

基于“肾虚血瘀”理论探讨五味子-丹参药对通过调控线粒体-内质网结构偶联改善糖尿病肾病的机制

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摘 要

中医学认为“肾虚血瘀”是糖尿病肾病(Diabetic Kidney Disease, DKD)的关键病机。肾主封藏、司水液代谢, 其功能与线粒体-内质网结构偶联(Mitochondria-Associated endoplasmic reticulum Membranes, MAMs)都与机体的能量代谢相关, 在生理上均关乎机体物质能量代谢平衡; 在病理上, 肾虚导致的精气亏虚、水湿壅滞与线粒体能量代谢障碍、内质网应激产生的代谢毒性产物存在契合之处。当肾虚推动无力致瘀血内生, 瘀血痹阻肾络, DKD将进展为肾虚血瘀证候。MAMs失调是加速DKD肾脏损伤的重要因素, 肾虚血瘀形成的“精气耗损-瘀阻络脉”病理循环与其介导的细胞代谢紊乱和氧化损伤存在内在关联。因此, 通过揭示“肾虚血瘀”病机与MAMs的关系, 并以五味子-丹参药对践行“补肾为要、活血为辅”治法, 可为调控DKD代谢失衡及靶向干预提供中西医结合的理论依据。

关键词

糖尿病肾病, 线粒体-内质网结构偶联, “肾虚血瘀”, 补肾活血, 五味子, 丹参

Discussion on the Mechanism of Schisandra Chinensis and Salvia Miltiorrhiza Drug Pairing to Improve Diabetic Kidney Disease by Regulating Mitochondria-Endoplasmic Reticulum Structural Coupling Based on the Theory of “Kidney Deficiency and Blood Stasis”

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Abstract

Traditional Chinese medicine considers “kidney deficiency and blood stasis” as the key pathogenesis of Diabetic Kidney Disease (DKD). Kidney is the main sealing and storage, water and fluid metabolism, its function and Mitochondria-Associated endoplasmic reticulum Membranes (MAMs) are related to the energy metabolism of the body, and physiologically related to the balance of the body’s energy metabolism; Pathologically, the deficiency of essence and qi and the congestion of water-dampness caused by kidney deficiency coincide with the mitochondrial energy metabolism disorder and the metabolic toxic products produced by endoplasmic reticulum stress. When the inability to promote kidney deficiency leads to internalization of blood stasis and paralysis of the kidney channels by blood stasis, DKD will progress to the syndrome of “kidney deficiency and blood stasis”. MAMs dysregulation is an important factor accelerating renal injury in DKD, and the pathological cycle of “essence depletion and stasis” formed by renal deficiency and blood stasis is intrinsically related to the cellular metabolic disorders and oxidative damage mediated by MAMs. Therefore, by revealing the relationship between the pathogenesis of “kidney deficiency and blood stasis” and MAMs, and practicing the treatment of “tonifying the kidney and activating the blood” with the Wuweizi-Danshen medicinal pairing, we can provide the theoretical basis for the combination of traditional Chinese and Western medicines to regulate the metabolic imbalance of DKD and to target the intervention.

Keywords

Diabetic Nephropathy, Mitochondria-Associated Endoplasmic Reticulum Membranes, “Kidney Deficiency and Blood Stasis”, Invigorate the Kidneys and Promote Blood Circulation, Schisandrae Fructus, Salvia Miltiorrhiza

