特约评述

DOI: 10.12211/2096-8280.2024-076

生物合成红景天苷的研究进展

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摘要：红景天苷是一种具有抗缺氧、抗氧化、抗衰老和抗肿瘤等活性的天然产物，被广泛应用于化妆品与医药领域。目前获取红景天苷的主要方式是从红景天属植物的根茎和块茎中提取，由于其含量稀少，日益增长的市场需求导致植物资源逐渐匮乏。因此，开发新的合成方法成为了研究热点。红景天苷的天然生物合成路径已被解析，随着合成生物学的发展，采用合成生物技术构建微生物细胞工厂合成红景天苷成为缓解当前供需失衡和资源紧缺状况的有效途径。本文针对红景天苷的药理活性、植物合成路径、途径酶的挖掘与筛选、大肠杆菌和酿酒酵母的生物合成现状等相关研究进展进行系统性的综述，探讨了红景天苷的分离提纯方法以及它作为合成中间体在制备其他化合物方面的应用潜力，以期助力对红景天苷合成路径与相关工程改造策略的理解，并推动红景天苷绿色、高效的生物合成。

关键词：红景天苷；微生物合成；合成生物学；代谢工程；化妆品

中图分类号：Q819　　**文献标志码：**A

Research progress in the biosynthesis of salidroside

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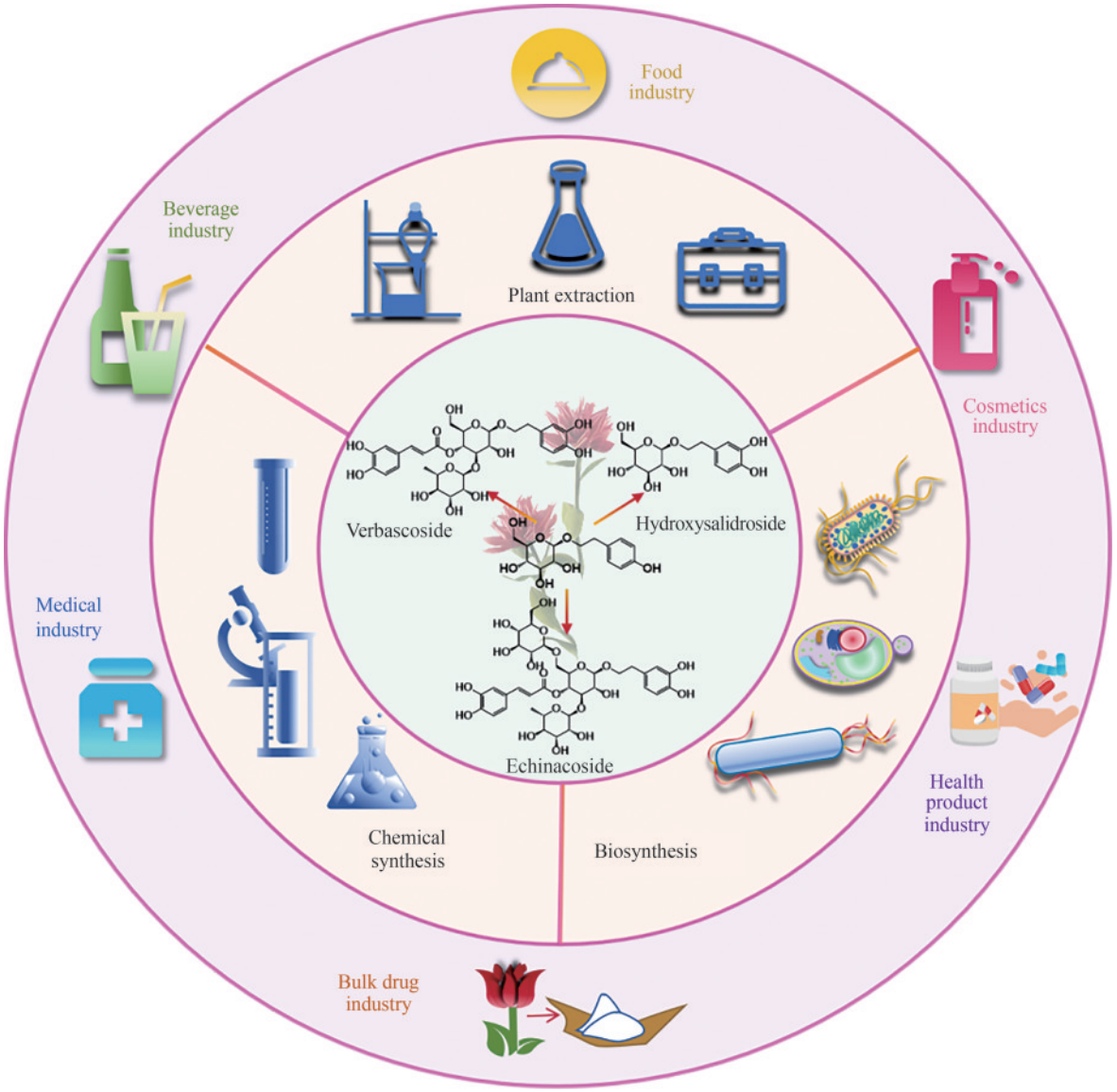
Abstract: Salidroside, a natural product known for its anti-hypoxia, anti-oxidation, anti-inflammatory, anti-aging, and anti-tumor properties, is extensively utilized in the food, cosmetics and pharmaceutical industries. Traditionally, salidroside has been obtained through the extraction from the rhizomes and tubers of *Rhodiola* species, including water extraction, two-phase aqueous extraction, supercritical CO_2 extraction and microwave assisted extraction. However, its low natural abundance (with the salidroside content in rhizomes and tubers of *Rhodiola* species ranging from 0.5% to 0.8%), coupled with escalating demand, has led to a progressive depletion of these plant resources. Given the broad

收稿日期：2024-10-18 修回日期：2025-03-09
基金项目：国家自然科学基金（32471492）；物质绿色创造与制造海河实验室（24HHWCSS00006）；广东省重点研发计划（2020B0303070002）
引用本文：黄姝涵，马赫，罗云孜. 生物合成红景天苷的研究进展[J]. 合成生物学，2025，6(2)：391-407
Citation：HUANG Shuhan，MA He，LUO Yunzi. Research progress in the biosynthesis of salidroside[J]. Synthetic Biology Journal，2025，6(2)：391-407

