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Microbial resources management 微生物资源管理

短梗霉资源应用：生物制造与可持续发展

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摘　要：短梗霉(*Aureobasidium* spp.)是一种具有极强生态适应性和抗逆性的真菌，广泛分布于植物等自然环境中，且能在极端条件下生存。短梗霉的基因组展现出特异性分化特征，其菌株在发酵过程中具有明显优势，能够利用广谱碳源并产生丰富多样的代谢产物。短梗霉及其代谢产物在生物医药、生物防治和食品加工等多个领域展现出显著的应用潜力。本文综述了短梗霉属菌株的分布、分类、主要代谢产物以及多领域的应用情况。未来随着基因组编辑、智能生物制造等多学科领域的不断发展，短梗霉有望在生物制造和可持续发展产业中发挥重要作用。

关键词：短梗霉；代谢产物；基因组学；生物制造

Applications of *Aureobasidium* spp. resources: biomanufacturing and sustainable development

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Abstract: *Aureobasidium* spp. are a group of fungi with remarkable ecological adaptability and stress tolerance. They are ubiquitous in natural environments such as plants and can survive under extreme conditions. The genomes of *Aureobasidium* spp. show specific differentiation characteristics, and the strains have obviously advantage characteristics in fermentation. *Aureobasidium* spp. can utilize a broad spectrum of carbon sources and produce a rich variety of

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metabolites. *Aureobasidium* spp. and their metabolites have significant application potential in fields such as biomedicine, biocontrol, and food processing. This article introduces the distribution, classification, main metabolites, and multidisciplinary applications of *Aureobasidium* spp. In the future, with the advancement in multidisciplinary fields such as genome editing and intelligent biomanufacturing, *Aureobasidium* spp. are expected to play an important role in biomanufacturing and sustainable development industries.

Keywords: *Aureobasidium* spp.; metabolites; genomics; biomanufacturing

短梗霉(*Aureobasidium* spp.)是一种广泛分布于自然环境中的酵母样真菌，能够在酸性、高渗透压和寡营养等极端环境条件下生存，展现出极强的生态适应性和抗逆性[1-2]。目前已报道的短梗霉菌超过 50 种，其中多数为出芽短梗霉(*A. pullulans*)和产黑色素短梗霉(*A. melanogenum*)。短梗霉在进化过程中积累了丰富的遗传多样性，能够利用多种广谱碳源，并产生一系列代谢产物，如聚苹果酸、普鲁兰多糖、富马酸、黑色素、胞外酶等(图 1)[3-6]。短梗霉基因组中存在大量与碳水化合物代谢相关的基因及调控元件，这是其代谢多样性和环境适应性强的重要内在机制[2]。

短梗霉菌株在生物制造领域被视为极具潜力的底盘生物工厂，它们具有广谱碳源利用能力，能够以廉价的生物质为原料，如玉米芯、木糖结晶母液等进行生物转化[7]。此外，短梗霉菌株在培养过程中主要呈现为单细胞形态，具备出色的抗逆性能，能够适应低 pH 值、高渗透压、高剪切力等极端发酵环境，展现出优异的工业菌株鲁棒性。短梗霉的代谢产物，如聚苹果酸和普鲁兰多糖等高分子聚合物，在药物递送和食品加工保鲜中被广泛应用(图 1B、1D)。同时，短梗霉丰富的次级代谢产物在植物病害防控中也发挥着重要作用，可有效抑制植物病原菌(图 1C)。因此，本文对短梗霉菌株的分布、分类特征、代谢产物其在生物医药、农业和食品工业中的应用进行系统综述，并探讨其在未来生物制造领域的应用前景。

1 短梗霉资源分布与分类

1.1 资源分布与生态适应性

短梗霉在自然界中分布极为广泛，常作为附生或内生真菌存在于植物的叶片等部位，并与植物形成共生关系，在生态系统中发挥着不可或缺的生态功能[8-9]。已报道在冰川、红树林、海洋、沙漠等多种极端环境中也发现了短梗霉属菌株的存在[1,10-14]。短梗霉在高盐、低酸、高温等极端环境中同样表现出卓越的生存和适应能力，这主要归因于其细胞具有的特定生理适应分子机制。短梗霉合成的黑色素有助于细胞应对热胁迫、氧化应激和紫外线辐射等特殊环境压力[15]。例如，从塔克拉玛干沙漠中分离得到的产黑色素短梗霉 XJ5-1 就具备产黑色素的能力[16]。短梗霉的环境耐受性还依赖于普鲁兰多糖等聚合物类产物，这些产物可维持细胞水分并增强细胞的抗氧化能力[17]。此外，高渗透压和低温等环境因素会激活短梗霉的丝裂原活化蛋白激酶(mitogen-activated protein kinase, MAPK)信号通路，诱导细胞内甘油积累以应对渗透压胁迫[18]。同时，高渗透压和低 pH 值等环境因素还会引起钙调磷酸酶信号通路下游基因的转录激活，进而对细胞生物膜的形成和细胞壁的完整性进行调节，从而提高细胞的耐受性[7,19-21]。这些适应性机制为短梗霉能够在多种极端环境下生存奠定了基础。

