

# 植物类黄酮生物合成相关 UDP - 糖基转移酶研究进展

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**摘 要:** 类黄酮是人类膳食和观赏园艺植物中重要的多酚类物质, 因其广泛的生物活性及重要的生物学功能而倍受关注。植物尿苷二磷酸糖基转移酶 (Uridine diphosphate glycosyltransferase, UGT) 催化类黄酮生物合成的最后一步从而形成多种多样的糖苷衍生物。近年来, 大量 UGT 基因家族被分析, 类黄酮合成相关糖基转移酶也陆续被鉴别报道。本文综述了植物类黄酮生物合成相关 UGT 的生物化学及分子生物学研究进展, 重点对参与不同类黄酮糖基化的 UGT 体外重组蛋白活性及转基因功能分析等试验证据进行归纳, 并介绍了相关的微生物工程, 以期对植物类黄酮代谢及其调控原理及生物技术研究提供参考。

**关键词:** 类黄酮; 生物合成; UDP - 糖基转移酶; 生物学功能

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## Plant UDP-glycosyltransferases in Flavonoids Biosynthesis

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**Abstract:** Flavonoids are important polyphenols for human diet and ornamental horticulture. Flavonoids attract attention for their wide range of biological activities and important biological functions. Uridine diphosphate glycosyltransferases (UGT) catalyze the final step of flavonoid biosynthesis to form various glycoside derivatives. Recently, with the development of plant genomics, many flavonoid biosynthesis related UGTs were analyzed and identified. Here, research progress on plant UGTs involved in flavonoids glycosylation modification was summarized from biochemical and molecular biological points of view. Important evidence illustrating enzymatic activities of flavonoid biosynthesis related-UGTs, functional characterization, as well as bioengineering of flavonoids with key UGTs were listed, which may provide theoretical foundation for regulation on flavonoid biosynthesis in the future.

**Keywords:** flavonoid; biosynthesis; UDP-glycosyltransferase; biological function

类黄酮是人类膳食和观赏园艺植物中重要的多酚类物质。大量研究表明, 类黄酮在预防或辅助治疗癌症、糖尿病和心血管疾病等慢性非传染性疾病中发挥重要作用 (Williams et al., 2004; Perez-Vizcaino

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& Duarte, 2010; Ekström et al., 2011; Deng et al., 2013; Xiao, 2017), 同时类黄酮参与植物生长发育和抵抗胁迫的过程, 其生物学功能受到广泛关注 (Falcone Ferreyra et al., 2012; Silva-Navas et al., 2016; Henry-Kirk et al., 2018)。

根据化学结构, 类黄酮可分为 6 大类: 黄酮醇、花色苷、黄烷酮、黄酮、异黄酮和黄烷醇。它们通常以  $\alpha$  或  $\beta$  糖苷形式存在, 如类黄酮葡萄糖苷、半乳糖苷、鼠李糖苷、阿拉伯糖苷等单糖苷, 芸香糖苷 (6-O- $\alpha$ -L-鼠李糖-D-葡萄糖)、新橙皮苷 (2-O- $\alpha$ -L-鼠李糖-D-葡萄糖) 等二糖苷及多糖苷 (Peterson & Dwyer, 1998; Xiao, 2017)。类黄酮糖基化主要发生在 3-O 或 7-O 位, 但在 5-O 和 4'-O 等位置也可发生糖基化, 此外还有类黄酮 C-糖苷 (Rayyan et al., 2005; Barreca et al., 2011; Xiao et al., 2014)。糖基化可以改变受体分子的亲水性, 增加其溶解度和化学稳定性, 有助于其在细胞内和生物体内的储存和转运, 并最终影响其生物学功能的发挥 (Plaza et al., 2014)。

糖基转移酶 (Glycosyltransferase, GT, EC 2.4.x.y) 催化生物体内糖基化反应, 它们将糖基从活化的供体分子转移到受体分子, 从而形成多种多样的糖苷化合物 (Vogt & Jones, 2000)。类黄酮糖基化主要由尿苷二磷酸 (Uridine diphosphate, UDP) 糖基依赖的转移酶 (UDP glycosyltransferase, UGT) 催化。近年来, 随着基因组学的发展, 越来越多的植物 UGT 基因家族被分析报道 (Li et al., 2001; Caputi et al., 2012; Huang et al., 2015), 部分类黄酮糖基化相关的 UGT 在矮牵牛、拟南芥、葡萄、桃等重要模式植物和园艺作物中得到鉴别 (Miller et al., 1999; Jones et al., 2003; Ono et al., 2010a; Cheng et al., 2014)。本文综述了植物类黄酮生物合成相关 UGT 的生物化学及分子生物学研究进展, 重点对参与不同类黄酮糖基化的 UGT 体外重组蛋白活性及转基因功能分析等试验证据进行归纳, 以期对植物类黄酮代谢调控及生物技术研究提供参考。

## 1 尿苷二磷酸糖基转移酶 (UGT) 简介

有关糖基转移酶 (GT) 超家族的系统分类收录在 CAZy 数据库中 (Carbohydrate Active enzymes Database, CAZy, <http://www.cazy.org>)。植物 UGT 属于 GT1 家族, 其 C 末端含有 1 个由 44 个氨基酸组成的保守序列 PSPG box, 该保守序列被认为是与 UDP-糖供体结合的区域 (Mackenzie et al., 1997; Shao et al., 2005)。植物 UGT 主要以类黄酮、酚酸、萜类以及植物激素等小分子化合物为糖基受体, 以 UDP-葡萄糖、UDP-半乳糖或 UDP-鼠李糖等为糖基供体 (Lim et al., 2004; Bowles et al., 2006)。

植物第 1 个 UGT 是诺贝尔奖获得者 Barbara McClintock 在研究玉米转座子遗传不稳定性时意外发现的, 赋予玉米籽粒暗色素沉着的 *Bronze1* 基因 (X13500) 后来被证明编码类黄酮糖基转移酶 (Uridine diphosphate flavonoid glycosyltransferase, UFGT) (Dooner & Nelson, 1977)。随着生物技术的发展, 生物化学、分子生物学和遗传学等方法都成功地被运用于 UGT 的克隆、鉴定与功能分析。传统生物化学方法通过分离纯化具有特定糖基转移酶活性的蛋白, 然后根据蛋白质序列克隆相应的基因序列。遗传学方法主要通过突变体筛选分离目的基因。近年来, 以二代测序技术为主的高通量测序技术被逐渐应用于 UGT 鉴定, 全基因组分析、转录组测序等技术极大地加速了不同物种中 UGT 家族的系统性分析与鉴定 (表 1)。

