专家述评

中药治疗糖尿病肾病的疗效及作用机制

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【摘　要】经过长期的临床实践，中药治疗糖尿病肾病已形成较为成熟的治疗体系，中药是治疗糖尿病肾病的重要组成部分。中药常常含有多种生物活性物质，并且具有多分子作用靶点的优势，还可以根据病人的具体情况改变配伍，可发挥不同的疗效，这些特点使中药治疗糖尿病肾病具有极大的潜力。此外，随着分子生物学技术和各种组学等实验技术的发展，越来越多的研究在不断地探索中药治疗糖尿病肾病的具体机制，例如自噬、炎症、氧化应激、糖代谢等。本文将从中药在临床试验中治疗糖尿病肾病的疗效，以及中药治疗糖尿病肾病的作用机制两个方面进行述评，以期对中药的临床和基础研究提供新思路。

【关键词】中药；糖尿病肾病；疗效

【中图分类号】R587.1　　文献标志码 A　　DOI：10.3969/j.issn.2096-3351.2022.06.002

Effect and mechanism of traditional Chinese medicine on diabetic nephropathy

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【**Abstract**】After long-term clinical practice，traditional Chinese medicine（TCM）has formed a relatively mature treatment system for diabetic nephropathy，which is an important part of the treatment of diabetic nephropathy. TCM often contains a variety of bioactive substances，and has the advantage of multi-molecular targets. It can also change the compatibility according to the specific situation of patients to bring about different curative effects. These characteristics make TCM have great potential in the treatment of diabetic nephropathy. In addition，with the development of molecular biology technology and various experimental technologies such as omics，more and more studies are constantly exploring the specific mechanism of TCM treatment of diabetic nephropathy，such as autophagy，inflammation，oxidative stress and glucose metabolism，etc. This review will provide insights into the curative effect and the mechanism of TCM in the treatment of diabetic nephropathy. Hopefully，this review could provide insights into clinical and basic research of TCM.

【**Key words**】Traditional Chinese medicine；Diabetic nephropathy；Curative effect



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中医治疗糖尿病及其并发症具有非常悠久的历史。在中医里，糖尿病被称为“消渴”，早在春秋战国时期就有糖尿病的记载。而关于糖尿病肾病（diabetic nephropathy ，DN）的记载最早可追溯到汉代（公元前206年至公元220年），并且中医认为DN的本质是本虚虚实相杂证[1]。本虚证随病程动态变化，可以分为三个阶段：阴不足和干热的早期阶段；气阴不足在中期，阴损伤阳和发展到阳虚或阴阳两虚证在后期[2]。表虚证主要包括湿证、血瘀证、痰证虚证[2]。经过长期的临床实践，中药治疗DN已形成较为成熟的治疗体系。中医认为血瘀的发病机制贯穿于DN的发病过程中，治疗DN应注意活血化瘀以改善血液循环[3]，这与西医中使用血管紧张素转化酶抑制剂（angiotensin converting enzyme inhibitirs.ACEI）/血管紧张素Ⅱ受体拮抗剂（angiotensin

基金项目：四川大学华西医院学科卓越发展1.3.5工程项目（ZYGD18027）

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引用本文：付平，陈馨韵. 中药治疗糖尿病肾病的疗效及作用机制[J]. 西南医科大学学报，2022，45（6）：466-473.DOI：10.3969/j.issn.2096-3351.2022.06.002