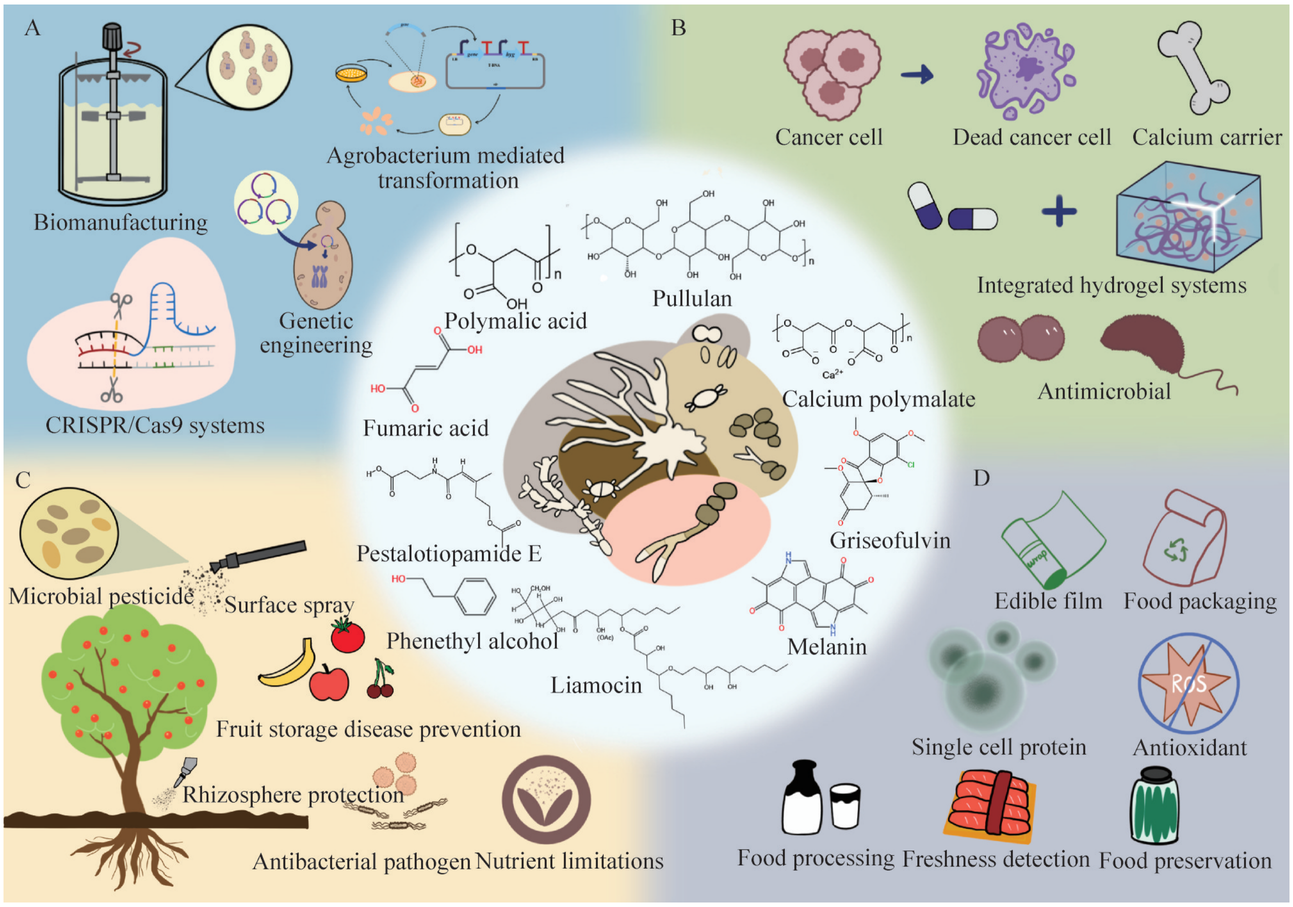

图1　短梗霉及其代谢产物的多领域应用。A：短梗霉底盘生物技术和应用；B：代谢产物在药物递送与抑菌治疗的应用；C：活体细胞及代谢产物在农业防治的应用；D：代谢产物在食品加工保鲜中的应用。

Figure 1　Multi-disciplinary applications of *Aureobasidium* spp. and its metabolites. A: Biotechnology and applications of *Aureobasidium* spp. chassis; B: Applications of metabolites in drug delivery and antibacterial treatments; C: Applications of living cells and metabolites in agricultural control; D: Applications of metabolites in food processing and preservation.

1.2　系统分类学与基因组特征

在系统分类学上，短梗霉隶属于子囊菌门(*Ascomycota*)、座囊菌纲(*Dothideomycetes*)、座囊菌目(*Dothideales*)、*Saccotheciaceae*[22]。最早由 Viala 和 Boyer 在葡萄叶上发现并命名为 *A. vitis*，曾被归入 *Dothioraceae* 和 *Aureobasidiaceae*[23-26]。出芽短梗霉最初被记录为 *Dematium pullulans*，被描述为一种极端耐受的酵母样真菌，可通过透明分生孢子的同步产生与 *Hormonema* spp. 进行区分，并以产普鲁兰多糖广为人知[27-28]。近年来短梗霉属已成为研究热点。2018 年后被鉴定的新种超过 20 个，短梗霉的细胞形态呈现多态性，由酵母状细胞、芽生孢子、膨胀细胞、厚垣孢子、菌丝及假菌丝组成，分生孢子透明、光滑且呈椭圆形，部分可见黑色素沉着[29]，见表 1。细胞的多态性和细胞分化受到 pH、温度、营养条件等多种因素的影响[57]。在发酵培养阶段细胞多表现为单细胞形态，主要为酵母状细胞和膨胀细胞。

表1 已经报道的短梗霉菌种

Table 1 The reported strains of *Aureobasidium* spp.

