黄芪及其方剂配伍干预糖尿病肾病研究进展

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摘要: 糖尿病肾病 (diabetic kidney disease, DKD) 是一种进行性肾脏并发症, 目前尚缺乏有效逆转病情的治疗策略。中医药基于“扶正祛邪”原则, 在控制血糖、改善肾功能等方面展现出多靶点、整体调节的优势。黄芪作为补气要药, 功擅补气升阳、利水消肿, 与DKD“气虚浊留”核心病机高度契合, 已成为临床防治DKD的高频药物。本文系统总结相关文献发现, 黄芪凭借其活性成分如黄芪甲苷、黄芪多糖、毛蕊异黄酮, 药对如黄芪−山药、黄芪−山茱萸、黄芪−金雀根等, 配伍方剂如参芪地黄汤、玉液汤、黄芪葛根汤、黄芪六一汤、黄芪汤等和相关中成药如渴络欣胶囊、参芪降糖颗粒、尿毒清颗粒等在DKD防治中表现出良好潜力, 其作用机制涉及调节糖脂代谢、抑制氧化应激与炎症反应、改善胰岛素抵抗、调控多种程序性细胞死亡 (焦亡/凋亡/铁死亡/自噬)、抗肾脏纤维化及减轻内质网应激等多个环节。该综述系统梳理了黄芪及其方剂配伍干预DKD的研究进展, 旨在初步阐释黄芪“补气利水”功效的现代科学内涵, 为其临床应用与深入研究提供参考。

关键词: 黄芪; 补气利水; 糖尿病肾病; 气虚浊留; 方剂配伍; 作用机制

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Research progress on *Astragalus membranaceus* and its formulations in the management of diabetic kidney disease

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Abstract: Diabetic kidney disease (DKD) is a progressive renal complication for which effective reversal strategies remain elusive. Traditional Chinese medicine (TCM), based on the principle of "strengthening the body's defenses and expelling pathogens" demonstrates advantages in multi-targeted, holistic regulation for controlling

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blood glucose and improving renal function. *Astragalus membranaceus*, a key Qi-tonifying herb, excels at replenishing Qi, elevating Yang, promoting diuresis, and reducing edema. Its properties align closely with the core pathogenesis of DKD—Qi deficiency with retention of turbidity—making it a frequently used clinical agent for preventing and treating DKD. This systematic review of relevant literature reveals that *Astragalus membranaceus*, through its active components (e. g., astragaloside IV, astragalus polysaccharide, and calycosin), synergistic combinations (e. g., *Astragalus membranaceus-Dioscorea opposita*, *Astragalus membranaceus-Cornus officinalis*, *Astragalus membranaceus-Caragana sinica*), and formulae (e. g., Shenqi Dihuang Decoction, Yuye Decoction, Huangqi Gegen Decoction, Huangqi Liuyi Decoction, Huangqi Decoction), and related proprietary Chinese medicines like Keluxin Capsule, Shenqi Jiangtang Capsule, and Niaoduqing Granule demonstrate promising potential in DKD prevention and treatment. Its mechanisms involve regulating glucose and lipid metabolism, inhibiting oxidative stress and inflammatory responses, improving insulin resistance, and modulating multiple pathways of programmed cell death (pyroptosis/apoptosis/ferroptosis/autophagy), counteracting renal fibrosis, and alleviating endoplasmic reticulum stress. This review systematically summarizes research progress on *Astragalus membranaceus* and its formula combinations in intervening DKD, aiming to preliminarily elucidate the modern scientific implications of *Astragalus membranaceus*'s "Qi-tonifying and water-draining" efficacy, providing reference for its clinical application and further investigation.

Key words: *Astragalus membranaceus*; Qi-tonifying and diuretic; diabetic kidney disease; Qi deficiency with retention of turbidity; formula composition; mechanism of action

糖尿病肾病 (diabetic kidney disease, DKD) 作为糖尿病 (diabetes mellitus, DM) 的一种重要的血管并发症, 其特征是长时间患糖尿病导致的蛋白尿以及肾小球滤过率 (glomerular filtration rate, GFR) 进行性降低, 最终可发展为终末期肾脏病[1]。DKD在DM患者中的发生率约为20%～40%[2]。近年来, DKD已成为亚太地区重大医疗负担, 是导致肾衰竭患者需肾脏替代治疗的主要病因[3]。目前对于DKD复杂发病机制的认识尚不清晰, 这使得针对DKD的治疗策略缺乏特异性指向。因此, 探索有效延缓甚至逆转DKD进展的防治策略, 已成为当前糖尿病管理中的重要内容。而中医药治疗DKD可有效改善临床症状, 保护肾功能[4]。

DKD在中医学中归于“消渴”“肾消”“下消”“水肿”“尿浊”等范畴[5],《证治准绳》载消渴“渴而便数有膏为下消”;《圣济总录》言消渴日久“肾气虚衰……精微不固而致小便至甜, 有膏, 能为水肿”。既往临床研究表明, DKD患者常见气虚血瘀、水湿内停等基本病机, 其中气虚被认为是DKD发生、发展的核心因素[6]。气虚推动无力, 血行不畅则瘀阻肾络; 水液失于输布, 聚为湿浊, 损伤肾络, 导致蛋白尿及肾功能进行性下降, 此即“气虚浊留”之证[7]。因此, 以“扶正祛邪”为基本治则, 从益气活血、利湿泄浊入手, 是防治DKD的关键环节。

黄芪为豆科植物蒙古黄芪*Astragalus membranaceus* (Fisch.) Bge. var. *mongholicus* (Bge.) Hsiao或膜荚黄芪*Astragalus membranaceus* (Fisch.) Bge.的干燥根, 其味甘性温, 功擅补气升阳、利水消肿、行滞通痹。《名医别录》记载黄芪: “补丈夫虚损, 五劳羸瘦, 止渴。”《得配本草》云其: “助气补血, 固腠理, 益脾胃……配茯苓, 治气虚白浊”与DKD“气虚浊留”之病机相契合。前期数据挖掘研究表明, 黄芪是治疗DKD用药频数最多的中药[8]。现代药理研究及临床研究证实, 黄芪及其复方具有调节糖代谢、减轻炎症反应、抑制肾纤维化及保护足细胞等多重作用[9,10], 在DKD临床实践中获得广泛应用, 尤其适用于气虚水停、肾络瘀阻型DKD患者[11,12]; 此外, 在慢性肾脏病、高血压肾损害等疾病中亦显示出显著的肾脏保护效应[13,14]。为此, 本研究系统总结黄芪及其组方配伍在治疗DKD中的作用机制(图1), 有利于揭示黄芪“补气利水”传统功效的科学内涵, 以期为黄芪及其复方干预DKD的临床应用与深入研究提供参考。

1 黄芪及其活性成分改善糖尿病肾病的研究

1.1 黄芪改善糖尿病肾病的活性成分

黄芪现已分离鉴定出200余种化合物, 主要包括皂苷类、黄酮类、多糖类、氨基酸类等[15,16], 其中治疗DKD的有效活性成分是黄芪皂苷、黄芪多糖和黄酮类物质[17]。临床研究证实, 在常规治疗外, 辅助使用黄芪制剂, 包括片剂、颗粒、煎剂、提取物液体和注射剂, 可减少DKD患者的白蛋白尿、蛋白尿和血清肌酐 (serum creatinine, Scr) 水平[18]。黄芪甲苷作为黄芪中最重要的皂苷类成分之一, 在改善DKD的过程中具有重要作用[19,20]。机制研究显示, 黄芪甲苷能够直接作用于肾脏细胞, 通过保护足细胞功能、抑制上皮细胞–间充质转分化 (epithelial-mesenchymal transition,