application potential of salidroside, the rapid growth of market demand, and the increasing scarcity of natural resources, there is an urgent need to develop innovative synthetic approaches for this valuable compound. Chemical synthesis of salidroside is characterized by its efficiency and rapid processing time. However, the use of strong acids, bases, and catalysts with heavy metal ions in the synthesis process poses challenges for the separation of salidroside with environmental risks. In recent years, with the advancements in synthetic biology, the construction of microbial cell factories for the biosynthesis of salidroside has become a viable strategy for addressing the current supply-demand imbalance and resource scarcity associated with the natural biosynthetic pathway of salidroside. To enhance the production of salidroside biosynthesis, two major strategies can be employed. First, metabolic engineering approaches can be used to overexpress key genes in the synthesis pathways while knocking out or downregulating the expression of genes related to the bypass routes, thereby increasing precursor accumulation and enhancing the metabolic flux. Second, enzyme engineering can be applied to improve the catalytic efficiency and regioselectivity of natural glycosyltransferases, which often exhibit low activity and poor selectivity. Sequence alignment techniques can be used to identify and screen potential glycosyltransferases from various biological genomes. Additionally, protein engineering combined with computational approaches can be utilized to optimize these enzymes to meet specific requirements,



ultimately improving the production of salidroside. In this comprehensive review, we systematically assess the pharmacological activities of salidroside, the plant biosynthetic pathway, the mining and screening of the enzymes, and the biosynthetic advancements in *Escherichia coli* and *Saccharomyces cerevisiae*. Additionally, we discuss the separation and purification methods of salidroside and its application potential as a synthetic intermediate in the preparation of other compounds, such as hydroxysalidroside, verbascoside and echinacoside. This review aims to enhance the understanding of the biosynthetic pathway of salidroside, thereby promoting a greener and more efficient biosynthetic approach to salidroside production.

Keywords: salidroside; microbial synthesis; synthetic biology; metabolic engineering; cosmetics

红景天苷（酪醇8-*O*-β-D-葡萄糖苷）是一种来源于红景天属植物的糖苷类化合物，主要分布在红景天属植物的根茎和块茎中[1-3]。研究表明，红景天苷不仅具有强大的抗氧化、抗疲劳和抗衰老活性[4-7]，而且其展现出的抗癌[8]、抗炎[9]以及神经系统保护活性[10]，使其在化妆品、保健品以及医学领域应用广泛。日益增长的药物需求，促使科研工作者不断探索红景天苷新的合成方法，包括化学合成和生物合成等[11]。在化学合成方面，主要采用Koenigs-Knorr法合成红景天苷[12]，即在碱性条件下，溴代四乙酰基葡萄糖与酪醇直接缩合，而后通过脱乙酰基处理，得到红景天苷。截至目前，史明明[13]获得的红景天苷产量较高，达到61.8%。然而，化学合成过程涉及强酸、强碱和重金属离子等物质，往往会对环境造成一定污染，并且所产生的副产物也易给后续分离过程造成困难[14]。因此，随着合成生物学的发展，开发绿色、高效的生物合成方法成为合成红景天苷的研究热点。

本文对红景天苷的理化性质和药理活性、生物合成路径以及微生物合成现状进行了系统性综述，并基于相关研究进展探讨当前红景天苷合成研究面临的技术挑战及未来前景，以期助力对红景天苷合成路径与相关工程改造策略的理解，并推动红景天苷的绿色、高效生物合成。

1 红景天苷的理化性质和药理活性

红景天苷是从红景天属植物中提取出来的糖苷类化合物[15]，外观呈白色。其理化性质稳定，具有良好的水溶性与生物相容性。研究表明红景天苷展现出多方面的药理活性[16]，包括抗疲劳[17]、抗缺氧、抗衰老[18-19]、抗氧化[20]、抗癌[21]、抗炎[22-24]、心脑血管和神经系统保护活性[10]等，这些特性使其在生物医学领域和化妆品领域具有广泛应用。

1.1 抗衰老和抗缺氧活性

在抗衰老方面，Mao等[25]基于建立的小鼠衰老模型，验证红景天苷可以抑制随衰老过程而积累的晚期糖基化终末产物（advanced glycation end-product，AGE）[26-28]的形成，从而逆转D-半乳糖诱导的神经系统和免疫系统的衰老效应，发挥抗衰老作用；同时，Mao等[29]发现红景天苷可以通过调节氧化状态从而防止H_2O_2诱导的人成纤维细胞过早衰老。另外，红景天苷也可以缓解人支气管上皮细胞的衰老[19]。

在抗缺氧方面，红景天苷可以作为红细胞生成辅助剂用于治疗贫血和缺氧不良等症状[30]。此外，红景天苷还可以拮抗$CoCl_2$的细胞毒性，避免H9c2细胞因缺氧而死亡[7]。同时，红景天苷可以通过提高氧的利用率来实现抗缺氧活性，Zhong等[31]研究发现红景天苷通过调节多种信号通路来拮抗缺氧细胞的毒作用，包括抑制哺乳动物雷帕霉素靶蛋白（mammalian target of rapamycin，mTOR）信号通路等。

由于红景天苷具有延缓机体衰老的活性，因此在护肤品中应用广泛，如国内知名的品牌相宜本草等。含有红景天苷的保湿抗衰乳在调节皮肤新陈代谢、抗老防衰方面具有显著效果[32]。

1.2 抗氧化活性

在抗氧化方面，Lu等[33]发现红景天苷可以减少高葡萄糖诱导的活性氧生成，从而抑制细胞凋亡；Lin等[34]发现红景天苷可以通过抵抗氧化应激和保护线粒体使肝脏免受CCl_4诱导的损伤；Xing等[35]发现红景天苷可以通过促进线粒体的形成来保护内皮细胞免受H_2O_2诱导损伤，从而防止氧化应激相关下游信号通路的过度激活；黎明华等[36]研究发现，红景天苷还可以通过增加超氧化物歧化酶和谷胱甘肽过氧化物酶的活性来抑制活性氧介导的心血管疾病。基于红景天苷的抗氧化机制，可将其应用到护肤品中，通过抑制自由基生成，提高皮肤抗氧化能力，并实现抑菌和紧致保湿等护肤效果[37]。

1.3 其他活性

在癌症治疗方面，红景天苷可通过诱导癌细胞的凋亡与自噬对结直肠癌细胞[38]、乳腺癌细胞[39]、膀胱癌细胞[40]以及胃癌细胞[41]的生长产生抑制作用，从而治疗癌症。此外，红景天苷还可以通过减轻大鼠糖尿病诱导的心脏氧化应激，抑制炎症反应，从而缓解心肌细胞的凋亡，改善心脏功能，并通过促进钙激活钾离子通道依赖性细胞凋亡和延缓脑血管衰老样重塑等方式来实现对心脑血管的保护活性[42-43]。在神经系统保护活性中，红景天苷可显著抑制脂多糖与中枢神经系统炎症所诱导的认知功能障碍，恢复神经元损伤，在治疗神经退行性疾病如阿尔兹海默病、帕金森病等方面具有潜在的作用[44-45]。