种名 Species name	来源 Source	位置 Location	菌株号 Strain number	有效记录年份 Year of effective record	参考文献 References
A. acericola	紫花槭叶 Leaves of *Acer pseudosieboldianum*	韩国 Korea	MB836925	2021	[30]
A. aerium	空气 Air	中国北京 Beijing, China	MB843527, CFCC 50324	2022	[26]
A. aleuritis	N/A	N/A	MB309377	1977	[28]
A. apocryptum	N/A	N/A	MB309378	1977	[28]
A. aurantiacum	N/A	N/A	MB902111	2024	[31]
A. australiense	N/A	N/A	MB501787	1896	[32]
A. bupleuri	直布罗陀柴胡花 Flowers of *Bupleurum gibraltarium*	西班牙 Spain	MB835676, CBS 131304	2021	[33]
A. castaneae	锥栗叶斑 Leaf spots of *Castanea henryi*	中国湖南 Hunan, China	MB838314	2021	[34]
A. caulivorum	三叶草 *Trifolium* spp.	英国 UK	MB326817	1962	[35]
A. dalgeri	桉树叶 Leaves of *Eucalyptus*	突尼斯 Tunisia	MB309379	1977	[28]
A. faidherbiae	环荚合欢叶 Leaves of *Faidherbia albida*	纳米比亚 Namibia	MB848079	2023	[36]
A. foliicola	N/A	N/A	MB326818	1964	[37]
A. hainanensis	秋茄叶 Leaves of *Kandelia candel*	中国海南 Hainan, China	RZIQ01000000	2019	[38]
A. harposporum	白果槲寄生 *Viscum album*	西班牙马德里 Madrid, Spain	MB309380, CBS 122914	1977	[28]
A. indicum	N/A	N/A	MB103074	1985	[39]
A. insectorum	沫蝉 Spittle insects	中国 China	MB571251	2023	[40]
A. intercalariosporum	叶 Leaf	中国 China	MB571252	2023	[40]
A. iranianum	竹子 Bamboo	伊朗 Iran	MB800705, CCTU 268	2012	[41]
A. khasianum	美丽桐叶 Leaves of *Wightia speciosissima*	印度 India	MB828278	2018	[42]
A. leucospermi	灰针垫花叶 Leaves of *Leucospermum conocarpodendron*	南非斯泰伦博斯 Stellenbosch, South Africa	MB560556, CBS 130593	2011	[43]
A. lilii	植物 Plant	N/A	MB326819	1964	[44]
A. lini	亚麻 *Linum usitatissimum*	英国 UK	MB283371, CBS 125.21	1977	[28]
A. mangrovei	海榄雌 *Avicennia marina*	伊朗 Iran	MB823444	2018	[12]
A. mansonii	N/A	N/A	MB326820	1962	[35]
A. melanogenum	N/A	N/A	MB807698, CBS 105.22	2014	[2]
A. microstictum	N/A	N/A	MB326821	1962	[35]
A. microstromoides	美国梓树 *Catalpa bignonioides*	匈牙利 Hungary	MB326822	1962	[35]
A. microtermitis	白蚁 Termite	印度古吉拉特邦 Gujarat, India	MB839078, GTS2.7	2021	[45]

(待续)

(续表1)

种名 Species name	来源 Source	位置 Location	菌株号 Strain number	有效记录年份 Year of effective record	参考文献 References
A. motuoense	叶 Leaf	中国 China	MB571263, OP856710	2023	[40]
A. mustum	葡萄 *Vitis vinifera*	南澳大利亚州 South Australia	MB836845	2020	[46]
A. namibiae	白云质大理岩 Dolomitic marble	纳米比亚 Namibia	MB807701, CBS 147.97	2014	[2]
A. nigricans	箭舌豌豆 *Vicia sativa*	N/A	MB326823	1962	[35]
A. pini	松叶 Pine needle	中国 China	MB828664, CFCC 52778	2019	[47]
A. planticola	叶 Leaf	中国 China	MB571262	2023	[40]
A. proteae	瓶中美人帝王花 *Protea Sylvia*	南非 South Africa	MB560557, CBS 114273	2011	[43]
A. prunicola	北美稠李 *Prunus virginiana*	美国威斯康星州 Wisconsin, USA	MB309382	1977	[28]
A. prunorum	N/A	N/A	MB309383	1973	[48]
A. pullulans	葡萄 *Vitis vinifera*	法国 France	MB101771	1910	[49]
A. ribis	黑茶藨子叶 Leaves of *Ribes nigrum*	N/A	MB309384	1977	[28]
A. salmonis	N/A	N/A	MB309385	1967	[50]
A. sanguinariae	血根草叶 Leaves of *Sanguinaria canadensis*	美国西弗吉尼亚州 West Virginia, USA	MB309386	1977	[28]
A. subglaciale	海水亚冰川 Subglacial ice from sea water	挪威 Norway	MB807700, CBS 123387	2014	[2]
A. thailandense	木材表面 Surface of wood	泰国 Thailand	MB801148, NRRL 58543	2013	[51]
A. thujae-plicatae	植物 Plant	N/A	MB309387	1978	[32]
A. tremulum	实验室培养污染物 Culture contaminant in a laboratory	印度马哈拉施特拉邦 Maharashtra, India	MB829941	2019	[52]
A. umbellulariae	加州桂叶 Leaves of *Umbellularia californica*	美国加利福尼亚州 California, USA	MB309388	1977	[28]
A. uvarum	葡萄汁 Grape juice	南澳大利亚州 South Australia	MB836846	2020	[46]
A. vaccinii	植物 Plant	N/A	MB126507	1989	[32]
A. vineae	葡萄汁 Grape juice	南澳大利亚州 South Australia	MB836849	2020	[46]
A. vitis	N/A	N/A	MB168679	1891	[53]
A. vitis var. *tuberculatum*	N/A	N/A	MB168866	1898	[54]
A. welwitschiae	百岁兰叶 Leaves of *Welwitschia mirabilis*	纳米比亚 Namibia	MB848078	2023	[36]
A. xishuangbannaense	华南水鼠耳蝠 *Myotis laniger*	中国云南 Yunnan, China	MB849254	2023	[55]
A. zeae	玉米叶 Leaves of *Zea mays*	德国 Germany	MB283372, CBS 767.71	1973	[56]

N/A：无相关信息。

N/A: Not applicable.

