

木姜叶柯提取物二氢查尔酮治疗 2 型糖尿病及其并发症的研究进展

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[摘要] 2 型糖尿病(type 2 diabetes mellitus, T2DM)是一种常见的代谢性和内分泌疾病,长期高血糖水平会导致多种严重的慢性并发症,给社会 and 患者带来巨大的经济负担。尽管目前有多种降糖药物可供临床使用,但它们往往无法满足 T2DM 并发症的治疗需求。因此,迫切需要寻找新的治疗策略和药物。木姜叶柯被誉为集茶、糖、药于一体的“树上虫草”,在传统医学中具有悠久的使用历史。研究发现,木姜叶柯提取物富含二氢查尔酮类化合物,主要包括三叶苷、根皮苷和根皮素,具有抗炎、抗氧化、降血糖、降血脂、肝脏保护及心脏保护等多种药理活性,这使得它们在治疗 T2DM 及其并发症方面具有潜在的应用价值。该综述系统收集并整理了近十年关于木姜叶柯提取物中二氢查尔酮类化合物(三叶苷、根皮苷和根皮素)的相关文献,重点阐述了它们通过降低胰岛素抵抗、调节葡萄糖转运、改善糖脂代谢、调控酶类活性、调节肠道菌群,以及抗炎和抗氧化损伤等机制治疗 T2DM 及其并发症方面的最新研究进展。旨在为木姜叶柯提取物中的二氢查尔酮(三叶苷、根皮苷和根皮素)防治 T2DM 及其并发症的进一步研究提供参考和依据。

[关键词] 木姜叶柯; 二氢查尔酮; 三叶苷; 根皮苷; 根皮素; 2 型糖尿病; 并发症

Research progress on dihydrochalcones from *Lithocarpus litseifolius* extracts in treatment of type 2 diabetes mellitus and its complications

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[Abstract] Type 2 diabetes mellitus (T2DM) is a prevalent metabolic and endocrine disorder. Long-term hyperglycemia can lead to severe chronic complications, imposing substantial economic burdens on both society and patients. Despite the availability of various hypoglycemic agents for clinical use, these agents often fail to meet the therapeutic needs of T2DM and its complications. Consequently, there is an urgent need for novel therapeutic strategies and drugs. *Lithocarpus litseifolius* (*L. litseifolius*), commonly referred to as "cordyceps on trees", has a long history of use in traditional medicine and can be applied in tea, sugar, and medicine. Research indicates that *L. litseifolius* extracts are rich in dihydrochalcones, including trilobatin, phloridzin, and phloretin, which exhibit a range of pharmacological activities, such as anti-inflammatory, antioxidant, hypoglycemic, hypolipidemic, hepatoprotective, and cardioprotective effects. These properties suggest potential applications in the treatment of T2DM and its complications. This review systematically compiled and organized the relevant literature from the past decade on dihydrochalcones (trilobatin, phloridzin, and phloretin) from *L. litseifolius* extracts. It highlighted recent research progress regarding their role in treating T2DM and its complications through mechanisms such as reducing insulin resistance, regulating glucose transport, improving glucose and lipid metabolism, modulating enzyme activity, regulating gut microbiota, and alleviating inflammation and oxidative damage. The purpose of

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this review is to provide a reference and basis for future research on the prevention and treatment of T2DM and its complications using dihydrochalcones (trilobatin, phloridzin, and phloretin) from *L. litseifolius* extracts.

[Key words] *Lithocarpus litseifolius*; dihydrochalcones; trilobatin; phloridzin; phloretin; type 2 diabetes mellitus; complications

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2 型糖尿病(type 2 diabetes mellitus, T2DM)的发病率正在急剧上升,已成为全球性的公共卫生问题^[1]。长期高血糖水平会损害器官,引发心血管疾病、肾病、视网膜病变等多种并发症^[2-3]。根据国际糖尿病联盟的数据,2021 年全球约有 5.4 亿成年人患有糖尿病,其中超过 90% 为 T2DM,且 670 万人因糖尿病或其并发症死亡^[4-5]。目前临床上主要依靠西药来控制血糖,但这些药物无法满足 T2DM 并发症的治疗需求。因此,迫切需要开发一种能够同时针对 T2DM 及其并发症的有效预防或治疗药物。

木姜叶柯是一种在中国南方广受欢迎的茶饮^[6],在我国已有 1 500 年的使用历史,并于 2017 年被批准为新食品资源植物。木姜叶柯富含二氢查尔酮,具有抗氧化、抗炎、降血糖、降血脂、肝保护、心脏保护等多种健康益处,特别是在治疗糖尿病方面具有显著的降血糖作用^[7-8],这些作用主要与二氢查尔酮中的三叶苷、根皮苷和根皮素(主要成分化学结构见中国知网本文增强出版附加材料)有关^[7,9]。这些机制涉及不同的分子靶点和信号通路的调节,表明二氢查尔酮具有多靶点、多途径、多层次的治疗优势,其综合治疗潜力值得进一步研究和开发。