Ⅱ receptor blockers，ARB）治疗DN的想法不谋而合。本文将从中药治疗DN的疗效和中药治疗DN的作用机制两个方面进行述评。

1 中药治疗DN的疗效

目前DN的治疗策略是采用多因素管理，主要包括使用肾素-血管紧张素系统（renin-angiotensin-aldosterone system ，RASS）抑制剂和降糖药物如胰岛素、钠葡萄糖共转运蛋白2型（Sodium-glucose Cotransporter-2，SGLT2）抑制剂、胰高血糖素样肽1（glucagon like peptide 1，GLP1）等，饮食控制和生活管理[4]。除此之外，中药治疗DN也已成为不可缺少的一部分，在临床实践中广泛应用。中药常常含有多种生物活性物质，并且具有多分子作用靶点的优势，这些特点使中药治疗DN具有极大的潜力。越来越多的随机对照临床试验（randomized controlled trial，RCT）证实了中药方剂治疗DN的效果，如桂枝茯苓丸、六味地黄丸和温脾汤等[5-10]。有Meta分析指出，ACEI或ARB联合中药治疗DN的疗效优于安慰剂联合ACEI或ARB[11-12]。而一些中药的有效成分或者提取物，例如雷公藤多甙、白藜芦醇、小檗碱治疗DN的疗效也被证实[13-15]。

许多临床试验都验证了传统中药复方治疗DN具有良好的治疗效果。例如，在一个招募了180名DN病人的多中心RCT试验中，随机给予DN病人汤参颗粒剂组或安慰剂治疗24周后，汤参颗粒剂组的24 h尿蛋白显著低于安慰剂组，肾小球滤过率也有所上升[16]。在一项纳入204名DN病人的临床研究中，随机给予DN病人肾衰宁颗粒或替米沙坦治疗12周后，与替米沙坦治疗组相比，肾衰宁颗粒联合替米沙坦治疗组的24 h尿微量白蛋白和血肌酐水平更低[17]。除此之外，一项纳入了18个RCT试验和1 275名病人的Meta分析结果显示，标准治疗加上六味地黄丸组与标准治疗组比，病人的尿蛋白、尿素氮、血肌酐、空腹血糖等指标改善更显著[18]。

此外，也有许多的研究关注了中药复方中发挥治疗作用的活性成分。一项纳入12个RCT研究包含829名病人的Meta分析结果显示，雷公藤多甙（Tripterygium glycosides）联合缬沙坦对血肌酐水平影响不大，但可以更好地降低24 h尿蛋白水平[19]。另外一个纳入35项RCT包含2 320名DN病人的Meta分析显示，与对照组相比，灯盏花素（breviscapine）注射液对DN病人有肾脏保护和调节血脂的作用，其可以降低病人的尿蛋白、血肌酐、胆固醇和甘油三酯水平[20]。

综上，这些临床试验结果都提示了中药治疗DN的有效性和潜力。但是，此类临床研究仍有许多不足之处有待改进：许多临床试验设计有漏洞，质量欠佳，极大地影响了试验结果的可靠性与准确性。首先，这些试验大多规模小，纳入人数较少，并且纳入人群存在各种偏倚，使试验结果不具有普遍性。其次，在选择对照组的治疗方案上不具有统一性，例如有的试验使用安慰剂作为对照，有的试验选用ACEI/ARB药物作为对照，有的使用二甲双胍作为对照，还有的试验联合几种药物作为对照。因而不同的试验结果之间无法相互比较。最后，许多临床试验设计不严谨规范，治疗周期有长有短，缺乏长期的临床随访，无法验证药物对DN的长期预后是否有影响。因此，未来需要规模更大、设计更加严谨、随访时间较长的RCT研究进一步明确中药治疗DN的效果。

2 中药治疗DN的作用机制

随着分子生物学技术和各种组学等实验技术的发展，人们对中药治疗DN的研究不再停留在宏观层面，越来越多的研究探究了中药治疗DN的分子机制。DN的发病机制较为复杂，由多因素共同影响。本文将从自噬、炎症、氧化应激、糖代谢四个方面探讨中药治疗DN的作用机制。

