

茶与糖尿病视网膜病变的相关研究

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摘 要

糖尿病视网膜病变(DR)是糖尿病(DM)患者常见的慢性并发症之一, 已经成为全世界面临的较为严重的公共卫生负担。越来越多的证据表明, 氧化应激和慢性炎症在DR的发展中起主导作用。目前, 还没有可以预测和完全阻止DR进展的方法, 为了避免不必要的视力损害, DR的预防和早期治疗必须引起重视。研究表明, 茶除了具有抗氧化活性、减缓氧化应激和血管损伤的作用, 能够通过影响新生血管、清除自由基减少视网膜损伤, 此外, 还具有抗炎作用, 能减轻因高血糖引起的慢性炎症反应。本文将对茶在DR发生发展中的作用及其对DR的治疗作用和机制研究进展进行综述, 为DR防治提供了新思路。

关键词

糖尿病视网膜病变, 茶, 儿茶素, 茶多酚, 表没食子儿茶素没食子酸酯

Study on the Correlation between Tea and Diabetic Retinopathy

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Abstract

Diabetic retinopathy (DR) is one of the common chronic complications in patients with diabetes mellitus (DM) and has become one of the more serious public health burdens facing the world. There is growing evidence that oxidative stress and chronic inflammation play a dominant role in the development of DR. Currently, there is no method to predict and completely stop the progression

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of DR, and prevention and early treatment of DR must be emphasized in order to avoid unnecessary vision damage. Studies have shown that in addition to its antioxidant activity, slowing oxidative stress and vascular damage, tea is able to reduce retinal damage by affecting neovascularization and scavenging free radicals, in addition to its anti-inflammatory effect, which reduces chronic inflammatory responses due to hyperglycemia. This paper will review the role of tea in the development of DR and its therapeutic effects on DR and the progress of mechanism research, which provides new ideas in the prevention and treatment of DR.

Keywords

Diabetic Retinopathy, Tea, Catechins, Tea Polyphenols, (-)-Epigallocatechin-3-Gallate

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1. 引言

糖尿病视网膜病变(DR)是糖尿病导致的常见微血管并发症,严重时可导致失明,是引发不可逆视力损害的主要原因之一[1][2]。DR分为非增殖期和增殖期两个阶段,非增殖期视网膜病变表现为微血管损伤,如微动脉瘤、出血和渗出,而增殖期则是视网膜新生血管形成,进而导致严重的视网膜出血、视网膜脱落甚至失明[3]。早期控制血糖水平和改善生活方式,有助于减缓病变进程。虽然目前的治疗方法如激光治疗和抗血管内皮生长因子(抗 VEGF)药物注射等能够缓解病情,但效果有限且伴有一定风险,因此寻找新的治疗策略尤为重要[4]。近年许多研究发现,茶叶中的茶多酚具有显著的抗氧化和抗炎作用,能够有效减轻氧化应激、抑制视网膜炎症反应,减轻视网膜细胞的凋亡,增强血管的稳定性,可能有助于延缓病变进程,从而降低 DR 的发生风险[5][6]。总之,茶作为天然抗氧化剂,能够在一定程度上减缓 DR 的病情发展。本文综述了茶与 DR 的相关性,旨在为 DR 的预防与治疗提供新的思路 and 方案,让患者能够接受低成本、低风险的 DR 治疗。

2. 糖尿病视网膜病变和茶的相关性

DM 是全球最常见的代谢性疾病之一,慢性高血糖常常伴随着微血管并发症(例如:视网膜病变、周围神经病变、慢性肾脏疾病)。大约三分之一的 DM 患者会出现 DR,而其中的三分之一可能会面临视力威胁,甚至完全失明[3][7]。DR 的发病机制复杂,主要涉及微血管病变、炎症反应、氧化应激、活性氧自由基(ROS)积聚、线粒体功能障碍、自噬失调等诸多因素均参与了 DR 的发展[8]。治疗中晚期 DR 的方法有玻璃体内注射抗血管内皮生长因子、激光治疗和玻璃体手术[9][10]。然而,这些方法都具有较高的侵入性和费用,给个人和社会带来显著的财政负担。现用于治疗 DR 的方法很少,且大多效果欠佳,常有严重的副作用。因此,迫切需要辅助或补充治疗。