2 红景天苷的植物合成

2.1 红景天苷植物提取

目前，获取红景天苷的主要方式是植物提取，包括热回流萃取法、索氏萃取法、超声辅助提取法、微波辅助提取法、红外辅助提取法等[46-52]。此外，通过培养植物细胞或植物愈伤组织合成红景天苷是当前探索的一种新型方式。利用细胞系筛选、培养条件优化、引入额外碳源[53]、前体喂养[54]、添加诱导剂[55]、建立紧凑的愈伤组织聚集体[56]等策略可提高植物细胞中红景天苷的含量[57]。然而，依赖植物提取红景天苷的工业生产方法面临着诸多挑战：一方面，红景天苷在红景天属植物中的含量较低，仅为0.5%～0.8%，难以满足日益增长的需求[58]；另一方面，植物生长周期较长导致时间成本较高[16]，限制了红景天苷的工业化生产和应用。因此，探究新的合成方法是解决上述问题的关键，其中解析红景天苷的生物合成途径并挖掘关键酶，为开发创新合成方法提供了重要的理论依据和技术支持。

2.2 天然合成途径

红景天苷在自然界中主要由红景天属植物合成，其代谢路径目前已被解析（图1）。首先磷酸烯醇式丙酮酸（phosphoenolpyruvate，PEP）和赤藓糖-4-磷酸（erythrose-4-phosphate，E4P）在3-脱氧-D-阿拉伯-庚酮酸-7-磷酸酯合成酶（3-deoxy-D-arabino-heptulosonate-7-phosphate synthase，DAHPS）催化下合成3-脱氧-D-阿拉伯-庚酮酸-7-磷酸酯（3-deoxy-D-arabino-heptulosonate-7-phosphate，DAHP），然后经过3-脱氢奎宁合成酶（3-dehydroquinate synthase，DHQS）催化合成3-脱氢奎宁（3-dehydroquinate，DHQ），再由3-脱氢奎尼酸脱水酶（3-dehydroquinate dehydratase，DHD）催化得到3-脱氢莽草酸盐（3-dehydroshikimate，DHS）。接下来3-脱氢莽草酸盐经过莽草酸脱氢酶（shikimate dehydrogenase，SDH）、莽草酸激酶（shikimate kinase，SK）、5-烯醇式丙酮酸莽草酸-3-磷酸合成酶（5-enolpyruvylshikimate-3-phosphate synthase，EPSPS）、分支酸合成酶（chorismate synthase，CS），分支酸变位酶（chorismate mutase，CM）、苯丙氨酸转氨酶（prephenate aminotransferase，PPA-AT），前酪氨酸脱氢酶（arogenate dehydrogenase，ArDH）一系列酶的催化作用合成酪氨酸。酪氨酸可在酪氨酸脱羧酶（tyrosine decarboxylase，TDC）和酪胺氧化酶（tyramine oxidase，TYO）的催化下合成4-羟基苯乙醛。此两步反应也可由芳香醛合成酶（aromatic aldehyde synthase，AAS）催化一步完成。4-羟基苯乙醛随后在醇脱氢酶（alcohol

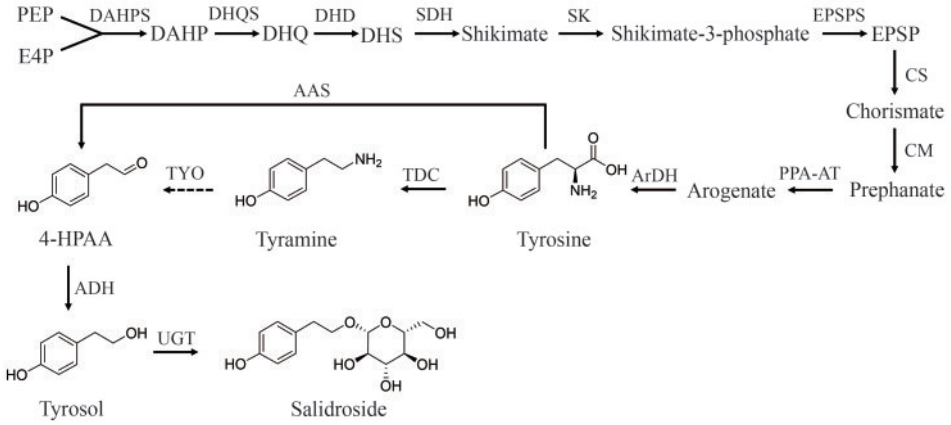


图1 植物中红景天苷的生物合成途径

（PEP—磷酸烯醇式丙酮酸；E4P—赤藓糖-4-磷酸；DAHP—3-脱氧-D-阿拉伯-庚酮酸-7-磷酸酯；DHQ—3-脱氢奎宁；DHS—3-脱氢莽草酸盐；EPSP—5-烯醇式丙酮酸莽草酸-3-磷酸；4-HPAA—4-羟基苯乙醛；DAHPS—3-脱氧-D-阿拉伯-庚酮酸-7-磷酸酯合成酶；DHQS—3-脱氢奎宁合成酶；DHD—3-脱氢奎尼酸脱水酶；SDH—莽草酸脱氢酶；SK—莽草酸激酶；EPSPS—5-烯醇式丙酮酸莽草酸-3-磷酸合成酶；CS—分支酸合成酶；CM—分支酸变位酶；PPA-AT—苯丙氨酸转氨酶；ArDH—前酪氨酸脱氢酶；TDC—酪氨酸脱羧酶；TYO—酪胺氧化酶；AAS—芳香醛合成酶；ADH—醇脱氢酶；UGT—尿苷二磷酸糖基转移酶）

Fig. 1 Biosynthetic pathways of salidroside in plants

(PEP—phosphoenolpyruvate; E4P—erythrose-4-phosphate; DAHP—3-deoxy-D-arabino-heptulosonate-7-phosphate; DHQ—3-dehydroquinate; DHS—3-dehydroshikimate; EPSP—5-enolpyruvylshikimate-3-phosphate; 4-HPAA—4-hydroxyphenylacetaldehyde; DAHPS—3-deoxy-D-arabino-heptulosonate-7-phosphate synthase; DHQS—3-dehydroquinate synthase; DHD—3-dehydroquinate dehydratase; SDH—shikimate dehydrogenase; SK—shikimate kinase; EPSPS—5-enolpyruvylshikimate-3-phosphate synthase; CS—chorismate synthase; CM—chorismate mutase; PPA-AT—prephenate aminotransferase; ArDH—arogenate dehydrogenase; TDC—tyrosine decarboxylase; TYO—tyramine oxidase; AAS—aromatic aldehyde synthase; ADH—alcohol dehydrogenase; UGT—uridine diphosphate glycosyltransferase)

dehydrogenase，ADH）催化下合成酪醇，最后在尿苷二磷酸糖基转移酶（uridine diphosphate glycosyltransferase，UGT）催化下合成红景天苷。

2.3 途径酶挖掘

在红景天苷的生物合成途径中，糖基转移酶作为催化最后一步反应的关键酶[59]，其活性直接影响红景天苷的生成效率。因此，通过优化筛选策略获得高活性糖基转移酶，是提升红景天苷产量的重要途径（表1）。

Torrens-Spence等[60]首先从蔷薇红景天挖掘得到4-羟基苯乙醛合酶*Rr*4HPAAS，而后将34个糖基转移酶候选基因分别转化至异源表达*Rr*4HPAAS