1 木姜叶柯提取物中主要二氢查尔酮(三叶苷、根皮苷和根皮素)对 T2DM 的作用机制

1.1 通过降低胰岛素抵抗(insulin resistance, IR)治疗 T2DM IR 作为 T2DM 的主要发病机制,贯穿整个疾病过程^[10]。其作用机制与机体胰岛素信号传导异常有关^[11]。高血糖会诱导胰岛细胞释放胰岛素进入血液中,激活肝脏、肌肉和脂肪等靶组织细胞膜上的胰岛素受体,启动胰岛素信号传导,并促使葡萄糖转运蛋白 4(glucose transporter type 4, GLUT4)从细胞内转移到细胞表面,促进其摄取葡萄糖(相关机制图见中国知网本文增强出版附加材料)。在肥胖动物模型中,胰岛素受体底物(insulin receptor substrate, IRS)/蛋白激酶 B(protein kinase B, Akt)/GLUT4 信号通路在 IR 的进展中发挥重要作用^[12-14]。研究表明,三叶苷可通过 IRS/Akt/GLUT4 信号通路改善 C2C12 肌管和 T2DM 小鼠的 IR,提高葡萄糖耐量,降低空腹血糖和胰岛素水平^[15]。根皮素与二甲双胍联用可增加 T2DM 大鼠骨骼肌和肝脏中胰岛素受体底物 1(insulin receptor substrate 1, IRS-1)、磷脂酰肌醇 3-激酶(phosphatidylinositol 3-kinase, PI3K)、磷酸化蛋白激酶 B(phospho-protein kinase B, p-Akt)和 GLUT4 的表达,从而有助于预防和治疗 T2DM^[16]。在 T2DM 大鼠和 L6 肌管中,根皮苷通过上调 Akt、PI3K、IRS-1 和 GLUT4 的表达,在体内外均表现出降血糖作用^[17]。

氧化应激可导致胰岛素诱导的葡萄糖转运和胰岛素信号传导通路的功能障碍,进而导致 IR^[18]。因此,缓解氧化应激和抑制异常的胰岛素信号传导是治疗 T2DM 的重要策略。研究发现,根皮素通过没食子酸水凝胶肠道释放,减轻糖尿病的氧化应激^[19]。核因子 E2 相关因子 2(nuclear factor erythroid 2-related factor 2, Nrf2)是调节氧化应激反应的关键转录因子,Nrf2/抗氧化反应元件(antioxidant response element, ARE)信号通路的激活在抗氧化应激中起关键作用^[20]。研究表明,在 T2DM 小鼠中,三叶苷通过激活 Nrf2/ARE 信号通路,介导胰岛素信号传导,改善 IR,表现出显著的抗 T2DM 作用^[21]。

抑制细胞周期蛋白依赖性激酶 5(cyclin-dependent kinase 5, Cdk5)介导的过氧化物酶体增殖物激活受体 γ (peroxisome proliferator-activated receptor gamma, PPAR γ) Ser273 位点的磷酸化是治疗 T2DM IR 的关键策略。生物活性植物分子长期以来一直被认为是 PPAR γ 治疗 IR 和 T2DM 的天然调节剂^[22]。研究发现,在 3T3L1 细胞中,根皮素和根皮苷通过抑制 Cdk5 的激活和随后 PPAR γ 在 Ser273 位点的磷酸化,调节胰岛素敏感性和脂质代谢相关基因的表达来减轻 IR^[23]。在 T2DM 小鼠中,根皮苷和根皮素可通过抑制 PPAR γ S273/Cdk5 的相互作用来减轻炎症应激,改善脂肪和肝脏的 IR^[24]。

巨核细胞蛋白酪氨酸磷酸酶-微管相关蛋白 2(protein tyrosine phosphatase-microtubule-associated protein 2, PTP-MEG2)通过拮抗胰岛素功能导致 T2DM 相关的 IR^[25-26]。研究发现,根皮苷可通过抑制 PTP-MEG2 的催化活性,激活腺苷酸激活蛋白激酶(adenosine monophosphate-activated protein kinase, AMPK)和 Akt 信号通路,促进细胞摄取葡萄糖并改善 IR^[27]。

1.2 通过改善糖脂代谢紊乱治疗 T2DM 糖脂代谢紊乱是 T2DM 最基础的病理表现特征,也是疾病恶化的主要原因和各种致命并发症的诱因^[28-30]。AMPK 在肝脏糖脂代谢的调节中起着关键作用^[31],并已成为治疗 T2DM 的重要靶点。研究显示,三叶苷可通过改善糖耐量、肝组织中的 IR、脂肪肝、血脂和空腹血糖水平,显著缓解 T2DM 小鼠的糖脂代谢紊乱,其机制可能与 AMPK/磷酸烯醇式丙酮酸羧激酶(phosphoenolpyruvate carboxykinase, PEPCK)/葡萄糖-6-磷酸酶(glucose-6-phosphatase, G6Pase)信号通路及 AMPK/乙酰辅酶 A 羧化酶(acetyl-CoA carboxylase, ACC)/肉碱棕榈酰转移酶-1(carnitine palmitoyltransferase-1, CPT-1)信号通路的调控有关^[32]。根皮苷可抑制 IR 型 HepG2(insulin-re-

sistant HepG2, IR-HepG2) 细胞的 G6Pase 表达和葡萄糖摄取,并可降低小鼠和大鼠的血糖,改善血脂水平,减少肝细胞中的脂肪沉积,对高血糖及高血脂均具有治疗和预防作用^[33-34]。

PPAR γ 可调节多种生物过程,如炎症反应及葡萄糖和脂肪酸代谢^[35-36]。刺激 PPAR γ 磷酸化会导致血脂异常、高血糖及 IR,最终导致 T2DM^[37]。根皮苷和根皮素可通过阻断 PPAR γ 磷酸化来抑制炎症反应、脂肪酸摄取和脂肪生成,降低肿瘤坏死因子(tumor necrosis factor, TNF)- α 、白细胞介素-6(interleukin-6, IL-6)和单核细胞趋化蛋白-1(monocyte chemoattractant protein-1, MCP-1)水平,增加脂联素分泌和胰岛素敏感性,改善 T2DM 小鼠空腹血糖和血脂谱[高密度脂蛋白(high-density lipoprotein, HDL)、低密度脂蛋白(low-density lipoprotein, LDL)、总胆固醇(total cholesterol, TC)和甘油三酯(triglycerides, TG)]的失调^[24]。三叶苷通过减轻炎症反应和细胞焦亡,恢复糖尿病小鼠的糖代谢紊乱和肝功能,并减轻脂质积累^[38]。