茶是全球最常消费饮品之一,由于各种制造工艺造成的特征和发酵程度不同,可分为六大类,包括未发酵绿茶、轻度发酵白茶、部分发酵黄茶、半发酵乌龙茶、完全发酵红茶和后发酵黑茶[11]。茶含有许多生物活性成分,尤其是多酚类(如儿茶素、绿原酸等)、黄嘌呤类(如茶黄素、茶碱等)和酰胺类化合物(茶氨酸)的主要来源,这些成分具有抗氧化、抗炎、降脂、抗糖化等健康益处[12]-[14]。茶因其丰富的生物活性成分尤其受到关注,儿茶素占茶叶成分的 30%,能通过减轻氧化应激、改善胰岛素抵抗、调节线粒体功能等多途径帮助缓解 DM 及其并发症[15][16]。随着 DM 患者对视网膜病变预防的关注增加,日常

饮品的安全性成为热门话题, 茶饮成为 DR 治疗研究的新方向[17]。已有研究证明定期饮茶有助于改善 DM 患者的血糖控制, 不同类型的茶在体内和体外都表现出抗糖尿病的作用, 甚至可以延缓视网膜病变的发展[18] [19]。最近的研究还表明, 富含多酚的茶能延缓甚至改善 DR 的发生、进展与预后。

在一项基于人群的横断面研究中, Xu 等人发现与不喝茶的人相比, 长期饮茶(≥ 20 年)是中国老年 DM 居民发生 DR 的保护因素[20]。同样, Ma 及其同事对中国 DM 人群进行的一项病例对照研究报告了绿茶摄入量与 DR 患病率之间的保护关系[21]。已有大量研究表明, 茶中的多酚类对 DR 有保护作用[22]。一项来自中国的病例对照研究显示, 长期饮用绿茶的 DM 患者可以预防 DR, 发现其风险可以降低 50% ($OR = 0.49, 95\%CI (0.26 \sim 0.90)$) [21]。换句话说, 相比不饮用者, 常饮绿茶的人患此病的风险显著较低。有动物实验表明, 绿茶提取物能够显著降低糖尿病大鼠眼部的氧化应激标志物, 并改善其视网膜结构, 虽然这些研究多集中于动物模型, 但为人类患者提供了潜在的治疗策略[18]。另外, 乌龙茶作为半发酵茶, 既具有绿茶的抗氧化功能, 也具有黑茶的调节血糖作用, 可以改善血糖波动同时也减少高血糖引起的视网膜慢性炎症的风险[23]。流行病学和实验研究均表明, 茶叶尤其是绿茶、红茶和乌龙茶, 具有显著的抗氧化和抗炎作用, 有助于改善胰岛素抵抗, 减轻氧化应激, 调节炎症反应, 这些效果可能有助于预防 DR [22] [24] [25]。