UGT 家族的分类和命名采用 GT 命名委员会所建立的体系 (Mackenzie et al., 1997)。UGT 后面的阿拉伯数字表示家族, 其中 1~50 为动物源 UGT, 51~70 为酵母源, 71~100 为植物源, 101~200 家族为细菌源; 数字后面字母表示亚家族; 字母后的数字表示基因家族成员 (Mackenzie et al.,

1997)。拟南芥 UGT 家族中有 107 个成员, 根据序列同源性被划分为 14 个系统发育组, 命名为 A~N (Li et al., 2001), 随后在毛果杨、葡萄、苹果、茶和玉米等植物中发现了 O、P、Q 和 R 组 (Caputi et al., 2012; Cui et al., 2016)。苹果中有 241 个 UGT 家族成员, 是目前最大的 UGT 家族 (Caputi et al., 2012)。在高等植物的进化中, A、D、E、G 和 L 组扩展较快; D 组和 E 组是植物中较大的群组 (Caputi et al., 2012)。目前, 与类黄酮生物合成相关的 UGT 在 B、D、E、F 和 L 组中均有报道 (Osmani et al., 2009)。

表 1 不同植物中的 UGT 家族成员数  
Table 1 Number of plant UGTs in different phylogenetic group

物种	系统发育组 Phylogenetic group																			总数	参考文献
Species	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P	Q	R	Total	Reference	
拟南芥	14	3	3	13	22	3	6	19	1	2	2	17	1	1	-	-	-	-	107	Li et al., 2001	
<i>Arabidopsis thaliana</i>																					
葡萄	23	3	4	8	46	5	15	7	14	4	2	31	5	1	2	11	-	-	181	Caputi et al., 2012	
<i>Vitis vinifera</i>																					
黄瓜	10	1	2	12	13	-	11	5	-	2	1	17	2	1	3	5	-	-	85	Caputi et al., 2012	
<i>Cucumis sativus</i>																					
苹果	33	4	7	13	55	6	40	14	11	12	6	16	13	1	5	5	-	-	241	Caputi et al., 2012	
<i>Malus × domestica</i>																					
毛果杨	12	2	6	14	49	-	42	5	5	6	2	23	6	1	3	2	-	-	178	Caputi et al., 2012	
<i>Populus trichocarpa</i>																					
水稻	14	9	8	26	38	-	20	7	9	3	1	23	5	2	6	9	-	-	180	Caputi et al., 2012	
<i>Oryza sativa</i>																					
高粱	10	4	6	24	50	-	17	12	8	3	1	26	6	3	8	2	-	-	180	Caputi et al., 2012	
<i>Sorghum bicolor</i>																					
大豆	25	3	1	43	36	1	15	3	18	3	2	19	4	1	5	3	-	-	182	Caputi et al., 2012	
<i>Glycine max</i>																					
亚麻	16	5	6	21	22	1	19	6	9	4	5	19	3	1	-	-	-	-	137	Barvkar et al., 2012	
<i>Linum usitatissimum</i>																					
玉米	8	3	5	18	34	2	12	9	9	3	1	23	3	4	5	1	7	-	147	Li et al., 2014b	
<i>Zea mays</i>																					
陆地棉	17	12	-	36	38	8	20	16	10	4	2	18	2	2	1	10	-	-	196	Huang et al., 2015	
<i>Gossypium hirsutum</i>																					
木本棉	20	8	3	21	28	7	13	7	7	4	1	13	4	1	1	8	-	-	146	Huang et al., 2015	
<i>Gossypium arboreum</i>																					
雷蒙德氏棉	15	9	2	20	30	8	5	8	7	4	1	15	4	1	1	12	-	-	142	Huang et al., 2015	
<i>Gossypium raimondii</i>																					
茶	15	5	2	20	23	2	13	2	2	2	1	27	3	-	6	6	-	3	132	Cui et al., 2016	
<i>Camellia sinensis</i>																					
桃	10	2	4	19	29	4	34	9	5	7	7	18	14	1	1	4	-	-	168	Wu et al., 2017	
<i>Prunus persica</i>																					
百脉根	7	2	-	19	15	1	4	1	7	1	-	8	1	-	5	-	-	-	71	Yin et al., 2017a	
<i>Lotus japonicus</i>																					
小麦	22	3	2	17	37	2	4	5	7	5	-	19	3	1	3	13	36	-	179	He et al., 2018	
<i>Triticum aestivum</i>																					

2 类黄酮的糖基化

UGT 催化的类黄酮糖基化反应主要发生在细胞质中, 是很多次生代谢产物生物合成的最后一步, 也代表着植物次生代谢产物一种普遍的修饰方式 (Vogt & Jones, 2000; Bowles et al., 2006)。

体外酶活性研究表明, 不同 UGT 具有不同的底物偏好性, 其中包括糖受体和糖供体的多样性和特异性 (Hofer, 2016)。糖受体方面, 黄酮醇、花色素、黄烷酮、黄酮、异黄酮和黄烷醇等苷元可被不同或相同的 UGT 催化生成相应的糖苷。糖供体方面, UDP - 葡萄糖是最常见的活化的糖供体分子, 此外, UDP - 半乳糖、UDP - 鼠李糖、UDP - 阿拉伯糖和 UDP - 葡萄糖醛酸等也可被 UGT 所利用催化生成相应的类黄酮糖苷 (Bowles et al., 2006)。不同 UGT 在类黄酮糖基化反应中具有不同的区域选择性, 根据其催化位点的不同, 可分为 3 - O - 糖基转移酶、5 - O - 糖基转移酶、7 - O - 糖基转移酶和催化生成二糖苷的糖基转移酶, 此外还发现有类黄酮 C - 糖基转移酶 (Noguchi et al., 2008; Brazier-Hicks et al., 2009; Falcone Ferreyra et al., 2013)。表 2 中列出了拟南芥及园艺作物中已鉴定的参与类黄酮生物合成的 UGT。