2.1 中药对自噬的调节作用

自噬是一种依赖溶酶体的参与，清除、降解和回收细胞质中靶物质的过程，同时也是细胞重要的自卫机制，可以保护细胞免受各种应激反应等的影响[21]。正常状态下，自噬会被严格调控，以确保细胞成分的合成和降解、使用和循环之间的最佳平衡。在一些疾病状态下，例如细胞内营养过剩时，自噬被下调。尽管这种下调在短时间内是对细胞有益的，但自噬水平的不足最终可能会导致细胞损伤[22]。中药方剂或提取物可以促提高不同疾病的自噬水平。以黄芪中提取的皂苷化合物黄芪甲苷（astragaloside iv）为例，黄芪甲苷可以促进脑缺血再灌注大鼠模型的自噬水平并改善神经功能缺损评分[23]；黄芪甲苷还可以通过促进自噬来抑制星形细胞衰老，进而预防帕金森病中多巴胺能神经退行性变[24]。此外，黄芪甲苷还可以通过促进自噬水平缓解脂多糖（Lipopolysaccharide，LPS）诱导的肺上皮细胞损伤[25]、阿霉素引起的心肌损伤[26]以及LPS诱导的心功能障碍等[27]。

越来越多的证据表明，自噬功能的缺陷与DN的发病机制息息相关，自噬水平在DN时被明显抑制，DN病人的肾小球和肾小管细胞自噬受损，链脲佐菌素（Streptozotocin，STZ）诱导的DN大鼠近端小管的自噬被抑制[28]。腺苷酸活化蛋白激酶（adenosine 5-monophosphate-activated protein kinase，AMPK）、雷帕霉素靶蛋白（mammalian target of rapamycin，mTOR）和NAD-依赖性去乙酰化酶Sirtuin-1(NAD-dependent deacetylase sirtuin-1，SIRT1)是著名的能量代谢通路相关靶点，在细胞内营养过剩的状态下，葡萄糖和胰岛素

水平的增加会激活mTOR；在细胞内营养不足的状态下，细胞内AMP和NAD+会激活AMPK和SIRT1[29]。而糖尿病状态下AMPK、mTOR和SIRT1通路的变化可损害自噬活性[30]。体内和体外实验发现，中药治疗DN时可影响自噬水平，进而对肾脏发挥保护作用[31]。首先，中药可通过AMPK通路影响自噬进而发挥肾脏保护作用。研究发现，黄茂甲苷可通过增加糖尿病小鼠肾脏AMPK磷酸化及自噬水平，进而缓解蛋白尿并减轻肾小球硬化[32]。小檗碱（berberin）也可通过AMPK的磷酸化增加自噬并保护足细胞[15]。此外，许多中药或提取物，例如雷公藤甲素[33]、芒果苷[34]等还可通过mTOR通路调节自噬。SIRT1也是中药调节自噬治疗DN的重要靶点。例如，白藜芦醇可增加SIRT1的表达促进自噬并保护肾脏[35]。值得注意的是，这些中药或提取物不是仅仅作用于细胞的自噬水平。自噬与包括凋亡在内的多种细胞活动都有密切的联系，它们共享许多相同的调节信号，可以互相调节和影响。而我们前面所提到的AMPK、mTOR、SIRT1等通路，也作用于其他细胞途径。此外，正如我们前面所讲到的中药的多靶点作用，中药或提取物可以同时影响多种途径，这些都给予了中药治疗DN无限的潜力。

2.2 中药对炎症反应的调节作用

炎症反应的异常也是DN发病因素的重要环节之一。高血糖、RAAS激活和晚期糖基化终末产物（advanced glycation end products，AGE）等刺激均可诱发炎症反应。DN是微炎症（microinflammation）反应，DN的肾脏组织有炎症细胞的积聚，有粘附分子、趋化因子和促炎细胞因子的过度表达，以及一些炎症相关的信号通路被激活，但这和感染引起的炎症不同，被称为“微炎症”[36]。无论是肾脏固有细胞（如肾脏的足细胞、内皮细胞、系膜细胞和肾小管上皮细胞）还是其他细胞（如淋巴细胞、巨噬细胞），均可参与DN的炎症反应，并分泌相关的促炎细胞因子和趋化因子，如白细胞介素1β（interleukin-1β，IL1β）、白细胞介素-6（interleukin 6，IL6）、白细胞介素-18（interleukin 18，IL18）和肿瘤坏死因子α（tumor necrosis factor-α，TNF-α）、单核细胞趋化蛋白-1（monocyte chemotactic-protein 1，MCP-1）[2,37]。近年来，调节炎症反应已成为中药治疗的重要策略。