1.3 通过重建肠道菌群稳态治疗 T2DM 肠道菌群失调和肠道屏障损伤与 IR、慢性炎症和脂质代谢异常密切相关,是 T2DM 发病的重要因素^[39-41]。肠道微生物群失调可能导致肠道屏障功能受损^[42-43],使肠道衍生物脂多糖(lipopolysaccharide, LPS)进入血液,从而引发内毒素血症^[44]。此外,肠道菌群失调还会导致巨噬细胞在脂肪组织中聚集,促进炎症因子的释放,诱导 IRS-1 异常磷酸化,最终引发 IR^[45]。然而,某些肠道微生物对由 LPS 引起的内毒素血症和炎症反应具有保护作用。例如,阿克曼黏液菌通过调节细胞外囊泡降低肠道通透性,激活肠上皮细胞中的 AMPK,从而改善肠道紧密连接和完整性,增强肠道防御能力,并降低 LPS 水平^[46-47]。短链脂肪酸(short-chain fatty acids, SCFAs)作为肠道菌群与宿主之间的信号分子,通过抑制炎症反应和氧化应激来调节脂质代谢^[48]。SCFAs 还可以通过抑制内毒素相关炎症和保护肠黏膜屏障来降低 IR^[43]。根皮苷可通过增加阿克曼黏液菌和普氏菌的数量,调节肠道微生物群落结构和肠道屏障完整性,降低血清 LPS 和 IR 水平,提高 SCFAs 水平,进而调节 T2DM 小鼠的血糖水平^[43, 49]。

中药与肠道菌群之间相互作用,在预防或治疗疾病、促进人体健康方面拥有巨大的潜力^[50]。但目前肠道菌与 T2DM 的关系以及木姜叶柯提取物二氢查尔酮与肠道菌相互作用的机制、代谢产物等仍需进一步研究探索,需整合研究方法和多组学技术,系统阐明肠道微生物与人体的相互关系并筛选出影响中药活性成分疗效的肠道菌。

1.4 通过抑制葡萄糖转运治疗 T2DM 钠-葡萄糖共转运体(sodium-glucose cotransporter, SGLT)和易化葡萄糖转运体(glucose transporter, GLUT)是体内葡萄糖的主要转运载体。SGLT 通过促进肾脏对葡萄糖的重吸收,引起糖尿病患者体内的葡萄糖无法通过尿液排出,从而导致血糖浓度升高。三

叶苷是一种钠-葡萄糖共转运体 1/2(sodium-glucose cotransporter 1/2, SGLT1/2)抑制剂^[51],适用于治疗 T2DM 餐后高血糖。根皮素也是一种高效的 SGLT1/2 抑制剂^[52],有助于促使糖尿病大鼠通过尿液排泄葡萄糖。根皮苷通过特异性和竞争性抑制 SGLT1/2,阻断葡萄糖的吸收或重吸收,从而使血糖水平恢复正常^[53-55]。然而,由于根皮苷在体内难以吸收及代谢成根皮素等原因,其治疗作用受到限制。此外,根皮苷的 SGLT1 抑制作用可能导致睾丸吸收功能下降,因此,根皮苷不能单独作为糖尿病的治疗药物^[56],通常作为生理学工具被广泛应用于 SGLT 潜在机制的研究^[57]。

1.5 通过抑制 α -葡萄糖苷酶活性治疗 T2DM α -葡萄糖苷酶是一种肠上皮分泌的碳水化合物水解酶,在人体小肠中将淀粉和碳水化合物水解为葡萄糖和单体糖来帮助消化^[58]。因此, α -葡萄糖苷酶是导致机体血糖升高的直接因素^[59]。 α -葡萄糖苷酶抑制剂被证明是治疗 T2DM 的一种有效策略^[60]。抑制 α -葡萄糖苷酶能够延缓葡萄糖进入血液,从而控制餐后高血糖^[61]。在临床应用中,常用的 α -葡萄糖苷酶抑制剂包括阿卡波糖、米格列醇和伏格列波糖,对治疗 T2DM 有显著的疗效^[62-65]。然而,由于其对 α -淀粉酶强烈的抑制作用,可引起患者出现胀气、腹泻等不良反应^[66-68]。目前,利用天然活性物质开发 α -葡萄糖苷酶抑制剂已经成为研究的热点。根皮苷及其十二烷基酰化衍生物能够抑制 α -葡萄糖苷酶活性^[69]。三叶苷作为一种较强的 α -葡萄糖苷酶抑制剂,有助于改善 T2DM 的血糖水平^[8, 70],同时,它对 α -淀粉酶的抑制作用较弱^[71]。这使得三叶苷既能有效控制 T2DM 的餐后血糖,又能避免因过度抑制 α -淀粉酶而引起的副作用。

木姜叶柯提取物中主要二氢查尔酮(三叶苷、根皮苷和根皮素)对糖尿病的作用机制总结见表 1。

2 木姜叶柯提取物中主要二氢查尔酮(三叶苷、根皮苷和根皮素)对 T2DM 并发症的作用机制

2.1 糖尿病肾病 在糖尿病肾病(diabetic nephropathy, DN)的发病机制中,足细胞损伤起关键作用^[72-73]。足细胞在维持肾小球滤过屏障(glomerular filtration barrier, GFB)的结构和功能中发挥重要作用^[74-76]。损害 GFB 的完整性可导致蛋白尿^[77-78],这是 DN 的关键临床特征之一。在肾损伤的 T2DM 小鼠模型中,低剂量的根皮素治疗可保护肾小球足细胞免受损伤,并改善肾小球基底膜增厚和足细胞足突消失^[79]。

免疫炎症反应和氧化应激是 DN 发病的重要病理机制^[80-82]。研究发现,根皮素可降低肾细胞中 TNF- α 和白细胞介素-8(interleukin-8, IL-8)诱导的炎症反应^[83]。根皮苷可通过减少氧化应激和改善脂质代谢来降低肾小球和肾小管功能障碍^[84],还可减轻 T2DM 大鼠的肾小球硬化、肾小管再生和炎症^[85]。