表 2 拟南芥和园艺作物类黄酮生物合成糖基转移酶

Table 2 Glycosyltransferases involved in flavonoid biosynthesis in <i>Arabidopsis thaliana</i> and horticultural plants					
物种 Species	糖基转移酶 UGT	登录号 Accession No.	底物 Acceptor substrate	糖供体 Donor substrate	产物 Product
拟南芥 <sup>1</sup> <i>Arabidopsis thaliana</i>	UGT78D1	AT1G30530	山柰酚、槲皮素、异鼠李素 Kaempferol, quercetin, isorhamnetin	UDP - 鼠李糖 UDP-Rha	3 - O - 鼠李糖苷 3-O-Rha
	UGT78D2	AT5G17050	山柰酚、槲皮素、异鼠李素 Kaempferol, quercetin, isorhamnetin	UDP - 葡萄糖 UDP-Glc	3 - O - 葡萄糖苷 3-O-Glc
	UGT78D3	AT5G17030	槲皮素 Quercetin	UDP - 阿拉伯糖 UDP-Ara	3 - O - 阿拉伯糖苷 3-O-Ara
	UGT73C6	AT2G36790	山柰酚 3 - O - 鼠李糖苷、槲皮素 3 - O - 鼠李糖苷 kaempferol 3-O-Rha, quercetin 3-O-Rha	UDP - 葡萄糖 UDP-Glc	3 - O - 鼠李糖基 - 7 - O - 葡萄糖苷 3-O-Rha-7-O-Glc
	UGT79B2	AT4G27560	矢车菊素、矢车菊素 3 - O - 葡萄糖苷、槲皮素、山柰酚 Cyanidin, cyanidin 3-O-Glc, quercetin, kaempferol	UDP - 鼠李糖 UDP-Rha	3 - O - 鼠李糖苷 3-O-Rha
	UGT79B3	AT4G27570	矢车菊素、矢车菊素 3 - O - 葡萄糖苷、槲皮素、山柰酚 Cyanidin, cyanidin 3-O-Glc, quercetin, kaempferol	UDP - 鼠李糖 UDP-Rha	3 - O - 鼠李糖苷 3-O-Rha
	UGT79B6	AT5G54010	山柰酚 3 - O - 葡萄糖苷、槲皮素 3 - O - 葡萄糖苷 Kaempferol 3-O-Glc, quercetin 3-O-Glc	UDP - 葡萄糖 UDP-Glc	3 - O - 葡萄糖基 - (1→2) - 葡萄糖苷 3-O-Glc-(1→2)-Glc
	UGT89C1	AT1G06000	黄酮醇 3 - O - 葡萄糖苷 Flavonol 3-O-glycosides	UDP - 鼠李糖 UDP-Rha	7 - O - 鼠李糖苷 7-O-Rha
	F3GalT	AAD55985	山柰酚、槲皮素 Kaempferol, quercetin	UDP - 半乳糖 UDP-Gal	3 - O - 半乳糖苷 3-O-Gal
	PH1	AB027455	飞燕草素 3 - (p - 酰基) - 芸香糖苷 Delphinidin 3-(p-Coumaroyl)-Rut	UDP - 葡萄糖 UDP-Glc	飞燕草素 3 - (p - 酰基) - 芸香糖基 - 5 - O - 葡萄糖苷 Delphinidin 3-(p-Coumaroyl)-Rut-5-O-Glc
矮牵牛 <sup>2</sup> <i>Petunia hybrida</i>	PGT8	AB027454	黄酮醇、花色素 Flavonol, anthocyanidin	UDP - 葡萄糖 UDP-Glc	黄酮醇 3 - O - 葡萄糖苷, 花色素 3 - O - 葡萄糖苷 Flavonol 3-O-Glc, Anthocyanidin 3-O-Glc
	F3GT	BBE29003	山柰酚 3 - O - 半乳糖苷/葡萄糖苷 Kaempferol 3-O-Gal/Glc	UDP - 葡萄糖 UDP-Glc	山柰酚 3 - O - 葡萄糖基 - (1→2) - 半乳糖苷/葡萄糖苷 Kaempferol 3-O-Glc-(1→2)-Gal/Glc
	UGT72AM1	KY399734	黄酮醇、柚皮素 Flavonol, naringenin	UDP - 葡萄糖 UDP-Glc	3 - O - 葡萄糖苷, 4' - O - 葡萄糖苷, 7 - O - 葡萄糖苷 3-O-Glc, 4'-O-Glc, 7-O-Glc
	UGT75L12	ALO19892	柚皮素、芹菜素、金雀异黄素、山柰酚 Naringenin, apigenin, genistein, kaempferol	UDP - 葡萄糖 UDP-Glc	7 - O - 葡萄糖苷 7-O-Glc
茶 <sup>3</sup> <i>Camellia sinensis</i>	UGT78A14	KP682360	槲皮素、山柰酚、杨梅素 Quercetin, kaempferol, myricetin	UDP - 葡萄糖 UDP-Glc	3 - O - 葡萄糖苷 3-O-Glc
	UGT78A15	KP682361	槲皮素、山柰酚、杨梅素 Quercetin, kaempferol, myricetin	UDP - 半乳糖 UDP-Gal	3 - O - 半乳糖苷 3-O-Gal
	FaGT1	AY663784	黄酮醇、花色素 Flavonol, anthocyanidin	UDP - 葡萄糖 UDP-Glc	3 - O - 葡萄糖苷 3-O-Glc
	FaGT6	DQ289587	山柰酚、槲皮素、异鼠李素 Kaempferol, quercetin, isorhamnetin	UDP - 葡萄糖 UDP-Glc	3 - O - 葡萄糖苷, 7 - O - 葡萄糖苷, 4' - O - 葡萄糖苷, 二葡萄糖苷 3-O-Glc, 7-O-Glc, 4'-O-Glc, Diglucoside
草莓 <sup>4</sup> <i>Fragaria × ananassa</i>	FaGT7	DQ289588	山柰酚、槲皮素、异鼠李素 Kaempferol, quercetin, isorhamnetin	UDP - 葡萄糖 UDP-Glc	3 - O - 葡萄糖苷, 7 - O - 葡萄糖苷 3-O-Glc, 7-O-Glc
	F3GT1	GU079683	矢车菊素 Cyanidin	UDP - 半乳糖 UDP-Gal	矢车菊素 3 - O - 半乳糖苷 Cyanidin 3-O-Gal
	F3GGT1	FG404013	矢车菊素 3 - O - 半乳糖苷 Cyanidin 3-O-Gal	UDP - 木糖 UDP-Xyl	矢车菊素 3 - O - 木糖基 - 半乳糖苷 Cyanidin 3-O-Xyl-Gal
	AcUFGT3a	AYJ72756	矢车菊素 Cyanidin	UDP - 半乳糖 UDP-Gal	矢车菊素 3 - O - 半乳糖苷 Cyanidin 3-O-Gal
葡萄 <sup>6</sup> <i>Vitis vinifera</i>	VvGT5	AB499074	山柰酚、槲皮素、异鼠李素 Kaempferol, quercetin, isorhamnetin	UDP - 葡萄糖醛酸 UDP-Glc A	3 - O - 葡萄糖醛酸 3-O-Glc A
	VvGT6	AB499075	山柰酚、槲皮素、异鼠李素 Kaempferol, quercetin, isorhamnetin	UDP - 葡萄糖, UDP - 半乳糖 UDP-Glc, UDP-Gal	3 - O - 葡萄糖苷, 3 - O - 半乳糖苷 3-O-Glc, 3-O-Gal