中医根据治疗效果将中草药分为温、热、凉和冷四种属性。其中，清凉或寒性的草药可用于治疗以发热、潮热、出汗、口干、口渴、舌红、脉快为症状的热证疾病。清热草药的化学成分主要包括有机酸、类黄酮、糖苷、生物碱等，这些成分具有抗菌和抗炎功效，主要通过NF-κB、TLR和JAK/STAT等信号通路缓解肾脏炎症水平。

2.2.1 中药及其提取物通过NF-kB缓解炎症 正常状态下，IκB（inhibitor of NFκB）可与细胞质NF-κB结合，使其保持非活性状态。但在高糖刺激下细胞会聚集晚期糖基化终末产物，使IκBα-NF-κB p65-p50复合物解离，NF-κB p65-50易位到细胞核中，并促进多种促炎细胞因子的生成[38]。多种中药及其提取物通过NF-κB通路缓解炎症。例如，白芍提取物芍药苷（paeoniflorin）是清热草药的化学成分之一，芍药苷可以缓解晚期糖基化终产物对肾脏系膜细胞的炎症作用，并抑制DN大鼠模型和高糖刺激的系膜细胞中NF-κB p65的磷酸化[39]。三子固本颗粒（Sanziguben Granule）由一种金樱子、余甘子、五味子、绞股蓝等组成治疗糖尿病肾病的经验处方[40]，可以缓解NF-κB的表达并减少DN大鼠的24 h尿蛋白[41-42]。此外，补阳还五汤（Buyang Huanwu decoction）[43]、牛蒡子蛋白（arctigenin）[44]等也可以通过影响NF-κB信号通路缓解DN小鼠的肾脏损伤。

2.2.2 中药及其提取物通过TLRs通路缓解炎症 Toll受体（Toll-like receptor，TLRs）是一个保守的模式识别受体家族，由非微生物来源的内源性配体激活[45-46]。代谢应激或糖尿病状态下内源性配体可激活TLRs，TLRs招募不同的适配器蛋白例如MyD88，然后在转录因子NF-κB或IRF-3的参与下启动下游的级联信号，促进下游的促炎细胞因子和趋化因子产生，进一步募集巨噬细胞和促进成纤维细胞增殖，最终导致肾小管间质纤维化和肾小球硬化[47]。TLRs信号通路的激活，尤其是TRL2和TRL4通路的激活是DN的重要发病机制之一，也是中药治疗的重要靶点。例如，芍药苷可以缓解1型和2型糖尿病小鼠的巨噬细胞浸润和活化，并降低蛋白尿水平[48-50]。但芍药苷不是直接抑制巨噬细胞的活化，而是通过降低TLR2/4及其下游的信号通路，在体内和体外抑制iNOS的表达以及TNF-α、IL-1β和MCP-1的产生来影响巨噬细胞[48-50]。

2.2.3 中药及其提取物通过JAK/STAT通路缓解炎症 Janus激酶（Janus kinase，JAK）家族是一组非跨膜酪氨酸激酶[51]。JAK激活以后可以磷酸化信号转导及转录激活蛋白（signal transducer and activator of transcription，STAT），STAT形成二聚体后通过核膜进入细胞核，并与DNA序列的特定调节区结合，以激活或抑制靶基因的转录[51-52]。JAK和STAT的多个亚型在DN病人的肾小球和肾小管间质样本表达水平显著高于对照组[53-54]。JAK/STAT通路也是中药治疗DN的重要靶点。芍药的主要活性成分白芍总苷（total glucosides of paeony）能显著抑制糖尿病大鼠肾脏中的p-JAK2、p-STAT3蛋白水平，并抑制巨噬细胞的聚集和增殖，进而降低24小时尿白蛋白排泄率[55]。此外，还有研究表明，汤参复方（Tangshen formula）、青藤碱（sinomenine）、肉桂醛（cinnamaldehyde）、丹栀降糖胶囊（Danzhi Jiangtang Capsule）等能通过调节JAK/STAT信号通路改善糖尿病动物模型的肾脏损伤[56-60]。