在 DN 中,AMPK 活性的受损会加速 DN 的进展^[86]。肾

表 1 木姜叶柯提取物中主要二氢查尔酮(三叶苷、根皮苷和根皮素)对糖尿病的作用机制

 Table 1 Action mechanisms of major dihydrochalcones (phlorizin, phloretin, and trilobatin) from *Lithocarpus litseifolius* extracts in alleviating diabetes mellitus

成分	模型	药物剂量	主要效应及相关机制	文献
三叶苷	链脲佐菌素(STZ)诱导小鼠糖尿病, C2C12 细胞胰岛素抵抗	10 mg·kg ⁻¹ , 0.1、1.0、10 μmol·L ⁻¹	通过 IRS/Akt/GLUT4 信号通路改善 C2C12 细胞肌管和雄性 ob/ob 小鼠的胰岛素抵抗	[15]
三叶苷	KK-Ay 型小鼠	10、20 mg·kg ⁻¹	通过 Nrf2/ARE 和 IRS-1/GLUT2 信号通路发挥抗 T2DM 作用	[21]
根皮苷/根皮素	小鼠 3T3-L1 成纤维细胞	5、10、20 μmol·L ⁻¹	破坏分化的脂肪细胞中 PPARγ/Cdk5 相互作用来改善胰岛素敏感性并增强葡萄糖摄取	[23]
根皮苷	C2C12 肌细胞及 3T3-L1 前脂肪细胞	1、10 μmol·L ⁻¹	通过激活 AMPK 和 Akt 信号通路,刺激葡萄糖摄取	[27]
根皮苷/根皮素	高脂饮食(HFD)诱导小鼠 T2DM	50、100 mg·kg ⁻¹	消除 PPARγ S273/Cdk5 的相互作用来减轻炎症应激,改善脂肪和肝脏的胰岛素抵抗	[24]
三叶苷	HFD 与 STZ 联合诱导的小鼠 T2DM	75、150 mg·kg ⁻¹	通过刺激 AMPK 和 ACC 磷酸化,抑制 PGC-1α、PCK1 和 G6Pase 的表达,抑制 AMPK 介导的糖异生和脂肪酸合成,从而改善糖脂代谢紊乱	[32]
根皮苷	db/db 小鼠	20 mg·kg ⁻¹	改变肠道微生物群,降低宿主的脂多糖负荷,产生较高水平的有益细菌,增强胰岛素敏感性	[49]
根皮苷	HFD 喂养的 C57BL/6J 小鼠	80 mg·kg ⁻¹	靶向肠道微生物群和肠道屏障的完整性,增强短链脂肪酸产生,改善内毒血症和胰岛素抵抗	[43]
三叶苷	斯特恩-沃尔默方程	0~180 μmol·L ⁻¹	三叶苷是一种较强的 α-葡萄糖苷酶抑制剂,可有助于改善 T2DM	[8]
三叶苷	HFD 联合 STZ 诱导小鼠糖尿病	20、60 mg·kg ⁻¹	通过减轻炎症反应和细胞焦亡,恢复糖尿病小鼠的葡萄糖代谢紊乱和肝功能,减轻脂质积累	[38]
根皮苷	诱导 HepG2 细胞和昆明小鼠胰岛素抵抗	40、60、80 mg·kg ⁻¹	抑制 IR-HepG2 细胞的 G6Pase 表达和葡萄糖摄取,增强小鼠葡萄糖耐量,降低餐后血糖水平,对稳定血糖和糖尿病辅助治疗效果良好	[34]
根皮苷	HFD 联合 STZ 诱导 SD 大鼠糖尿病	30、60、120 mg·kg ⁻¹	降低空腹血糖,保护胰岛免受损伤,减少肝细胞中的脂肪沉积,对糖尿病大鼠的高血脂和高血糖具有防治效果	[33]
根皮苷	肥胖型 T2DM 小鼠	400 mg·kg ⁻¹	作为 SGLT1/2 抑制剂,不仅用于控制血糖,还可减轻非酒精性脂肪性肝病的发展和/或进展	[55]
根皮素	STZ 联合高脂高糖诱导 SD 大鼠	100 mg·kg ⁻¹	与二甲双胍联合使用,可增加骨骼肌和肝脏中 IRS-1、PI3K、p-Akt 和 GLUT4 的表达	[16]
根皮素	诱导大鼠 T2DM 和 L6 肌细胞	100 mg·kg ⁻¹ 100 μmol·L ⁻¹	上调 Akt、PI3K、IRS-1 和 GLUT4 的表达,在体内和体外均具有降血糖作用	[17]
根皮苷及其十二烷基醚衍生物	肠道 Caco-2 细胞	0.3 μmol·L ⁻¹	根皮苷抑制 α-葡萄糖苷酶活性,抑制肠道葡萄糖的吸收	[69]
三叶苷	利文韦-伯克曲线,斯特恩-沃尔默方程	0.062 5、0.125、1 mg·kg ⁻¹	α-葡萄糖苷酶和 α-淀粉酶抑制剂,其 α-葡萄糖苷酶抑制作用超过阿卡波糖,有助于预防和治疗 T2DM	[70]
根皮素	Wistar 型大鼠	60、110、160、210 mg·mL ⁻¹	用于肠道释放根皮素的没食子酸水凝胶,是减少慢性糖尿病氧化应激的有前途的治疗策略	[19]

脏中 AMPK 的活性与 SGLT2 的表达呈负相关^[87]。抑制 SGLT2 可通过增加尿葡萄糖的排泄来诱导葡萄糖剥夺状态,从而激活能量传感器 AMPK,逆转 DN 的代谢紊乱,并改善肾脏炎症和纤维化^[88]。根皮苷和根皮素作为 SGLT1/2 的抑制