续表 2

物种 Species	糖基转移酶 UGT	登录号 Accession number	底物 Acceptor substrate	糖供体 Donor substrate	产物 Product
桃 <sup>7</sup> <i>Prunus persica</i>	PpUGT78A1	ONI27510	矢车菊素 Cyanidin	UDP - 半乳糖 UDP-Gal	矢车菊素 3 - O - 半乳糖苷 Cyanidin 3-O-Gal
	PpUGT78A2	XP_007224129	矢车菊素 Cyanidin	UDP - 葡萄糖 UDP-Glc	矢车菊素 3 - O - 葡萄糖苷 Cyanidin 3-O-Glc
柚 <sup>8</sup> <i>Citrus maxima</i>	1,2-RhaT	AY048882	黄烷酮 7 - O - 葡萄糖苷 Flavanone 7-O-Glc	UDP - 鼠李糖 UDP-Rha	黄烷酮 7 - O - 鼠李糖基 - (1→2) - 葡萄糖苷 Flavanone 7-O-Rha-(1→2)- Glc
甜橙 <sup>9</sup> <i>Citrus sinensis</i>	1,6-RhaT	DQ119035	黄烷酮 7 - O - 葡萄糖苷 Flavanone 7-O-Glc	UDP - 鼠李糖 UDP-Rha	黄烷酮 7 - O - 鼠李糖基 - (1 →6) - 葡萄糖苷 Flavanone 7-O- Rha-(1→6)-Glc
	CsUGT76F1	KDO69246	槲皮素、山奈酚 Quercetin, kaempferol	UDP - 鼠李糖 UDP-Rha	7 - O - 鼠李糖苷 7-O-Rha
葡萄柚 <sup>10</sup> <i>Citrus paradisi</i>	Cp3GT	ACS15351	槲皮素、山奈酚、杨梅素 Quercetin, kaempferol, myricetin	UDP - 葡萄糖 UDP-Glc	3 - O - 葡萄糖苷 3-O-Glc
温州蜜柑 <sup>11</sup> <i>Citrus unshiu</i>	CuCGT	LC131334	2 - 羟基黄烷酮、二氢查儿酮、单 - C - 葡萄糖苷 2-Hydroxyflavanones, dihydrochalcone, mono-C-glucosides	UDP - 葡萄糖 UDP-Glc	二 - C - 葡萄糖苷 Di-C-Glc
金柑 <sup>11</sup> <i>Fortunella crassifolia</i>	FcCGT	LC131333	2 - 羟基黄烷酮、二氢查儿酮、单 - C - 葡萄糖苷 2-Hydroxyflavanones, dihydrochalcone, mono-C-glucosides	UDP - 葡萄糖 UDP-Glc	二 - C - 葡萄糖苷 Di-C-Glc
玫瑰 <sup>12</sup> <i>Rosa hybrida</i>	RhGT1	AB201048	矢车菊素、矢车菊素 5 - O - 葡萄糖苷 Cyanidin, cyanidin 5-O-Glc	UDP - 葡萄糖 UDP-Glc	矢车菊素 5 - O - 葡萄糖苷, 矢车菊素 3,5 - O - 葡萄糖苷 Cyanidin 5-O-Glc,Cyanidin 3,5-O-Glc
柿 <sup>13</sup> <i>Diospyros kaki</i>	DkFGT	BAI40148	花色素、黄酮醇 Anthocyanidin, flavonol	UDP - 半乳糖 UDP-Gal	3 - O - 半乳糖苷 3-Gal
银杏 <sup>14</sup> <i>Ginkgo biloba</i>	UGT716A1	KX371617	黄酮醇、黄烷酮、黄酮 Flavonol, flavanone, flavone	UDP - 葡萄糖 UDP-Glc	3 - O - 葡萄糖苷, 4' - O - 葡 萄糖苷, 7 - O - 葡萄糖苷 3-O-Glc,4'-O-Glc,7-O-Glc

注: 1. Jones et al., 2003; Tohge et al., 2005; Yonekura-Sakakibara et al., 2007, 2008, 2014; Li et al., 2017; Ishihara et al., 2016; 2. Miller et al., 1999; Yamazaki et al., 2002; Knoch et al., 2018; 3. Cui et al., 2016; Dai et al., 2017; Zhao et al., 2017; 4. Griesser et al., 2008a, 2008b; 5. Montefiori et al., 2011; Liu et al., 2018; 6. Ono et al., 2010a; 7. Cheng et al., 2014; 8. Frydman et al., 2004; 9. Frydman et al., 2013; Liu et al., 2018; 10. Owens & McIntosh , 2009; 11. Ito et al., 2017; 12. Ogata et al., 2005; 13. Ikegami et al., 2009; 14. Su et al., 2017.

