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6,8-二异戊烯基染料木素(6,8-Diprenylgenistein)的生物活性研究进展

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摘 要

6,8-二异戊烯基染料木素(6,8-Diprenylgenistein)，一种源自豆科植物的天然异黄酮类化合物，其主要来源包括甘草和刺桐等植物。该化合物的独特之处在于其分子结构中包含两个异戊烯基侧链，这种结构的特殊性赋予了其独特的生物活性和药理作用。本文旨在综述该化合物在生物活性研究方面的最新进展。

关键词

6,8-二异戊烯基染料木素，天然产物，生物活性

Research Progress on the Biological Activity of 6,8-Diprenylgenistein

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Abstract

6,8-Diprenylgenistein is a natural isoflavone compound derived from leguminous plants, mainly from plants such as licorice and Erythrina. The uniqueness of this compound lies in the fact that its molecular structure contains two isopentenyl side chains, which endows it with unique biological activity and pharmacological effects. This article aims to review the latest progress in the study of the biological activity of this compound.

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Keywords

6,8-Diprenylgenistein, Natural Product, Biological Activity

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1. 引言

6,8-二异戊烯基染料木素(6,8-Diprenylgenistein)也叫 6,8-二异戊烯基金雀异黄素(见图 1)是从豆科植物中提取的一种天然异黄酮类化合物，主要来源于甘草、刺桐等植物。

甘草(*Glycyrrhiza uralensis* Fisch.) (豆科甘草属)是中国传统医学中最古老的药物之一[1]，其主要来源于乌拉尔甘草、胀果甘草和光果甘草的根和根茎，用于治疗咳嗽、流感和癌症[2] [3]。在过去的几十年里，一些研究小组研究了甘草根部的化学成分和生物活性。通过先前的化学研究已鉴定出约 100 种酚类化合物，其中许多是异戊二烯取代的酚类结构[4] [5]。

被子植物刺桐属(Erythrina) (豆科)约有 200 多种种类，主要分布在热带和亚热带地区，其中在中国有十余种野生和人工栽培的刺桐。刺桐(*Erythrina variegata* L.)是一种灌木，可长到 12~15 米高，广泛分布于东亚和东南亚。作为一种民间药物，其树皮和叶子用于治疗咳嗽、蠕虫、痢疾、发烧、失眠、脾病以及产后呕吐[6] [7]。提取物具有一系列有趣的生物活性，例如驱虫、细胞毒性、抗氧化和抗糖尿病等特性[8] [9]。

从甘草、刺桐中提取的 6,8-Diprenylgenistein 是一种具有独特化学结构的异黄酮类化合物，其结构中包含两个异戊烯基侧链，分别位于 A 环的 6 位和 8 位。这种结构的特殊性赋予了它独特的生物活性和药理作用[10]。

