现因金黄色葡萄球菌感染引起腹泻、发热等症状，导致猪陆续死亡[26]。2021年西藏自治区报道了羊群被感染，导致羊内脏多处损伤[27]。2022年云南省昆明市发现鹅被感染的现象[28]，在福建省发现鸡被感染的现象[29]。此外，在伴侣动物猫狗的子宫黏液、泪液等也检测出金黄色葡萄球菌[30]。由此可见，我国多种动物均有金黄色葡萄球菌感染情况，需进一步加强对金黄色葡萄球菌的监测。

2 畜禽金黄色葡萄球菌耐药现状

目前，我国不仅存在金黄色葡萄球菌感染各种动物的病例，而且在临床治疗中表现出严重的耐药性。耐药性的产生与耐药基因的产生有密切关系。本文对近10年来分离自我国各种动物、人及食品的金黄色葡萄球菌的耐药性和相关耐药基因检出率进行汇总(表2)。由表2可知，来源于动物的金黄色葡萄球菌中四环素类*tet*族、大环内酯类*erm*族、氨基糖苷类*aac*(*6′*)-*aph*(*2″*)等耐药基因检出率较高[27-36]。在来源于人的金黄色葡萄球菌中检测出氟喹诺酮类耐药基因 *grlA* (100.0%)、大环内酯类耐药基因 *ermC* (95.0%)、四环素类 *tetM* (77.78%)、*tetK* (80.0%)等耐药基因[37]。另外在食品中也检测出大环内酯类、氨基糖苷类耐药基因[38-39]，这很有可能是造成耐药菌在人畜之间传播的关键途径。

表 1　其他动物感染金黄色葡萄球菌病例

Table 1　Other cases of *Staphylococcus aureus* infection in other animals

感染症状 Symptoms of infection	来源 Source	采集地点 Collection location	检测时间 Detection time	参考文献 Reference
流鼻涕继而咳嗽气喘 Runny nose followed by coughing and wheezing	猪 Pig	内蒙古自治区呼和浩特市郊区 A suburb of Hohhot, Inner Mongolia Autonomous Region	2018 年 5 月 May 2018	[25]
体温升高、毛粗乱，采食量下降，同时伴有腹泻和发抖症状 Elevated body temperature, coarse coat, decreased feed intake, and diarrhea and shivering are present	猪 Pig	北京市 Beijing	2020 年 6 月 June 2020	[26]
羊心包有积血，心脏、肝脏和肾脏肿大，肝脏边缘有部分坏死，肺脏发生肉变 There is hemopericardium, enlargement of the heart, liver, and kidneys, partial necrosis of the liver margins, and flesh changes of the lungs	羊 Sheep	西藏自治区日喀则市 Shigatse, Xizang Autonomous Region	2021 年 4 月 April 2021	[27]
精神不振、关节肿大、跛行、腹泻 Lack of energy, swollen joints, claudication, diarrhea	鹅 Goose	昆明市东川区 Dongchuan district, Kunming	2022 年 10 月 October 2022	[28]
脚关节发炎肿胀充血，爪掌出现溃烂呈乌黑色痂，趾关节肿胀 The joints of the feet are inflamed, swollen and congested, the palms of the claws are ulcerated and blackened, and the joints of the toes are swollen	鸡 Chicken	福建省 Fujian Province	–	[29]
–	猫、狗 Cat and dog	沈阳市 Shenyang	2020–2021 年 2020–2021	[30]

–：未提及

–: Not mentioned.

