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茶的活性成分对延缓慢性肾脏病进展的作用

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摘　要

茶是世界上最古老、最受欢迎的饮料之一，其有益的保健作用已经引起了全世界的极大关注。研究表明，茶中的某些化合物，如茶多酚、儿茶素、茶色素等，由于其具有的抗氧化应激和抗炎作用，对慢性肾脏疾病(CKD)的进展具有潜在的保护作用。本文旨在通过分析茶的活性成分及其可能对肾脏作用的分子机制，对其延缓慢性肾脏病的进展和减轻其高危因素的潜在作用作一综述。

关键词

茶的活性成分，分子作用机制，慢性肾脏病

The Role of the Active Ingredients in Tea in Delaying the Progression of Chronic Kidney Disease

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Abstract

Tea is one of the oldest and most popular beverages in the world, and its beneficial health effects have attracted great attention around the world. Studies have shown that certain compounds in

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tea, such as tea polyphenols, catechins, tea pigments, etc., have potential protective effects on the progression of chronic kidney disease (CKD) due to their antioxidant stress and anti-inflammatory effects. This article aims to review the potential role of tea in delaying the progression of chronic kidney disease and alleviating its high-risk factors by analyzing the active ingredients of tea and its possible molecular mechanisms of effects on the kidneys.

Keywords

Active Ingredients of Tea, Molecular Mechanism of Action, Chronic Kidney Disease

1. 引言

慢性肾脏疾病是一个日益严重的公共卫生问题，影响着世界人口的 9%~16% [1]。在全球范围内，慢性肾脏病死亡人数已增至约 120 万人，从 1990 年到 2017 年[2]，所有年龄段的死亡率增加了 41.5%。慢性肾脏病与许多其他疾病的风险增加有关，包括认知障碍、肾性骨病、慢性贫血、败血症和心血管疾病死亡[3] [4]等。经研究发现，生活方式的因素，如吸烟、饮酒和肥胖，与疾病的更高风险相关[5] [6] [7]。除了这些因素，人们对饮食的重要作用越来越感兴趣[8]。许多饮食成分在保护肾功能和延缓 CKD 进展方面起到了作用[9] [10] [11]。作为饮食的重要组成部分，饮料可以影响一般健康和肾功能的维持，并能够抑制或者改善可能导致慢性肾脏病的高危因素(例如高血压、肥胖和糖尿病) [8] [12]。茶不仅在中国有着悠久的历史，也是世界上最受欢迎的饮料之一，有越来越多的研究讨论其对 CKD 患者的健康和肾功能的潜在影响。本文将从茶的活性成分及其可能的作用机制来阐述其对慢性肾脏病的进展及其高危因素的作用。

2. 茶的活性成分及其可能对肾脏作用的分子机制

茶叶含有丰富的功能成分，如茶多酚、儿茶素、茶色素、L-茶氨酸、茶多糖、咖啡因和其他生物活性物质[13] [14] [15]。其中，儿茶素是最重要的活性成分之一，其中以表没食子儿茶素没食子酸酯(Epigallocatechin-3-Gallate, EGCG)含量最高、活性最强[16] [17] [18]，具有减少氧化应激，抑制炎症反应等作用，从而可能对改善或保护肾功能有益。

总结以下几种潜在的生物学机制可能是茶的活性成分与肾脏损伤风险之间的负相关的基础。

1) **抗氧化应激**：越来越多的证据表明，活性氧(Reactive Oxygen Species, ROS)的产生在肾脏疾病的发病机制中发挥着重要作用。肾脏容易受到氧化还原失衡和氧化应激(Oxidative Stress, OS)的影响，因此 OS 可能导致肾脏血流改变、钠水潴留、肾脏炎症和纤维化改变，以及蛋白尿[19]。茶及其生物活性成分，如多酚、多糖和色素，被认为通过清除自由基、耗尽活性氧(ROS)、增加抗氧化剂含量和增强抗氧化酶活性来显示抗氧化活性，从而保护肾脏功能[20] [21]。

2) **抗炎作用**：炎症是肾功能障碍的另一个关键病理机制[22]。茶叶提取物及其生物活性成分可能会降低慢性肾脏病的风险，因为它们具有抗炎活性，包括调节促炎和抗炎因子，以及相关的信号通路[21]。

3) **脂代谢调节**：英国生物库最近的一项研究发现，较高的茶消费量(红茶和绿茶)与更有利的心脏代谢生物标志物水平相关，包括较低的 TC 和低密度脂蛋白胆固醇、载脂蛋白 B 和空腹甘油三酯，但较高