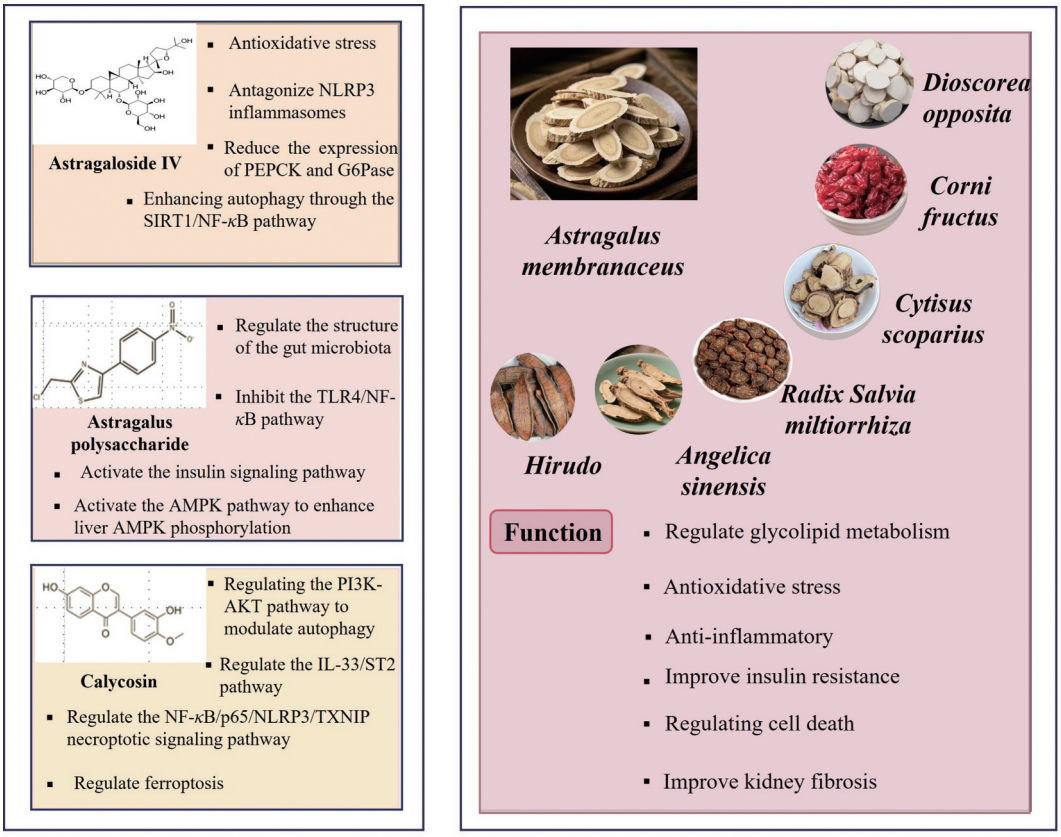


Figure 1 Mechanisms of *Astragalus membranaceus* treatment in DKD. DKD: Diabetic kidney disease; NLRP3: NOD-like receptor pyrin domain containing 3; PEPCK: Phosphoenolpyruvate carboxykinase; G6Pase: Glucose-6-phosphatase; SIRT1: Silent information regulator 1; NF-κB: Nuclear factor kappa-B; TLR4: Toll-like receptor 4; AMPK: Adenosine 5'-monophosphate-activated protein kinase; PI3K: Phosphoinositide 3-kinase; AKT: Protein kinase B; IL-33: Interleukin-33; ST2: Growth stimulation expressed gene 2; p65: RelA; TXNIP: Thioredoxin interacting protein

EMT)、减少细胞凋亡等多条信号通路, 对DKD的多个病理环节具有干预效果[21,22]。此外, 黄芪多糖作为黄芪的主要多糖成分, 在调节机体糖代谢、改善胰岛素敏感性方面贡献突出, 能从源头控制DKD的进展风险[23]; 而毛蕊异黄酮等黄酮类成分则被证实具有显著的抗炎和抗纤维化活性, 能够直接减轻肾脏的炎性损伤与细胞外基质 (extracellular matrix, ECM) 的积聚[24]。这些活性成分通过多成分、多靶点的协同作用, 共同构成了黄芪防治DKD的现代药理学基础。不同活性成分的体内代谢特征见表1[25-27]。

1.2 黄芪干预糖尿病肾病的作用机制

1.2.1 调节糖脂代谢 长期处于高血糖状态会导致晚期糖基化终末产物 (advanced glycation end products, AGEs) 大量产生, 其与肾脏细胞上的受体 (receptor for advanced glycation end products, RAGE) 结合后, 可激活核因子κB (nuclear factor kappa-B, NF-κB) 等炎症信号通路, 并诱发氧化应激, 直接损伤肾小球内皮细胞、足细胞和肾小管上皮细胞 (tubular epithelial cells, TECs), 加速肾脏纤维化进程[28,29]。同时, 脂质代谢异常引发的肾内脂质沉积, 即脂毒性, 可进一步诱导肾小球系膜细胞 (mesangial cell, MC) 增殖、ECM积聚和肾小管损伤, 共同推动DKD的进展[30,31]。

黄芪及其活性成分能够通过改善机体的糖脂代谢稳态, 降低血糖和血脂, 发挥肾脏保护作用。黄芪多糖可增强外周组织对葡萄糖的摄取与利用能力, 进而从根源上降低血糖水平, 有效缓解高血糖对肾脏所造成的持续性损害[32]。机制研究表明, 黄芪甲苷能够显著下调肝脏中磷酸烯醇丙酮酸羧激酶和葡萄糖-6-磷酸酶的活性, 抑制肝糖原过度输出, 实现非胰岛素依赖性血糖调控[33]。此外, 已有研究证实, 毛蕊异黄酮可以有效调节脂质代谢, 显著降低DKD模型动物血清总胆固醇 (serum total cholesterol, TC)、甘油三酯 (triglyceride, TG) 等水平, 减轻肾脏脂毒性损伤[34]。

1.2.2 抗氧化应激 氧化应激指促氧化剂与抗氧化剂平衡失调, 由活性氧 (reactive oxygen species, ROS) 及氮自由基过度生成引发[35]。在DKD病程中, 胰腺与肾

Table 1 Metabolic characteristics of active components from *Astragalus membranaceus in vivo*. CYP450: Cytochrome P450; SCFAs: Short-chain fatty acids

Active component	Absorption site	Metabolic pathway	Bioavailability	Ref.
Astragaloside	Mainly in the small intestine; partially absorbed after hydrolysis by intestinal microbiota	1. Gut microbiota metabolism: Hydrolysis to secondary aglycones; 2. Liver metabolism: Hydroxylation, demethylation *via* CYP450 enzymes; 3. Excretion: Mainly *via* bile and urine	Low (approximately 0.1%−2%) due to strong hydrophilicity, poor membrane permeability, and significant first-pass effect	[25]
Astragalus polysaccharide	Colon (minor absorption in small intestine), dependent on degradation by intestinal microbiota	1. Gut microbiota fermentation: Degradation to SCFAs; 2. Absorption into blood: Enters circulation as degradation products; 3. Immunomodulation: Partially directly acts on intestinal immune cells	Very low (minimal direct absorption); exerts systemic effects mainly through local intestinal actions and metabolites	[26]
Calycosin	Small intestine (passive diffusion or transporter-mediated)	1. Gut metabolism: Partially hydrolyzed by microbiota to aglycones; 2. Liver metabolism: Glucuronidation and sulfation *via* CYP450 enzymes; 3. Enterohepatic circulation: Conjugates hydrolyzed and reabsorbed in the intestine; 4. Excretion: Mainly *via* urine and feces	Moderate (approximately 10%−30%) due to high lipophilicity of the aglycone form, facilitating absorption	[27]

脏等靶器官存在高水平氧化应激[36]。过度氧化应激与细胞内不良事件相关, 高血糖促进细胞内AGEs生成, 进而诱发线粒体释放过量ROS, 最终引发肾脏炎症、肾细胞损伤及纤维化[37]。故而有效控制氧化应激水平对于肾脏功能的保护而言具有至关重要的意义。