目前分子标记技术已广泛应用于短梗霉的物种鉴定和进化分析，常用的标记基因包括内部转录间隔区(internal transcribed spacer, ITS)、核糖体大亚基(28S rRNA)、延伸因子-1α (elongation factor-1α, EF-1α)、RNA 聚合酶 II 第二大亚基(DNA-directed RNA polymerase II subunit, RPB2)和β-微管蛋白(β-tubulin)等。Gostinčar 等[2]通过多位点 DNA 序列分析，重新界定了出芽短梗霉、产黑色素短梗霉、*A. subglaciale* 和 *A. namibiae* 这 4 个种，说明短梗霉在基因组层面呈现出特异性分化特征；通过 DNA 序列差异可以快速识别具有遗传差异的新菌种。例如，对 45 个出芽短梗霉分离株进行的系统发育分析显示，不同分支呈现出不同的菌落特征、普鲁兰多糖产量和木聚糖酶活性[58]。在 NCBI 数据库中已上传的 182 个短梗霉基因组中，多数出芽短梗霉为单倍体，而产黑色素短梗霉为二倍体，这与 Černoša 等[59]的研究结果一致。此外，短梗霉基因组中含有大量不同家族的胞外酶和糖转运蛋白，以及高亲和力钾离子通道蛋白等，是其能够利用多种糖类物质的重要基础[2]。同时，基因组中还含有普鲁兰多糖、聚苹果酸、铁载体、低聚糖、黑色素等代谢产物合成关键的基因，其中普鲁兰多糖和聚苹果酸合成相关基因具有较高的保守性，但黑色素合成基因则表现出一定的差异[60]。此外，仍有大量基因未得到完全注释，可能含有与短梗霉环境适应性和代谢产物相关的新基因或调控元件。我们对耐热型短梗霉的基因组分析还发现，其含有丰富的抗氧化酶和热休克蛋白编码基因，这可能是应对热休克反应的重要遗传基础。

2 短梗霉的丰富代谢产物资源

2.1 短梗霉发酵特性

短梗霉基因组中存在大量与碳水化合物分解代谢相关的分泌蛋白和糖转运蛋白编码基因[2]。它能够利用葡萄糖、木糖等单糖以及分解淀粉、纤维素等多糖为小分子糖类[7,61-63]。例如，可以利用马铃薯废料合成普鲁兰多糖等[64]。短梗霉基因组包含由环境因素和细胞内信号途径介导的调控基因，当碳源、氮源等营养物质比例发生变化时，可触发基因表达调控网络，进而调节产物合成基因的转录和翻译水平[65]。与其他模式真菌相比，短梗霉的发酵温度在 25−30 °C之间，培养基成分相对简单；相较于丝状真菌，短梗霉细胞在发酵过程中呈单细胞形态，不易结块，混合传质效率高，易于进行工程发酵放大[66-67]。此外，短梗霉能够产生酿酒酵母无法合成的纤维素酶、木聚糖酶等多种生物质处理相关酶，这更有利于构建生物质综合炼制加工体系[68]。

2.2 短梗霉主要代谢产物

目前，关于短梗霉代谢产物的研究主要聚焦于菌株的代谢工程改造及过程优化。表 2 列举了短梗霉的主要产物及其发酵水平。普鲁兰多糖主要由出芽短梗霉发酵生产，多种工业加工废料均可作为底物。例如，出芽短梗霉 BL06 以蔗糖发酵可产 140.2 g/L 普鲁兰多糖，分子量达 3.3×10^6 Da[69]。出芽短梗霉与产黑色素短梗霉均具备较强的合成聚苹果酸的能力，且可利用的碳源种类多样。出芽短梗霉 7012D3N5 的聚苹果酸产量为已报道的短梗霉中最高水平，达 194.3 g/L[73]。产黑色素的菌种主要为产黑色素短梗霉，但部分出芽短梗霉的细胞壁中也可积累黑色素[76,82]。短梗霉还可产生结构多样的 liamocin 糖脂，这些糖脂具有不同的生物学活性[83]。此外，短梗霉还能合成富马酸，如出芽短梗霉 DH177 菌株可产 93.9 g/L 的富马酸[4]。这些研究表明，短梗霉在工业发酵生产中具有巨大的潜力。

表2 部分短梗霉主要产物

Table 2 The reported metabolites of *Aureobasidium* spp.