表1 红景天苷合成相关酶的名称及来源

Table 1 Names and sources of enzymes related to salidroside synthesis

酶的名称	酶的来源植物	酶的功能	红景天苷产量（mg/L）、干重（mg/g DW）或酶活 K_{cat}/K_m [L/（mmol·s）]	参考文献
*Rr*4HPAAS	蔷薇红景天	4-羟基苯乙醛合酶	11.71 L/（mmol·s）	[60]
*Rr*UGT29	蔷薇红景天	糖基转移酶	316.04 L/（mmol·s）	[60]
*Rr*UGT32	蔷薇红景天	糖基转移酶	NA	[60]
*Rr*UGT33	蔷薇红景天	糖基转移酶	420.60 L/（mmol·s）	[60]
*At*UGT73C5	拟南芥	糖基转移酶	NA	[61]
*At*UGT73C6	拟南芥	糖基转移酶	NA	[61]
*At*UGT85A1	拟南芥	糖基转移酶	288.00 mg/L	[61]
*Rs*UGT73B6	库页红景天	糖基转移酶	8.76 mg/g DW	[62]
*Rs*UGT72B14	库页红景天	糖基转移酶	19.81 mg/g DW	[62]
*Rs*UGT74R1	库页红景天	糖基转移酶	5.72 mg/g DW	[62]

注：NA—不适用。

Note: NA—Not applicable.

的酿酒酵母中，经筛选确定了3个来源于蔷薇红景天的具有醇羟基特异催化活性的糖基转移酶（*Rr*UGT29、*Rr*UGT32和*Rr*UGT33）。Chung等[61]通过外源添加酪醇筛选得到拟南芥（*Arabidopsis thaliana*）来源的*At*UGT73C5、*At*UGT73C6和*At*UGT85A1可以催化酪醇生成红景天苷。Grech-Baran等[62]从库页红景天（*Rhodiola sachalinensis*）中筛选出*Rs*UGT72B14和*Rs*UGT74R1两个糖基转移酶，并与此前筛选的*Rs*UGT73B6进行酶活比较，结果表明*Rs*UGT72B14对红景天苷的生产活性高于其他两个酶。通过对红景天苷植物合成路径中关键酶的挖掘与鉴定，为后续在微生物细胞中实现红景天苷合成路径的重构与从头合成奠定了重要基础。

3 红景天苷的微生物合成现状

随着红景天苷天然合成路径中关键酶功能的解析，利用合成生物技术构建微生物细胞工厂高效生产红景天苷成为可能。这一方法凭借较短的生产周期、灵活的过程调控以及潜在的大规模生产能力，为解决红景天苷供应问题提供了全新的方案。截至目前，红景天苷已在多种微生物中实现了从头合成，包括大肠杆菌、酿酒酵母以及红景天属植物内生菌。

3.1 大肠杆菌合成红景天苷

大肠杆菌[63-64]作为一种分子生物学领域的经典模式生物，具有清晰的遗传背景和高效的基因编辑系统。此外，其基因组序列已被解析，这为理解其代谢机制、预测基因功能以及设计遗传改造策略提供了基础。基于大肠杆菌的优点[65-71]（表2），将其作为底盘菌合成红景天苷成为了当前的研究热点。

通过在大肠杆菌中重构红景天苷的天然合成路径，目前已成功实现红景天苷的从头合成（图2），具体为：以葡萄糖为起始碳源，首先在磷酸转运系统（phosphotransferase system，pts）作用下转化为6-磷酸葡萄糖。随后，6-磷酸葡萄糖分流至两条关键路径。其一为UDP-葡萄糖的合成过程，6-磷酸葡萄糖经磷酸葡萄糖变位酶（phosphoglucose mutase，pgm）生成1-磷酸葡萄糖，而后经UDP-葡萄糖焦磷酸化酶（UDP-glucose pyrophosphorylase，galU）催化生成UDP-葡萄糖。其二，则是酪醇合成过程。首先，6-磷酸葡萄糖经糖酵解途径和磷酸戊糖途径生成前体E4P和PEP，二者在3-脱氧-D-阿拉伯-庚酮糖-7-磷酸合成酶（3-deoxy-D-arabino-heptulosonate-7-phosphate synthase，aroG）的催化下，缩合生成DAHP。随后，在3-脱氢奎尼酸合成酶（3-dehydroquinate synthase，aroB）、3-脱氢奎尼酸脱水酶（3-dehydroquinate dehydratase，aroD）、莽草酸脱氢酶（shikimate dehydrogenase，aroE）催化下生成莽草酸，莽草酸经莽草酸激酶Ⅰ/Ⅱ（shikimate kinase Ⅰ/Ⅱ，aroK/L）、EPSP合成酶（5-enolpyruvylshikimate-3-phosphate synthase，aroA）、分支酸合成酶（chorismate synthase，aroC）以及双功能分支酸变位酶/预苯酸脱水酶（the NAD^+-dependent chorismate mutase/prephenate dehydrogenase，tyrA）催化生成4-羟基苯丙酮酸，而后经来源于

表2 不同红景天苷合成底盘菌株的优缺点对比

Table 2 Comparison of different microbial chassis for being engineered with salidroside synthesis

名称	优点	缺点
大肠杆菌	应用广泛、适宜天然产物生产[65]	致病性大肠杆菌可能含有毒素[70]
	成熟的高密度细胞培养技术[66]	缺乏对部分植物来源酶的转录和翻译功能[71]
	生长速率快，具有多种系统代谢工程工具和策略[67]	
	可以结合和转导转移DNA，遗传物质可以水平转移[68]	
	开发了各种蛋白质表达系统，可以通过质粒大规模生产重组蛋白[69]	
酿酒酵母	易于基因操作，营养需求简单，无细胞内毒素，安全性高[72]	特征明确的启动子数量不足，动态范围差[76]
	高分泌能力，在多种碳源上的高生长速率[73]	异源蛋白表达量较少[77]
	具有翻译后修饰能力，对噬菌体等传染性病原体不敏感[74]	
	遗传易处理性和整体易用性[75]	