黄芪甲苷具有显著的抗氧化作用, 可通过激活过氧化物酶体增殖物激活受体γ (peroxisome proliferative activated receptor γ, PPARγ)-Klotho-叉头框转录因子O1 (forkhead box O1, FoxO1) 通路增强Klotho表达并抑制氧化应激, 从而减轻*db*/*db*小鼠的足细胞损伤[38]。体外实验结果与动物研究结果一致, 黄芪甲苷可降低ROS含量, 恢复Klotho表达, 增强FoxO1依赖的抗氧化活性, 并上调核因子E_2相关因子2 (nuclear factor erythroid 2-related factor 2, Nrf2)-抗氧化反应元件 (antioxidant response element, ARE)/线粒体转录因子A (transcription factor A, mitochondrial, TFAM) 以抵抗氧化应激损伤, 进而使暴露于高葡萄糖 (high glucose, HG) 的足细胞免于凋亡[39,40]。毛蕊异黄酮及其衍生物毛蕊异黄酮-7-*O*-*β*-*D*-葡萄糖苷作为黄芪的代表性成分, 其抗氧化作用亦已得到证实。使用毛蕊异黄酮干预2型糖尿病 (type 2 diabetes mellitus, T2DM) 大鼠, 能够降低ROS、丙二醛 (malondialdehyde, MDA) 及硫氧还蛋白互作蛋白 (thioredoxin interacting protein, TXNIP) 水平, 且升高Nrf2和总抗氧化能力 (total antioxidant capacity, TAC) 水平, 进而恢复线粒体活力, 证明其缓解氧化应激的潜力[41-43]。

1.2.3 抗炎 根据全基因组转录组分析, 在DKD病程中可观察到多种炎症途径[44]。NF-κB作为经典的炎症相关信号通路, 其激活及特定促炎性趋化因子的转录被证实是DKD进展的生物标志物[45]。Toll样受体4 (toll-like receptor 4, TLR4) 同样被发现在DKD肾组织中高表达[46]。核苷酸结合寡聚化结构域样受体 (nucleotide-binding oligomerization domain-like receptor, NLR) 蛋白家族作为模式识别受体, 可介导细胞损伤与应激的初始先天免疫反应[47]。已知某些NLR会形成称为炎性小体的多蛋白复合体, 其由NLR家族嘌呤结构域蛋白 (NOD-like receptor pyrin domain containing, NLRP)、凋亡相关斑点样蛋白及半胱天冬酶-1 (cysteinyl aspartate specific proteinase-1, Caspase-1) 构成[48]。无论在DM患者和小鼠体内, 还是体外实验中, 均检测到内皮细胞和足细胞中存在炎性小体激活[49]。此外, 部分促炎细胞因子已被证实参与DKD发病机制, 包括白细胞介素 (interleukin, IL)-1、IL-6、IL-18及肿瘤坏死因子 (tumor necrosis factor, TNF)[50]。尽管炎症在DKD进展过程中的具体作用尚待阐明, 但已有研究明确表明靶向炎症相关信号通路可改善DKD进程。

研究证实, 黄芪甲苷可下调DKD大鼠体内IL-1*β*、IL-4、TNF-*α*、单核细胞趋化因子-1 (monocyte chemoattractant protein-1, MCP-1) 和细胞间黏附分子-1 (intercellular cell adhesion molecule-1, ICAM-1) 的过度表达, 表明其通过调控NF-κB介导的炎症基因表达来减轻肾损伤[51,52]。黄芪多糖和毛蕊异黄酮亦能通过调控NF-κB依赖性途径来缓解DKD肾脏的炎症, 具体通过TLR4的下调、抑制IκB*α*和NF-κB p65的磷酸

化以及降低TNF-α、IL-1β和MCP-1的表达发挥作用, 该效应在糖尿病大鼠/小鼠、AGEs处理的小鼠TECs及HG处理的小鼠足细胞中均得到验证[53,54]。此外, 黄芪甲苷可通过抑制NLR信号通路, 调节肾脏中DKD改变的基因转录谱, 进而改善大鼠血糖水平、肾功能及肾脏病理变化[55]。NLRP3炎症小体作为研究最深入的炎症小体之一, 抑制其活性能减轻DKD中的氧化应激、炎症及纤维化[56]。黄芪甲苷具有拮抗由NLRP3炎症小体所介导的炎症反应的能力, 通过这一机制改善*db*/*db*小鼠的肾功能指标, 同时有效减轻足细胞损伤[57]。

1.2.4 改善胰岛素抵抗 在肾脏中, 胰岛素信号通路不仅调控细胞的代谢与存活, 还直接影响足细胞功能、肾小球滤过和肾小管重吸收[58]。DKD状态下, 肾脏局部会出现胰岛素信号转导障碍, 其特征是胰岛素受体底物1 (insulin receptor substrate 1, IRS-1)的酪氨酸磷酸化水平下降, 进而导致下游的磷酸肌醇3-激酶(phosphoinositide 3-kinase, PI3K)/蛋白激酶B (protein kinase B, PKB/AKT)途径被抑制[59]。此通路的失活会加剧肾脏细胞的代谢应激, 促进炎症因子释放和ECM积聚, 最终加速肾纤维化进程[60]。由此可见, 改善全身及肾脏局部的胰岛素抵抗(insulin resistance, IR), 成为遏制DKD病情进展的关键策略。

研究显示, 黄芪甲苷可激活PI3K/AKT途径, 抑制氧化应激与NF-κB介导的炎症反应, 并增强足细胞自噬能力, 进而改善IR, 减轻DKD所导致的肾脏损伤[61]。一方面, 黄芪多糖可通过上调胰岛素受体(insulin receptor, InsR)/IRS-1/葡萄糖转运蛋白4 (glucose transporter 4, GLUT4)表达, 降低ROS、TNF-α、IL-6水平, 并调节脂代谢紊乱, 有效缓解IR, 进而减轻肾脏氧化损伤、炎症浸润及尿微量白蛋白(urinary microalbumin, U-mALB)排泄, 保护肾小管结构[62]。另一方面, 黄芪多糖被证实可通过调节T2DM大鼠体内的磷酸腺苷活化蛋白激酶(adenosine 5'-monophosphate-activated protein kinase, AMPK)信号通路, 增强胰岛素敏感性, 并抑制糖异生关键酶的活性[63]。此外, 毛蕊异黄酮、毛蕊异黄酮苷等活性成分亦可影响PI3K/AKT/哺乳动物雷帕霉素靶蛋白(mechanistic target of rapamycin, mTOR)及AMPK途径, 进而发挥改善IR状态的重要功能[64]。

1.2.5 调控细胞死亡 细胞死亡是涉及多种信号通路的复杂生物学过程, 主要包括凋亡、铁死亡、焦亡及自噬等多种形式。在生理状态下, 细胞死亡参与维持组织稳态、清除异常或衰老细胞; 然而, 在DKD等病理条件下, HG、氧化应激及炎症等因素可导致细胞死亡机制失调, 进而诱发肾实质细胞的过度丧失与肾功能损伤。研究表明, 不同类型的细胞死亡在DKD进展中扮演不同角色[65]。具体而言, 细胞焦亡由NLRP3炎性小体介导, 通过激活Caspase-1切割焦亡效应蛋白消皮素D形成膜孔, 释放IL-1β和IL-18, 加剧炎症反应[66]; 细胞凋亡则依赖于线粒体途径, 表现为促凋亡蛋白B细胞淋巴瘤/白血病-2基因(B-cell lymphoma 2, Bcl-2)相关X蛋白(Bcl-2-associated X protein, BAX)/抗凋亡蛋白Bcl-2比例失衡, 促使细胞色素C释放并激活Caspase级联反应; 铁死亡以脂质过氧化和铁代谢紊乱为核心特征, 涉及胱氨酸/谷氨酸逆向转运体/谷胱甘肽过氧化物酶4 (glutathione peroxidase 4, GPX4)通路失调, 导致ROS积累和细胞膜损伤; 而自噬作为细胞自我保护机制, 在HG环境下被抑制, 导致有害物质堆积, 进一步加重肾细胞损伤[67]。这些细胞死亡机制相互影响, 共同促进DKD的肾脏功能丧失和纤维化进展[68]。因此, 干预这些异常的程序性细胞死亡是保护肾细胞、延缓DKD进展的重要策略。