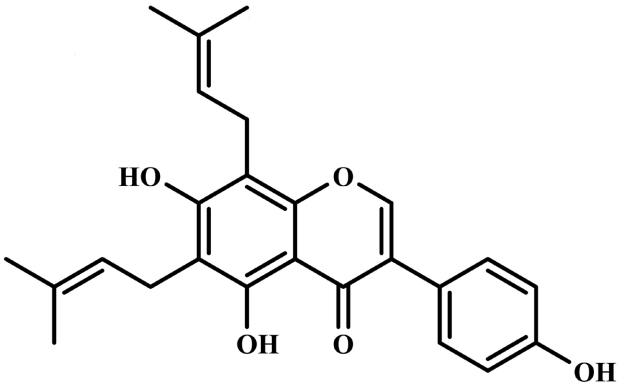

Figure 1. 6,8-Diprenylgenistein
图 1. 6,8-二异戊烯基染料木素

2. 抗糖尿病活性

2 型糖尿病(T2DM)是一种异质性代谢紊乱，其特征是胰腺 β 细胞胰岛素分泌受损，以及肝脏、脂肪组织和骨骼肌等外周组织出现胰岛素抵抗[11]。

在胰岛素刺激条件下，骨骼肌约占葡萄糖吸收的 75%，体外和体内均观察到 2 型糖尿病患者骨骼肌

在胰岛素刺激下葡萄糖摄取减少[12] [13]。

在当前市场上，一些广泛使用的降糖抗糖尿病药物，例如二甲双胍、罗格列酮和吡格列酮，已被证实能够促进骨骼肌对葡萄糖的摄取[14] [15]。因此，肌肉对葡萄糖的摄取可被视为治疗 2 型糖尿病的一个极佳靶点。葡萄糖进入组织的过程在很大程度上是由一系列促进载体蛋白的成员介导的，这些蛋白被称为葡萄糖转运蛋白(GLUT) 1~12 [16]。GLUT4 在骨骼肌细胞中高度表达，这些细胞表现出受调节的胰岛素反应性葡萄糖摄取。GLUT4 表达的增加已被证明可以降低血糖，增强骨骼肌中的葡萄糖转运和葡萄糖利用[17]。GLUT1 被认为是作用于与 AMPK 激活相关的基础葡萄糖转运的主要部分[18] [19]。L6 成肌细胞和转基因小鼠中 GLUT1 的过度表达导致基础葡萄糖摄取率增加[20] [21]。因此，基础和胰岛素刺激的骨骼肌葡萄糖摄取可能至少部分受肌肉组织中 GLUT1 和 GLUT4 表达水平的调节。蛋白酪氨酸磷酸酶 1B (PTP1B)负向调节胰岛素信号，并参与葡萄糖摄取途径[22]。转基因小鼠中 PTP1B 的过度表达使葡萄糖摄取活性降低 40%~50% [23]。小鼠中 PTP1B 的整体缺失会导致全身胰岛素敏感性增加、骨骼肌对葡萄糖的摄取增强以及葡萄糖耐受性改善[24]。因此，PTP1B 和 GLUT 抑制剂被认为是治疗 2 型糖尿病的高度有效靶点[25]。

抗 PTP1B 活性

Table 1. Inhibitory activities of 6,8-Diprenylgenistein and compounds 1~27 against PTP1B
表 1. 6,8-Diprenylgenistein 和化合物 1~27 的 PTP1B 抑制活性

compound	inhibition (%)[a]	IC50 (μM)[b]	compound	inhibition (%)[a]	IC50 (μM)[b]
1	37.50 ± 5.59		(+)-1`R,2`R-15a	68.27 ± 2.90	18.24 ± 2.74
(+)-2S,3R-2a	24.76 ± 8.65		(−)-1`S,2`S-15b	82.66 ± 2.30	14.70 ± 4.61
(−)-2R,3S-2b	40.92 ± 4.60		16	46.87 ± 0.00	
3	86.17 ± 8.05	8.99 ± 1.07	17	31.72 ± 7.70	
(+)-R-4a	47.54 ± 1.75		18	84.79 ± 11.51	12.61 ± 0.74
(−)-S-4b	47.68 ± 1.15		19	82.66 ± 0.76	10.98 ± 1.76
5	27.59 ± 9.65		20	82.10 ± 9.20	8.18 ± 2.12
6	42.89 ± 3.14		21	86.45 ± 10.40	11.32 ± 1.51
7	47.63 ± 12.65		22	32.28 ± 5.40	
8	46.05 ± 0.36		6,8-Diprenylgenistein	83.2 ± 14.91	14.42 ± 7.70
9	32.54 ± 3.45		24	84.82 ± 3.45	3.21 ± 0.24
10	35.62 ± 0.20		25	37.50 ± 0.24	
11	83.73 ± 1.75	12.13 ± 0.59	26	28.16 ± 6.55	
12	65.02 ± 1.15	15.25 ± 0.85	27	79.41 ± 0.80	19.17 ± 4.30
13	84.45 ± 13.37	13.80 ± 1.65	Oleanolic acid[c]		2.62 ± 0.07
14	36.32 ± 4.05				

a: The preliminary screening concentration at 20 μM; b: Values were determined by regression analysis and expressed as mean ± SD, n = 3; c: Positive control.