3. 茶对糖尿病视网膜病变的防治作用

3.1. 茶对糖代谢异常的改善作用

茶对糖尿病及其并发症的作用已被广泛研究。流行病学研究发现, 饮茶与糖尿病及其并发症的风险呈负相关[26]。一项病例对照研究发现, 茶的饮用可以显著降低越南成年人患 2 型糖尿病(T2DM)的风险 ($OR = 0.66, 95\%CI (0.49 \sim 0.89)$) [27]。另一项研究表明, 长期饮用绿茶对 DR 具有预防作用($OR = 0.49, 95\%CI (0.26 \sim 0.90)$), 在经常饮用绿茶的人群, DR 的发生风险比不饮用绿茶的人群低 50% [28]。在中国汕头进行的一项基于人群的病例对照研究显示, 长期饮用乌龙茶能够显著降低南方地区高胆固醇血症和甘油三酯的风险($OR = 0.10, 95\%CI (0.06 \sim 0.16)$) [29]。此外, 一项描述性研究发现, 长期饮茶与塞浦路斯地区 T2DM 呈负相关[30]。绿茶中的主要有效成分为儿茶素, 尤其是表没食子儿茶素没食子酸酯(EGCG), 通过抑制体外炎症因子和减少 ROS 的产生, 有助于保护胰腺 β 细胞的功能, 还能下调诱导型一氧化氮合酶(iNOS)的表达, 从而进一步保护胰岛 β 细胞[31]。另一方面, EGCG 能够激活 5'-腺苷酸活化蛋白激酶 (AMPK)通路, 改善胰岛素受体底物-1 (IRS-1)磷酸化, 从而改善肝癌细胞系 HepG2 中的胰岛素抵抗状态 [32]。绿茶中的阿拉伯半乳聚糖则通过环磷酸腺苷-Akt (cAMP-Akt)通路, 增加葡萄糖刺激的胰岛素分泌 [33]。此外, 绿茶还被发现能够通过促进糖尿病小鼠胰岛 β 细胞分泌更多胰岛素, 从而降低血糖水平[34]。黑茶中的没食子酸(GC)则通过刺激蛋白激酶 B (AktB)的磷酸化, 在胰岛素缺乏的情况下, 促进骨骼肌葡萄糖的摄取[35]。综上, 茶从多方面对糖代谢异常有明确的改善作用和对 DM 的防治作用。

3.2. 茶对氧化应激反应的抑制作用

DM 患者在高血糖状态下, 容易引发氧化应激、线粒体功能受损、晚期糖基化终产物(AGEs)和 ROS 的积累, 这些因素会激活多种致病途径, 最终导致血管和神经的损伤, 从而增加 DR 的风险[36]。过去的多数研究已证明, 茶作为一种天然的抗氧化剂, 在改善糖代谢的过程中还具有重要的抗氧化作用。绿茶中的 EGCG 能够通过清除 ROS 来改善胰岛素抵抗, 从而通过降低肿瘤坏死因子- α (TNF- α)诱导的 c-jun NH2-末端激酶(JNK)的磷酸化, 阻断胰岛素信号的转导, 阻止 IRS-1 与胰岛素受体的结合[37]。绿茶的抗氧化作用还体现在其能够通过降低氧化应激相关的标志物, 减少炎症反应对胰岛 β 细胞的损伤。此外, 红茶含有丰富的茶黄素, 茶黄素具有抗氧化作用, 能够抑制单线态氧、超氧化物和羟基自由基等活性氧的作用, 从而

在一定程度上起到延缓 DR 发展的作用[38]。白茶比红茶含有更高水平的茶多酚, 展现出更强的抗氧化活性来表现其抗氧化应激的作用[39]。因此, 茶能够通过减轻氧化应激反应来延缓 DR 的发生发展。

3.3. 茶对炎症因子表达的抑制作用

DR 已被证实是慢性炎症性疾病, 涉及小胶质细胞、单核-巨噬细胞、中性粒细胞和淋巴细胞的激活以及炎症介质的分泌, 包括白细胞介素-6 (IL-6)、TNF- α 、单核细胞趋化蛋白-1 (MCP-1) 和 VEGF, 故有研究提出了抗炎策略[40]。茶叶中的茶多酚还具有抗炎作用, 可以有效抑制因高血糖引起的慢性炎症反应, 这也是预防 DR 发生的重要机制之一[22]。白茶富含的天然抗氧化物质中儿茶素和多酚类成分具有强大的抗氧化性能, 能有效减少氧化应激对视网膜微血管的损害, 从而降低糖尿病患者的视力损伤风险[41]。茶多酚, 尤其是在抗炎方面表现出显著作用, 通过下调诱导型 iNOS 的表达, 抑制炎症因子的释放, 进而减少慢性低度炎症反应对胰岛 β 细胞的破坏[42][43]。槲皮素是白茶中发现的一种重要的类黄酮, 它可以通过抑制炎症通路, 特别是 PKC ζ /JNK/核因子- κ B 信号传导, 预防胰岛素缺乏和抵抗中的糖尿病血管并发症[44]。研究表明, 绿茶和黑茶通过其丰富的多酚成分, 能够抑制与 DM 相关的炎症因子, 例如 TNF- α 、IL-6 等, 降低其在体内的水平[45]。此外, 红茶和白茶也通过抗氧化和抗炎作用, 帮助减轻氧化应激和炎症反应, 从而降低糖尿病相关并发症的发病风险[46]。通过这些机制, 茶对 DR 的防治作用可能在很大程度上得益于其对炎症因子表达的抑制作用, 因此, 抑制这些炎症因子的产生可能成为延缓 DR 发展的有效策略。