表 2　近 10 年耐药金黄色葡萄球菌耐药基因检出率

Table 2　In the past decade, the detection rate of drug-resistant *Staphylococcus aureus* resistance genes

来源 Source	耐药基因 Drug resistance gene	耐药基因检出率 Detection rate of drug resistance gene (%)	耐药情况 Drug resistance	参考文献 Reference
牛 Cattle	*blaZ* *grlA* *gyrA* *norA*	64.5 95.7 97.9 97.9	青霉素、头孢西丁、苯唑西林、克林霉素、庆大霉素、红霉素、替米考星 Penicillin, cefoxitin, oxacillin, clindamycin, gentamicin, erythromycin, timicoxin	[31-32]
羊 Sheep	–	–	对氨苄西林、多黏菌素 B、四环素、新霉素、卡那霉素、青霉素、克林霉素和红霉素 p-ampicillin, polymyxin B, tetracycline, neomycin, kanamycin, penicillin, clindamycin, and erythromycin	[27]
猪 Pig	*blaZ* *grlA* *tetM* *tetK*	96.9 100.0 93.8 100.0	林可霉素、青霉素、阿莫西林、氨苄西林、四环素、多黏菌素 B、磺胺嘧啶 Lincomycin, penicillin, amoxicillin, ampicillin, tetracycline, polymyxin B, sulfadiazine	[33]

(待续)

(续表 2)

来源 Source	耐药基因 Drug resistance gene	耐药基因检出率 Detection rate of drug resistance gene (%)	耐药情况 Drug resistance	参考文献 Reference
	Lin(*A*)	89.2		
	sull	72.3		
	ermA	83.0		
	aac(*6′*)-*aph*(*2″*)	100.0		
兔 Rabbit	*tet*	70.7	氨苄西林、青霉素、妥布霉素、红霉素、四环素、多西环素、万古霉素、头孢他啶、头孢氨苄、庆大霉素、丁胺卡那、卡那霉素 Ampicillin, penicillin, tobramycin, erythromycin, tetracycline, doxycycline, vancomycin, ceftazidime, cephalexin, gentamicin, amikacin, kanamycin	[34-35]
	erm	53.7		
	aph(*3′*)-*IIIa*	53.7		
	aac(*6′*)-*aph*(*2″*)	92.7		
禽 Fowl	*ermA*	13.6	大观霉素、头孢他啶、卡那霉素、氨苄西林、阿莫西林、四环素、红霉素、阿奇霉素、链霉素、萘啶酸、磺胺复合物、氧氟沙星、环丙沙星、诺氟沙星 Spectinomycin, ceftazidime, kanamycin, ampicillin, amoxicillin, tetracycline, erythromycin, azithromycin, streptomycin, nalidixic acid, sulfonamide complex, ofloxacin, ciprofloxacin, norfloxacin	[28-29,36]
	aac(*6′*)-*aph*(*2″*)	76.7		
猫狗 Cat and dog	*tetM*	81.8	林可霉素、青霉素、四环素、氨苄西林、阿莫西林、阿奇霉素、多西环素、红霉素、泰乐菌素、杆菌肽、氟苯尼考、环丙沙星、恩诺沙星、氧氟沙星、头孢唑林、头孢噻夫、头孢喹肟、庆大霉素 Lincomycin, penicillin, tetracycline, ampicillin, amoxicillin, azithromycin, doxycycline, erythromycin, tylosin, bacitracin, florfenicol, ciprofloxacin, enrofloxacin, ofloxacin, cefazolin, cefotaxif, cefquinome, gentamicin	[30]
	tetK	70.9		
	ermC	65.5		
	aac(*6′*)-*aph*(*2″*)	82.7		
人 Human	*blaZ*	60.0	青霉素、红霉素、四环素、克林霉素、环丙沙星、苯唑西林、头孢西丁、庆大霉素、氯霉素、复方新诺明、头孢唑啉 Penicillin, erythromycin, tetracycline, clindamycin, ciprofloxacin, oxacillin, cefoxitin, gentamicin, chloramphenicol, cotrimoxazole, cefazolin	[37]
	grlA	100.0		
	gyrA	100.0		
	tetM	77.78		
	tetK	80.0		
	Lin(*A*)	30.0		
	ermA	80.6		
	ermC	95.0		
食品 Food	*ermA*	14.3	红霉素、克林霉素、四环素、氯霉素、环丙沙星、庆大霉素、复方新诺明、青霉素、苯唑西林、头孢西丁 Erythromycin, clindamycin, tetracycline, Chloramphenicol, ciprofloxacin , gentamicin, cotrimoxazole, penicillin, oxacillin, cefoxitin	[38-39]
	ermC	19.6		
	aph(*3′*)-*IIIa*	5.4		
	aac(*6′*)-*aph*(*2″*)	10.7		

–：未提及

–: Not mentioned.