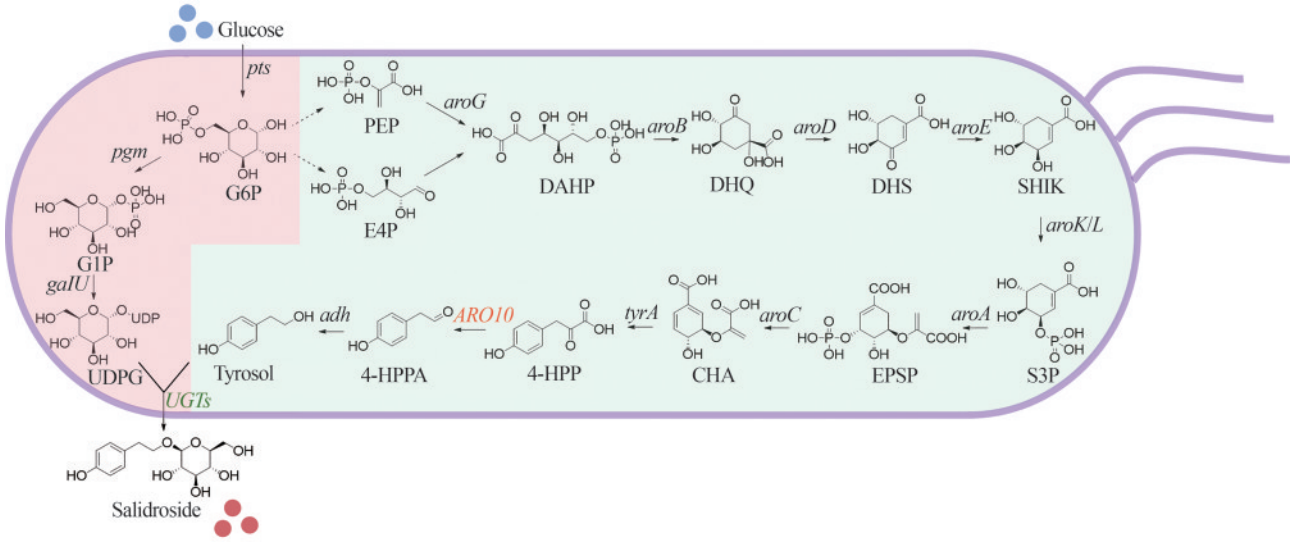


图 2　大肠杆菌中红景天苷的生物合成途径

（化合物和基因分别用正体字母和斜体字母表示，基因中黑色表示大肠杆菌内源基因，橙色表示酿酒酵母来源的基因，绿色表示植物来源的基因）

Fig. 2　Biosynthetic pathways of salidroside in *Escherichia coli*

(Compounds and genes are represented by straight and italic letters, respectively. The black letters represent endogenous genes of *Escherichia coli*, the orange letters represent genes from *Saccharomyces cerevisiae*, and the green letters represent genes from plants.)

酿酒酵母的苯丙酮酸脱羧酶（phenylpyruvate decarboxylase，ARO10）以及内源乙醇脱氢酶（alcohol dehydrogenase，adh）催化下生成酪醇。最后，酪醇与先前合成的尿苷二磷酸葡萄糖在尿苷二磷酸葡萄糖醛酸转移酶（uridine diphosphate glycosyltransferase，UGT）的催化下，发生缩合反应，生成目标产物红景天苷。

在利用大肠杆菌合成红景天苷的过程中，一方面，前体酪醇的积累量是影响红景天苷产量的关键因素。因此，为提高酪醇的积累量，研究人员通常利用代谢工程策略对菌株进行改造，调控碳代谢流，实现酪醇产量的提升。例如，Xue 等[78]在大肠杆菌中异源表达酿酒酵母来源的基因 *ARO10* 与 *ARO8*，敲除基因 *pheA* 和 *feaB*，以 10 mmol/L 酪氨酸为底物，通过摇瓶培养，可获得 8.71 mmol/L 的酪醇。此外，苯丙酮酸脱羧酶 ARO10 是酪醇合成过程中的关键酶，因此 Yang 等[79]对酿酒酵母来源的 *ARO10* 基因进行密码子优化并在大肠杆菌中异源表达，在进一步敲除酪醇合成过程中的竞争途径基因 *pheA*、*feaB*、*tyrB*、*tyrR* 后，将酪醇产量提高到 1316.30 mg/L。酪氨酸作为酪醇合成过程中的前体，提高其积累量是构建酪醇高产菌株的基础，因此 Shen 等[80]构建了一种具有更高酪氨酸生产力的工程菌株，利用 *T7* 启动子控制表达选定的酪氨酸脱羧酶、酪胺氧化酶和中链脱氢酶/还原酶，在 5 mL 试管培养后，酪醇的最终产量达到 2.42 g/L。沈玉平等[81]在整合苯丙酮酸脱羧酶突变体 $ARO10^{F138L/D218G}$ 的基础上，优选醇脱氢酶，应用基因敲除技术，敲除了 4-羟基苯乙酸竞争途径关键基因 *feaB*，阻断了酪醇合成的竞争途径，同时采用群体感应系统动态调控酪醇合成，由此构建的工程菌使酪醇产量达到 4.22 g/L。另一方面，糖基转移酶作为红景天苷合成过程中的限速酶，其催化活性和底物特异性至关重要。为了筛选高效且特异的糖基转移酶，提升酪醇的糖基化效率，研究人员对其进行了不断的挖掘与优化（表 3）。

Xue 等[82]在大肠杆菌中异源表达经密码子优化后的糖基转移酶基因 *UGT72B14*，经分批补料发酵可获得 6.70 mg/L 的红景天苷。Bai 等[83]通过在大肠杆菌中过表达酵母来源的 *ARO10* 及一系列内源基因 *tyrA*（$tyrA^{*syn}$）、*aroG*（$aroG^{*syn}$）、*ppsA*、*tktA*、*aroE*、*aroD* 和 $aroB^{op}$，并敲除旁路基因 *tyrR*、*pykA*、*pykF* 和 *pheA*，构建高产酪醇重组菌株，在此基础上引入红景天来源的糖基转移酶基因 *UGT73B6*，经摇瓶发酵可获得 56.90 mg/L 的红景天苷。Chung 等[61]通过异源表达拟南芥来源的

表3 微生物细胞合成红景天苷的产量和相关途径改造策略

Table 3 Production of salidroside through microbial biosynthesis and strategies for optimizing associated pathways