3.4. 茶对视网膜血管内皮细胞的保护作用

DR 主要表现为血管通透性增加、水肿、炎症细胞浸润、新生血管形成和血管生成因子的表达[47]。此外, 玻璃体内注射抗 vegf 药物已显示出良好的治疗效果[44]。最近有报道称, T2DM 患者存在细胞内 ROS 水平升高, 而 ROS 可以激活炎症反应, 增加 TNF- α 、白细胞介素等炎症因子水平, 造成微血管损害[48]。新生血管的形成与血管内皮细胞增殖之间的联系密不可分, 茶氨酸对高浓度葡萄糖刺激后的人视网膜血管内皮细胞的增殖方面具有抑制作用, 并且能够下调 VEGF 蛋白表达, 从而遏制视网膜病理性新生血管生成, 这一作用与 VEGF 的表达水平降低有关, 体现出茶氨酸在 DR 的防治方面具有一定作用[49]。许多研究提到, 茶的抗氧化和抗炎特性被认为对 DR 具有保护作用。绿茶通过增加谷氨酸转运体的表达、重建细胞间连接和恢复谷氨酰胺/谷氨酸循环, 减少 ROS 的产生, 进一步保护视网膜神经, 并调节视网膜下环境[48]。研究还发现, 极低剂量的绿茶能够改善抗氧化防御, 减少炎症标记物, 防止视网膜基底膜增厚, 从而减缓 DR 的发展[50]。此外, 红茶通过降低血糖水平, 有助于抑制糖尿病视网膜的病理生化发展, 从而抑制糖尿病引起的视网膜病变进程[51]。总体而言, 茶在 DR 的预防和治疗中, 发挥了显著的血管内皮细胞和神经保护作用。

4. 小结及展望

DR 作为一种常见的糖尿病并发症, 其发病机制复杂, 涉及血管炎症、氧化应激、新生血管形成、细胞凋亡等多个通路。目前, 研究者们对多种天然成分在 DR 治疗中的潜力进行了探索, 茶作为其中的重要研究方向之一, 吸引了广泛关注。茶叶中富含的天然成分, 如多酚类、黄嘌呤类和酰胺类化合物等, 已被证实具有抗氧化、抗炎、抑制新生血管形成等多重作用, 能够有效缓解 DR 的病理进展。虽然现有研究表明茶可能对 DR 具有保护作用, 但具体的分子机制尚未完全阐明, 且不同种类的茶和生物活性成分对 DR 的影响可能存在差异, 未来的研究需要进一步探索茶及其成分在 DR 中的作用。因此, 茶及其生物活性成分可能为糖尿病及其视网膜病变的预防和治疗提供新的治疗策略。随着对茶叶功能的深入理解, 未来可能为 DR 的治疗提供新的思路和方法, 但二者的因果关系及二者确切的具体关系仍需通过更为深入的研究来进一步确认。

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DR	diabetic retinopathy
EGCG(-)	-epigallocatechin-3-gallate
GC	gallic acid
ROS	reactive oxygen species
DM	diabetes mellitus
T2DM	type 2 diabetes mellitus
VEGF	vascular endothelial growth factor
iNOS	inducible nitric oxide synthase
AMPK	adenosine 5'-monophosphate (AMP)-activated protein kinase
IRS-1	insulin receptor substrate-1
TNF- α	tumor necrosis factor- α
IL-6	interleukin-6