2.1 黄酮醇的糖基化

黄酮醇是植物中分布最广泛的类黄酮之一，常见的苷元主要有山奈酚、槲皮素、杨梅素和异鼠李素等，一般以 3 - O - 糖苷的形式存在（Pollastri & Tattini，2011）。

利用矮牵牛（*Petunia hybrida*）花粉蛋白提取液，黄酮醇糖基转移酶 F3GalT（AAD55985）和 F3GT（BBE29003）能相继催化合成黄酮醇 3 - O - （2'' - O - 葡萄糖基） - 半乳糖苷，该黄酮醇二糖苷在花粉萌发中发挥重要作用（Vogt & Taylor，1995）。之后，矮牵牛 F3GalT（F3GalTase）和 F3GT（UGT79B31）相继被克隆分离，F3GalTase 重组蛋白特异识别 UDP - 半乳糖，催化合成黄酮醇 3 - O - 半乳糖苷；F3GT 重组蛋白可以催化合成黄酮醇 3 - O - （2'' - O - 葡萄糖基） - 半乳糖苷，并证实了该黄酮醇对花粉萌发的重要作用（Miller et al., 1999; Knoch et al., 2018）。

在拟南芥（*Arabidopsis thaliana*）中，UGT78D1（AT1G30530）、UGT78D2（AT5G17050）和 UGT78D3（AT5G17030）蛋白分别被鉴定为特异识别 UDP - 鼠李糖（Jones et al., 2003）、UDP - 葡萄糖（Tohge et al., 2005）和 UDP - 阿拉伯糖（Yonekura-Sakakibara et al., 2008）的黄酮醇糖基转移酶。相应地，拟南芥突变体 *ugt78d1*、*ugt78d2*、*ugt78d3* 中黄酮醇 - 3 - O - 鼠李糖 - 7 - O - 鼠李

糖苷、黄酮醇-3-O-葡萄糖苷、黄酮醇-3-O-阿拉伯糖苷含量显著减少(Jones et al., 2003; Tohge et al., 2005; Yonekura-Sakakibara et al., 2008; Yin et al., 2014)。拟南芥 *ugt78d1/ugt78d2* 双突变体中黄酮醇含量仅为野生型植株的 1/3, 利用该双突变体材料发现, 黄酮醇苷元未正常糖基化对苯丙烷代谢途径上游基因表达存在反馈抑制调控(Yin et al., 2012)。

在草莓(*Fragaria × ananassa*)中, FaGT6 (DQ289587) 可以催化槲皮素形成 3-O-葡萄糖苷, 此外还有少量的 7-O、4'-O、3'-O 葡萄糖苷和葡萄糖二糖苷, 而 FaGT7 (DQ289588) 则只能催化黄酮醇生成单糖苷(Griesser et al., 2008b)。葡萄柚(*Citrus paradisi*) Cp3GT (ACS15351) 可特异地催化黄酮醇如槲皮素、山奈酚和杨梅素 3-O 位葡萄糖基化(Owens & McIntosh, 2009; Devaiah et al., 2018)。在葡萄(*Vitis vinifera*)中, VvGT5 (AB499074) 具有黄酮醇 3-O-葡萄糖醛酸转移酶活性, 而 VvGT6 (AB499075) 以黄酮醇为底物, 具有 UDP-葡萄糖和 UDP-半乳糖双糖转移酶活性(Ono et al., 2010a)。茶树(*Camellia sinensis*)中 CsUGT78A14 (KP682360) 和 CsUGT78A15 (KP682361) 分别具有 UDP-葡萄糖和 UDP-半乳糖转移活性(Cui et al., 2016)。长春花(*Catharanthus roseus*) CaUGT3 (AB443870) 可以催化槲皮素的 1,6-糖基化, 并且具有葡萄糖基链延伸活性, 可形成龙胆二糖苷、龙胆三糖苷和龙胆四糖苷(Masada et al., 2009)。西红花(*Crocus sativus*)的 *UGT707B1* 基因(HE793682)在拟南芥中过量表达, 转基因植株的茎和花中山奈酚 3-O-槐糖苷和槲皮素 3-O-槐糖苷含量显著增加, 植株茎秆变粗, 开花延迟(Trapero et al., 2012)。大豆(*Glycine max*) *Fg2* 基因编码的 GmF3G6''Rt-a (I1LCI8) 是黄酮醇 3-O-葡萄糖苷(1→6)鼠李糖基转移酶(Rojas Rodas et al., 2014), 由 *Fg3* 基因编码的 GmF3G2''Gt 蛋白(A0A0G4DBR5) 具有黄酮醇 3-O-葡萄糖苷/半乳糖苷(1→2)葡萄糖基转移酶活性(Di et al., 2015), 由 *Fg1* 编码的 GmF3G6''Gt 蛋白(AB828193) 具有黄酮醇 3-O-葡萄糖苷/半乳糖苷(1→6)葡萄糖基转移酶活性(Rojas Rodas et al., 2016)。可见, UGT 对不同糖供体和黄酮醇苷元或糖苷存在较明显的偏好性。

## 2.2 花色素的糖基化

花色素(anthocyanin)是植物重要的水溶性色素, 在组织中可以产生红色、蓝色甚至接近黑色等色泽, 其色度与化学结构和 pH 值有关。植物中常见的花色素苷元主要有矢车菊素、飞燕草素、锦葵色素和天竺葵素等, 其糖苷多以 3-O-糖苷或是 3,5-O-二糖苷形式存在(Jaakola, 2013)。