通过实验表明 6,8-Diprenylgenistein 对 PTP1B 具有较好的抑制效果。Lee M S 等研究者对 *T. scandens* 的枝条进行了甲醇提取，并通过多种色谱技术分离得到了 6,8-Diprenylgenistein。该化合物首次被用于葡萄糖摄取实验，结果表明其对空白组和胰岛素处理组的葡萄糖摄取具有显著的剂量依赖性刺激作用，在 25 mM 浓度下分别实现了 161%和 247%的葡萄糖摄取率提升。此外，6,8-Diprenylgenistein 对 PTP1B 的抑制活性进行了测定，其 IC50 值为 28.13 ± 0.19 μM，显示出中等强度的抑制效果[26]。

并且对 α 葡萄糖苷酶(α-Glucosidase)同样具有活性。Fan J 等研究者对乌拉尔甘草地上部分的乙醇提取物进行了分析，发现 6,8-Diprenylgenistein 在 10 μM 浓度下对 α 葡萄糖苷酶的抑制活性超过 40%，同时对 PTP1B 的抑制率超过 80% [27]。这说明 6,8-Diprenylgenistein 对于抗糖尿病具有双靶点作用。

随后，Liu C Y 等研究者于 2023 年从刺桐(*Erythrina variegata* L.)的乙醇提取物中分离出 6,8-Diprenylgenistein，并在 20 μM 浓度下对其 PTP1B 抑制活性进行了测定，抑制率为 83.2% ± 14.91%，IC50 值为 14.42 ± 7.70 (μM) (见表 1) [28]。

综上所述，6,8-Diprenylgenistein 对治疗 T2DM 具有良好活性，可对其结构进一步衍生化，寻找治疗药物。

3. 抗菌活性

单核细胞增生李斯特菌(*Listeria monocytogenes*)是一种具有高度致病性的病原体，同时也是引发食源性疾病——李斯特菌病的主要病原体。该病主要影响免疫系统功能不全的人群、老年人、孕妇以及婴幼儿。尽管李斯特菌病的发病率相对较低，但其病死率却相对较高。根据欧洲食品安全局(EFSA)和欧洲疾病预防控制中心(ECDC)在 2021 年的报告，2020 年欧盟共记录了 1876 例确诊的侵袭性人类病例，病死率达到了 13.0% [29]。

单核细胞增生李斯特菌展现出极强的环境适应性，能在多种环境条件下生长和存活，导致其在食物链中持续存在[30]。该病原体能够在低温、低 pH 值、高盐浓度以及有氧或无氧条件下生长，这进一步突显了在食品及其相关环境中控制该病原体的复杂性[31]。

变形链球菌(*Streptococcus mutans*)为革兰氏染色阳性的球菌，是口腔天然菌群中占比例最大的链球菌属中的一种，为牙斑的主要成分之一，与龋齿的形成密切相关。鉴于此，开发能够有效抑制变形链球菌活性的新型抗菌剂显得尤为迫切[32]。

牙菌斑，作为口腔生物膜的一种，于牙齿表面形成，对龋齿的发病机制具有决定性影响。尽管口腔微生物群落种类繁杂且结构复杂，变形链球菌由于其在牙面形成生物膜的特殊能力，被广泛认定为导致人类龋齿的主要病原体[33] [34]。因此，抑制变形链球菌的活性及其生物膜的形成，已成为预防龋齿的关键策略之一。

3.1. 抗变形链球菌活性

He J 及其研究团队从乌拉尔甘草(*Glycyrrhiza uralensis*)根部的乙醇萃取物中成功分离出 6,8-Diprenylgenistein。该研究采用美国国家临床实验室标准委员会(NCCLS)推荐的最低抑菌浓度(MIC)测定方案[35]，并对其进行了适当调整[36]，以评价对革兰氏阳性口腔细菌——变形链球菌的体外抗菌效力。研究结果表明，该化合物对变形链球菌具有显著的抗菌活性，其最低抑菌浓度测定为 2 μg/mL [10]。

与之前研究相同，Ahn S J 等人同样从乌拉尔甘草根部的乙醇萃取物中分离得到 6,8-Diprenylgenistein，并测定了对变形链球菌 UA159 的 MIC 为 4 μg/mL。随后该课题组进行了四甲基偶氮唑盐分析法(MTT)，以评测葡萄糖酸氯己定(CHX)和 6,8-Diprenylgenistein 等化合物在对变形链球菌 UA159 具有抗菌作用的浓度下是否对正常人牙龈成纤维细胞(NHGF)具有细胞毒性。6,8-Diprenylgenistein 在 1 × MIC (4 μg/mL)的