耐药基因快速传播也是导致金黄色葡萄球菌多重耐药现状的重要原因之一。目前，金黄色葡萄球菌对青霉素耐药最为严重，其次是红霉素、四环素、庆大霉素、氨苄西林等临床常用药物[27-39]。在本文所统计的菌株中均表现出对 7 种以上的抗生素存在不同程度的耐药，这种多重耐药的现状对临床选用抗生素治疗金黄色葡萄球菌感染造成了巨大挑战。

3 耐药金黄色葡萄球菌感染分析

耐药基因的出现同时也促进了金黄色葡萄球菌耐药菌株不断演变。本文对金黄色葡萄球菌耐药菌株的发现时间、产生原因、主要的流行分型及目前感染情况等流行特征进行了分析(图 2)。

1942 年发现第一株 PRSA，该耐药株出现主要是由于 *blaZ* 耐药基因的广泛传播，噬菌体 80/81、MLST/ST30、CC30 分型是主要的流行分型[40]。

1962 年产生了第一株 MRSA，其产生原因与细菌 *mecA* 耐药基因的出现及对 β-内酰胺酶表达过量有关[41]，MRSA 的出现对畜牧业产生前所未有的挑战，尤其是奶牛业。奶牛一旦感染 MRSA 会引起产奶量及质量下降，造成巨大的经济损失[42]。根据我国 CHINET 网数据表明，在 2016 年之前 ST239-t030-III 为主要流行分型，2016 年之后以 ST59-t437-IV 为主要分型，并且流行分型具有地域差异性[43]。2004 年，荷兰首次报道了猪源 MRSA 感染人的案例[44]，此后，人们逐渐意识到 MRSA 是一种人畜共患