研究显示, 黄芪的活性成分对干预异常程序性细胞死亡具有多方面的调控作用, 黄芪甲苷可以抑制*db*/*db*小鼠肾皮质中NLRP3炎症小体、凋亡相关斑点样蛋白(apoptosis-associated speck-like protein containing a CARD, ASC)、Caspase-1和IL-1β的表达水平, 同时降低血清中TNF-α和MCP-1的浓度, 从而通过上调足细胞标志物足细胞裂隙膜蛋白podocin (由*NPHS2*基因编码)和突触足蛋白, 使足细胞免于焦亡[57,69]。同时, 黄芪甲苷具备的抗氧化能力还能逆转肾小管细胞的凋亡。使用黄芪甲苷干预HK-2细胞的研究表明, Bcl-2/Bax比值和Nrf2增加, 而裂解的Caspase-3减少[70]。并且黄芪甲苷还能通过沉默信息调节因子1 (silent information regulator 1, SIRT1)/NF-κB信号通路调节Beclin-1和自噬相关蛋白微管结合蛋白1轻链3II (microtubule-associated protein light chain 3-Ⅱ, LC3-II), 进而抑制MC增殖[71]。此外, 通过体内外研究证实, 毛蕊异黄酮能调节DKD中的铁死亡与自噬。毛蕊异黄酮可降低血尿素氮(blood urea nitrogen, BUN)和Scr水平, 缓解肾小管扩张与胶原沉积, 逆转*db*/*db*小鼠近端肾小管刷状缘的丧失; 并且毛蕊异黄酮能够通过上调GPX4、抑制ROS生成及核受体共激活因子4 (nuclear receptor coactivator 4, NCOA4)表达, 提升HG处理的HK-2细胞的存活率, 上述机制均与铁死亡密切相关[72]。在调节自噬方面, 毛蕊异黄酮通过调控PI3K-AKT途径, 增加LC3-II的表达, 降低P62水平, 增强TECs的自噬能力, 有效减轻DKD相关的细胞损伤[73]。

1.2.6 改善肾脏纤维化 肾纤维化的病理特征为肾小

管萎缩、间质慢性炎症及纤维生成、肾小球硬化等[74]。多种细胞生长因子如转化生长因子β (transforming growth factor-β, TGF-β)、血管紧张素II及其受体的异常激活是肾纤维化的介导因子[75]。对于肾小管, 在DKD过程中, 浸润的免疫细胞、糖尿和蛋白尿可诱导近端TECs分泌促炎和促纤维化介质, 导致间质炎症和纤维化[76]。在人类肾小球中, 足细胞损伤会导致其脱离和丧失, 这是肾小球损伤和肾小球硬化症的主要决定因素之一; 内皮细胞通过再生产生基底膜 (glomerular basement membrane, GBM) 并导致其增厚, 从而参与肾小球硬化形成; 同时, MC和壁上皮细胞的病理变化表现为再生、增殖并产生ECM, 这也可能导致肾小球硬化, 参与肾脏纤维化进程[77]。

对HK-2和NRK-52E细胞系的体外实验证实, 黄芪甲苷可逆转HG或糖化作用诱导的α-平滑肌肌动蛋白 (alpha smooth muscle actin, α-SMA) 表达上调, 并降低E-钙黏蛋白水平以减弱EMT[78,79]。研究表明, 黄芪甲苷能够通过TGF-β1/Smad/miR-192信号通路抑制TGF-β1及其下游介质果蝇母体抗五联体蛋白3 (SMAD family member 3, Smad3) 的表达, 增加Smad7的表达, 并下调微小RNA (microRNA, miR)-192、α-SMA及I型胶原 (type 1 collagen, Col-1) 的表达, 抑制MC异常增殖和GBM增厚, 进而改善DKD大鼠的肾纤维化[55,80]。此外, 体外与体内实验研究显示, 毛蕊异黄酮可抑制肾脏ECM沉积并调节其纤维化进程[43,81]。

1.2.7 调节内质网应激 内质网 (endoplasmic reticulum, ER) 的主要生理功能是合成蛋白质, 然而当ER蛋白折叠能力超负荷时, 细胞便会出现内质网应激 (endoplasmic reticulum stress, ERS) 反应。ERS会引发错误折叠和未折叠蛋白 (unfolded protein response, UPR) 的逐渐积累, 当这种积累超过ER所能承受的临界阈值时, 便会触发名为UPR的信号传导途径[82]。过度且持续的UPR上调可能引起细胞凋亡或坏死。HG状态会导致蛋白质糖基化异常, 并干扰蛋白质折叠, 使错误折叠和UPR在内质网中积累, 从而加剧ERS, 在长期过程中产生细胞毒性[83,84]。研究显示, ERS参与糖尿病并发症包括肾病的发病机制。ERS对DKD预后不良的影响具有多重机制, 在未缓解的ERS和稳态失衡状态下, UPR会触发细胞凋亡, 这是DKD发展的关键过程[85]。

黄芪甲苷已被证明能通过多个靶点减弱ERS, 其保护作用可能与抑制某些类型肾细胞中ERS诱导的凋亡有关。研究表明, 黄芪甲苷可通过下调蛋白激酶RNA样内质网激酶 (protein kinase RNA-like endoplasmic reticulum kinase, PERK)、激活下游转录本因子4 (activating transcription factor 4, ATF4) 和C/EBP同源蛋白 (C/EBP-homologous protein, CHOP) 等与ERS紧密相关的蛋白表达, 并恢复Bax与Bcl-2表达的平衡, 从而减轻DKD大鼠TECs的凋亡[86]。黄芪甲苷缓解ERS诱导的足细胞凋亡的机制亦与抑制PERK/ATF4/CHOP通路相关[87]。此外, 黄芪甲苷还能通过恢复肌浆网/内质网Ca^{2+}-ATP酶2 (sarcoplasmic/endoplasmic reticulum Ca^{2+} ATPase 2, SERCA2) 表达和活化, 减轻ERS, 从而缓解足细胞凋亡[88]。常见黄芪活性成分干预DKD相关基础研究见附表1。

2 黄芪药对干预糖尿病肾病的研究

基于单味药活性成分的研究为理解黄芪的药理作用奠定了基础, 然而中医药临床实践更注重药物间的配伍协同。药对作为中药配伍的最小单元, 深刻体现了方剂学的核心内涵。深入研究黄芪相关药对的配伍规律及作用机制, 不仅有助于阐释“益气活血、利湿泄浊”治法的科学内涵, 也为DKD的病理机制探讨、诊疗思路拓展及新药研发提供理论支撑与实践指导。

2.1 黄芪–山药

黄芪–山药的配伍源于《医学衷中参西录》玉液汤, 取其补脾固肾、益气生津之功, 一方面, 通过补脾益气, 促使脾气升发, 推动精微物质上达于肺, 进而输布津液以止渴; 另一方面, 借助固肾涩精之功, 使得精微封藏以缩尿。研究表明[89], 黄芪–山药能够通过调节T2DM大鼠的粪便代谢产物表达, 影响糖酵解、糖异生和丙酮酸代谢等过程, 改善糖脂代谢与氨基酸代谢紊乱。已有研究证实[90], 黄芪–山药可降低DKD大鼠的血糖水平, 减少U-mALB排泄, 降低BUN和Scr含量, 改善肾脏病理损伤。此外, 黄芪–山药还能提高抗氧化能力, 增强超氧化物歧化酶 (superoxide dismutase, SOD) 活性, 减少MDA含量, 进而降低氧化应激对DKD肾脏的损伤[91]。这些发现提示黄芪–山药药对可能通过调节多代谢通路和增强抗氧化作用, 保护肾脏功能, 延缓DKD的进展。

2.2 黄芪–山茱萸

黄芪–山茱萸药对源于《杂病犀烛》参芪地黄汤, 两者伍用益气固涩之功增强, 共奏调补脾肾之效。研究表明, 黄芪–山茱萸及其活性成分, 如黄芪中的毛蕊异黄酮、山茱萸中的环烯醚萜苷类, 可通过调节自噬、改善脂质代谢紊乱等多途径保护肾脏。黄芪–山茱萸能显著上调自噬标志蛋白LC3-II表达、降低P62积累, 并通过调控PI3K-AKT信号通路恢复自噬水平, 延缓肾纤维化及足细胞损伤[34]。代谢组学进一步揭示, 黄芪–山茱萸可回调花生四烯酸、*L*-苯丙氨酸、黄嘌呤等