剂,可抑制近端肾小管对葡萄糖的重吸收,减轻糖尿病引起的肾脏损伤^[52,54]。

虽然二氢查尔酮抑制肾葡萄糖重吸收的主要作用是抗高血糖,但先前的研究表明,SGLT2 抑制剂具有多效性作用,

这可能解释了其在临床试验中改善肾脏预后的机制^[89-90]。

2.2 糖尿病视网膜病变 (diabetic retinopathy, DR) DR 是糖尿病的一种常见并发症,常会导致视力迅速下降^[91]。根皮素可以通过介导核因子红细胞衍生 2 样 2 (nuclear factor, erythroid 2-like 2, NFE2L2) 和细胞外信号调节激酶 1/2 (extracellular signal-regulated kinases 1/2, ERK1/2) 途径,降低 IL-6 和 IL-8 的分泌,从而防止线粒体损伤引起的视网膜色素沉着^[92]。根皮苷还可以预防 T2DM 大鼠的年龄相关视网膜病变,如视网膜折叠和增厚,并减少白内障的形成^[85]。

研究发现,DR 硬渗出的严重程度与 TG、LDL 和 TC 水平呈正相关,而与 HDL 水平呈负相关^[93]。因此,控制血脂水平可以改善视网膜血管内皮细胞的功能,减少眼底微血管的炎症和渗漏,从而延缓 DR 的进展^[94]。三叶苷通过调控 AMPK/PEPCK/G6Pase 和 AMPK/ACC/CPT-1 信号通路,显著缓解 T2DM 小鼠的糖脂代谢紊乱^[32]。根皮苷和根皮素通过阻断 PPAR γ 磷酸化来抑制炎症反应、脂肪酸摄取和脂肪生成,从而改善 T2DM 小鼠的空腹血糖水平及血脂谱 (HDL、LDL、TC 和 TG) 的失调^[24]。

DR 的特点是血-视网膜屏障 (blood-retinal barrier, BRB) 的破坏及视网膜血管的渗漏。高血糖、缺血、缺氧、氧化应激及炎症是糖尿病导致 BRB 破坏的主要诱发因素^[95]。根皮素通过激活 Nrf2 减少 IL-8 的分泌,在人视网膜色素上皮细胞中表现出显著的抗炎作用^[96]。研究发现,高血糖会导致视网膜周细胞的功能及形态学改变。根皮苷作为一种非选择性 SGLT 抑制剂,可通过直接作用于视网膜周细胞而对 DR 起到保护作用^[97]。

2.3 糖尿病心肌病 (diabetic cardiomyopathy, DCM) T2DM 会导致过度的氧化应激^[98-99],这是由于活性氧 (reactive oxygen species, ROS) 产生与氧化清除系统之间失衡所致^[100]。ROS 会引起心肌细胞损伤和纤维化,这些是心力衰竭的病理基础^[101]。研究发现,激活 Nrf2 可以快速有效地清除体内过量的 ROS,减少氧化应激^[21,102]。这表明在高糖诱导的心肌细胞损伤中,抗炎和抗氧化机制与 Nrf2 通路有关,且 Nrf2 在 DCM 中具有保护作用^[103-105]。研究表明,根皮素通过激活 Kelch 样环氧氯丙烷相关蛋白-1 (Kelch-like ECH-associated protein 1, Keap1) 和 Nrf2 复合物并抑制氧化应激来预防 DCM^[103]。此外,过量的 ROS 会引起心肌损伤,增加乳酸脱氢酶 (lactate dehydrogenase, LDH)、肌酸激酶同工酶 (creatinine kinase-MB, CK-MB)、心肌肌钙蛋白 T (cardiac troponin T, cTn-T) 和心肌肌钙蛋白 I (cardiac troponin I, cTn I) 的水平^[106-108]。这些心肌损伤标志物的水平与心肌损伤及心力衰竭程度呈正相关^[109-110]。因此,降低心肌损伤标志物已成为评估 2 型糖尿病心肌病心肌损伤改善的重要指标之一。根皮素能够降低 CK-MB、LDH、天冬氨酸转氨酶 (aspartate aminotransferase, AST) 和丙氨酸转氨酶 (alanine aminotransferase, ALT),从而改善心肌损伤^[111]。

沉默信息调节因子 2 相关酶 1 (sirtuin 1, SIRT1) 是 T2DM 中减轻氧化应激的调节基因,可降低 DCM 中的氧化应激水平^[112-114]。研究发现,根皮素通过恢复 SIRT1 的表达,保护心肌细胞免受高糖诱导的炎症和纤维化损伤^[104]。

心肌细胞凋亡的增加是 DCM 发展中的主要事件^[115]。己糖激酶 1 (hexokinase 1, HK1) 是调节 NOD 样受体热蛋白结构域相关蛋白 3 (NOD-like receptor pyrin domain containing 3, NLRP3) 炎症小体激活的关键因子^[116]。HK1 是糖酵解过程中负责第一反应的限速酶,并在许多炎症反应中过度表达^[117-118]。研究发现,根皮苷通过抑制 HK1 介导的 NLRP3 炎症小体激活来抑制心肌细胞焦亡,从而改善心肌纤维化^[119]。DCM 的病理基础可能由多种信号通路的相互作用引起,这些信号通路之间的关系还需进一步研究。

2.4 糖尿病大血管病变 T2DM 的代谢紊乱和 IR 等病理改变可能导致内皮功能障碍和一氧化氮 (nitric oxide, NO) 水平下降,这被认为是 T2DM 大血管并发症的重要机制^[120-121]。内皮型一氧化氮合酶 (endothelial nitric oxide synthase, eNOS) 异常会导致 NO 生成减少,损害内皮功能并引发动脉粥样硬化^[122]。上调锌指样转录因子 2 (Kruppel-like factor 2, KLF2) 水平可以有效恢复糖尿病小鼠的 eNOS 活性,维持内皮功能^[123]。因此,KLF2 很可能作为动脉粥样硬化治疗的潜在靶点^[124]。研究表明,低剂量根皮素通过恢复 KLF2 水平,可以缓解糖尿病动脉粥样硬化^[125]。此外,eNOS 衍生的 NO 在预防血栓形成和动脉粥样硬化中起重要的生理作用^[126]。NO 生成的增加依赖于 PI3K/Akt 通路对 eNOS 的激活^[127-128]。研究发现,根皮苷可通过激活 PI3K/Akt/eNOS 信号通路增加 NO 水平,从而对内皮功能障碍具有直接的保护作用^[129]。