目前, 以矢车菊素为底物, 鉴定到的 UGT 分别参与了葡萄、矮牵牛、玫瑰花、桃花、红肉猕猴桃等红色植物组织的着色。继玉米中编码类黄酮糖基转移酶(UFGT)的 *Bronze1* 被报道后(Dooner & Nelson, 1977), Ford 等(1998)报道了葡萄 UFGT 参与果实成熟变色过程中矢车菊素 3-O-葡萄糖苷的合成。矮牵牛 PH1 (AB027455) 和 PGT8 (AB027454) 被分别鉴定为花色素 5-O-葡萄糖基转移酶(5GT)和类黄酮 3-O-葡萄糖基转移酶(3GT)(Yamazaki et al., 2002)。牵牛花(*Ipomoea purpurea*) *Duskish* 编码类黄酮 3-O-葡萄糖基转移酶(3GT) (LC019110), 在 *duskish-2* 突变体中花色素含量减少了 80%, 其花瓣显示白色(Morita et al., 2015)。玫瑰(*Rosa hybrida*)中 *RhGT1* 编码的蛋白(AB201048)可以相继催化矢车菊素形成不稳定的矢车菊素 5-O-葡萄糖苷和稳定的矢车菊素 3,5-O-二葡萄糖苷(Ogata et al., 2005)。桃花中, PpUGT78A1 (ONI27510) 和 PpUGT78A2 (XP\_007224129) 是花色素合成中重要的 3-O-糖基转移酶(3GT) (Cheng et al., 2014)。利用红肉猕猴桃 'HD22' 和 '红阳' 研究发现, F3GT1 (GU079683) 和 AcUFGT3a (AYJ72756) 均能特异催化合成矢车菊素 3-O-半乳糖苷, 而 F3GGT1 (FG404013) 则可进一步催化合成矢车菊素 3-O-木糖基-半乳糖苷; 在猕猴桃和苹果果实中瞬时表达 *AcUFGT3a* 能使果肉呈现红色

(Montefiori et al., 2011; Liu et al., 2017)。紫色甘薯 (*Ipomoea batatas*) 的 Ib3GGT (KF056328) 催化花色素 3-O-葡萄糖苷形成花色素 3-O-槐糖苷, 将 Ib3GGT 在野生型拟南芥和 *ugt79b1* 突变体中过量表达, 转基因植株均能产生 1 种新的矢车菊素 3-O-槐糖苷 (Wang et al., 2018)。拟南芥 UGT79B2 (AT4G27560) 和 UGT79B3 (AT4G27570) 编码花色素鼠李糖基转移酶, 它们可通过调节花色苷的积累而改变植物对低温、盐、干旱等非生物胁迫抗性 (Li et al., 2017)。

以飞燕草素和锦葵色素为底物, 目前鉴定到的 UGT 分别参与了龙胆花、豌豆花、山葡萄、半边莲等蓝紫色植物组织的着色。三花龙胆 (*Gentiana triflora*) 中花色素 3'-O-葡萄糖基转移酶 (3'GT) (AB076697) 能特异催化飞燕草素 3-O-葡萄糖基 5-O-葡萄糖苷 B 环的 3'-OH 葡萄糖基化, 参与合成深蓝色的龙胆翠雀花素 (Fukuchi-Mizutani et al., 2003)。在豌豆 (*Clitoria ternatea*) 花中, 花色苷 3',5'-O-葡萄糖基转移酶 (UA3'5'GT) 相继催化飞燕草素 3-O-(6"-乙二酰基)-葡萄糖生成飞燕草素 3-O-(6"-乙二酰基)-葡萄糖基-3'5'-O-二葡萄糖苷, 使豌豆花瓣呈现蓝色 (Kogawa et al., 2007)。在婆婆纳 (*Veronica persica*) 蓝色花中鉴定到的 UGT94F1 (AB465708) 参与了花色素 3-O-葡萄糖苷-2"-O-葡萄糖苷的生物合成 (Ono et al., 2010b)。小苍兰 (*Freesia hybrida*) Fh3GT1 (HM590645) 参与花色苷的生物合成, 将 Fh3GT1 RNAi 质粒转入矮牵牛植株中, 其花中总花色苷含量显著下降, 花色改变明显; 进一步生化分析表明, Fh3GT1 识别广泛的类黄酮底物, 能在飞燕草素的 3-O、4'-O 和 7-O 位发生糖基化, 将该基因转入拟南芥 *ugt78d2* 突变体可恢复其花色素的积累 (Sui et al., 2011; Sun et al., 2016)。在山葡萄 (*Vitis amurensis*) 中, Va5GT (AHL68667) 偏好锦葵色素 3-O-葡萄糖苷为底物, 催化形成锦葵色素 3,5-O-二葡萄糖苷 (He et al., 2015)。利用 'Aqua Blue' 和 'Aqua Lavender' 不同花色的半边莲 (*Lobelia erinus*) 为材料, 鉴定到编码鼠李糖基转移酶的 ABRT2 (LC131336) 和 ABRT4 (LC131337), 发现鼠李糖基转移酶对飞燕草素 3-O-葡萄糖苷的进一步糖基化修饰决定了不同品种间花瓣蓝色的差异 (Hsu et al., 2017)。

此外, 研究还发现 FaGT1 (AY663784) 参与草莓果实天竺葵素 3-O-葡萄糖苷等花色苷的合成, 在果实成熟发育过程中发挥重要作用 (Griesser et al., 2008a)。岩桐 (*Sinningia speciosa*) ScUGT5 编码的 3-脱氧花色素 5-O-葡萄糖基转移酶 (dA5GT, AB537182) 可特异催化合成植物罕见色素 3-脱氧花色苷 (Nakatsuka & Nishihara, 2010)。可见, UGT 对不同花色苷的生物合成具有显著调控作用。

## 2.3 黄烷酮的糖基化

黄烷酮主要存在于柑橘果实中, 如柚皮苷、新橙皮苷等, 是柑橘苦味物质的重要组成 (Tripoli et al., 2007; 陈嘉景 等, 2016)。黄烷酮苷元主要包括柚皮素、橙皮素、圣草酚等。

在柑橘中, 黄烷酮不同糖基化产物会直接影响果实风味, 如葡萄柚 (*Citrus paradisi*) 和柚 (*C. maxima*) 中因为积累大量黄烷酮 7-O-新橙皮苷, 所以有苦味, 而宽皮柑橘和甜橙中主要积累黄烷酮 7-O-芸香糖苷, 无明显苦味 (Frydman et al., 2004)。柑橘 7-GlcT 催化柚皮素、橙皮素等形成黄烷酮 7-O-葡萄糖苷 (Lewinsohn et al., 1989)。在此研究基础上, 在柚果实中鉴定出 Cml2-RhaT (AY048882) 编码鼠李糖转移酶, 催化黄烷酮 7-O-葡萄糖苷进一步形成带有苦味的柚皮苷、新橙皮苷等; 而甜橙 (*C. sinensis*) Cs1,6-RhaT (DQ119035) 则催化黄烷酮 7-O-葡萄糖苷形成无苦味的柚皮芸香苷和橙皮苷等 (Bar-Peld et al., 1993; Frydman et al., 2004, 2013)。最近 Chen 等 (2019) 利用不同风味的柑橘种质材料, 进一步研究发现鼠李糖基转移酶 Cit1,2RhaT 催化形成苦味的新橙皮苷, 两个 CitdGlcTs 被鉴定为类黄酮 7-O-二葡萄糖基转移酶, 可催化形成无苦味的柚皮素 7-O-