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1. 引言

糖尿病肾病(Diabetic Kidney Disease, DKD)是糖尿病最严重的微血管并发症之一，现在仍然是终末期肾病(End-Stage Renal Disease, ESRD)的主要病因[1]。流行病学数据显示，DKD 在糖尿病患者中的患病率持续升高，这给医疗保健系统带来了巨大压力[2]。中医学认为“肾虚血瘀”是 DKD 的核心病机，肾气亏虚则气化失司，精微不固而漏泄，久病入络则瘀血内阻，形成“虚 - 瘀”互结的病理格局[3]。现代研究表明，线粒体 - 内质网结构偶联(Mitochondria-Associated endoplasmic reticulum Membranes, MAMs)的紊乱是 DKD 的关键病理特征[4]-[6]。五味子与丹参作为中医治疗 DKD 的经典药对，前者补肾固精，后者活血化瘀，二者协同可标本兼顾[7]。研究表明五味子及其主要成分通过调节 OPA1/MFN2 改善线粒体融合，而丹参及其主要成分 抑制葡萄糖调节蛋白 78 (Glucose-Regulated Protein 78, GRP78)介导的内质网应激

(Endoplasmic Reticulum Stress, ERS), 共同维持 MAMs 结构完整性[1][8]。因此, 基于“肾虚血瘀”理论, 本研究提出五味子-丹参药对可能通过调控 MAMs 动态平衡, 从而调控 DKD “虚-瘀”的病机转化, 为阐释中医药多靶点干预 DKD 的分子机制提供新的研究角度。

2. “肾虚血瘀”是糖尿病肾病病机的关键

DKD 在中医古籍中无确切的病名, 据其临床表现, 可归属于“肾消”“尿浊”“水肿”“虚劳”等范畴[9], 糖尿病肾病病机复杂, 病性本虚而标实, 通常认为肾虚血瘀为病机之本[3]。《素问·六节藏象论》强调“肾者, 主蛰, 封藏之本, 精之处也”, 肾具有封藏和贮存精气的功能, 精气是人体生长、发育和生殖的物质基础[10]。肾主水, 主持和调节人体水液代谢的平衡[11]。正如《素问·逆调论》中所说: “肾者水脏, 主津液。”在正常生理状态下, 肾中精气充足, 肾的气化功能正常, 可促进和调节全身的水液代谢, 维持体内水液的平衡[12]。肾藏精, 精生髓, 髓化血, 肾精充足则血液生成有源, 肾中阳气具有推动血液运行的作用, 可保证血液在脉管内正常流动。若肾虚, 则肾的封藏、气化等功能则会出现失常。肾精亏虚, 不能充分化生血液, 导致血液生成不足; 肾阳虚弱, 无力推动血液运行, 可使血液运行迟缓, 出现血瘀之象[13]。正如《景岳全书》中记载: “凡人之气血犹源泉也, 盛则流畅, 少则壅滞。故气血不虚不滞, 虚则无有不滞者。”[14]《医林改错》亦指出: “元气既虚, 必不能达于血管, 血管无气必停留而为瘀。”[15]这些都强调了肾虚与血瘀相互影响的病理关系。此外, 禀赋不足、消渴迁延、情志失调、饮食不节等均可导致肾的气化、封藏、温煦功能失常, 致使血脉运行不畅, 瘀血阻痹肾络, 日久引发 DKD [16]。