在糖尿病患者中,高血糖和炎症是导致内皮细胞损伤的主要原因之一^[130-131]。内皮功能障碍可引起多种心血管并发症,包括血管纤维化和血管钙化。人骨形态发生蛋白 2 (bone morphogenetic protein 2, BMP2) 和破骨细胞分化因子 (receptor activator of nuclear factor kappa-B ligand, RANKL) 在血管钙化中^[132-133],转化生长因子 β (transforming growth factor β , TGF β) 在血管纤维化中起重要作用。根皮素在体内外均能降低 BMP2、TGF β 和 RANKL 的表达,表明其对糖尿病血管内皮损伤具有保护作用^[134]。此外,内皮细胞是首先受到高血糖破坏的细胞之一^[135]。在高糖、缺氧或炎症条件下,内皮细胞可能会失去其独特标记物血小板内皮细胞黏附分子-1 (platelet endothelial cell adhesion molecule-1, PECAM-1),并表达间充质干细胞标记物波形蛋白和细胞表面糖蛋白 (cell surface glycoprotein CD44)^[136]。这一过程被称为内皮细胞-间充质转分化 (endothelial-to-mesenchymal transition, EndMT)^[137]。因此,抑制 EndMT 可能是预防或改善糖尿病性心血管并发症的有前途的手段^[138]。研究表明,根皮素可以通过 AMPK 依赖的抗 EndMT 途径,逆转波形蛋白增加和 PE-

CAM-1 减少,从而改善糖尿病诱导的内皮损伤^[134]。

糖尿病和糖毒性通过加重内皮功能障碍、增加氧化应激、血脂异常和自主神经功能障碍,促进冠状动脉粥样硬化^[139]。巨噬细胞根据微环境的差异,可瞬态、可逆地极化为加剧炎症反应的 M1 表型及参与炎症反应改善的 M2 表型^[140-142]。M1 和 M2 型巨噬细胞平衡极化控制着炎症或损伤器官的命运^[141]。因此,巨噬细胞的扩增和向 M1 表型的极化是动脉粥样硬化发生的重要原因^[143]。研究发现,根皮苷、根皮素和三叶苷作为天然 SGLT1/2 抑制剂,可通过抑制 SGLT2,减少 M1 极化,增加 M2 极化^[51-54,144]。此外,糖尿病患者往往伴有血脂异常,其特征是 TG 和极低密度脂蛋白(very low-density lipoprotein, VLDL)升高、HDL 降低,从而增加心血管疾病风险^[145]。根皮苷治疗可以显著降低糖尿病小鼠的血糖和脂质水平,并通过改善肝脏胆固醇清除减少动脉粥样硬化病变^[146]。

2.5 糖尿病周围神经病变(diabetic peripheral neuropathy, DPN) 持续性高血糖和高血脂是导致外周神经元功能障碍的主要原因。高糖与糖基化和氧化应激直接相关,氧化应激可降低有髓鞘神经纤维的传导速度^[147]。IR 导致胰岛素在神经元中的作用降低,进而促进神经纤维的线粒体功能障碍^[148]。此外,糖尿病性血脂异常通过提高游离脂肪酸水平和影响雪旺细胞来促进神经元损伤^[52]。这些机制最终导致神经纤维的功能障碍和其他神经元的死亡。因此,控制高血糖、高血脂和改善 IR 成为治疗 DPN 的重要策略。根皮苷和根皮素可通过抑制 T2DM 小鼠中 PPAR γ S273/Cdk5 的相互作用来减轻炎症应激,改善脂肪和肝脏胰岛素抵抗,降低高血糖,调节脂代谢^[24]。根皮素具有良好的神经保护特性,低剂量的根皮素可防止甲基乙二醛诱导的晚期糖基化终产物生成,以保护细胞免受直接毒性^[52]。根皮苷可提高 T2DM 大鼠的坐骨神经传导速度和增强周围神经密度^[85]。此外,根皮素联合度洛西汀对糖尿病大鼠的 DPN 有良好的治疗作用^[52]。

2.6 糖尿病创面愈合延迟 在糖尿病患者中,高血糖会导致血管僵硬,阻碍血液循环,引起微血管功能障碍,最终导致组织缺氧^[149]。在这种情况下,过量的晚期糖基化终产物(advanced glycation end-products, AGEs)与其受体相结合,引发氧化应激和炎症,这是糖尿病血管损伤的关键因素^[150]。此外,高血糖还会延长炎症反应,抑制内皮细胞功能,损害血管生成,从而延迟伤口愈合^[151]。因此,抑制 AGEs 生成、增强抗氧化和抗炎作用以及控制血糖已成为促进伤口愈合的关键策略。

研究表明,根皮素可通过 Nrf2 依赖机制降低 AGEs 受体的表达,减少 AGEs 的生成^[152],这有助于促进伤口的愈合。根皮素还可以在高 ROS 浓度的高血糖环境中增强抗氧化作用,激活 PI3K/Akt 信号通路,增加 GLUT4 的易位和表达,从而改善葡萄糖的消耗和耐受性^[79,153-154]。此外,根皮素通过

没食子酸基水凝胶在肠道中释放,可有效缓解慢性糖尿病引起的氧化应激^[19]。

根皮苷也表现出抑制 AGEs 形成的潜力,通过阻断 AGEs 与晚期糖基化终产物受体的相互作用,降低肠道炎症的敏感性,并减少 AGEs 前体甲基乙二醛的生成^[155]。根皮苷还可通过增强抗氧化酶(如谷胱甘肽过氧化物酶、超氧化物歧化酶和过氧化氢酶)的活性,减少 HepG2 细胞在过氧化氢诱导下的凋亡,从而抑制氧化应激^[156]。