主要产物 Main product	菌种名 Strain	底物碳源 Substrate carbon source	发酵温度 Fermentation temperature (°C)	发酵时间 Fermentation time (h)	产量 Yield (g/L)	菌株来源 Strain source	参考文献 References
普鲁兰多糖 Pullulan	出芽短梗霉 *A. pullulans* BL06	蔗糖 Sucrose	28±2	120	140.2	落叶 Fallen leaves	[69]
	出芽短梗霉 *A. pullulans* MTCC 6994	脱油米糠 De-oiled rice bran	30	168	54.8	植物叶片 Plant leaves	[70]
	出芽短梗霉 *A. pullulans* 201253	马铃薯淀粉水解物 Potato starch hydrolysate	28	120	54.6	N/A	[71]
	出芽短梗霉 *A. pullulans* AZ-6	甘蔗糖蜜 Sugarcane molasses	28	N/A	33.6	橄榄 Olive	[72]
聚苹果酸 Poly(malic acid)	出芽短梗霉 *A. pullulans* 7012D3N5	葡萄糖 Glucose	25	156	194.3	植物 Plant	[73]
	产黑色素短梗霉 *A. melanogenum* GXZ-6	麦芽糖浆 Malt syrup	30	360	124.1	植物 Plant	[74]
	出芽短梗霉 *A. pullulans* YJ 6−11	木糖 Xylose	25	156	80.4	植物 Plant	[75]
黑色素 Melanin	产黑色素短梗霉 *A. melanogenum* XJ5-1	葡萄糖Glucose	N/A	N/A	N/A	沙漠土壤 Desert soil	[16]
	出芽短梗霉 *A. pullulans* 53LC7	蔗糖Sucrose	27	156	16.3	樱花 Cherry blossoms	[76]
Liamocin	产黑色素短梗霉 *A. melanogenum* M39	葡萄糖Glucose	28	156	43.0	红树林 Mangrove	[77]
	出芽短梗霉 *A. pullulans* NRRL 62042	蔗糖Sucrose	28	168	8.6	树叶 Leaf	[78]
	产黑色素短梗霉 *A. melanogenum* SK25	木糖Xylose	28	N/A	7.8	植物 Plant	[79]
	出芽短梗霉 *A. pullulans* NRRL 50380	多元醇Polyols	28	168	<4.0	N/A	[80]
富马酸 Fumaric acid	*A. pullulans* var. *aubasidani* DH177 e-PYC	葡萄糖Glucose	28	168	93.9	锦带花叶 Leaves of *Weigela florida*	[81]

N/A：无相关信息。

N/A: Not applicable.

2.3 其他次级代谢产物的发现

随着对短梗霉研究的不断深入，其次级代谢产物日益丰富，且具备显著的生物活性。例如，在摩洛哥叶来源的出芽短梗霉菌丝提取物中鉴定出了新的酰胺类物质 pestalotiopamide E 和相应的新酸类 pestalotiopin B，以及吲哚代谢物、异萘酸、氢萘衍生物[84]。从出芽短梗霉发酵产物中分离得到的新型灰黄霉素(griseofulvin)衍生物可抑制多种植物病原真菌[6]。在出芽短梗霉 S2 的挥发性有机化合物(volatile organic compounds, VOCs)中鉴定出的 2-苯乙醇、2-庚醇以及乙酸辛酯等还对灰霉病菌具有抑制作用[85]。从产黑色素短梗霉 LUO5 中分离出了新的 C_{10} 和 C_{12} 脂肪族 δ-内酯以及脂肪酸甲酯[86]。此外，短梗霉还可产生天然抗氧化剂麦角硫因[87]。这些发现不仅丰富了短梗霉代谢产物的种类，还拓宽了其工业应用场景，为开发新型生物制品和生物防治手段提供了思路和资源。

3 短梗霉资源的跨领域应用研究

3.1 短梗霉底盘细胞构建和生物技术应用研究

3.1.1 底盘细胞构建研究

短梗霉因其强大的环境适应性和广泛的碳源利用能力，在生物合成领域受到了广泛关注。随着基因组学技术的不断进步，短梗霉的底盘开发取得了显著进展。国内外多个研究团队已对不同种的短梗霉进行了深入的测序分析，揭示了其基因组特征和基因分布信息，并发现了一系列与关键代谢途径相关的基因，为后续的代谢工程提供了靶点。例如，Wang 等[88]通过对出芽短梗霉的基因组分析，成功鉴定出了重要的转录激活因子 Cmr1 和聚酮合酶(polyketide synthase, PKS)等下游关键基因，并通过敲除和过表达实验，进一步阐明了 Cmr1 在黑色素合成中的关键调控作用。

早期的短梗霉底盘开发主要依赖于同源重组技术。研究者们通过同源重组方法，成功将潮霉素磷酸转移酶(hygromycin phosphotranferase, HPT)基因靶向整合至出芽短梗霉 HN6.2 的 L-鸟氨酸-N^5-羟化酶基因 *SidA* 的开放阅读框中，从而有效破坏了该基因[89]。此外，基于同源重组的一步法还实现了 III 型 PKS 基因的敲除和糖脂转运蛋白基因 *GltP* 的敲入[90]。然而，同源重组技术存在效率低、工作量大等问题，且选择标记难以去除，这限制了进一步的基因操作。为此，研究者们引入了其他模式生物的基因操作技术并进行了改进。例如，借鉴真菌遗传转化中常用的根癌农杆菌(*Agrobacterium tumefaciens*)介导转化法，将外源 DNA 高效整合入出芽短梗霉基因组，并用于构建基因组突变库[91]。为了去除抗性标记，研究者们还构建了一种 Cre/loxP 重组系统，虽然该方法在多次基因敲除后能实现较高的抗性标记丢失率，但会在基因组上留下 loxP 位点[92]。随着 CRISPR/Cas9 系统的引入，短梗霉的基因编辑效率得到了显著提升，且实现了无标记的基因编辑。Zhang 等[93]利用尿苷 5′-单磷酸合成酶(uridine monophosphate synthetase, UMPS)基因作为反向选择标记，开发了出芽短梗霉的 CRISPR/Cas9 基因编辑方法，显著提高了敲除效率。此外，通过将 Cas9-RNA 复合物直接转入短梗霉菌株中，还可进行多重基因组编辑，并最大限度地降低了脱靶效应[94]。短梗霉底盘细胞构建的逐渐成熟，为其在生物合成领域的进一步应用奠定了坚实的基础。

3.1.2 代谢工程调控策略与应用

短梗霉的代谢工程调控策略主要集中在碳代谢和信号通路调控等领域。从碳源高效利用的角度来看，短梗霉凭借其独特的基因编码体系包括多种转运蛋白和代谢酶，能够广泛摄取和利用单糖、多糖以及复杂碳源。通过优化关键酶的表达和活性，可以进一步增强细胞的碳源利用率。例如，通过过表达短梗霉木糖代谢途径中的木糖还原酶和木糖脱氢酶，可以显著提高木糖的利用效率和脂质产物的积累[95]。