浓度下对 NHGF 细胞无细胞毒性作用(细胞存活率约为 95%)，在 2 × MIC (8 μg/mL)的浓度下细胞存活率为 77.9%。根据前人对细胞毒性的分类[37] [38]，6,8-Diprenylgenistein 可能适合在浓度高达 8 μg/ml 的体内使用[39]。综上所述，6,8-Diprenylgenistein 具有显著抗变形链球菌活性。

3.2. 抗李斯特菌活性

6,8-Diprenylgenistein 对李斯特菌也有较强抑制活性。在 2023 年 Bombelli A 等人对此进行了研究。多项研究表明，基质的温度和 pH 值的波动对抗菌化合物的活性具有显著影响，尤其对于单核细胞增生的李斯特菌而言，这一点尤为重要，因为该菌种能够适应多变的环境条件[40]-[42]。

李斯特菌适应环境变化的策略之一就是响应外部压力(如低温和低 pH 值等)从而调整其细胞质膜的组成[43] [44]，鉴于细胞质膜作为细胞的第一道防线，同时也是多种化合物的作用靶点，膜组成的改变能够显著地影响抗菌活性[45]。

因此有课题组研究了在不同温度(10℃到 37℃)、pH 值(5 和 7.2)和氧气浓度(有氧和无氧)的情况下对李斯特菌的抑制活性。在所有测试条件下，6,8-diprenylgenistein 的体外最低抑菌浓度在 0.8 至 12.5 μg/ mL 之间[46]。

综上所述，6,8-Diprenylgenistein 在不同环境条件下均对李斯特菌有较强抑制活性。

3.3. 其他抗菌活性

在 2004 年 Dastidar S G 等人筛选了 11 种异黄酮化合物，首先对 12 种已知的革兰氏阳性菌和革兰氏阴性菌的抗菌性能进行了评测，其中 6,8-Diprenylgenistein 表现出显著抗菌活性(表 2)。随后该课题组进行了小鼠体内实验，对照组 60 只小鼠在感染肠道沙门氏菌肠道亚种(*S. typhimurium* NCTC 74)后 100 小时内死亡 48 只，而经过不同剂量 6,8-Diprenylgenistein 治疗的小鼠均无死亡。表明该化合物对药物治疗组有显著保护作用[47]。

Table 2. Minimum inhibitory concentration (MIC) of 6,8-Diprenylgenistein
表 2. 6,8-Diprenylgenistein 的最低抑菌浓度(MIC)

Bacterial strain	No. tested	Minimum inhibitory concentration (mg/l)				
		25	50	100	200	>200
Staphylococcous aureus	39	5	12	9	10	3
Salmonella spp.	31	4	5	6	12	4
Shigella spp.	35	6	8	5	10	6
Klebsiella spp.	9			2	5	2
Pseudomonas spp.	11		1	3	7	
V. cholerae	69	6	8	24	24	7
V. parahaemolyticus	20	2	5	5	8	
Total	214	23	39	54	76	22

6,8-Diprenylgenistein 对多种真菌均有抑制活性(见表 2)。在 2011 年 Chukwujekwu J C 等人从南非刺桐(*Erythrina caffra* Thunb.)茎皮的丙酮提取物中分离得到了 6,8-diprenylgenistein，并对枯草芽孢杆菌(*Bacillus subtilis*)、肺炎克雷伯菌(*Klebsiella pneumoniae*)、大肠杆菌(*Escherichia coli*)、金黄色葡萄球菌(*Staphylococcus aureus*)进行了最低抑制浓度测定，结果分别为 15.6、7.8、7.8、7.8 (μg/ml) [48]。

4. 抗癌活性及抗肥胖活性

4.1. 抗癌活性

Bae M G 等学者于 2020 年开展了一项研究，旨在探究 6,8-Diprenylgenistein 对 VEGF-A 诱导的淋巴管生成的体外抑制效应。研究采用人淋巴微血管内皮细胞(HLMEC)作为实验对象，执行了细胞增殖、管腔形成及迁移实验(见图 2)。