在糖尿病中,高血糖环境会损害白细胞功能并限制其在伤口部位的循环,因为血管的改变增加了其对病原体的脆弱性,使其更容易受到感染^[149,157]。此外,周围神经病变还可引起受影响区域的麻木和疼痛感下降,导致伤口被忽视,未经适当治疗就变成慢性^[157]。这些都是导致 T2DM 伤口愈合延迟的重要原因。因此,抑制创面感染及周围神经病变已成为治疗创面愈合延迟的重要方法。研究发现,根皮素能够抑制革兰阳性菌,特别是金黄色葡萄球菌和甲氧西林耐药金黄色葡萄球菌的临床菌株^[158],其联合度洛西汀对糖尿病大鼠的 DPN 有显著治疗效果^[52]。

在 T2DM 和肥胖患者的循环系统中,二肽基肽酶-4(dipeptidyl peptidase-4, DPP-4)水平升高^[159]。DPP-4 的过度激活能够切割趋化因子和血管分泌因子基质细胞衍生因子-1 α /C-X-C 基序趋化因子配体 12,从而阻碍肉芽组织的血管化和生长^[160]。研究表明,在正常小鼠中使用 DPP-4 抑制剂可以加速伤口愈合,并减少瘢痕形成^[161]。因此,抑制 DPP-4 的活性已成为改善伤口愈合的关键策略之一。根皮苷作为 DPP-4 抑制剂,通过抑制 DPP-4 活性,增强胰岛素分泌和葡萄糖摄取,从而改善 T2DM 的血糖水平^[162]。这有助于促进糖尿病创面的愈合。

2.7 糖尿病其他并发症 脑源性神经营养因子(brain-derived neurotrophic factor, BDNF)与抑郁症之间的相关性已经确立^[163]。动物和人类的研究均已证明,BDNF 在 T2DM 及其相关神经问题中起着关键作用^[164-165]。在 T2DM 中,谷胱甘肽(glutathione, GSH)的合成减少取决于 IR 和高血糖的程度^[166-167]。研究表明,GSH 的降低被认为是抑郁行为的主要标志,并已证明抑郁症中存在氧化应激^[168]。因此,BDNF、GSH 和氧化应激是 T2DM 相关抑郁症的关键病理因素。研究表明,根皮苷可通过减轻氧化应激和上调 BDNF 水平来改善 T2DM 诱导的小鼠抑郁^[169]。

BDNF、氧化应激和胆碱能神经传递受损是导致 T2DM 大鼠记忆缺陷的关键因素。糖尿病损害胆碱能信号,促进淀粉样蛋白的积累,这是阿尔茨海默病发病的主要原因^[170-172]。研究发现,根皮苷可通过上调神经营养因子、减少氧化应激和增强大脑胆碱能信号通路,改善 T2DM 诱导的记忆缺陷^[173]。

木姜叶柯提取物中主要二氢查尔酮(三叶苷、根皮苷和根皮素)对糖尿病并发症的作用机制总结见表 2。

表 2 木姜叶柯提取物中主要二氢查尔酮(三叶苷、根皮苷和根皮素)对糖尿病并发症的作用机制

Table 2 Action mechanisms of major dihydrochalcones (trilobatin, phloridzin, and phloretin) from *Lithocarpus litseifolius* extracts in alleviating complications of diabetes mellitus

疾病	成分	模型	药物剂量	主要效应及相关机制	文献
DPN	根皮素	雄性 Wistar 大鼠腹腔注射通过链脲佐菌素 (STZ) 诱导糖尿病	25、50 mg·kg ⁻¹	通过抗氧化和抗炎活性发挥剂量依赖性的神经保护作用	[52]
DR	根皮素	人视网膜色素上皮细胞线粒体损伤诱导的炎症	100 μmol·L ⁻¹	通过 NFE2L2 和 ERK1/2 减少 IL-6 和 IL-8 的分泌,防止线粒体损伤引起的视网膜色素上皮细胞炎症	[92]
		人视网膜色素上皮细胞	100 μmol·L ⁻¹	通过激活 Nrf2 减少 IL-8 的分泌,在人视网膜色素上皮细胞中显示出显著抗炎作用	[96]
DR、DN 及 DPN	根皮苷	自发性糖尿病鸟居肥胖大鼠	100 mg·kg ⁻¹	预防与年龄相关的视网膜病变,如视网膜折叠和增厚,同时减少白内障的形成,增加坐骨神经传导速度,并减轻肾小球硬化、肾小管再生和炎症	[85]
DCM	根皮素	心脏 H9c2 细胞	10 mg·kg ⁻¹	通过解离 Keap1/Nrf2 复合物并抑制氧化应激来预防糖尿病性心脏病	[103]
		诱导雄性 Wistar 大鼠心脏损伤	240.3、480.6 mg·kg ⁻¹	通过抑制氧化应激和亚硝化应激来减轻诱导大鼠的心脏损伤	[111]
		STZ 诱导 C57BL/6 小鼠糖尿病和高糖诱导的 H9c2 细胞	20 mg·kg ⁻¹ 20 μmol·L ⁻¹	通过恢复 SIRT1 表达和发挥抗炎作用来抑制心脏损伤和重构	[104]
	根皮苷	诱导小鼠心肌纤维化	100、200 mg·kg ⁻¹	通过抑制 HK1 介导的 NLRP3 炎症小体激活来抑制细胞焦亡,从而改善心肌纤维化	[119]
动脉粥样硬化	根皮素	STZ 诱导的小鼠糖尿病和高糖培养基诱导的人脐血管内皮细胞损伤	20 mg·kg ⁻¹ 50、100 nmol·L ⁻¹	低剂量根皮素通过内皮细胞 KLF2 修复缓解糖尿病动脉粥样硬化	[125]
动脉粥样硬化	根皮苷	Ldr ^{-/-} 敲除糖尿病小鼠	400 mg·kg ⁻¹	通过改善肝脏胆固醇清除来减少动脉粥样硬化病变	[146]
		棕榈酸诱导人脐静脉内皮细胞功能障碍	50 nmol·L ⁻¹ 10 μmol·L ⁻¹	通过激活 PI3K/Akt/eNOS 信号通路和增加 NO,对棕榈酸诱导的内皮功能障碍具有直接保护作用	[129]
动脉粥样硬化	根皮素	高糖或晚期糖基化终产物诱导内皮细胞损伤和 STZ 诱导的糖尿病小鼠	25、75 mg·kg ⁻¹ 40 μmol·L ⁻¹	通过 AMPK 依赖性抗 EndMT 途径改善糖尿病引起的内皮损伤	[134]
DN	根皮素	STZ 和高脂饮食诱导载脂蛋白 E 敲除 T2DM 小鼠	20 mg·kg ⁻¹	通过抑制肾素和减少足细胞蛋白的非降糖作用来改善糖尿病肾病	[79]
		人胚肾 293-hTLR2 细胞和 Raw264.7 细胞	10、20 μmol·L ⁻¹	可减少 TLR2 诱导的炎症反应,并降低肾细胞中 TNF-α 和 IL-8 诱导的炎症反应	[83]
	根皮苷	db/db 糖尿病小鼠	20 mg·kg ⁻¹	通过减少氧化应激和改善脂质代谢来减轻肾小球和肾小管功能障碍	[84]
抑郁症	根皮苷	高脂饮食和 STZ 诱导的雄性 T2DM 小鼠	5、10、20 mg·kg ⁻¹	通过减轻氧化应激和调节脑源性神经营养因子来改善小鼠 T2DM 引起的抑郁症	[169]
记忆缺陷	根皮苷	高脂饮食和 STZ 诱导的 T2DM 大鼠	10、20 mg·kg ⁻¹	通过上调神经营养因子、减轻氧化应激和增加大脑胆碱能信号通路改善 T2DM 大鼠记忆缺陷	[173]