3. “肾虚血瘀”功能失司与 MAMs 的相关性

现代医学研究表明, MAMs 作为连接两大细胞器的动态亚细胞结构, 在钙离子稳态、能量代谢和氧化应激调控中具有核心作用[17]。这一发现为阐释中医“肾虚血瘀”理论的分子机制提供了全新视角。线粒体与内质网通过 MAMs 形成的结构-功能耦联, 本文认为这与中医理论中“肾为先天之本”与“血为生命之基”的互根互用关系相类似。在生理状态下, MAMs 通过协调内质网的蛋白质折叠功能与线粒体的能量生成功能, 维持着细胞内氧化还原平衡和能量代谢稳态[18]。这与中医“肾藏精, 主生殖发育”的生理功能相吻合。然而当 MAMs 结构偶联异常时, 导致 ERS 与线粒体功能障碍的恶性循环[19]。这主要表现为钙信号紊乱、活性氧(Reactive Oxygen Species, ROS)过度产生和 ATP 合成障碍[20], 以上这些病理改变与“肾虚血瘀”证候中出现的代谢紊乱、氧化损伤和能量供应不足等临床表现具有相关性。有研究显示, 在慢性肾脏病(Chronic Kidney Disease, CKD)发展过程中, MAMs 介导的线粒体-内质网通讯障碍会导致线粒体形态改变, 如嵴结构破坏、基质电子密度降低这些以及功能异常如膜电位下降、超氧化物歧化酶(Superoxide Dismutase, SOD)活性降低等[21], 而与此同时还会伴随 ERS 标志物 GRP78 表达上调[22], 以上这种“器质-功能”双重损伤的病理特征, 与中医“肾虚精亏, 瘀血内阻”的病机演变过程相类似。从分子层面看, MAMs 功能障碍引发的氧化应激级联反应尤为关键。一方面, ERS 通过肌醇需求酶(Inositol-Requiring Enzyme 1 α , IRE1 α)通路激活 NADPH 氧化酶, 导致 ROS 爆发[20]; 另一方面, 受损线粒体产生的过量超氧化物又会进一步加剧内质网蛋白折叠负荷[23], 这种“氧化应激-ERS”的恶性循环与“肾虚致瘀, 瘀久伤肾”的中医病理循环相类似。值得注意的是, 在肾纤维化进程中, MAMs 结构异常导致的线粒体自噬缺陷与内质网未折叠蛋白反应(Unfolded Protein Response, UPR)过度激活[24], 会共同促进肌成纤维细胞活化及细胞外基质(Extracellular Matrix, ECM)沉积[25], 这一病理过程与“肾虚血瘀”证候中“久病入络”的病变特点相类似。相关网络药理学研究揭示补肾活血类中药的活性成分多靶向作用于 MAMs 调控网络, 如丹参酮-IIA 则能抑制 CHOP 通路减轻 ERS[26][27]。这些发现从系统生物学角度印证了“肾虚血瘀”与 MAMs 功能障碍的内在关联。这种“线粒体-内质网-炎症体”的跨细胞器对话机制, 为理解“肾虚血瘀”状态下“久病必瘀”的炎症微环境形成提供了新思路。综上所述, MAMs

功能障碍所导致的能量代谢紊乱、氧化应激加剧和细胞死亡激活等病理过程[28],与中医“肾虚血瘀”理论中的核心病机存在对应关系。

4. 补肾活血法调控糖尿病肾病 MAMs

肾虚是 DKD 发病之本,而血瘀日久是 MAMs 异常的关键。在中医基础理论的指导下,结合现代医学的研究进展,从肾虚血瘀入手探讨 DKD 的 MAMs 治疗的相关机制具有重要意义。中医理论认为“肾为先天之本”,主司精微化生与气化功能,肾气亏虚则精微不固,水湿瘀浊内停,久则络脉瘀阻。现代研究表明,MAMs 作为线粒体与内质网的关键交互平台,其结构异常可导致线粒体分裂过度、ERS,进而诱发足细胞损伤和肾小管上皮细胞铁死亡[4][5]。补肾活血法通过“补肾以固本,活血以祛瘀”的双向调节,可干预 MAMs 介导的细胞器对话失衡。

5. 五味子-丹参药对通过补肾活血法调控糖尿病肾病 MAMs 的核心策略

5.1. 补肾为要

五味子性温味酸甘,归肺、肾、心经,具有“收敛固涩、益气生津、补肾宁心”之效。《本草纲目》载其“补元气不足,收耗散之气”,《神农本草经》将其列为上品,谓其“主益气,咳逆上气,劳伤羸瘦,补不足,强阴,益男子精”[29]。在 DKD 治疗中,五味子通过补肾填精、固摄下焦,可有效改善肾虚所致的精微外泄的蛋白尿以及水液代谢紊乱而导致的水肿[30][31],现代药理学研究揭示,五味子活性成分如五味子乙素通过调控肾小管上皮细胞线粒体动力学,促进融合蛋白 OPA1、MFN1/2 表达、抑制 ERS 标志物 GRP78,显著减轻 db/db 小鼠肾脏损伤[1],这些研究印证了其“补肾固本”的科学内涵。