的高密度脂蛋白-C 水平[23]。考虑到脂代谢的异常改变可能会导致肾脏疾病的发病和进展[24]，推测茶的活性成分可能有部分通过改善脂代谢来保护肾功能。当然，也可能涉及其他机制，未来需要进一步研究，以进一步探索饮茶对肾脏健康的作用。

4) **对血流动力学的影响**：咖啡因可能通过阻断 A1 和 A2A 腺苷受体，同时增加肾内血管紧张素 II 水平和肾脏肾素－血管紧张素系统的活性，可能允许更大比例的系统血压传递到肾小球，从而导致肾脏损伤[25]。因此推测当咖啡因代谢受损时，茶的好处可能会被咖啡因的有害影响所抵消。

3. 茶的活性成分在肾脏疾病中的研究现状

1) **急性肾损伤**：急性肾损伤(AKI)是慢性肾脏病(CKD)发生和发展的重要危险因素。即使是轻微的 AKI 也可能产生不良后果，并可能发展为肾脏纤维化，这是所有终末期肾病的最终结果。AKI 后肾小管细胞可能通过多种途径导致肾功能减退和肾纤维化[26] [27] [28] [29]。肾纤维化是由于细胞外基质的过量产生和积累而造成肾组织瘢痕。目前还没有针对肾脏纤维化和慢性肾脏病的特异和有效的治疗方法。Wang 等人[30] [31] [32]广泛研究了 EGCG 对单侧输尿管梗阻的小鼠(Unilateral Ureteral Obstruction, UUO)的肾的保护作用，单侧输尿管梗阻是常见的肾纤维化动物模型。他们最初证明，Smad 依赖的 TGF-β1 信号通路被激活，与上皮间充质转化相关，从而导致肾纤维化[30]。组织病理学研究显示肾小球和肾小管损伤伴巨噬细胞浸润，提示 UUO 组肾脏炎症，并伴有趋化因子(单核细胞趋化蛋白 1 和 3)和促炎细胞因子(肿瘤坏死因子-α 和 IL-1β)增加[30]。然而，这些特征可以被 EGCG 所逆转[30]。这一结果也被 TGF-β1 处理的细胞株[30]的体外实验所证实。EGCG 还可通过减少髓过氧化物酶活性和促炎细胞因子(即肿瘤坏死因子-α、IL-6 和 IL-1β)的释放而减轻 UUO 诱导的炎症反应。

2) **肾小球肾炎**：是一种常见的肾脏疾病，与终末期肾病相关。肾小球肾炎最具侵袭性的形式之一是抗肾小球基底膜肾炎[33] [34] [35]，其特征是肾小球基底膜上形成新月形免疫复合体[36]。在国外 Rattiyaporn Kanlaya 等人的一项研究首次报道了在抗肾小球基底膜肾炎的动物模型[37]中，EGCG 治疗肾小球肾炎潜力的证据，与给药小鼠相比，EGCG 可显著减少肾小球和肾小管间质损伤并降低死亡率。此外，在 EGCG 治疗组中，氧化应激标志物(丙二醛、髓过氧化物酶和过氧化氢)、NAD(P)和抗氧化酶(谷胱甘肽过氧化物酶和过氧化氢酶)恢复到基线水平[38]。EGCG 对实验性新月体肾炎的肾保护作用[39]不仅与过氧化物酶体增殖物激活受体 γ 相关，还有 Nrf2 信号通路也参与其中。

3) **慢性肾脏病(CKD)**：在 Mengyi Liu 等人的一项大规模人群的前瞻性研究中，观察到无糖茶的摄入量与新发 CKD 的风险呈负相关，但无论是否在茶中添加牛奶，或是含糖茶的摄入量与新发 CKD 的风险无关。与此同时，CARDIA (Coronary Artery Risk Development in Young Adults)研究中的验证分析一致发现，与无糖茶相关的新发 CKD 的风险显著降低[40]。另外在 Yangchang Zhang 等人的一项由两个样本组成的 MR 研究使用了来自英国生物库和 CKDGen 联盟数据的 MR 分析表明，茶摄入量的增加似乎对慢性肾脏病、EGFR 和蛋白尿具有保护作用。在不同的敏感性分析中，这些影响是相似的。因此，饮茶有益于肾功能[41]。另外在目前的纵向和横断面研究中，茶摄入量和慢性肾脏病风险之间的关联仍然不一致。在 Doetinchem 队列研究中，包括 4722 名年龄在 26~65 岁的人，茶的消费与 EGFR 的变化没有明显的关联[42]。然而，在另一个西班牙队列中，包括 5851 名患有 METS 的超重/肥胖老年人、患有 METS 的超重/肥胖成年人以及茶的高摄入量(每天至少 1 杯)在一年内 EGFR 下降更大[43]。广州生物银行的一项队列研究包括 12,428 名老年人，没有发现绿茶或红茶与 EGFR 之间的显著关联。然而，另一项研究发现乌龙茶的摄入量与 EGFR 呈负相关[44]。