关键代谢物, 干预亚油酸、甘油磷脂、苯丙氨酸等多条代谢途径, 从而改善DKD代谢紊乱[92]。值得关注的是, Cai课题组[93,94]在挑选出黄芪−山茱萸干预DKD精准药对 (CG_6, 多糖−黄酮−皂苷−环烯醚萜苷2∶3∶1∶2)的基础上, 得到山茱萸酒制优化后的炮制药对P-CG5 (2∶2∶3∶1) 疗效最优, 体现了炮制与配伍在增强药效中的协同作用。

2.3 黄芪−金雀根

黄芪−金雀根的配伍源于中医“肾络瘀阻”理论, 以“健脾益气、利湿泄浊通络”为核心治法, 金雀根清肺益脾、活血通络, 与黄芪相伍有益气活血通络、清热利湿泄浊之功。研究表明[95,96], 黄芪−金雀根配伍可通过多通路协同作用发挥肾脏保护效应: 一方面, 干预PTEN诱导激酶1 (PTEN induced kinase 1, PINK1)/线粒体融合蛋白2 (mitofusin 2, MFN2)/Parkin RBR E3泛素蛋白连接酶 (Parkin RBR E3 ubiquitin protein ligase, Parkin) 途径, 增强线粒体自噬, 改善氧化应激, 减少MDA生成并提升SOD活性; 另一方面, 调控c-Jun氨基末端激酶 (c-Jun N-terminal kinase, JNK)/应激活化蛋白激酶 (stress-activated protein kinase, SAPK) 途径活化, 降低分化群68 (cluster of differentiation 68, CD68) 和诱导型一氧化氮合酶 (inducible nitric oxide synthase, iNOS) 的表达, 降低TNF-α、IL-1β和ICAM-1等因子水平, 改善肾脏炎症和病理损伤。此外, 该配伍在改善U-mALB、Scr和BUN水平方面表现出协同增效作用, 其疗效优于单药应用。

2.4 黄芪−丹参

黄芪−丹参药对源于中医“益气活血”治法, 是治疗DKD的经典配伍, 广泛应用于临床。网络药理学分析预测[97], 黄芪−丹参可能通过多种机制干预DKD, 涉及缺氧诱导因子1 (hypoxia-inducible factor 1, HIF-1)、胰岛素、丝裂原活化蛋白激酶 (mitogen activated protein kinase, MAPK) 等途径, 关键靶点包括转录激活因子3 (signal transducer and activator of transcription 3, STAT3)、AKT1、JUN等。实验研究表明[98], 黄芪−丹参能够提高腺嘌呤核苷三磷酸 (adenosine triphosphate, ATP) 和二磷酸腺苷 (adenosine diphosphate, ADP) 含量, 提高线粒体呼吸控制率, 进而保护DKD大鼠肾脏。并且黄芪−丹参可通过上调TECs巨蛋白表达, 增强肾小管对蛋白质的重吸收能力, 减少蛋白尿, 并改善肾组织氧化应激指标[99]。代谢组学研究表明[100], 黄芪−丹参可协同调节乳酸、黄嘌呤、柠檬酸、胆氨酸等代谢物, 影响糖、氨基酸及能量代谢通路。这些证据表明, 黄芪−丹参可能通过改善线粒体能量代谢、增强肾小管重吸收功能、调节代谢紊乱及抗炎抗氧化等多途径, 综合发挥肾脏保护作用。

2.5 黄芪−当归

黄芪−当归药对源于《内外伤辨惑论》当归补血汤, 乃益气活血经典配伍[101]。该药对契合DKD气虚血瘀之基本病机, 临床研究证实其可改善DKD患者肾功能, 减少蛋白尿。药理研究表明, 当归补血汤可作用于AGE/RAGE信号通路, 抑制HG诱导的HK-2细胞炎症反应及NF-κB等核心蛋白表达, 达到治疗DKD的目的[102]。进一步研究显示, 当归补血汤通过抑制PERK/ATF4/CHOP ERS通路, 减少足细胞Bax、剪切型半胱天冬酶-3 (cleaved Caspase-3) 的表达, 增强podocin、synaptopodin表达, 从而保护肾小球滤过屏障[103]。此外, 黄芪−当归药对能激活Nrf2/血红素氧合酶1 (heme oxygenase-1, HO-1) 通路, 提升抗氧化酶SOD、过氧化氢酶 (catalase, CAT)、谷胱甘肽过氧化物酶 (glutathione peroxidase, GSH-PX) 活性, 减轻糖尿病小鼠肾脏氧化损伤[104]。综上, 黄芪−当归药对可能借助抗炎、抗氧化及抑制ERS等多途径延缓DKD病情发展。

2.6 黄芪−水蛭

水蛭破血逐瘀、通经利水, 与黄芪相合既可益气活血, 又有祛瘀生新之效。实验研究显示[105,106], 黄芪−水蛭能够显著降低DKD大鼠的空腹血糖、24小时尿蛋白 (24-hour urinary total protein, 24 h-UTP) 及U-mALB, 减少尿视黄醇结合蛋白、β2-微球蛋白等肾损伤标志物的排泄。同时, 该药对通过抑制肾脏组织中TGF-β1、Col-4、纤维连接蛋白 (fibronectin, FN) 及IL-1β的表达, 减少ECM沉积, 减轻肾纤维化程度。

2.7 其他

除上述与黄芪配伍的经典药对外, 尚有部分未深入开展研究的药对被应用于DKD的干预中。一系列网络药理学分析表明, 黄芪−党参可能通过作用于AKT1、TNF等靶点, 调控AGE-RAGE、MAPK等途径, 从而发挥干预DKD的效果[107]; 筛选出黄芪−熟地黄的20个活性成分, 作用于TNF、血管内皮生长因子 (vascular endothelial growth factor, VEGF) 等139个靶点, 参与PI3K-AKT、HIF-1等信号通路, 提示其具有改善DKD炎症反应与缺氧状态的作用[108]; 黄芪−黄精的关键成分薯蓣皂苷、芒柄花黄素等可通过AKT1、TP53、RELA等靶点, 影响AGE-RAGE、IL-17等途径, 对DKD具有潜在治疗价值[109]; 此外, 黄芪−大黄可能通过TP53、AKT1、TNF等核心靶点调控AGE-RAGE、PI3K-AKT等通路, 发挥抗炎、抗纤维化等效果, 进而改善DKD[110]。尽管关于以上黄芪药对治疗DKD的相关研究较少, 但均已开展的网络药理学研究为后续作用机制研究的探索与验证提供了方向。汇总黄芪与不

同药物配伍形成的药对在DKD中的实验研究证据见附表2。

3 黄芪组方在改善糖尿病肾病中的应用

在药对研究的基础上, 由多味中药组成的复方更能体现中医药整体调节、复方配伍的特色。黄芪作为益气利水要药, 是众多防治DKD经典名方及现代中成药的核心组成。以下将系统梳理含黄芪的经典方剂及中成药在DKD防治中的临床应用与作用机制研究进展。

3.1 参芪地黄汤

参芪地黄汤经《沈氏尊生书》改良后, 由黄芪、人参、熟地黄、山药、山茱萸、牡丹皮、茯苓、泽泻组成。本方擅益气养阴、补脾益肾, 为《糖尿病肾病病证结合诊疗指南》中期气阴两虚证推荐方[111]。临床研究表明[112], 参芪地黄汤加减可改善DKD患者中医证候积分, 提高细胞免疫功能, 降低胰岛素抵抗指数(homeostatic model assessment of insulin resistance, HOMA-IR) 及炎症因子水平, 并减少尿蛋白、Scr和BUN。联合羟苯磺酸钙应用时, 还能进一步改善老年DKD患者内生肌酐清除率、血清SOD水平及微循环指标NO、ET-1, 减轻氧化应激和肾纤维化[113]。