二葡萄糖苷。

## 2.4 黄酮的糖基化

黄酮苷元主要包括芹菜素及其羟基或甲基化产物木犀草素、黄芩素等,其糖基化 UGT 也在长春花、婆婆纳等不同药用或观赏植物中被陆续报道。

长春花中的 CaUGT3 (Masada et al., 2009)、婆婆纳蓝色花中的 UGT88D8 (AB465708) (Ono et al., 2010b)、粉蝶花 (*Nemophila menziesii*) 的 NmF4'GT (LC328827) 和 NmF4'GGT (LC328828) (Okitsu et al., 2018) 都可以芹菜素为底物,分别催化合成芹菜素 7-O-龙胆葡萄糖苷、芹菜素 7-O-葡萄糖醛酸、以及芹菜素 7,4'-O-二葡萄糖苷。多品种水稻 (*Oryza sativa*) 全基因组关联分析表明,OsUGT706D1 (BAB68093) 和 OsUGT707A2 分别具有黄酮 7-O-葡萄糖基转移酶和黄酮 5-O-葡萄糖基转移酶活性,参与芹菜素的糖基化,并能提高水稻对紫外辐射的耐受性 (Peng et al., 2017)。绿毛山柳菊 (*Hieracium pilosella*) 中的 UGT95A1 (EU561020) 和 UGT90A7 (EU561019) 偏好木犀草素作为底物,分别催化其 3-O 和 4'-O 位的糖基化,UGT2B11 (EU561016) 则可催化广泛的底物,如黄酮和黄酮醇等 (Witte et al., 2009)。此外,长春花 CaUGT3 蛋白还可以催化黄芩素的 7-O-葡萄糖苷形成龙胆糖苷 (Masada et al., 2009)。

除了 O-糖苷,植物中还存在类黄酮 C-糖苷。水稻 OsCGT (FM179712) 能催化芹菜素和木犀草素等形成 6-C-葡萄糖苷 (Brazier-Hicks et al., 2009); 玉米 UGT708A6 (GRMZM2G162783) 则具有黄酮 C-和 O-双功能糖基转移酶活性 (Falcone Ferreyra et al., 2013)。最近,金柑 (*Fortunella crassifolia*) FcCGT (LC131333) 和温州蜜柑 (*C. unshiu*) CuCGT (LC131334) 都被鉴定为 C-糖基转移酶,能催化二氢柚皮素、二氢查儿酮形成单糖苷及二糖苷 (Ito et al., 2017)。

## 2.5 异黄酮和黄烷醇的糖基化

异黄酮苷元包括大豆苷元和金雀异黄素等,在豆类、葛根等植物特定组织部位的含量较为丰富。目前鉴定到的异黄酮糖基转移酶均为 7-O 位的葡萄糖转移酶,包括大豆 GmUGT73C20 (XP\_003554403) 和 GmUGT88E19 (XP\_003533968) (Yin et al., 2017b)、葛根 (*Pueraria lobata*) PIUGT1 (KC473565) (Li et al., 2014a)、水稻 OsUGT709A4 (BAC80066) (Ko et al., 2008) 和南非醉茄 (*Withania somnifera*) WsGT (FJ560880) (Kumar et al., 2013),它们均能催化大豆苷元和金雀异黄素形成相应 7-O-葡萄糖苷。

植物中黄烷醇类物质包括儿茶素、表儿茶素、原花青素、茶黄素等,自然界部分黄烷醇也存在糖基化现象。苜蓿 (*Medicago truncatula*) UGT72L1 (EU434684) (Pang et al., 2008) 和大豆 GmUGT88A13 (XP\_003533971) (Yin et al., 2017b) 均可催化(-)-表儿茶素糖基化,参与表儿茶素 3'-O-葡萄糖苷的生物合成。更多异黄酮和黄烷醇生物合成相关的 UGT 有待鉴定。

## 3 UGT 对糖供体的偏好性

对 UGT 晶体结构研究表明: PSPG box 区域最后 1 个氨基酸残基,即第 44 个氨基酸对于 UDP-糖供体的偏好至关重要,若它是谷氨酰胺 (Gln, Q),则 UGT 偏好以 UDP-葡萄糖作为糖供体,如拟南芥 UGT78D2 (Tohge et al., 2005)、茶 CsUGT78A14 (Cui et al., 2016)、草莓 FaGT6 和 FaGT7 (Griesser et al., 2008b) 等。在彩虹菊 (*Dorotheanthus bellidiformis*) 中,该氨基酸残基 (Gln378) 和靠近 N 端的组氨酸 (His22) 替换会使 UGT73A5 丧失 UDP-葡萄糖转移酶活性 (Hans et al., 2004);



黄芩 (*Scutellaria baicalensis*) 类黄酮葡萄糖基转移酶 UBG1 (AB031274) 该位点 (Gln382) 突变为组氨酸 (His382) 之后, 葡萄糖转移酶活性明显下降 (Kubo et al., 2004); 茶 CsUGT78A15 和 CsUGT78A14 蛋白定点突变结果也表明, PSPG box 区域最后一个氨基酸残基对于类黄酮 UGT 葡萄糖转移活性至关重要 (Cui et al., 2016)。

对已鉴定的植物半乳糖转移酶序列分析显示: PSPG box 最后一个氨基酸残基多为组氨酸 (His), 如矮牵牛 F3GalT (Miller et al., 1999)、茶 CsUGT78A15 (Cui et al., 2016) 和猕猴桃 F3GT1 (Montefiori et al., 2011) 等。将土当归 (*Aralia cordata*) 花色素半乳糖基转移酶 ACGaT (AB103471) 的该位点 (His374) 突变为谷氨酰胺 (Gln374), ACGaT 有了葡萄糖和半乳糖双功能转移活性 (Kubo et al., 2004)。