在碳通量和限速步骤调控方面，通过调控代谢途径中的关键酶活性以及阻断竞争代谢途径，可以优化代谢流。糖酵解中的关键酶和副产物合成相关基因均会对普鲁兰多糖的合成产生影响[96]。其中，UDP-葡萄糖焦磷酸化酶作为

关键限速酶，受到环磷酸腺苷-蛋白激酶 A (cyclic adenosine monophosphate-protein kinase A, cAMP-PKA)信号通路中转录激活因子 Msn2 的调控[97]。此外，敲除聚苹果酸合酶(polymalate synthase, PMAs)基因和 PKS 基因也对普鲁兰多糖产量的提升发挥积极作用[69]。在聚苹果酸合成方面，通过敲除普鲁兰合成酶、黑色素合成酶和甘氨酸合成酶的编码基因，可以将碳通量导向聚苹果酸合成途径，从而极大提高聚苹果酸的生产率，产量可达 194.3 g/L，且回收后的苹果酸纯度可达 99.7%[73]。同时，还原型 TCA 循环(reductive tricarboxylic acid cycle, rTCA)中辅因子与 CO_2 的参与可调节苹果酸的代谢通量，进而影响聚苹果酸的合成[98]。在以甘油和乙醇为底物进行发酵时，启动子工程可有效平衡甘油代谢和 rTCA 通路中的代谢通量，并维持底物利用和聚苹果酸合成的高效性及稳定性[99]。在工业生产中，黑色素作为副产物会影响下游产品的外观和纯化，因此通过紫外诱变和副产物通路敲除等方法可以减少黑色素的生成，从而提高产品质量和效益[73,100]。

转录调控在短梗霉的代谢过程中也起着关键作用。聚苹果酸的合成受到钙调磷酸酶响应锌指转录因子(calcineurin-responsive zinc finger transcription factor, CRZ1)、雷帕霉素靶蛋白复合物(target of rapamycin complex 1, Torc1)、磷酸泛酰巯基乙胺基转移酶(phosphopantetheinyl transferases, PPTase)和 GATA 型转录因子 Gat1 等多重调节[101-103]。特异性转录激活因子 Cat8 还可通过调节乙醛酸分流途径，提高以乙醇为底物时聚苹果酸的产量[104]。细胞壁完整性(cell wall integrity, CWI)信号通路中的转录激活因子 Cmr1 可特异性结合 PKS1，从而调控黑色素的生物合成[105]。同时，PKS 还受到 PPTase 的激活和调控，且 PPTase 编码基因 *Npg1* 和 *Pks1* 受到氮源和葡萄糖的抑制[106]。GATA 型转录因子 NsdD 负向调控黑色素的合成，但正向调控聚苹果酸和普鲁兰多糖的生物合成[107]。这些研究表明，通过协同调控代谢过程，可以精准调节产物的合成，从而充分发挥底盘的优势和潜力。

3.2 短梗霉代谢产物在药物递送与治疗领域的应用

3.2.1 高分子产物在药物递送体系中的应用

普鲁兰多糖和聚苹果酸等高分子材料作为药物缓释载体，在提升药效和降低毒副作用方面具有重要意义。普鲁兰多糖因其高亲水性和生物可降解性，被广泛应用于制备药物载体，以实现药物的控释、改善药物的稳定性和增强生物利用度[108-110]。例如，在 DNA 递送方面，聚乙烯亚胺与普鲁兰多糖偶联制备的载体可将 DNA 高效递送至靶细胞[111]。质粒 DNA 偶联普鲁兰多糖和精胺的非病毒基因载体，可在肿瘤细胞中有效表达[112]。叶酸-聚乙烯亚胺修饰的普鲁兰多糖还可用于 pDNA/siRNA 的靶向递送，且具备良好的靶向性和低细胞毒性[113]。此外，以普鲁兰多糖制备的改性天然聚合物材料，能够递送水飞蓟素等黄酮类化合物，并提升药物的吸附和释放速率[114]。

聚苹果酸因其生物可降解性、低免疫原性和可修饰性等特性，在癌症诊断和药物靶向运送研究中展现出广泛应用前景[110]。例如，通过β-聚-L-苹果酸纳米平台共价连接吗啉反义寡核苷酸(antisense oligonucleotides, AONs)、靶向抗 TfR 单克隆抗体及赫赛汀(曲妥珠单抗)，实现了对 HER2/neu 阳性乳腺癌的有效治疗[115]。基于β-聚-L-苹果酸的新型纳米成像剂能够穿过血脑屏障，对癌细胞实施高效纳米成像并完成特异性 AONs 的递送[116]。此外，聚苹果酸还可用作骨质疏松症治疗的钙载体，聚苹果酸钙治疗能够减轻骨质疏松模型小鼠的运动疲劳程度，缓

解骨质疏松症状并改善成骨细胞分化[117]。然而，这些高分子产物在体内的长期稳定性、潜在的免疫原性和细胞毒性等方面仍有待进一步的评估与研究。

3.2.2 生物活性产物的应用

短梗霉的代谢产物和改性产物具有抗菌抗炎、抗癌和免疫调节等多种生物活性。基于普鲁兰多糖、聚赖氨酸衍生物、茶多酚等制备的多功能水凝胶可用于感染性伤口的修复[118]。由氧化普鲁兰多糖、季铵化壳聚糖和小球藻等制备的复合水凝胶还可用于伤口的抗菌消炎和慢性愈合监测[119]。Liamocin 具备抗链球菌感染活性，且不同多元醇头基的 liamocins 展现出差异化的抗菌和抗癌活性，因此对 liamocin 进行结构改造和功能化修饰有望推动其在抗菌药物定向开发中的应用[80,120]。此外，liamocin 还可转化为马索亚内酯，其对多种丝状真菌和酵母菌具有抗菌活性，同时还具备抗癌、抗病毒和抗炎潜力[121-122]。