中药通过改善炎症水平治疗DN的研究还有许多，这里就不在一一列举了。清热抗炎类中药种类繁多。哪些中药可以改善DN的肾脏炎症，以及其具体的抗炎机制，这都需要在将来不断地进行探索。

2.3 中药对氧化应激的调节作用

细胞内的氧分子经历一系列还原性生物合成步骤后，会形成几种活性氧中间体，具有不稳定和高活性的特点，并被称为活性氧（reactive oxygen species，ROS）。在生理状态下，内源性和外源性抗氧化剂都与ROS相互作用，以抵消对细胞的氧化损伤[61]。许多研究关注了中药的抗氧化作用。例如，有研究发现丹参（salvia miltiorrhiza）可通过抑制氧化酶，减少超氧化物的产生，抑制低密度脂蛋白（low-density lipoprotein，LDL）的氧化修饰和改善线粒体氧化应激来减少ROS的产生[62-63]。也有文献报道了黄芪甙（astragalin）可通过改善氧化应激水平来缓解大鼠的急性肺损伤[64]。

ROS的过度产生和抗氧化防御机制的损伤是DN的发生发展的关键因素之一。在生理状态下，ROS可作为第二信使影响对氧化还原敏感的信号通路[65]。但在DN状态下，慢性高血糖和其他刺激物（例如AGEs、AngII和TGF-β），可增加NOX的表达和活性，生成大量的ROS，对肾脏组织造成氧化损伤[66-69]。越来越多的证据证明，恢复氧化应激和抗氧化防御系统之间的平衡是中药治疗DN的潜在治疗靶点。

2.3.1 中药及其提取物通过Nrf2缓解氧化应激

核因子E2相关因子2（nuclear factor erythroid 2-related factor 2，Nrf2）是抗氧化作用相关基因的主要转录调节因子[70-73]。在生理状态下，Nrf2在细胞质中通过与Kelch样ECH联合蛋白1（Kelch-like ECH-associated protein 1，KEAP1）结合保持不活跃状态[74-75]。当Nrf2被激活时，Nrf2与KEAP1分离后转移到细胞核中，介导下游分子的调控[76-77]。已有研究证明中药复方或其提取物可以通过Nrf2通路发挥作用。例如，吴茱萸次碱（rutaecarpine）可激活Nrf2并改善葡聚糖硫酸钠诱导的结肠炎[78]。丹参酮I通过调节Nrf2信号通路抑制氧化应激诱导的心肌细胞损伤[79]。健脾补血方通过上调NRF2/HO1/NQO1信号通路缓解环磷酰胺诱导的骨髓抑制[80]。

Nrf2表达的降低可能是DN病人肾脏的氧化损伤和发病机制之一[81]。短时间内的高糖刺激可暂时升高Nrf2的表达；但在慢性高血糖刺激下，Nrf2的表达降低[82]。与非糖尿病病人相比，DN病人肾组织的Nrf2蛋白水平均较低[83]。在糖尿病动物模型中，*Nrf2*基因敲除小鼠的氧化应激水平增加，肾损伤更为显著[84-85]。

Nrf2相关通路也是中药治疗DN的重要靶点。例如，复方积雪草可以上调DN大鼠肾脏中KEAP1和Nrf2的表达，进而降低了尿蛋白水平，缓解肾脏损伤[86]。三子固本颗粒可以防止DN大鼠肾脏过氧化氢酶活性的破坏，并通过Nrf2通路抑制上皮间质转化（EMT）[41]。此外，黄芩苷（baicalin）[87]和黄连碱（coptisine）[88]也通过激活Nrf2通路缓解DN的氧化应激。