微生物类别	产量	发酵方式	改造策略	参考文献
大肠杆菌	6.70 mg/L	摇瓶培养	高效表达 *UGT72B14*	[82]
	56.90 mg/L	摇瓶培养	异源表达红景天来源的 *UGT73B6*、酵母的 *ARO10*，构建共养大肠杆菌，过表达 *tyrA*（$tyrA^{*syn}$）、*aroG*（$aroG^{*syn}$）等酪醇内源合成途径基因，敲除 *tyrR*、*pykA* 等旁路基因	[83]
	288.00 mg/L	摇瓶培养	异源表达 *AtUGT85A1* 和 *PcAAS*	[61]
	1.04 g/L	摇瓶培养	异源表达地衣芽孢杆菌ZSP01来源的 $UGT_{BL}1$	[84]
	8.17 g/L	5 L发酵罐	构建了UDP-葡萄糖循环再生系统，整合糖基转移酶基因 *UGT33*	[85]
	9.48 g/L	5 L发酵罐	增加大肠杆菌中 *UGT85A1* 的拷贝数	[86]
	7.50 g/L	摇瓶发酵	过表达UDP-葡萄糖合成路径中的基因 *pgm* 和 *galU*，并利用酶工程策略对糖基转移酶UGT85A1进行改造，整合突变体基因 $UGT85A1^{A21G}$	[87]
	16.80 g/L	5 L发酵罐		
酿酒酵母	640.00 mg/L	摇瓶培养	整合 $ARO4^{K229L}$ 和 $ARO7^{T266I}$ 到酵母菌上，过表达 *TYR1* 和 *ARO10*，异源表达 *OsUGT13*	[88]
	732.50 mg/L	5 L发酵罐	过表达 $ARO4^{K229L}$、$ARO7^{G141S}$、*aroL*，而后引入 $PcAAS^{syn}$ 和 $AtUGT85A1^{syn}$	[14]
	1575.45 mg/L	摇瓶培养	过表达 *RKI1*、*TKL1*、$ARO3^{K222L}$、$ARO4^{K229L}$、$ARO7^{G141S}$ 突变体、分支酸合成酶 *ARO2* 与苯丙氨酸脱羧酶 *ARO10* 并敲除酪醇竞争路径中的 *PDC1*、*PHA2*，整合 *RrU8GT33*	[89]
	26.55 g /L	5 L发酵罐		
	1.82 g/L	3 L发酵罐	敲除 *PDC1*、*PHA2* 和 *TRP3*，异源表达 *PcAAS*、$EcTyrA^{M53I/A354V}$，异源表达 *Xfpk*、*UGT85A1*	[90]
	2.40 g/L	摇瓶培养	将突变体 $ARO3^{D154N}$ 整合到酿酒酵母工程菌中	[91]
植物内生菌	2.34 mg/L	摇瓶培养	筛选了347种内生菌，最终获得目标菌株 *Phialocephala fortinii* Rac56，并在此基础上优化了其发酵条件	[92]
混菌培养	3.80 g/L	摇瓶培养	酿酒酵母中共表达 *GmSUS* 和 *RrUGT33*，大肠杆菌中异源表达 *AAS*，建立共培养体系并优化发酵条件	[93]
	6.03 g/L	5 L发酵罐	在两株大肠杆菌中分别表达 *KDC4* 和 *UGT85A1* 构建酪醇生产菌株与红景天苷生产菌株，并对两种菌株的碳源利用进行优化	[94]

UGT85A1，利用大肠杆菌全细胞反应来生产红景天苷，产量达288.00 mg/L。Fan等[84]将地衣芽孢杆菌来源的 $UGT_{BL}1$ 转入大肠杆菌中，通过摇瓶培养得到了1.04 g/L的红景天苷。魏晨昱等[85]为提高UDP-葡萄糖的含量，在大肠杆菌中构建了UDP-葡萄糖循环再生系统，整合活性较高的糖基转移酶基因 *UGT33* 后得到的重组菌株可高效催化酪醇糖基化生产红景天苷，经5 L发酵罐培养，红景天苷产量可达8.17 g/L。Liu等[86]通过增加 *UGT85A1* 基因拷贝数构建大肠杆菌工程菌株，在5 L发酵罐中产量达9.48 g/L。为了进一步提升红景天苷产量，Zeng等[87]首先利用代谢工程策略结合适应性进化改造大肠杆菌，获得3.30 g/L酪醇，在此基础上过表达UDP-葡萄糖合成路径中的基因 *pgm* 和 *galU*，解决UDP-葡萄糖供应不足的问题，最后利用酶工程策略对糖基转移酶UGT85A1进行改造，整合突变体 $UGT85A1^{A21G}$ 的重组菌株经摇瓶发酵和分批补料发酵，红景天苷产量分别达到7.50 g/L、16.80 g/L，是目前以大肠杆菌为底盘菌生产红景天苷的最高产量。

3.2 酿酒酵母合成红景天苷

酿酒酵母[95]作为一种特性良好的模式生物，其生物转化能力和生产潜力巨大，从传统的发酵食品到现代的生物制药，其应用领域不断拓展[96-99]。随着酵母遗传研究的不断深入，目前已开发出许多基因编辑工具[100-102]，为遗传操作提供了便利。此外，酿酒酵母作为公认安全（generally recognized as safe，GRAS）菌株，无内毒素，其表达产物不需经过大量宿主安全性实验[103]。基于其高分泌能力、易表达真核来源蛋白以及遗传易处理性等特点[72-77]，酿酒酵母可作为生产红景天苷的优良宿主（表2）。

目前红景天苷的完整代谢通路在酿酒酵母中也已实现重构，其生物合成途径始于体外添加的葡萄糖（图3）。首先，葡萄糖在磷酸激酶催化下转化为6-磷酸葡萄糖，随后该底物经两条路径分别产生红景天苷所需的糖基供体和糖基受体。第一条路径聚焦于葡萄糖的磷酸化和尿苷化，6-磷酸葡萄糖经过