肾虚状态下,线粒体能量代谢障碍与 ERS 相互促进,形成“ERS-线粒体损伤-炎症/氧化应激”病理轴。丹酚酸 B 可显著抑制高糖诱导的肾小管上皮细胞间质转化(Epithelial-Mesenchymal Transition, EMT),下调线粒体分裂蛋白动力相关蛋白 1 (Dynammin-related protein 1, Drp1),同时上调融合蛋白 MFN2,恢复线粒体网络完整性[32]。有动物实验表明,五味子提取物能提高糖尿病模型小鼠肾脏组织中 ATP 生成效率,ROS 水平,减轻氧化应激对肾组织的损伤[33][34]。

ERS 是 DKD 肾小球足细胞凋亡的关键诱因,五味子多糖通过下调 ERS 标志物 CHOP、激活转录因子 4 (Activating Transcription Factor 4, ATF4)及半胱天冬酶-12 (CysteinyI aspartate specific proteinase-12, Caspase-12)的表达,未折叠蛋白质反应(Unfolded Protein Response, UPR)过度激活,从而保护足细胞结构和功能[31]。此外,五味子甲素可通过调节 IRE1-XBP1s 通路,减轻 ERS 诱导的肾脏纤维化[34]。

传统中医理论强调认为“肾主水,瘀阻水停,血不利则为水”,肾虚与血瘀互为因果。五味子在补肾的同时,兼具“活血”潜能。其活性成分可通过抑制 TGF- β /Smad3 信号通路,减少肾脏纤维化标志物,如 α -平滑肌肌动蛋白(alpha-Smooth Muscle Actin, α -SMA)、纤连蛋白(Fibronectin, FN)的表达[35]。此外,其还能下调炎症因子如肿瘤坏死因子- α (Tumor Necrosis Factor- α , TNF- α)、白细胞介素-6 (Interleukin-6, IL-6)和氧化应激产物如丙二醛(Malondialdehyde, MDA)、8-羟基脱氧鸟苷(8-Hydroxy-2'-deoxyguanosine, 8-OHdG),改善肾脏微炎症状态[36]。

结合以上研究,五味子以“补肾为要”,通过多成分、多靶点调控 MAMs,从能量代谢、氧化应激、炎症反应等层面来调控 DKD 的“肾虚血瘀”病理基础。这一策略不仅体现了中医“治病求本”的思想,也为开发基于 MAMs 调控的 DKD 治疗新药提供了理论依据。

5.2. 活血为辅

丹参作为活血化瘀类中药的代表性药物,在 DKD 的治疗中具有重要作用。中医理论认为,DKD 的

病理基础在于“肾虚血瘀”，而丹参以其“活血祛瘀、通经止痛”的功效，能够有效改善肾脏微循环障碍，减轻肾小球硬化和肾小管间质纤维化[37]。丹参归心、肝经，具有“活血而不伤正”的特点，能够疏通肾脏络脉瘀阻，改善“血不利则为水”的病理性水肿。在 DKD 中，丹参通过活血化瘀作用，可减轻肾小球高滤过状态和肾小管缺氧性损伤，从而保护肾功能。此外，丹参的“通络”功效与现代医学中改善微循环障碍、抑制血小板聚集等作用相契合，进一步体现了其中医理论的科学内涵[38][39]。现代药理学研究表明，丹参的主要活性成分包括水溶性丹酚酸类代表成分如丹酚酸，和脂溶性丹参酮类，代表成分如丹参酮 IIA，这些成分通过多靶点、多途径发挥抗炎、抗氧化、调节 MAMs 等作用，从而延缓 DKD 的进展[40][41]。近年研究发现，MAMs 紊乱是 DKD 中细胞应激和炎症反应的关键环节。Tan-IIA 能够显著抑制高糖诱导的足细胞线粒体分裂，并通过调节 MAMs 稳定性减少 ERS 和 ROS 的过度产生[42]。丹酚酸 B 可改善氧化应激与线粒体功能障碍，通过激活 Nrf2/HO-1 信号通路，增强抗氧化酶活性，同时抑制线粒体膜电位下降和细胞色素 C 释放，保护肾小球系膜细胞免受高糖损伤[43]。