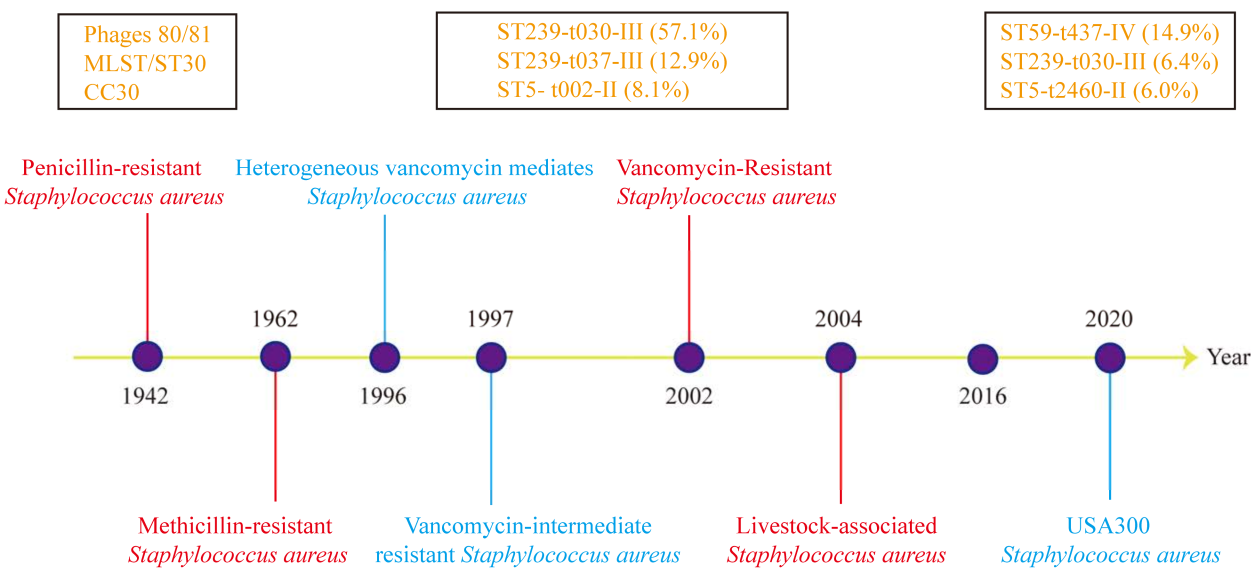

图 2 金黄色葡萄球菌耐药菌株流行历史[40-50] 金黄色葡萄球菌耐药菌株不断发展，流行分型也不断变化. 20 世纪 50 年代以噬菌体 80/81、MLST/ST30、CC30 为流行分型，直到 2016 年以 ST239-t030-III 分型为主，2016 年后以 ST59-t437-IV 分型为主

Figure 2 Development of resistant strains of *Staphylococcus aureus*[40-50]. Resistant strains of *Staphylococcus aureus* are constantly evolving, and the epidemic typology is constantly changing. In the 1950s, phages 80/81, MLST/ST30, CC30 were used as popular types, and then ST239-t030-III were mainly classified until 2016, and ST59-t437-IV were prevalent after 2016.

条件致病菌。据统计，与家畜相关的耐甲氧西林金黄葡萄球菌(livestock-associated methicillin-resistant *Staphylococcus aureus*, LA-MRSA)在欧洲和北美国家的流行分型是 ST398，而在中国则是 ST9-t899[45]。随着耐药菌株不断进化，USA300 MRSA 分离株正逐渐广泛流行，该流行菌株的出现加重了 MRSA 的感染数量及感染程度[46]。

万古霉素是治疗超级耐药菌 MRSA 的最后一道防线，但近年来 MRSA 对万古霉素的敏感性也逐渐降低，甚至产生了耐药性。1996 年，于一名日本肺癌患者的痰中检测出第一株万古霉素耐药的原代金黄色葡萄球菌菌株(heteroresistant vancomycin-intermediate *Staphylococcus aureus*, hVISA)，但其耐药性的产生与耐药基因无关，主要是由于细胞壁增厚阻滞了万古霉素到达作用靶点[47]。随后，1997 年，日本报道了第一株万古霉素中度耐药的金黄色葡萄球菌(vancomycin-intermediate resistant *Staphylococcus aureus*, VISA)，其耐药机制尚不明确，但研究者从遗传分析中推测其可能与控制细菌细胞壁生物合成的决定簇和/或核糖体基因 *rpoB* 的突变密切相关[48]。2002 年从一名慢性肾衰的美国糖尿病患者体内检测出第一株万古霉素高度耐药的金黄色葡萄球菌，VRSA 被世界卫生组织确定为“高优先级抗生素耐药病原体”，该病原菌耐药性的产生主要是由于转座子 Tn1546 上编码的 *van*A 操纵子和其他 *van* 基因簇遗传元件改变细胞壁结构，阻止了万古霉素对细胞壁合成的抑制作用[49]。据统计，2006–2020 年，VRSA 的感染率增加了 3.5 倍，VRSA 的患病率在亚洲为 5%，在欧洲为 1%，在美洲为 4%，在南美洲为 3%，在非洲为 16%[50]。2013 年，我国发现第一株 VISA，尚无 VRSA 的报道[51]。

4 中草药防控耐药金黄色葡萄球菌的策略

金黄色葡萄球菌具有传播范围广、突变速度快、多重耐药等特点，如何有效抑制耐药金黄色葡萄球菌已成为现在的研究热点。当前，用于治疗多重耐药金黄色葡萄球菌感染的新抗菌药物利奈唑胺[52]，或半合成药物如替加环素、达巴万星、奥利万星、伊克拉普林、塞红霉素和德拉沙星[53]在临床治疗中得到了应用。除了使用新抗生素治疗外，抗生素联合使用均被证实具有很好的抑菌效果。如夫西地酸联合多西环素使用[54]，头孢喹肟和恩诺沙星、庆大霉素、卡那霉素合用[55]，万古霉素与左氧氟沙星、利福平、磷霉素[56]或亚胺培南[57]联合使用。但依靠原有的抗生素来解决细菌耐药性问题远远不够，仍须探索新的用药策略。目前，大量减抗替抗的中草药抗菌药物被证实有良好的效果，为解决细菌耐药性提供了新的选择。因此，本文对中草药防控耐药金黄色葡萄球菌的策略进行了归纳总结，为研发新型抗生素提供理论基础。