4) **糖尿病肾病(Diabetic Nephropathy, DN)**：DN 是糖尿病的主要微血管并发症，也是慢性肾脏病和终末期肾病的主要病因之一。发生糖尿病肾病的患者还会出现其他微血管并发症，包括晚期糖基化终产

物(AGEs)、丝裂原活化蛋白激酶(MAPKs)和蛋白激酶 C 的激活，以及各种细胞因子、趋化因子和生长因子的过度产生[45] [46]。早期诊断和医疗处理是至关重要的，可能会减轻或延缓糖尿病肾病的进展。EGCG 对糖尿病肾病的有益作用最初是在链脲佐菌素诱导的肾大部切除的糖尿病大鼠中进行的[47]，研究结果表明，糖尿病大鼠长期使用 EGCG 治疗 50 天，可显著减少肾脏病变，抑制高血糖、蛋白尿、脂质过氧化[47]。此外，EGCG 还可以减少积聚的 AGE (Advanced Glycation End Products)和抗炎分子[47]。另一项对链脲佐菌素诱导的糖尿病小鼠中的研究结果一致表明，EGCG 对糖尿病肾病具有肾脏保护作用[48]。EGCG 还改善了肾功能，如降低血清肌酐和血尿素氮，减少蛋白尿和肾组织损伤[48]。

4. 茶的活性成分对抑制或改善慢性肾脏病高危因素的影响

慢性肾脏疾病(CKD)起病隐匿，早期长无症状，疾病进展过程中可出现高血压、矿物质骨代谢紊乱、心脑血管疾病事件等多种并发症。研究发现茶中的某些活性成分可以发挥调节血压、改善血糖、脂代谢、尿酸水平等作用，通过抑制或者改善这些可能导致慢性肾脏病的高危因素，从而延缓 CKD 的进展，减少并发症的发生。

4.1. 降低心血管疾病风险、调节脂代谢

CKD 患者中心血管疾病的高发生率可归因于高血压、血脂异常、高尿酸血症、糖代谢异常、肥胖、全身炎症和氧化应激的高患病率。在日本的一项研究表明绿茶摄入量与各种原因死亡和心血管疾病的风险之间存在负相关。该研究对 76,979 名年龄在 40~79 岁之间的人进行了研究，发现每天喝 6 杯或更多绿茶的女性与不喝绿茶的女性相比，死于冠心病的风险降低 58% [49]。C 反应蛋白是预测心血管危险的重要生物标志物。关于绿茶和 CRP 的研究表明，绿茶可能通过降低 2 型糖尿病患者的 CRP 浓度来降低心血管疾病的风险[50]。另一项对 240 名年龄大于 18 岁的中国男性和女性进行的随机双盲试验表明，每天服用绿茶提取物胶囊(375 毫克)可降低循环中的总胆固醇和低密度脂蛋白胆固醇水平，升高高密度脂蛋白胆固醇水平[51]。以及日本另一项对 240 名年龄在 25~55 岁的男性和女性进行的随机双盲试验表明，补充含有 583 毫克儿茶素的绿茶(干预组)与只含有 96 毫克儿茶素的绿茶(对照组)相比，能更大程度地降低体脂、血压和低密度脂蛋白胆固醇[52]。

4.2. 降低糖尿病患病风险、调节血糖水平、改善胰岛素抵抗

糖尿病肾病(Diabetic Nephropathy, DN)是糖尿病的微血管并发症，是 2 型糖尿病最常见的并发症[53]，是全球终末期肾病发生的主要原因之一，近年 DN 的发病率和死亡率呈逐年递增趋势[54]。在诊断出 2 型糖尿病的十年后[55]，大约 40%的糖尿病患者会出现 DN [56]。因此早期诊断和治疗是预防 DN 发生发展的有效手段。DN 的进展与氧化应激有关，但在 DN 的早期阶段，人类和实验动物的糖尿病肾脏中参与对抗氧化应激的抗氧化防御系统的主调节因子 Nrf2 出现了上调。尽管表达量增加，但该蛋白转运到细胞核的能力却减弱了，这表明 Nrf2 的功能受损，意味着氧化还原失衡。因此，在治 DN 时，促进 Nrf2 转位的药物可能比那些定量过表达 Nrf2 的药物更有益。EGCG 就是这样一种植物化学物质，它通过影响 Nrf2/ARE 通路阻止 DN 的发展，显示出有益的作用[57]。另外在一项关于 50 万中国成年人队列研究中，与过去一年不喝茶的人相比，每天喝绿茶与患 2 型糖尿病的风险降低 8%相关。而在糖尿病患者中，每天喝绿茶与死亡风险降低 10%相关[58]。另外来自体外和动物体内研究的数据表明，茶及其活性成分可能通过几种可能的机制影响葡萄糖代谢和胰岛素信号[59] [60]。其中儿茶素，包括表儿茶素-3-没食子酸酯、表儿茶素-3-没食子酸酯、单宁和茶黄素，可通过抑制兔肠道中的碳水化合物消化酶 α-淀粉酶、肠道蔗糖和 α-葡萄糖苷酶来降低葡萄糖和胰岛素浓度[61] [62]。特别是表没食子儿茶素-3-没食子酸酯，被证明可