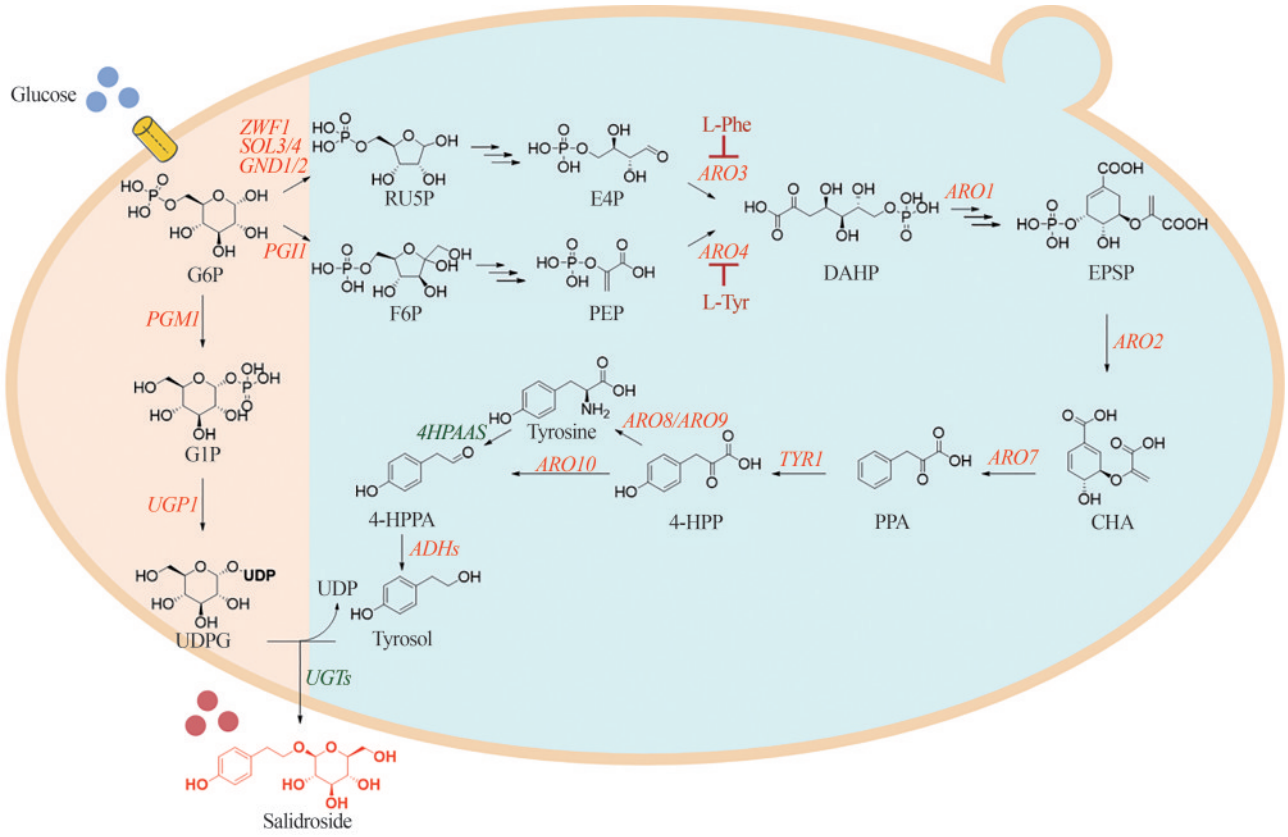


图 3　酿酒酵母中红景天苷的合成途径

（橙色字母表示酿酒酵母内源基因，绿色字母表示植物来源基因）

Fig.3　Biosynthetic pathways of salidroside in *Saccharomyces cerevisiae*

(The orange letters represent the endogenous genes of *S. cerevisiae*, and the green letters represent the plant-derived genes.)

磷酸葡萄糖变位酶（phosphoglycerate mutase 1，PGM1）和 UDP-葡萄糖焦磷酸化酶（UDP-glucose pyrophosphorylase 1，UGP1）两步反应生成尿苷二磷酸葡萄糖（uridine diphosphate glucose，UDPG）。作为糖基供体，尿苷二磷酸葡萄糖将在后续步骤中与酪醇结合，形成红景天苷的骨架。第二条路径则聚焦于芳香族化合物的合成，具体地，6-磷酸葡萄糖经糖酵解途径和磷酸戊糖途径生成莽草酸途径的重要前体 E4P 和 PEP。随后，二者在 DAHP 合酶（feedback-insensitive DAHP synthases，ARO3/4）、五功能型芳香酶（pentafunctional aromatic enzyme，ARO1）、分支酸合成酶（chorismate synthase，ARO2）和分支酸变位酶（feedback-insensitive chorismate mutase，ARO7）的催化下生成预苯酸，预苯酸经预苯酸脱氢酶（prephenate dehydrogenase，TYR1）催化生成 4-羟基苯丙酮酸，该中间体可通过酪氨酸途径生成酪醇前体 4-羟基苯乙醛，也可在苯丙酮酸脱羧酶催化下直接生成 4-羟基苯乙醛。而后在乙醇脱氢酶（alcohol dehydrogenase，ADH）催化下，4-羟基苯乙醛转化为酪醇。最终，来自两条路径生成的糖基受体酪醇与糖基供体尿苷二磷酸葡萄糖，在尿苷二磷酸葡萄糖基转移酶的催化下，发生缩合反应并释放出一个尿苷二磷酸分子，从而合成目标产物红景天苷。

基于上述路径，可分别通过优化前体酪醇的代谢通量与糖基转移酶的催化活性实现红景天苷的产量提升（表 3）。在优化前体酪醇的代谢通量方面，Kallscheuer 等[88]将突变体 *ARO4*^{K229L} 和 *ARO7*^{T266I} 整合到酵母基因组中替代受 L-苯丙氨酸反馈抑制的同工酶基因 *ARO3*，并通过过表达 *TYR1* 和 *ARO10* 促使碳通量流向酪醇。此外，由于酿酒酵母中含有 Ehrlich 途径[104]，Jiang 等[14]首先在酿酒酵母中过表达 *ARO4*^{K229L} 和 *ARO7*^{G141S} 以及大肠来源的 *aroL* 以增强前体酪氨酸的供应，而后引入欧

芹来源的*PcAAS*^{syn}，增强酪氨酸至酪醇的转化。研究表明，由PEP与E4P等比缩合的DAHP是莽草酸途径的重要前体，而酵母体内的E4P的含量远低于PEP的含量[105-106]。因此，为提高E4P的生成量，Guo等[90]通过异源表达*Xfpk*，双途径合成E4P，并敲除基因*PDC1*、*PHA2*和*TRP3*抑制乙醇、苯丙氨酸和色氨酸的生物合成，同时引入*PcAAS*和*EcTyrA*$^{M53I/A354V}$提高酪醇的产量。在此前研究的基础上，为进一步提高酪醇的产量，本课题组[89]利用模块化工程策略改造酿酒酵母：一方面，针对前体E4P与PEP供应不足的问题，过表达基因*RKI1*与*TKL1*来促进前体中碳通量的流入；另一方面，过表达*ARO3*^{K222L}、*ARO4*^{K229L}与*ARO7*^{G141S}突变体来解除关键酶的反馈抑制；最后，过表达途径基因*ARO2*与*ARO10*并敲除酪醇竞争路径中的基因*PDC1*和*PHA2*促使代谢流流向酪醇，以此获得的工程菌株酪醇产量可达702.30 mg/L。然而，进一步研究发现DAHP合酶中*ARO3*^{K222L}突变体在解除L-苯丙氨酸反馈抑制时效果不理想，仍然限制酪醇的产量。因此，针对*ARO3*^{K222L}的不足，本课题组获取了*ARO3*的晶体结构，并与抑制剂L-苯丙氨酸进行亲和力分析，获得可有效解除L-苯丙氨酸反馈抑制的突变体*ARO3*^{D154N}，并将其整合到酿酒酵母工程菌中，经摇瓶发酵可使酪醇和红景天苷产量分别提升至1.30 g/L和2.40 g/L[91]。

在对糖基转移酶的优化方面，Kallscheuer等[88]通过对三种糖基转移酶基因*RsUGT72B14*、*RsUGT73B6*和*OsUGT13*进行筛选得到催化活性较强的*OsUGT13*，并将其引入酿酒酵母工程菌后经摇瓶培养得到640.00 mg/L的红景天苷。Jiang等[14]筛选了*RsUGT73B6*、*RsUGT74R1*、*AtUGT73C5*和*AtUGT85A1*四种糖基转移酶基因，将效果较好的*AtUGT85A1*整合到酵母染色体上构建红景天苷生产菌株，并通过5 L发酵罐分批补料发酵使红景天苷与酪醇的产量分别提升至732.50 mg/L与1394.60 mg/L，为工业级生产奠定了基础。Guo等[90]在构建的高产酪醇菌株中异源表达拟南芥来源的糖基转移酶基因*UGT85A1*，经3 L发酵罐发酵得到8.48 g/L的酪醇和1.82 g/L的红景天苷。本课题组[89]比较筛选了三种不同来源的糖基转移酶基因*RsUGT72B14*、*BsYjiC*与*RrU8GT33*，结果表明整合*RrU8GT33*的工程菌株红景天苷产量最高，经摇瓶发酵与5 L发酵罐分批补料发酵，工程菌株的红景天苷产量分别为1575.45 mg/L、26.55 g/L，是目前报道的红景天苷生物合成的最高产量。