4.1 直接抗菌作用

4.1.1 中草药抑制耐药金黄色葡萄球菌生物膜的形成

一些中草药被证实可以改变 MRSA 细胞膜的通透性，使得药物更好地进入胞内，导致胞内 DNA、RNA 外泄，从而抑制了细菌的生长，如地榆皂苷II[58]、桂千金子提取物[59]。但细菌生物膜的形成可增强细菌对药物的抵抗力并且降低宿主细胞的免疫反应[60]，因此，有效抑制金黄色葡萄球菌生物膜的形成是耐药菌防控的一个关键靶点。生物膜的形成主要有黏附、聚集、成熟和扩散 4 个过程[61]，一些中草药活性成分可在金黄色葡萄球菌生物膜形成的不同阶段发挥抑制作用。大蒜素、香芹酚和黄芩素通

过降低生物膜 *ica* 家族基因转录水平，进而抑制多糖细胞间黏附素的合成，阻滞了细菌生物膜黏附过程[62-64]。丁香酚可以抑制细菌黏附 *fnbA* 和 *fnbB* 基因的表达，从而阻碍了细菌定殖，干扰金黄色葡萄球菌生物膜的形成[65]。

4.1.2 中草药抑制耐药金黄色葡萄球菌毒力因子的表达

在耐药危机的大背景下，抗毒素的药物研发备受关注。金黄色葡萄球菌具有 α-溶血素[66]、酚可溶性蛋白[67]、去角质毒素[68]、肠毒素[69]、毒性休克毒素-1[70]、表皮剥落性毒素[66]等致病性毒素，这些毒素可导致发热、中毒、肺炎、皮炎等炎症，严重时可引起脓血症、败血症等疾病(表 3)。五味子酮、黄芩苷、儿茶素、山奈酚、槲皮素、芍药苷衍生物对 α-溶血素具有抑制作用，小鼠肺炎模型表明，药物作用后小鼠肺部的损伤程度明显减轻，并且降低了炎症因子 TNF-α、IL-1β 和 IL-6 的含量[71-73]。青蒿琥酯和茶黄素-3,3′-二甲酸酯还被证实是通过 Agr 调控系统来抑制 α-溶血素的合成[74-75]。香茅醛、桃

表 3 金黄色葡萄球葡萄球菌毒素以及引起的相关疾病

Table 3 *Staphylococcus aureus* toxins and related diseases

毒素 Toxin	功能 Function	相关疾病 Associated disease	中草药活性成分 Active ingredient in Chinese herbal medicine	参考文献 Reference
α-溶血素 α-hemolysin	裂解细胞、参与细胞信号传导、增殖、免疫调节、溶血 Lysed cells, involved in cell signaling, proliferation, immunomodulation, hemolysis	败血症、肺炎 Sepsis, pneumonia	五味子酮、黄芩苷、儿茶素、山奈酚、槲皮素、青蒿琥酯、茶黄素-3,3′-二甲酸酯、芍药苷衍生物 Schizandra ketone, baicalin, catechin, kaempferol, quercetin, artesunate, theaflavin-3,3′-diplus ester, paeoniflorin derivative	[66, 71-75]
酚可溶性蛋白 Phenol soluble protein	诱导炎症反应、影响免疫细胞功能、参与细菌免疫逃逸 Inducing inflammatory response, affects immune cell function, and participates in bacterial immune escape	皮炎、肺炎、脓毒症、骨髓炎 Dermatitis, pneumonia, sepsis, osteomyelitis	–	[67]
去角质毒素 Exfoliating toxins	内皮细胞破裂 Endothelial cells rupture	糖尿病足溃疡 Diabetic foot ulcers	–	[68]
肠毒素 Enterotoxin	T 淋巴细胞激活剂、致敏 T lymphocyte activator, sensitization	支气管扩张、食物中毒 Bronchiectasis, food poisoning	香茅醛、桃柁酚 Citronellal, totarol	[69,76-77]
毒性休克毒素-1 Toxic shock syndrome toxin-1	致热原性超抗原 Pyrogenic superantigen	发热、脱屑性皮疹、休克 Fever, desquamative rash, shock	姜黄素、山莨菪碱、单月桂酸甘油酯 Curcumin, hyoscyamine, glyceryl monolaurate	[70,78]
表皮剥落性毒素 Exfoliating epidermal toxins	识别并水解皮肤中的桥粒蛋白 Recognizes and hydrolyzes desmosomlein in the skin	里特氏病 Ritter's disease	–	[66]