研究显示[114], 参芪地黄汤通过核心成分槲皮素、山柰酚等作用于AKT1、CASP3等关键靶点, 调控PI3K/AKT途径, 调节糖脂代谢和肾功能。细胞实验显示[115], 参芪地黄汤能干预HG诱导的TECs铁死亡, 其机制与调控Nrf2/HO-1/GPX4抗氧化轴、上调xCT和GPX4表达、降低Fe^{2+}、MDA及ROS水平有关。另一项研究表明[116], 参芪地黄汤通过调控长链酰基辅酶A合成酶4 (acyl CoA synthetase long chain family member 4, ACSL4)/溶血磷脂酰胆碱酰基转移酶3 (lysophosphatidylcholine acyltransferase 3, LPCAT3)/花生四烯酸脂氧合酶-15 (arachidonate 15-lipoxygenase, ALOX15) 轴抑制花生四烯酸相关性铁死亡, 减轻DKD小鼠肾脏病理损伤和纤维化。

3.2 玉液汤

玉液汤出自《医学衷中参西录》, 由黄芪、山药、葛根、知母、天花粉、五味子、鸡内金组成。该方具有益气生津、健脾固肾之效, 为《2型糖尿病病证结合诊疗指南》气阴两虚证推荐方[117]。临床研究显示, 玉液汤可显著改善DKD患者气阴两虚证候, 并改善肾功能。一项对DKD III和IV期患者的临床观察显示[118], 加味玉液汤能降低患者24 h-UTP、Scr和BUN水平, 提高血清白蛋白 (albumin, ALB) 和GFR; 加味玉液汤联合常规治疗DKD慢性肾衰竭, 可降低超敏C反应蛋白 (high-sensitivity c-reactive protein, hs-CRP)、IL-6等微炎症指标, 提升SOD活性, 改善氧化应激[119]。

研究显示[120], 玉液汤活性成分葛根素、芒果苷、毛蕊异黄酮葡萄糖苷等可通过调控lncRNA-miRNA-mRNA转录网络, 影响细胞凋亡、NOD样受体、IL-17和PI3K-AKT等途径, 从而改善肾脏炎症与纤维化。此外, 玉液汤还能改善肠道菌群结构, 提高拟杆菌门丰度、降低厚壁菌门比例, 修复肠黏膜屏障, 上调occludin、ZO-1蛋白表达, 减少结肠和肾脏组织中TNF-α、IL-6等炎症因子释放, 从而调节DKD大鼠的糖脂代谢和肾损伤[121]。

3.3 黄芪葛根汤

黄芪葛根汤出自《证治汇补》, 由黄芪、葛根两味药组成, 功擅益气升阳、利水活血、健脾养阴, 正合DKD脾肾气虚、瘀水互结之病机。临床研究表明[122], 黄芪葛根汤加减联合胰激肽原酶治疗DKD可降低患者24小时尿白蛋白排泄率 (urinary albumin excretion rates, UAER)、BUN水平和血浆黏度, 改善血液流变学; 黄芪葛根汤联合达格列净干预DKD的总有效率显著提高, 患者糖脂代谢指标、U-mALB、尿蛋白定量及多种炎性因子水平均明显改善[123]。

网络药理学预测黄芪葛根汤的核心靶点包括CASP3、VEGFA等, 调控AGE-RAGE、HIF-1等途径。实验研究进一步证实, 黄芪葛根汤可干预AGE-RAGE途径, 降低血清AGEs、TNF-α、MCP-1、ICAM-1等炎症因子水平, 抑制核转录因子-κB p65及其受体RAGE的表达, 减轻DKD大鼠肾脏组织纤维化[124]。此外, 黄芪葛根汤能调节DKD大鼠血液流变学状态, 降低血脂, 调节胱抑素C、hs-CRP、同型半胱氨酸 (homocysteine, Hcy) 等指标, 并上调肾组织SIRT1、LC3B-II蛋白表达[125]。

3.4 黄芪六一汤

黄芪六一汤出自《太平惠民和剂局方》, 由黄芪、甘草组成, 比例严谨, 具调和脾胃、平补气血、滋益肾水之效。DKD患者气虚血弱易出现虚劳、水肿等症, 黄芪六一汤以其平补气血、安和五脏之功, 切中病机, 临床可用于DKD的治疗。临床研究显示, 黄芪六一汤在调节DKD患者的肾功能及糖代谢方面有着一定优势。使用加味黄芪六一汤联合卡格列净干预气阴亏虚型DKD, 患者的空腹血糖、糖化血红蛋白、Scr、BUN、24 h-UTP及中医症状等方面均明显改善[126]。

Liu课题组[127]关注于黄芪六一汤对DKD的干预作用, 首先对其进行了系统药效组分研究, 从中分离出黄芪总皂苷、黄芪总黄酮、黄芪多糖和甘草酸等主要活性成分, 并证实这些组分在DKD小鼠中可显著降低血糖、尿蛋白、Scr等指标, 减轻肾纤维化程度, 提示其为

黄芪六一汤防治DKD的主要药效物质基础。为深入揭示其机制, 网络药理学分析结合动物实验验证表明[128], 黄芪六一汤药效组分可通过抑制PI3K/AKT/mTOR信号通路活化, 上调自噬关键蛋白Beclin-1与LC3-II/I的表达, 促进TECs自噬, 减轻肾损伤。此外, 通过构建药动学−药效学结合模型, 又揭示了芒柄花苷、毛蕊异黄酮等6个入血成分与炎症因子TNF-α、VEGF等水平的动态关联, 表明黄芪六一汤的抗DKD作用与其抑制炎症因子分泌、调节机体炎症状态密切相关[129]。

3.5 黄芪汤

黄芪汤出自北宋·杨士瀛《仁斋直指方论》, 由黄芪、生地黄、茯苓、瓜蒌根、麦门冬、五味子、炙甘草组成。临床研究表明, 黄芪汤能显著改善气阴两虚型DKD III期患者的中医证候, 减少尿白蛋白/肌酐比值(urinary albumin-to-creatinine ratio, UACR), 并有效调节空腹血糖(fasting blood glucose, FBG)、餐后2小时血糖(2-hour postprandial glucose, 2 hPG)、糖化血红蛋白(glycated hemoglobin A1c, HbA1c)及血脂水平, 且安全性良好[130]。黄芪汤联合厄贝沙坦干预DKD可显著降低24 h-UTP、UACR及炎症因子TNF-α、hs-CRP等水平, 改善肾功能指标BUN、Scr、Hcy, 且不增加不良反应风险[131]。

实验研究证实[132], 黄芪汤能够剂量依赖性地调节DKD小鼠代谢紊乱, 改善葡萄糖耐量, 降低血糖、HbA1c及HOMA-IR, 同时减少尿蛋白, 提高GFR, 进而改善肾损伤。另有研究表明[133], 黄芪汤可下调TLR4/NF-κB途径活化, 降低磷酸化kappa B抑制因子激酶α/β (IκB kinase α/β, IKKα/β)、NF-κB及下游炎症因子IL-6、TNF-α、IL-1β、COX2等的表达, 从而减轻肾脏炎症反应及肾小球硬化。

3.6 防己黄芪汤

防己黄芪汤源于《金匮要略》, 此方由防己、黄芪、白术、甘草组成, 在DKD治疗中应用广泛。临床研究表明[134], 防己黄芪汤联合贝那普利可显著提高早期DKD患者的总有效率, 降低Scr、BUN等肾功能指标及CRP、TNF-α等炎症因子水平, 且不增加不良反应, 安全性良好。前瞻性研究表明[135], 防己黄芪汤加减联合氯沙坦钾可改善DKD患者主症评分、血糖及血脂水平, 并下调IL-1β、TNF-α、IL-6及Toll样受体TLR4、TLR7表达。

研究显示[136], 防己黄芪汤可通过有效成分槲皮素、山柰酚靶向TP53、AKT1、STAT3等核心靶点, 主要调控AGE-RAGE、MAPK、NF-κB等途径, 实现抗炎、改善糖脂代谢及保护肾功能的多重功效。另一项研究证实[137], 防己黄芪汤可减轻DKD大鼠肾损伤, 降低BUN、Scr水平, 提高SOD活性, 减少ROS、MDA生成, 保护肾组织病理形态及足细胞超微结构, 并促进podocin、nephrin表达以修复足细胞所受损伤。