而针对 UDP-葡萄糖醛酸转移酶的分析表明: UGT 序列中特定定位点的精氨酸 (Arg) 残基与葡萄糖醛酸转移活性有关。葡萄 VvGT5 序列上的 Arg140、雏菊 (*Bellis perennis*) BpUGT94B1 (Q5NTH0) 序列中 Arg25 对于其葡萄糖醛酸转移活性至关重要 (Osmani et al., 2008); 在光紫黄芩 (*Scutellaria laeteviolacea*) 中, 将 F7GAT 序列 PSPG box 中的 Arg350 突变为色氨酸 (Trp350), 可使其由葡萄糖醛酸转移活性转变为葡萄糖转移活性 (Noguchi et al., 2009)。

然而, UGT 对于糖供体的偏好性也不完全由单个氨基酸决定, 目前已在拟南芥、葡萄等植物中发现不符合上述规律的类黄酮 UGT。例如, 拟南芥 UGT78D3 蛋白序列 PSPG box 最后一个氨基酸是谷氨酰胺, 但它却催化 UDP-阿拉伯糖的转移 (Yonekura-Sakakibara et al., 2008); 葡萄 VvGT6 序列中的谷氨酰胺 (Gln373) 和脯氨酸 (Pro19) 对其葡萄糖和半乳糖双功能活性起重要作用 (Ono et al., 2010a)。基于植物中大量 UGT 的存在, 不同成员对糖供体的偏好性有待继续探索。

## 4 类黄酮糖苷的合成生物学

从植物中分离纯化类黄酮糖苷的提取工艺复杂且获得率较低。随着合成生物技术的发展, 利用大肠杆菌和酵母等作为细胞工厂合成天然产物成为热点。与分离纯化法和化学合成法相比, 通过微生物转化合成类黄酮, 反应条件温和, 且具有区域选择性高, 所得产物产量和纯度高等优点 (Hofer, 2016)。

将不同底物特异性的 UGT 导入微生物中, 可催化合成多种多样的类黄酮糖苷衍生物。在大肠杆菌中过量表达 91 个拟南芥 UGT 基因, 发现仅 29 个 UGT 对槲皮素有催化活性, 检测到了 3-O-、7-O-、3'-O- 和 4'-O- 单葡萄糖苷、3,7-二-O-葡萄糖苷以及 7,3'-O-二葡萄糖苷等多种槲皮素葡萄糖苷 (Lim et al., 2004)。将拟南芥鼠李糖基转移酶基因在大肠杆菌中过量表达, 可大量合成类黄酮鼠李糖苷, 如过量表达 UGT78D1 可合成槲皮素 3-O-鼠李糖苷 (Kim et al., 2012a)、过量表达 AtUGT78D1/AtUGT89C1 基因可合成槲皮素 3,7-O-二鼠李糖苷 (Kim et al., 2013)、过量表达 ArGT-3 基因可合成杨梅素 3-O- $\alpha$ -L-鼠李糖苷 (Thuan et al., 2013)。将拟南芥葡萄糖转移酶基因在大肠杆菌中过量表达, 可大量合成类黄酮葡萄糖苷, 如过量表达 AtUGT73B3 和 AtUGT84B1 可分别合成槲皮素 3-O-葡萄糖苷和槲皮素 7-O-葡萄糖苷 (Xia & Eiteman, 2017)、过量表达 AtUGT78D2/AtUGT89C1 可合成槲皮素 3-O-葡萄糖苷-7-O-鼠李糖苷 (Kim et al., 2013), 在大肠杆菌核苷糖代谢相关突变体 galU 中过量表达 AtUGT78D2, 可大量合成槲皮素 3-O-N-乙酰氨基葡萄糖苷 (Kim et al., 2012b)。此外, 将拟南芥阿拉伯糖基转移酶基因 UGT78D3 在大肠杆菌中过量表达, 可大量合成槲皮素阿拉伯糖苷 (Kim et al., 2010)。

近年来, 利用其他植物来源 UGT 进行黄酮醇的微生物转化合成也有报道。如在大肠杆菌中分

别过量表达大豆 *GmUGT78K1* (Malla et al., 2013) 和长春花 *CaUGT* (Cho et al., 2016) 可大量合成黄酮醇糖苷; 其中在大肠杆菌中过量表达矮牵牛 *PhUGT* 可使槲皮素 3 - O - 半乳糖苷的产量达到 280 mg · L<sup>-1</sup> (Kim et al., 2015)。

此外, 酵母 (*Saccharomyces cerevisiae*) 也被用于进行类黄酮糖苷生物合成。将康乃馨 (*Dianthus caryophyllus*) 黄酮糖基转移酶基因 *DicGT4* 在酿酒酵母中表达, 可大量合成柚皮素 7 - O - 葡萄糖苷和柚皮素 4' - O - 葡萄糖苷 (Werner & Morgan, 2010); 将甘草 (*Radix glycyrrhizae*) 黄烷酮 2 - 羟化酶基因 *F2H* 和水稻 C - 糖基转移酶基因 *OsCGT* 转入酵母中, 可大量合成 2 - 羟基柚皮素 - C - 葡萄糖苷 (Brazier-Hicks & Edwards, 2013)。

## 5 展望

随着基因组学的发展, 大量植物 UGT 家族成员被报道, 然而目前得到充分功能验证的成员尚少。UGT 对受体和糖供体的偏好性及催化位点决定了次生代谢产物的多样性, 然而其偏好性机制复杂, 尚有很大研究空间, 目前的研究多停留在酶的体外催化活性、生化特征分析等水平, 仅少数 UGT 成员的研究涉及转基因等植物体内功能验证。此外, UGT 相关的转录调控鲜有研究。随着分子生物学的发展, 基因过表达或敲除以及基因编辑技术取得突破, 从遗传学角度深入研究并验证不同 UGT 的生物学功能更为高效准确, 这对将来通过基因工程进行农作物的改良育种来说具有重要意义。

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