–：未提及

–: Not mentioned.

柁酚可抑制肠毒素的分泌，并且可以限制金黄色葡萄球菌的生长[76-77]。姜黄素、山莨菪碱和单月桂酸甘油酯对毒性休克综合征毒素-1 有抑制作用，并且可以抑制干扰素的表达[78]。因此，通过抑制金黄色葡萄球菌的毒素，可以减小细菌的致病力及对宿主的侵袭力。

4.1.3 中草药活性成分抑制金黄色葡萄球菌分选酶 A

细菌分选酶 A 是一种细菌细胞膜锚定酶，在毒力因子锚定到细菌细胞壁过程中起关键作用，实验证明缺少该酶可降低金黄色葡萄球菌的毒力并增加宿主对病原菌的敏感性[79]。许多中草药的提取物经酶活试验和细菌侵袭试验被证明可以靶向抑制分选酶 A (sorting enzyme A, SrtA)。例如，土木香提取物与金黄色葡萄球菌 SrtA 共孵育后可有效降低酶的催化活性，并且加入土木香提取物还可降低细菌对宿主细胞的侵袭[80]。扁桃酸是桃树叶和柳树叶的提取物，经过分子对接表明扁桃酸通过氢键与 SrtA 稳定结合，酶活试验表明其可降低酶催化活性[81]。黄连根茎提取物小檗碱以及白桦提取物中的 β-谷甾醇-3-O-吡喃葡萄糖苷都是 SrtA 潜在抑制剂[82]。

4.2 抗菌增效作用

中草药除了可以直接发挥抗菌作用外，还与某些抗生素具有协同作用。中草药不仅可以增加抗菌效果，还可以有效减缓细菌耐药性。中药单体原花青素与头孢噻呋钠联合用药后，最小抑菌浓度从 32 μg/mL 降低到 4 μg/mL，小鼠大腿肌肉感染金黄色葡萄球菌模型表明，联合用药抗菌效果优于单独用药[83]，在体内外均有抗菌增效的作用。黄芩素与阿莫西林联用 24 h 后可观察到细菌全部死亡且防突变浓度降低, 有效减缓金黄色葡萄球菌耐药性的发生[84]。此外，生物碱类、类黄酮类化合物可以帮助利血平规避细菌外排泵的作用，降低药物的外排，从而增加了药物的抑菌作用[85]。

4.3 扶正宿主作用

中草药不仅可以直接抗菌，还可以通过激活宿主的免疫能力或调控宿主细胞代谢而发挥抗菌作用[86-87]。秘鲁树皮中活性成分贝达奎林可激活宿主先天免疫来增加杀菌能力[88]。牡荆素通过抑制活性氧(reactive oxygen species, ROS)的产生缓解内质网应激，通过 MAPK 和 NF-κB 信号通路抑制细胞凋亡[89]。虎杖甙抑制 TLR2 介导的 MAPK/NF-κB 激活，从而下调促炎细胞因子的水平[90]。雷公藤红素可以靶向与脯氨酸代谢过程中的 Δ1-吡咯啉-5-羧酸脱氢酶结合，激活宿主的氧化应激，还阻断了细菌脯氨酸的合成与分解，进而抑制了细菌的生长[91]。宿主导向性抗菌药物的研发是新趋势，可以发现药物-病原体-宿主之间的潜在机制, 为更好地防控耐药菌提供新思路。