以增强胰岛素敏感性，以及通过增加脂肪细胞中胰岛素刺激葡萄糖摄取而产生的促胰岛素活性[63] [64] [65]。以及目前研究已表明绿茶儿茶素可以减少低密度脂蛋白氧化和改善脂肪的胰岛素抵抗[66]。此外，一项结合 22 项临床试验的荟萃分析表明，摄入绿茶儿茶素可以显著降低人类的空腹血糖浓度[67]。另一项[68]对 17 项随机对照试验进行的荟萃分析也表明，绿茶的摄入与空腹血糖和糖化血红蛋白浓度的降低有关。

4.3. 调节血压水平

CKD 与高血压相互影响会加重患者肾功能衰竭、心血管疾病的发生，最终引起死亡率的增加 EGCG 对包括肾血管性高血压[69]和自发性高血压[70]在内的多种高血压疾病都有良好的疗效。EGCG 已被报道在几种肾脏疾病模型[71]中保护肾功能，例如急性肾损伤[72]、顺铂肾毒性[73]和梗阻性肾病[74]。另一项研究中观察到 EGCG 治疗可以降低盐敏感性高血压 Dahl 大鼠的收缩压(SBP)，减少蛋白尿，改善肾脏纤维化，并通过肾脏保护作用减轻盐诱导的高血压。进一步的研究表明，EGCG 的降压和肾脏保护作用归因于其抗氧化、抗炎和诱导细胞凋亡的作用[75]。

4.4. 调节尿酸水平

高尿酸血症为慢性肾脏病常见并发症之一，由于尿排泄减少，会导致慢性肾脏病患者体内尿酸水平升高。血清尿酸水平达到 446 μmol·L^{-1} 是 CKD 进展加速的独立危险因素[76]。绿茶多酚(GTP)是绿茶中具有多种药理功能的主要活性部分，在一项 GTP 对氧酸钾(Potassium Oxonate, PO)诱导的高尿酸血症小鼠血清尿酸水平影响的研究中，GTP 以剂量依赖性方式显着降低高尿酸血症小鼠血清尿酸水平，表明 GTP 具有通过减少尿酸产生和增加尿酸排泄来降低尿酸的作用[77]。

5. 结论

茶的活性成分对于延缓慢性肾脏病(CKD)进展和减轻其高危因素具有潜在的作用。主要机制包括抗氧化应激、抗炎作用，茶中的多酚类化合物能够减少肾脏的氧化应激和炎症反应。此外，茶叶的多酚类化合物成分还可以通过调节血压、改善血糖、脂代谢、尿酸水平来发挥作用，通过抑制或者改善这些可能导致慢性肾脏病的高危因素，对于延缓 CKD 的进展尤为重要。然而，关于饮茶与 CKD 风险之间对的相关研究结果存在差异，原因可能是世界各地不同的茶文化对茶的消费方式有所不同，例如，在消费牛奶、糖或柠檬时添加茶，甜味剂本身可能通过引起肾小球压力和加压素的改变，增加自由基的产生，改变氧化剂/抗氧化剂的平衡，从而导致肾小球和肾小管损伤[78] [79]。另外摄入不同种类的茶(红茶、乌龙茶或绿茶)、制备方法和茶中茶多酚有效浓度与肾功能之间的关系存在异质性。另外需要考虑到观察性研究设计的固有局限性，不能排除由于未测量或未知因素造成残留混杂或偏差的可能性。另外通过问卷调查对茶摄入数据进行评估，也可能存在回忆偏差。

因此，尽管有研究表明茶中的活性成分可为慢性肾脏病患者带来益处，但在未来的研究中需要通过临床试验来获得茶中的活性成分对肾脏疾病的肾脏保护作用的确凿证据。并且还需要根据茶叶种类、饮用模式和患者个体特征的不同，进行更有针对性的研究，并提供具体的饮用指南。

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