2.3.2 中药及其提取物通过NOX4缓解氧化应激

NOX4是DN中研究最广泛的NOX亚型[67,89]。线粒体和NOX4是肾脏中生成ROS的主要来源[90-91]。NOX4主要影响H_2O_2的生成，对维持肾脏的某些生理功能中起着重要作用[89,92]。慢性高糖刺激可诱导和激活NOX氧化酶。高糖刺激下，系膜细胞中NOX4表达增加并引起的ROS水平升高[93]。同时高血糖所导致的一些介质如Ang II和TGF-β也可促进NOX4的表达[94]。DN大鼠的肾小球中NOX4表达的增加[69]，而使用*NOX4*基因敲除小鼠或者使用NOX1/4抑制剂GKT137831可减少蛋白尿、减弱肾脏系膜扩张和肾小球硬化[95-96]。NOX4是中药治疗DN的重要靶点。例如，白藜芦醇可显著降低高糖刺激肾脏成纤维细胞NOX4的表达[97]，并降低db/db小鼠NOX4的表达[97]。也有文献报道了葛根（radix puerariae）可降低STZ诱导eNOS-/-小鼠和高糖刺激的小鼠足细胞的NOX4水平，发挥抗氧化作用保护肾脏[98]。

2.4 中药对糖代谢的调节作用

肾脏是调节血糖稳态的重要脏器，不仅负责将过滤后的葡萄糖重新吸收，还通过糖异生作用产生葡萄糖，并通过氧化磷酸化和糖酵解途径将葡萄糖用作燃料[99]。高血糖是DN发病的关键因素。正常情况下，肾脏糖原水平非常低，但DN病人的肾组织中有明显的肾糖原积累[100-101]。治疗高血糖能有效缓解DN。一项名为DCCT（The Diabetes Control and Complications Trial）的试验表明，使用胰岛素强化控制血糖可将微白蛋白尿的风险降低39%[102]。另一项名为UKPDS（The United Kingdom Prospective Diabetes Study）的研究表明，在12年内强化血糖控制能降低了约33%的蛋白尿风险[103]。研究表明，中药或中药提取物也具有降低血糖的功效，特别是含有苷、多糖、生物碱和黄酮类活性成分的中药[104]。有临床研究发现，与服用二甲双胍或安慰剂相比，联合服用二甲双胍和小檗碱可显著改善血糖控制[105]。另一项临床研究表明，由知母、苦瓜、黄连、芦荟和红曲米等八种中草药组成的复方可以有效降低2型糖尿病病人的血糖和血脂[106]。此外，也有研究报道了葛根芩连汤（Gegen Qinlian decoction，GQD）的降低血糖的作用[107]。

越来越多的研究探究中药对DN糖代谢的作用机制。首先，中药能改变肠道微生物群的多样性，改变胆汁酸代谢，增加短链脂肪酸的产生，从而有助于改善糖代谢[108]。其次，中药还能通过调节“营养传感器”的表达和活性，增加AMPK和SIRT表达和活性、降低mTOR

的表达和活性，调节血糖，进而发挥肾脏保护作用[109-112]。例如，梓醇（catalpol）[113]、京尼平-1-β-d-龙胆苷（Genipin-1-β-d-gentiobioside）[114]、消渴饮水复方[115]等中药或提取物可影响AMPK通路，进而发挥DN肾脏保护作用。除此之外，中药方剂或其提取物还可以影响晚期糖基化终产物（advanced glycation end products，AGEs）的水平。例如，杜仲[116]、地黄[117]、马钱苷[118]、黄连解毒汤[119]、小檗碱[120]等均可以抑制AGEs形成和RAGE表达，进而改善DN小鼠的肾损伤。

3　小结和展望

中药治疗DN具有悠久的历史。越来越多的研究证实了中药治疗DN的作用。中药的治疗作用具有多靶点的特点，并且不同的配伍可发挥不同的疗效。此外，中药可以根据不同病人的具体情况设计个性化的治疗方案，以更好的发挥治疗功效。我们期待更严谨、更深入的临床和基础研究来探索中药治疗DN的作用机制。

（利益冲突：无）

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(2022-08-04 收稿,2022-09-07 修回)