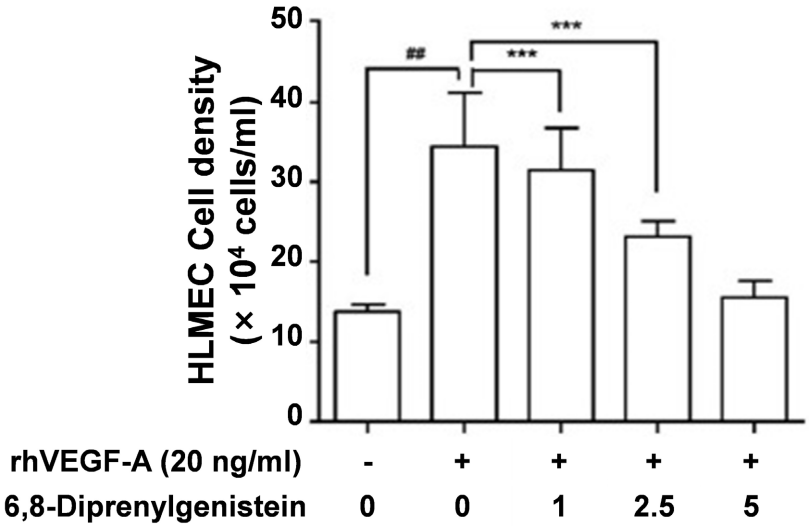

Figure 2. Effects of 6,8-DG on VEGF-A-induced human lymphatic microvascular endothelial cells (HLMEC) proliferation. Cells were detached and counted using a hemocytometer. Data are presented as a mean ± S.D. of three independent experiments ($^{\#\#}p < 0.001$, $^{***}p < 0.001$)
图 2. 6,8-Diprenylgenistein 对 VEGF-A 诱导的人淋巴管内皮细胞增殖的影响。分离细胞并用血细胞计数器计数，数据表示为三个独立实验的平均标准差($^{\#\#}p < 0.001$，$^{***}p < 0.001$)

通过实时定量聚合酶链反应(RT-PCR)、蛋白质印迹(Western blot)、免疫共沉淀、酶联免疫吸附测定(ELISA)以及共免疫沉淀技术，对 6,8-Diprenylgenistein 的蛋白表达水平及其作用机制进行了深入分析。此外，研究还利用前哨淋巴结口腔癌(OCSLN)动物模型，评估了 6,8-Diprenylgenistein 在体内的抑制效果。研究结果显示，6,8-Diprenylgenistein 在体内外均能有效抑制 VEGF-A 诱导的淋巴管生成及淋巴结转移。进一步的机制研究表明，6,8-Diprenylgenistein 的抑制作用可能与其在癌细胞中抑制 VEGF-A 表达以及在 HLMEC 中阻断 VEGFA/VEGFR-2 信号通路有关[49]。

基于上述发现，6,8-Diprenylgenistein 有潜力成为预防和治疗口腔癌转移的新型且具有重要价值的治疗药物。

4.2. 抗肥胖活性

6,8-Diprenylgenistein (DPG)同样对抗肥胖具有活性。在 2015 年 Jo Y H 等人从柘树果实(*Cudrania tricuspidata*)中成功分离出并进行抗肥胖活性研究。该研究采用高脂饮食(HFD)诱导的肥胖小鼠模型，以 10 mg/kg 和 30 mg/kg 剂量对 DPG 的抗肥胖效应进行了为期六周的连续研究。研究结果显示，DPG 治疗组的体重显著低于 HFD 对照组。

此外，HFD 与 DPG 联合处理组的附睾脂肪组织和肝脏中的脂肪沉积显著减少。与食物摄入量相等的 HFD 对照组相比，HFD 与 DPG 联合处理组的食物效率比亦有所降低。HFD 对照组中升高的代谢参数在 HFD 与 DPG 联合处理组中得到降低。进一步的机制研究表明，DPG 通过调节转录因子，如过氧化物

酶体增殖物激活受体γ(PPARγ)和CCAAT/增强子结合蛋白α(C/EBPα)，以及激素，如瘦素和脂联素，有效抑制脂肪生成基因的表达。DPG还通过激活AMP活化蛋白激酶(AMPK)来调节乙酰辅酶A羧化酶(ACC)和羟基-3-甲基戊二酰辅酶A还原酶(HMGCR)。综上所述，DPG对于调节肥胖，特别是由高脂肪摄入引起的肥胖具有积极的调节作用[50]。

5. 结语

6,8-二异戊烯基染料木素在治疗高血糖方面具有潜在的应用价值，具有多种生物活性，包括抗菌、抗癌、抗PTP1B等作用，且不良反应低，细胞毒性小。因此6,8-二异戊烯基染料木素有望成为一种广谱新型活性药物。

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