6. 五味子 - 丹参药对配伍理论的现代阐释

中药配伍是中医方剂学的核心理论之一，其强调药物之间的协同、制约或增效作用。五味子 - 丹参药对是传统中药复方的核心配伍，在“补肾活血”治法中具有良好的协同增效基础。从现代药学角度分析，二者在药代动力学和药效学层面均表现出良好的互补性与协同性。

6.1. 药代动力学层面的相互作用

研究证实，五味子与丹参联用时，其木脂素成分，如 Schisandrin B 能显著抑制肠道 P-gp 的外排功能，P-gp 是一种关键的外排转运蛋白，负责将药物泵出细胞外，这种抑制可增强丹参中水溶性成分丹酚酸 B 的口服生物利用度，改善其吸收率，避免因首过效应导致的损失。丹参的丹参酮类成分，如 Tanshinone II 可调节肝脏 CYP450 酶系活性，特别是对 CYP3A 亚型产生抑制作用，这减缓了五味子活性成分的代谢速率，延长其在体内的半衰期，从而提升组织分布浓度和药效持续时间[44]。药代动力学研究表明，这种相互作用机制归因于草药成分间的互补效应，五味子木脂素通过抑制 P-gp 减少外排，而丹参酮则通过调控代谢酶通路减少清除率[45]，在细胞水平实现协同增效。此外，这类相互作用支持了二者在慢性疾病治疗中的协同应用，通过提升关键活性成分的生物利用度，强化药效动力学表现，如减少剂量依赖毒性并增强整体治疗效果[46]。这种在药代动力学层面的互补，为二者在体内协同发挥“补肾活血”效应提供了物质基础。

6.2. 药效学层面的多靶点协同机制

在药效学层面，五味子与丹参分别作用于 MAMs 调控网络的不同节点，形成多靶点、多通路的协同调控。五味子侧重于调控线粒体功能，通过上调 OPA1、MFN2 等融合蛋白表达，改善线粒体动力学，增强 ATP 生成[47][48]，从“补肾”角度改善能量代谢障碍。丹参则侧重于抑制内质网应激，通过下调 GRP78、CHOP 等 ERS 标志物，减轻未折叠蛋白反应过度激活[49]，从“活血”角度缓解氧化应激与炎症反应。二者联用后，可在 MAMs 结构域形成“线粒体 - 内质网”双重调控，共同恢复细胞器间钙信号、ROS 平衡及自噬流，从而更全面地干预 DKD “虚 - 瘀”病机转化过程中的代谢紊乱与纤维化进程。

7. 讨论

糖尿病肾病病程长，中医药在治疗 DKD 方面有其独特的优势。本文基于“肾虚血瘀”理论，探讨五味子 - 丹参药对通过调控 MAMs 改善 DKD 的作用机制。研究发现，MAMs 功能障碍所导致的能量代谢紊乱、氧化应激加剧和细胞死亡激活等病理过程，与中医“肾虚血瘀”理论中的核心病机存在对应关系。

五味子-丹参药对通过补肾活血,多成分、多靶点调控 MAMs,从能量代谢、氧化应激、炎症反应等多层面来调控 DKD 的病理基础。然而,研究尚存在不足,如糖尿病肾病动物模型的标准化及评价体系尚需完善。未来研究需进一步明确五味子-丹参药对不同活性成分的靶点交互网络,优化其在补肾活血复方中的应用,更系统揭示“肾虚血瘀”与 MAMs 的内在联系,为补肾活血法的精准应用提供实验依据和理论支撑。

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