3.7 补阳还五汤

补阳还五汤源于《医林改错》, 此方由黄芪、当归、赤芍、川芎、桃仁、红花、地龙组成, 具有补气活血、化瘀通络之效, 契合DKD“气虚血瘀”的病机, 为临床治疗DKD气虚血瘀证的常用方剂。临床研究表明, 补阳还五汤联合西药干预DKD具有协同增效作用。补阳还五汤联合达格列净、缬沙坦可显著改善DKD患者U-mALB、UACR, 并调节血液流变学状态, 抑制炎性因子水平[138]; 补阳还五汤联合达格列净、羟苯磺酸钙可显著缓解气阴两虚型DKD患者的中医证候, 有效降低BUN、Scr水平, 改善III型前胶原肽、Col-4等肾纤维化标志物[139]。

在方剂优化方面, Li课题组[140]结合表观遗传测序与网络药理学研究对补阳还五汤进行化裁, 动物实验证实, 补阳还五汤加减通过调控PSMA6、RAD51B等表观遗传靶点, 改善肾功能, 抑制fibronectin、α-SMA表达下调, 从而改善肾纤维化。补阳还五汤可通过活化DKD小鼠肾组织TGF-β1/Smad3及NF-κB途径, 下调E3泛素连接酶Arkadia、恢复Smad7水平, 从而减轻肾纤维化与炎症反应[141]。进一步研究发现[142], 补阳还五汤能激活Nrf2/HO-1途径, 干预ACSL4介导的铁死亡, 减少足细胞desmin表达, 恢复nephrin、podocalyxin等表达, 从而减轻HG诱导的足细胞损伤。

3.8 黄芪桂枝五物汤

黄芪桂枝五物汤载于《金匮要略》, 由黄芪、桂枝、白芍、生姜、大枣组成, 具益气养血、温经通络之效, 是糖尿病周围神经病变气虚血瘀证指南推荐方[143]。临床研究表明[144], 黄芪桂枝五物汤联合缬沙坦、羟苯磺酸钙可显著降低DKD患者中医证候评分, 减少U-mALB和UACR, 提升GFR, 且不良反应发生率较低。针对DKD IV～V期患者, 加味黄芪桂枝五物汤可进一步降低其Scr、BUN及24 h-UTP定量, 调节TG和TC水平, 中医证候较纯西药组显著改善[145]。

网络药理学分析表明[145], 黄芪桂枝五物汤的活性成分糖皮素、木犀草素等可通过调控ALB、IL-6、EGFR等关键靶点, 调节PI3K-AKT、AGE-RAGE及p53途径, 进而作用于DKD。动物实验进一步揭示[146], 黄芪桂枝五物汤能上调组蛋白去乙酰化酶4活性, 改善糖尿病血管内皮功能障碍, 降低微血管通透性, 提高下肢血流灌注, 进而缓解肾脏的血管损伤。空间代谢组学研究显示[147], 黄芪桂枝五物汤可调节DKD肾皮质代

谢紊乱, 特别是核黄素代谢和精氨酸生物合成通路, 恢复肾小球结构, 改善高血糖和HbA1c水平。

3.9 中成药

除经典名方外, 多种以黄芪为主要组方成分的中成药在DKD治疗中也显示出良好的应用价值, 其中以渴络欣胶囊、参芪降糖颗粒 (胶囊/片)、尿毒清颗粒、肾康注射液、益肾化湿颗粒、芪明颗粒等的研究较为系统和深入[148,149]。

渴络欣胶囊由黄芪、太子参、枸杞子、女贞子、水蛭、大黄组成, 是我国首个获批DKD适应症的中成药。多项临床研究表明[150], 在常规西药治疗基础上联合渴络欣胶囊, 可显著降低患者24 h-UTP、UAER、Scr、BUN及FBG水平, 延缓肾功能进展。药物经济学评价显示[151], 其日均费用处于同类中成药中较低水平, 具备良好的经济性。基础研究进一步揭示[152], 渴络欣胶囊可通过下调肾脏SGLT1、SGLT2表达, 促进钠钾氯共转运蛋白2 (Na-K-2Cl cotransporter 2, NKCC) 及A1AR表达, 调节管球反馈机制, 从而改善DKD早期的高滤过状态。该药已被多部DKD中西医结合诊疗指南推荐使用, 体现了其在临床中的广泛认可度。

参芪降糖颗粒 (胶囊/片) 由人参 (茎叶) 皂苷、黄芪、五味子、山药、麦冬等11味药组成, 具有益气养阴、滋脾补肾功效, 为《国家糖尿病基层中医防治管理指南 (2022)》T2DM气阴两虚证推荐方[153]。临床研究表明[154], 参芪降糖片联合胰岛素干预脾肾两虚型DKD可显著提高总有效率, 调节血糖和肾功能指标; Meta分析表明[155], 参芪降糖颗粒/胶囊在降低UAER、BUN和24 h-UTP方面优于西药组治疗。实验研究证实[156,157], 参芪降糖颗粒/片能够降低DKD大鼠的血糖、Scr、BUN, 减轻MC基质增生、肾小管萎缩及间质纤维化等病理损伤; 机制研究表明[158], 参芪降糖颗粒通过调节IR、抑制炎症、抗氧化应激和抗纤维化等多途径发挥肾脏保护作用。

尿毒清颗粒由大黄、黄芪、桑白皮、苦参、白术、茯苓等10味中药组成, 已纳入慢性肾脏病规范化治疗方案, 适用于脾虚湿浊证、脾虚血瘀证患者; 临床研究表明[159,160], 尿毒清颗粒联合利格列汀能显著调节DKD患者肾功能, 减轻炎症, 且不良反应发生率与西药组相当; 网络药理联合实验研究显示[161,162], 尿毒清颗粒关键成分包括糖皮质素、β-谷甾醇、山柰酚等, 通过干预AGE-RAGE、MAPK、TNF等途径, 在抑制炎症、减轻氧化应激、调控细胞凋亡、保护足细胞结构和功能、减少蛋白尿方面均表现出对DKD的治疗潜力。

肾康注射液为常用中成药, 由黄芪、红花、丹参、大黄组成, 临床主治慢性肾功能衰竭湿浊血瘀证, 研究表明[163,164], 肾康注射液可提高DKD患者的临床总有效率, 降低临床症状积分, 控制Scr、尿β2-微球蛋白、24 h-UTP及TGF-β1和sICAM-1水平, 且不良反应发生率低; 实验证实[165-167], 肾康注射液能够调控葡萄糖调节蛋白78 (glucose-regulated protein 78, GRP78)/CHOP途径抑制ERS及足细胞凋亡, 通过Kelch样ECH相关蛋白1 (Kelch like ECH associated protein 1, Keap1)/Nrf2/HO-1信号通路减轻氧化应激, 通过p38 MAPK/NF-κB/MCP-1/C-C基序趋化因子受体2 (C-C motif chemokine receptor 2, CCR2) 通路抑制炎症反应, 从而改善DKD的肾脏功能和病理损伤。

益肾化湿颗粒由人参、黄芪、白术、茯苓、泽泻等16味药组成, 适用于慢性肾小球肾炎脾虚湿盛证, 临床研究表明[168,169], 益肾化湿颗粒可降低早期DKD患者的UAER、Scr和BUN水平, 改善肾功能及心功能指标, 且总有效率显著高于常规西药治疗; 实验证实[170-172], 益肾化湿颗粒能够通过调控Janus激酶2 (Janus kinase 2, JAK2)/STAT3/SHP2、p38 MAPK及PI3K/AKT/mTOR等信号通路, 抑制炎症因子MCP-1、CCR2表达, 减轻氧化应激和肾纤维化, 保护肾小球滤过屏障完整性。