5 中草药在养殖场中的应用

随着对中草药资源的不断开发及研究的深入，越来越多的中草药作为抗生素替代品和饲料添加剂在畜禽养殖中得到应用，据统计，目前兽用中药有 1 000 余种，其中含有 60 多种兽医专用中药[92]。例如，2011 年批准上市的博落回散具有抗金黄色葡萄球菌、肠杆菌的作用[93]。功苋止痢散被批准用于治疗大肠杆菌感染引起的仔猪湿热泻痢。苦参、木槿皮、白鲜、土茯苓、青蒿、虎杖、黄柏、穿心莲、大蒜素、马齿苋等中草药在临床研究中被发现抑制细菌感染作用显著[94-95]。中草药饲料添加剂能够显著促进畜禽生长，增强免疫力，降低肉料比，提高生产性能[96]。目前也有许多中草药饲料添加剂批准上市，如以黄芩为主要成分的金肥素、以甘草为主要成分的清根素、以姜黄为主要成分的加富强等。此外，一些中草药的残渣、非药用

部位也作为饲料添加剂进行使用，如豆蔻渣可以提高蛋鸡的鸡蛋质量[97]，极大地提高了经济效益。

6 讨论与展望

我国当前畜牧业金黄色葡萄球菌感染情况多发，以奶牛感染最为严重，多种动物均有感染现象，可能与病原菌在动物间不断传播演化有关[98]。多数耐药菌株对 7 种以上抗生素耐药，耐药性不断加剧，这与耐药基因的产生密切相关。此外，药物残留也是很重要的一环，需要加强对其监管，我国已于 2008 年成立动物源细菌耐药性检测系统，目前，已经检测出 50 多种金黄色葡萄球菌耐药基因[99]。金黄色葡萄球菌耐药株不断演变，从 1942 年至今依次出现了 PRSA、MRSA 与 VRSA 等耐药菌株，其中以 MRSA 感染最为严重。

继续使用传统抗生素治疗金黄色葡萄球菌感染已经有些不合时宜，开发新型抗生素以及找到新抑菌靶点极为关键。中草药在防控耐药金黄色葡萄球菌方面具有良好的应用前景，可以通过有效抑制细菌生物膜的形成、抑制毒力因子的表达、抑制细菌关键酶活性直接杀菌，并且与传统抗生素联合抗菌效果更好，还可以调控宿主功能来增加宿主抵抗病原菌感染的能力。除了使用中草药代替治疗外，抗体-抗生素缀合物(antibody-antibiotic conjugates, AAC)[100]、抗菌肽(antimicrobial peptides, AMP)[101]、特异性抗体[102]、噬菌体[103]等先进技术也在金黄色葡萄球菌感染治疗中发挥了重要作用。与此同时，也要加强畜禽感染金黄色葡萄球菌的预防工作，基因工程疫苗、亚单位疫苗、核酸疫苗[104-106]均被证实可以有效防控金黄色葡萄球菌的感染。总之，未来需要将金黄色葡萄球菌检测手段、预防策略和传统、新型药物联合治疗综合一体，不断探究防控金黄色葡萄球菌的更多用药策略和更完善的临床治疗方案，最终达到金黄色葡萄球菌的综合防控，推动畜牧业向安全、绿色方向发展。

中草药在兽用抗生素和饲料添加剂方面取得了一定的研究成果，但仍面临着有效成分不明确、用药剂量大、靶向性差、药物作用机制复杂，毒理学评价欠缺、提取工艺步骤烦琐、研发速度慢、成果转化慢等问题。今后应该着力开发药食同源、兽医专用中草药，以及中草药非药用部位生物活性的开发，从而为兽用中草药提供更丰富的资源，同时减轻与人用药物资料的争夺。此外，还须应用大数据筛选平台和化学合成提取工艺来优化有效成分的结构，结合先进的组学技术进行深度的机制研究。另外，国家部门也应该制定中草药生产标准、统一的提取技术及全面的药效检测指标，以便规范我国中草药资源的合理性研发及应用。

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