3 木姜叶柯与其他中药配伍的研究情况

木姜叶柯富含二氢查尔酮等黄酮类活性物质。据古籍记载,其可用于治疗湿热泻痢、肺热咳嗽、痈疽疮疡及皮肤瘙痒。现代药理学研究表明,其药理活性与其所含黄酮类化合

物密切相关,其中研究最广泛的单体化合物是三叶苷和根皮苷^[174]。研究发现,甘草中的甘草多糖及黄酮、异黄酮类化合物具有抗炎、降血糖、治疗心脑血管疾病、抗菌及抗氧化等功能,并且与木姜叶柯配伍时可产生协同作用^[174-175]。黄酮类化合物和低聚原花青素是山楂中的 2 种重要活性成分。它们具有降血压、治疗心脑血管疾病、抗氧化及降血糖等功能,与木姜叶柯配伍时可产生协同作用^[174,176]。菊花中的黄酮类化合物、挥发油及绿原酸与其药理活性密切相关。它们赋予菊花抗菌、抗炎、抗氧化、降血脂、降血糖及保肝、抗肿瘤等多种功能,与木姜叶柯配伍时可产生协同作用^[174,177]。陈皮及生姜具有温肺化痰的功效^[178]。它们与木姜叶柯配伍后可生成具有降血糖等多种功效的产品,未来可能成为新的发展方向。

4 结论与展望

糖尿病在中医中被归类为“消渴病”,其基本病理机制为“阴虚为本,燥热为标”。根据国际糖尿病联盟的数据,2021 年全球成年人的糖尿病患病率为 10.5%,医疗支出约为 9 660 亿美元。预计到 2045 年,糖尿病患病率将上升至 12.2%,医疗支出将达到 10 540 亿美元,给社会带来巨大的医疗负担。目前,许多降糖药物可以控制患者的血糖水平,但在治疗糖尿病相关的靶器官损伤方面缺乏有效手段。因此,开发更安全、经济且有效的治疗糖尿病及其并发症的新药物显得尤为重要。

木姜叶柯集药用、茶用和食用等多种用途于一体,历代本草著作和文献中均未记载木姜叶柯有药食禁忌和毒性。现代研究也表明,木姜叶柯无细胞毒性,可用于提取甜味剂和食用色素。据《中华本草》《中药大辞典》《全国中草药汇编》等本草典籍的记载,木姜叶柯性平,味甘,归肝经,具有清热解毒、生津止渴、利湿化痰、祛风止痒、滋润肝肾、活血止痛、和胃降逆、滋阴补肾、利尿止泻等功效,可用于气阴两虚证、脾肾气虚证和湿热内蕴证等不同证型的糖尿病患者及痰湿体质者。现有研究表明,木姜叶柯提取物具有抗炎、抗氧化损伤、降血糖和降血脂等药理作用。本综述从胰岛素抵抗、葡萄糖转运、糖脂代谢、酶类活性调控、肠道菌群调节和抗氧化损伤等方面,概述了木姜叶柯提取物中二氢查尔酮类化合物(三叶苷、根皮苷和根皮素)在治疗 T2DM 及其并发症的研究进展,并阐述其相关分子机制。

尽管对木姜叶柯提取物中主要二氢查尔酮的研究取得了一些令人鼓舞的结果,但相关研究仍处于初步阶段,大多数文献样本量较小,现有证据主要基于动物模型或细胞实验。目前仍缺乏长期、多中心和良好控制的临床试验来评估其疗效和安全性。此外,由于个体差异,其确切剂量尚不明确,不同有效成分是单独作用还是以特定比例组合对 T2DM 及其并发症有更好的治疗效果,尚需进一步研究。因此,进一步研究木姜叶柯提取物中主要二氢查尔酮(三叶苷、根皮苷和根皮素)的植物化学和药理特性,对其安全有效的应用

具有重要意义。同时,其在治疗 T2DM 及其并发症的多靶点效应方面,仍有很大的研究和开发潜力。

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