芪明颗粒由黄芪、葛根、生地黄、枸杞子、决明子、菟蔚子、蒲黄、水蛭组成, 共奏益气养阴、活血通络之功, 是我国首个获批糖尿病视网膜病变 (DR) 适应症的中成药。近年来芪明颗粒亦被用于DKD的干预, 临床研究显示[173], 芪明颗粒联合常规治疗可显著改善气阴两虚型DKD患者肾功能指标及氧化应激状态, 对DR和DKD具有“眼肾同治”作用; Meta分析进一步证实[174], 芪明颗粒能有效调节患者UAER、水肿评分及糖脂代谢指标。实验研究表明[175], 芪明颗粒通过调控NF-κB/NLRP3信号通路, 抑制磷酸化NF-κB p65、NLRP3炎症小体及其下游蛋白ASC、Caspase-1表达, 减少IL-1β和IL-18释放, 从而减轻DM大鼠肾组织病理变化; 网络药理学研究提示[176], 其核心成分槲皮素、金色酰胺醇酯等可通过多靶点作用于PI3K/AKT、AGEs/RAGE等信号通路, 协同调节氧化应激、细胞凋亡和血管生成。分别从临床与基础研究层面汇总含黄芪的经典方剂及中成药干预DKD的证据见附表3、4。

4 小结与展望

根据国际糖尿病联盟统计, 全球成年DM患病率现已超过10%, 达到全球大流行规模[177]。流行病学调查显示, 我国约20%～40%的DM患者会进展为DKD[178]。研究表明, 与非DKD患者相比, DKD患者发展至终末期肾病的风险增加约12倍, 死亡率显著升高[179]。一旦进入大量蛋白尿期, 肾功能将呈进行性下

降, 极大地增加了心血管事件风险及医疗支出[180]。由此可见, 积极寻求有效延缓DKD进展的策略是临床亟待解决的重要问题。当前, DKD的发病机制复杂多元, 西医治疗以控制血糖、血压及阻断肾素−血管紧张素−醛固酮系统为主, 但仍有部分患者病情持续进展[181]。在此背景下, 基于益气固本、活血利水等治法, 具有多成分、多靶点整体调节优势的黄芪及其复方展现出较好的应用潜力。

DKD其核心病机围绕“气虚”展开, 由气虚推动无力, 衍生出血瘀、水停、湿浊内留等病理变化, 形成“气虚浊留”之证[182]。中医药治疗上遵循“扶正祛邪”原则, 以益气活血、利湿泄浊为基本治法。黄芪作为“补气利水”之要药, 其味甘性温, 功擅补气升阳、利水消肿, 正合DKD脾肾气虚、水湿瘀阻之证候, 故成为临床干预DKD的高频药物。本文系统梳理发现, 黄芪及其活性成分可通过多途径、多靶点发挥肾脏保护作用。如表1总结, 黄芪甲苷、黄芪多糖、毛蕊异黄酮三类主要活性成分, 共同覆盖了糖脂代谢、氧化应激、炎症、胰岛素抵抗、细胞死亡、纤维化及内质网应激等DKD关键病理环节。其中, 黄芪甲苷的研究最为深入, 机制覆盖最广, 凸显其作为核心效应成分的地位; 黄芪多糖在调节糖代谢与胰岛素抵抗方面作用突出; 而毛蕊异黄酮则在抗炎、抗纤维化及调控铁死亡等方面显示出独特价值。黄芪常通过配伍形成药对以增强疗效, 其配伍规律体现了在“益气”基础上辨证施治的思路。结合表2的分析可见, 黄芪与不同药物的配伍各有侧重: 如黄芪−丹参、黄芪−当归侧重于“活血”, 以改善微循环与能量代谢; 黄芪−山药、黄芪−山茱萸侧重“养阴”, 以调节代谢紊乱与自噬; 黄芪−金雀根则“通络”特色鲜明, 善于改善线粒体动力学与抑制炎症; 而黄芪−水蛭等配伍则重在“泄浊”。不同药对作用机制的差异化, 丰富了黄芪干预DKD的途径。进一步地, 含黄芪的经典方剂及中成药在临床与基础研究中均积累了扎实证据。表3、4的汇总表明, 在临床层面, 各类黄芪组方在改善DKD患者症状、降低蛋白尿、保护肾功能等方面普遍有效, 且与西药联用常表现出协同增效作用。在机制研究层面, 这些复方展现了多成分、多靶点、多通路的整合调节特点, 全面涵盖DKD核心病理环节, 且不同方剂因组成不同而各有侧重: 如参芪地黄汤在调节铁死亡方面研究深入, 玉液汤关注肠道菌群−肾脏轴, 补阳还五汤则侧重活血通络与抗纤维化, 充分体现了中医辨证论治与方证对应的思想。相关中成药的广泛应用与系统研究, 也为黄芪及其复方防治DKD提供了有力的临床与实验证据。

然而, 尽管黄芪及其复方在防治DKD方面展现出较好前景, 当前研究仍存在若干关键问题与挑战, 亟待未来研究予以突破。① 循证证据级别有待提升: 现有临床研究多为小样本、单中心观察性研究或随机对照试验 (randomized controlled trial, RCT), 缺乏大规模、多中心、长期随访的高质量RCT证据, 尤其缺乏以硬终点 (如终末期肾病、心血管事件、全因死亡率) 为主要结局的研究, 限制了其在国际指南中的推荐级别; ② 药效物质基础与体内过程不明: 黄芪活性成分如黄芪甲苷、黄芪多糖、毛蕊异黄酮的生物利用度普遍较低, 其在体内的吸收、分布、代谢、排泄过程及入肾机制尚未完全阐明。复方中“君臣佐使”配伍如何影响关键成分的药代动力学行为, 以及成分−成分间是否存在相互作用, 研究仍很薄弱; ③ 研究维度不均衡: 现有机制研究高度集中于黄芪甲苷、黄芪多糖、毛蕊异黄酮等少数成分, 对黄芪中其他潜在活性成分 (如环黄芪醇、芒柄花素等) 及复方中非黄芪成分的研究相对不足。同时, 研究多聚焦于细胞凋亡、炎症、氧化应激等经典通路, 对新兴机制如细胞外囊泡通讯、表观遗传调控、微生物−宿主互作等在黄芪干预DKD中的作用探索尚未深入; ④ 复方整体调控网络解析不足: 现有网络药理学预测较多, 但实验验证往往局限于单一或少数通路, 对复方如何通过多成分协同作用于疾病调控网络, 实现“系统−系统”对话的整体效应, 缺乏系统性的整合解析。

基于现有研究的不足之处, 提出以下未来研究的策略与方向建议: ① 推动高质量临床研究: 精心设计并实施大样本、多中心、随机双盲、安慰剂对照的临床试验, 采用复合终点指标, 并积极开展真实世界研究, 积累高级别循证医学证据。同时, 结合组学技术开展临床生物标志物研究, 实现疗效的精准预测与评估; ② 深化药效物质基础与复方配伍机制研究: 综合利用代谢组学、蛋白质组学、转录组学等多组学技术, 结合高分辨质谱与成像技术, 动态追踪黄芪及其复方中多成分的体内命运, 明确入肾成分及效应物质。运用谱效关系、定量组效关系等方法, 解析复方配伍的化学基础与协同/拮抗规律; ③ 拓展机制研究的广度与深度: 在继续深入现有优势机制 (如铁死亡、自噬) 研究的同时, 积极开拓新的研究维度。如利用空间转录组、单细胞测序等技术, 研究黄芪对肾脏不同细胞亚群的特异性保护作用; 探讨黄芪通过调节肠道菌群及其代谢物 (如短链脂肪酸) 干预DKD的肠−肾轴机制[183]; 研究黄芪成分对肾脏细胞表观遗传修饰 (如DNA甲基化、组蛋白修饰、非编码RNA) 的调控作用; ④ 加强转化医学与前沿技术应用: 推动基础研究成果向临床应用转化。利用类器官、器官芯片等新型模型模拟人类DKD

病理环境, 提高临床前研究的预测价值。探索黄芪有效成分的结构优化与新型递药系统 (如纳米制剂) 的开发, 以提高其生物利用度及靶向性。结合人工智能与大数据, 构建“成分–靶点–通路–疾病”多维网络模型, 预测并验证新的作用靶点与联合治疗策略。

综上所述, 黄芪及其复方配伍在干预DKD领域展现出广阔的研究价值与应用前景。基于“气虚浊留”中医理论, 深入探讨黄芪及其配伍干预DKD的现代生物学机制, 不仅为揭示黄芪“补气利水”传统功效的科学内涵提供了支撑, 更为深入挖掘黄芪及其复方在DKD防治中的临床应用潜力与现代转化研究提供了坚实支撑。

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