3.3 其他方式合成红景天苷

在探索红景天苷的生物合成途径时，工程菌株的选取已经不再局限于大肠杆菌与酿酒酵母。近年来，红景天属植物的内生菌因其潜在的生物合成能力而逐渐进入研究视野[107]（表3）。杨欣等[108]在深入探索大花红景天的根部微生物资源时，成功分离并鉴定出一株独特的水生拉恩氏菌（*Rahnella aquatilis*），通过摇瓶培养，该菌株的酪醇产量达到15.68 mg/L。此外，Cui等[92]从高山红景天内生菌分离得到的福廷瓶头霉菌（*Phialocephala fortinii*），经过发酵条件的优化，实现了红景天苷与酪醇的生产，经摇瓶培养产量分别达到2.34 mg/L和2.00 mg/L。

除单一菌株发酵培养外，近年来发展的混菌培养体系可通过协同代谢、诱导等作用实现红景天苷的高效生产（表3）。Zhou等[93]首先在大肠杆菌中异源表达*PcAAS*构建酪醇生产菌株，而后将经密码子优化的基因*GmSUS*与*RrUGT33*整合到酿酒酵母中，并敲除己糖转运蛋白基因*HXT1-HXT7*和*GAL2*，构建了一个以蔗糖为碳源的体内UDP-葡萄糖再生系统，将上述两种菌株共培养，通过调节蔗糖与葡萄糖比例及两株菌的接种率来提升红景天苷的产量，经摇瓶培养红景天苷产量可达3.80 g/L。Liu等[94]通过在两株大肠杆菌中分别表达脱羧酶基因*KDC4*和糖基转移酶基因*UGT85A1*构建酪醇生产菌株与红景天苷生产菌株，并对两种菌株的碳源利用进行优化，最终采用共培养方式和分批补料发酵，在5 L发酵罐中红景天苷的产量为6.03 g/L。

4 展 望

红景天苷作为珍贵中药和藏药红景天的主要生物活性成分，具有抗氧化、抗衰老和抗缺氧等药理作用，被广泛应用于药品、保健品、化妆品

等多个领域，市场需求持续增长[109]。

合成生物学助力构建微生物细胞工厂生产红景天苷，以其绿色、高效、可持续的优点，推动了红景天苷的工业化生产。一方面，通过以廉价碳源为底物，将可再生资源转化为高附加值产品，可以降低生产成本，促进生物经济发展。另一方面，利用微生物发酵技术获取红景天苷，不仅减少了对化石燃料的依赖，还能有效降低碳排放，符合国家“碳达峰”和“碳中和”战略需求，推动可持续发展。目前，生物合成红景天苷已经取得显著成果，然而，这其中仍有问题亟待解决：一方面是前体积累量不足导致红景天苷产量难以进一步提升，另一方面是在酪醇的糖基化过程中，天然糖基转移酶的低催化活性同样也成为制约产量的重要因素。随着信息学的不断发展，借助人工智能对工程菌株的代谢网络进行模拟与分析，可帮助调整代谢策略、控制代谢流向，进而提高产量。此外，通过生物信息学的手段，以现有酶为基础，挖掘具有更高催化活性和更强底物选择性的糖基转移酶，或者利用机器学习、定向进化等手段对现有的糖基转移酶加以改造，并应用于微生物底盘菌株中，同样可提升微生物合成红景天苷的工业化能力。在此基础上，为了进一步降低成本，促使红景天苷的工业化生产，利用更廉价的碳源已成为微生物发酵的未来趋势。Zhou等[93]使用较为廉价的蔗糖为碳源，开发了用于生产红景天苷的大肠杆菌-酿酒酵母共培养系统，成本降低约93%，红景天苷产量达到3.80 g/L，为红景天苷的工业化生产提供了新的思路。Lai等[110]分别利用对香豆酸和甘油作为碳源替代葡萄糖，酪醇浓度分别为649.39 mg/L和545.51 mg/L，进一步扩大了酪醇生产的底物范围，为合成酪醇及红景天苷提供了更为经济的途径。

此外，红景天苷还可以作为中间体生成其他具有抗氧化、抗炎、抗肿瘤等活性的化合物分子，如毛蕊花糖苷、松果菊苷和羟基红景天苷等。其中，毛蕊花糖苷[111-113]是一种来源于毛蕊花的苯乙醇苷，具有抗炎、抗癌、抗氧化等药理活性，松果菊苷[114-119]则是从狭叶松果菊中分离出来的一种天然活性化合物，在抗菌、抗病毒方面具有一定活性，而羟基红景天苷[120]是羟基酪醇的糖苷化产物，最早从胡黄连中分离得来，具有神经保护等作用。目前，以大肠杆菌为底盘成功实现了毛蕊花糖苷和羟基红景天苷的生物合成，Yang等[121]通过筛选不同来源的酰基转移酶、鼠李糖基转移酶和羟化酶，并在大肠杆菌中进行异源表达，实现了毛蕊花糖苷的合成；Choo等[120]利用糖基转移酶UGT85A1实现了在大肠杆菌工程菌中以羟基酪醇为底物合成羟基红景天苷。此外，松果菊苷的微生物合成也有进展，Xu等[122]研究得到女贞（*Ligustrum lucidum* Ait.）叶片上的植物内生菌（*Penicillium* sp. H1）可以实现松果菊苷的生产；而Bai等[123]的最新研究表明构建的酿酒酵母工程菌株也可有效实现复杂苯乙醇糖苷类化合物的生产，经分批补料发酵可得到4497.90 mg/L的毛蕊花糖苷和3617.40 mg/L的松果菊苷。随着下游糖苷类化合物合成关键酶的不断挖掘，在红景天苷工业化生产的基础上，构建微生物细胞工厂，实现对具有广泛药理活性的不同糖苷类化合物的工业化生产，将成为未来研究的主要方向。

现阶段，由于红景天苷提取方法的不断优化，生物合成红景天苷的安全性与可靠性也在逐渐提高。此外，除传统的水提取法、基于双水相系统的萃取法之外，结合了现代物理手段的超临界CO_2萃取-微波辅助提取法[124]的发展则显著提高了红景天苷的提取效率，促进红景天苷的提取与制剂开发技术达到产业化水平。多家企业，如伊犁疆宁生物技术有限公司、天津利安隆新材料股份有限公司以及南京春秋生物工程有限公司等均实现了红景天苷的工业化生产。因此，在未来，通过植物学、化学、酶学、合成生物学及计算生物学等多个科学领域的协同研究与持续努力，将会揭示更多关于其他复杂的苯乙醇苷类化合物的合成途径，推动微生物制造技术的发展和应用。

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