在抗癌与免疫调节方面，短梗霉的代谢产物同样展现出应用潜力。例如，从出芽短梗霉中提取的 1,3-β-D 葡聚糖能够在体外诱导 DBA/2 小鼠脾细胞分泌 Th1 细胞因子及 Th17 细胞因子，作为潜在的免疫刺激剂[123]。出芽短梗霉 TD-062 的发酵提取物在骨髓瘤和乳腺癌细胞中表现出与姜黄素相近的抗癌活性，其中含有角鲨烯、豆甾醇等抗癌成分[124]。

3.3 短梗霉活体细胞在生物防治与生态农业中的应用

3.3.1 短梗霉生物防治应用

当前我国在生物防治领域取得了显著进展。截至 2024 年 4 月，国内登记的 20 种微生物新农药中，解淀粉芽孢杆菌(*Bacillus amyloliquefaciens*)占据了 7 种，而真菌微生物仅有 5 种。生防微生物的应用受到环境因素的制约，如湿度、pH、温度等，这些因素会影响其生长代谢；真菌作为生防微生物体系的重要组成部分，在农业应用中也面临环境适应性挑战[125]。然而，短梗霉作为农业可用的真菌，因其极端环境的适应性和耐受性，展现出了巨大的生防潜力和优势。例如，在落叶分解生态系统中，短梗霉呈现出高丰度，并与多数核心细菌类群呈负相关，显示出其在生态竞争中的独特优势[126]。在欧洲甜樱桃病虫害的研究中，短梗霉与其他子囊菌门真菌在健康组织中丰度较高，被认为是樱桃胶质病的潜在拮抗剂[127]。

短梗霉在梨火疫病的防治中已有成功案例。Blossom Protect™ (出芽短梗霉)通过诱导植物全身获得性耐药途径基因的表达，提高了植物自身的防御和抗病性，有效降低了火疫病的发生率[128-129]。德国研发的 BoniProtect™ (出芽短梗霉)能够有效控制储存过程中病原体对果实的侵害[130]。在田间试验中，Blossom Protect™对梨火疫病的控制率高达 81%，优于对照生防菌株 *Cystofilobasidium infirmominiatum* 58% 的控制率[131]。部分研究表明，克雷伯氏菌(*Klebsiella* sp.) TN50、类芽孢杆菌(*Paenibacillus* sp.) HN89、假单胞杆菌(*Pseudomonas* sp.) SN37 和贝莱斯芽胞杆菌(*Bacillus velezensis*) JE4 对梨火疫病的防效分别为 64%、52%、36% 和 73%，而农用链霉素的防效为 61%[132-133]。由此可见，出芽短梗霉在防控梨火疫病方面具有明显优势。

短梗霉在果蔬采前和采后病害防治中也发挥着重要作用。例如，出芽短梗霉 L1 和 L8 能将褐腐病的发生率分别降低 95% 和 80%[134]。出芽短梗霉 AP2 和 PL5 则可有效降低接种白雾病致病菌的苹果在储存期和保质期内的发病率[135]。此外，出芽短梗霉产生的 VOCs 能抑制链核盘菌 (*Monilinia* spp.)、灰葡萄孢菌 (*Botrytis cinerea*)、青霉菌(*Penicillium* spp.)等病原菌的菌丝体生长和分生孢子萌发，从源头上降低了病

原菌的侵染风险[136-137]。

3.3.2 生物防治作用机制

短梗霉的生防作用机制具有多元性和复杂性的特点，涉及营养和空间竞争、铁载体和抗菌物质合成、植物抗性诱导以及果实机械防御强化等多个方面[137-140]。例如，多种短梗霉菌株的 VOCs 可抑制病原菌，其中 3-甲基-1-丁醇对灰霉病菌的拮抗效果尤为突出[138]。环境适应性、宿主抗性诱导、生物膜形成以及 VOCs 产生是出芽短梗霉 S2 防治番茄灰霉病菌的重要作用机制[85]。增加外源氨基酸浓度会使出芽短梗霉 Ach1-1 对扩展青霉的防治效果显著降低，表明营养竞争在其中发挥了重要作用[141]。短梗霉还能产生几丁质酶、β-1,3-葡聚糖酶及蛋白酶等多种酶类，增强了其对植物病原菌的抑制能力[142-143]。在控制苹果灰霉病菌和扩展青霉的研究中，出芽短梗霉提高了果实中 β-1,3-葡聚糖酶、几丁质酶和过氧化物酶的活性，有利于对病原体的拮抗[144]。

在促进植物健康和根际微生态调控方面，短梗霉与土壤中植物根系的共生有利于植物的健康生长和增产。例如，出芽短梗霉产生的吲哚-3-乙酸(indole-3-acetic acid, IAA)可改变拟南芥生长素诱导基因的表达，促进拟南芥侧根的形成，并增强根系对水分和养分的吸收[145]。出芽短梗霉 AP1 不仅能抑制莴苣病原菌 *Rhizoctonia solani*，还能促进莴苣叶和根的生长[146]。这些研究为短梗霉在农业中根际共生应用提供了理论依据和实践指导，并且利用微胶囊等制剂对短梗霉进行有效包裹，可增强其在复杂应用环境中的稳定性和存活率。

3.4 短梗霉及其代谢产物在食品工业中的应用

3.4.1 多糖类产物的应用

短梗霉合成的普鲁兰多糖和 β-1,3-1,6-葡聚糖在食品工业中得到了广泛应用。普鲁兰多糖含有大量羟基，具备良好的亲水性和保湿性，兼具无毒、无味、可降解等特点，已被注册为食品添加剂，凭借其良好的成膜性和稳定性，普鲁兰多糖还被用于食品包装，以延长食品的保鲜期[147]。例如，基于普鲁兰多糖、明胶和山梨酸钾制备的可食用薄膜对多种微生物具有抑菌活性，可防止食物腐败和霉变[148]。花青素封装于乳酸链球菌素/明胶/普鲁兰多糖生物气凝胶中，有利于抗氧化活性的稳定，并且能够响应 pH 变化，指示食品的新鲜度[149]。由普鲁兰多糖、结冷胶、楮实子等制备的 pH 响应活性薄膜具有抗氧化和抗菌能力，可应用于鱼类保鲜和新鲜度检测[150]。此外，将普鲁兰多糖添加到玉米淀粉中，能够保护其颗粒完整性，减少油炸后的吸油量，并提升食品的感官品质[151]。

β-1,3-1,6-葡聚糖作为天然免疫调节剂，可预防非酒精性脂肪肝和抗食物过敏，在功能性食品开发领域具有良好的应用潜力[152-155]。由出芽短梗霉产生的 β-1,3-1,6-葡聚糖相比其他来源的 β-葡聚糖，支化程度更高，功能作用相近[155-156]。市场上多品牌乳粉和饮品中均添加了酵母 β-葡聚糖。日本大创公司开发了来源于出芽短梗霉的 β-1,3-1,6-葡聚糖作为功能食品配料[157]。可以预见，短梗霉多糖类产物在食品创新与品质提升方面将带来新机遇。

3.4.2 食品加工中的应用潜力

短梗霉所产生的代谢酶类具有独特的功能特性。例如，出芽短梗霉产生的木聚糖酶具有耐盐、耐乙醇和嗜酸特性，可以应用于酿造和海产品加工[158]。产黑色素短梗霉来源的单宁酶具备热稳定性和高比活等特性，可高效催化各种没食子酸酯的降解[159]。出芽短梗霉 FRR 5284 能够用作全细胞生物催化剂，在胞内高效生产低聚果糖酶，将糖蜜转化为高附加值的低聚果

糖[160]。*A. leucospermi* 来源的丝氨酸肽酶在低温储存 210 d 后仍能保持较高的活性，可应用于奶酪加工[161]。此外，短梗霉还具备在短时间内大量积累生物量的能力，能够利用廉价底物生长合成蛋白质，在单细胞蛋白合成方面具有潜力。例如，出芽短梗霉发酵豆粕能提高其蛋白水平，可用于生产鱼类高蛋白饲料[162]。

4 总结与展望

在双碳目标的驱动下，绿色生物制造致力于以可持续的生物生产方式替代传统高能耗、高碳排放的工业制造模式，从源头上实现“碳减排”。短梗霉作为一类独特的酵母样真菌，是绿色生物制造的优势微生物资源。短梗霉能够利用非发酵性碳源(如甘油、乙醇等)合成生物可降解高分子聚合物，如聚苹果酸，是一种有效的碳经济生物合成方式。同时，在利用木质纤维素水解物、工业生产废料等可再生生物质资源合成一系列高值化合物方面，短梗霉也展现出了独特优势。例如，其具有天然的木糖代谢途径和多重代谢调节网络，对绿色生物制造具有重要意义。

为实现大规模绿色生产应用，菌株底盘的开发和设计仍需完善。例如，需要挖掘新的功能基因和调控元件，以实现底盘细胞的精准设计。同时，由于菌株代谢涉及多重调控机制，亟需开发更高效的全局调控策略。目前，研究主要集中于出芽短梗霉和产黑色素短梗霉，但仍有大量新种的生理生化特性和基因组相关工作尚待填补。由于工业生产中的菌种需适应温度波动、高渗透压、pH 变化、溶氧变化等环境因素，提高菌种的发酵鲁棒性至关重要。此外，尽管短梗霉能够利用廉价的工业加工废料，但底物转化效率低和细胞耐受性差等问题仍需解决。Li 等[7]通过实验室适应性进化策略，成功增强了出芽短梗霉对高盐和低 pH 值的细胞耐受性，并实现了无钙废物污染的苹果酸回收，为绿色可持续的生物炼制提供了一条可行路线。未来，随着人工智能和多组学技术的发展，构建智能代谢网络模型将为菌种设计提供更为科学的指导。

在发酵过程控制和产物分离纯化方面仍面临技术瓶颈。短梗霉生产过程中副产物的合成会降低目标产物的代谢流和产率。在下游分离纯化过程中，发酵液的高黏度以及蛋白质和无机盐等杂质的干扰，也是工业化进程的制约因素。通过代谢工程改造策略减少副产物可以从上游降低产物分离纯化的难度。Li 等[73]已通过代谢工程改造得到了一株高纯度聚苹果酸生产的出芽短梗霉菌株，通过水相结晶法提取的 L-苹果酸纯度高达 99.7%。未来，结合先进的过程控制技术，通过大数据挖掘和模型化控制，有望实现高效智能的规模化绿色生产。

从菌株和产品的安全性与有效性角度出发，短梗霉菌株和部分代谢产物在药理机制、临床验证以及生物防控机制等方面还需深入研究。在不同场景下应用的菌株需符合严格的法规和标准，并且需系统评估其代谢产物的毒理学特性，尤其是对人体健康和生态环境的长期影响。总之，短梗霉在未来生物制造领域和绿色低碳循环经济体系中具有广阔的应用前景。

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