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医药、卫生

基于 PERK-eIF2α-ATF4-CHOP 通路探讨中医药干预糖尿病肾病的作用机制

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摘 要 糖尿病肾病发病机制复杂,最终可进展为终末期肾病,给患者带来沉重负担,目前的治疗手段疗效有限。蛋白激酶 R 样内质网激酶(protein kinase RNA-like endoplasmic reticulum kinase, PERK)-真核翻译起始因子 2α 激酶(eukaryotic initiation factor-2α, eIF2α)-转录激活因子 4(activating transcription factor 4, ATF4)- C/EBP 同源蛋白 (C/EBP-homologous protein, CHOP)信号通路作为内质网应激的关键通路,其下游调控的细胞凋亡和自噬等病理过程与糖尿病肾病的进展关系密切。中医药通过益气养阴、健脾益肾、利水消肿、清热解毒、活血祛瘀等治法调控 PERK-eIF2α-ATF4-CHOP 通路,起到保护肾小球滤过屏障、减少毛细血管基底膜增厚、增加尿蛋白质重吸收、延缓肾间质纤维化的作用。阐释 PERK-eIF2α-ATF4-CHOP 信号通路在糖尿病肾病中的作用机制,归纳中医治法干预该通路的理论基础,总结中药有效成分干预该通路的作用机制的研究进展,旨在为中医药防治糖尿病肾病提供新的思路和方法。

关键词 中医药; 糖尿病肾病; 内质网应激; 蛋白激酶 R 样内质网激酶-C/EBP 同源蛋白(PERK-CHOP)信号通路
中图法分类号 R259 R277.5; **文献标志码** A

Mechanism of Action of Traditional Chinese Medicine in Intervention of Diabetic Nephropathy Based on PERK-eIF2α-ATF4-CHOP Pathway

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[**Abstract**] The pathogenesis of diabetic nephropathy is complex and can ultimately progress to end-stage renal disease, imposing a heavy burden on patients. Current treatment methods show limited efficacy. The protein kinase RNA-like endoplasmic reticulum kinase (PERK)-eukaryotic initiation factor-2α (eIF2α)-activating transcription factor 4 (ATF4)-C/EBP homologous protein (CHOP) signaling pathway serves as a critical pathway in endoplasmic reticulum stress, with downstream regulation of pathological processes such as apoptosis and autophagy closely related to the progression of diabetic nephropathy. Traditional Chinese medicine regulates the PERK-eIF2α-ATF4-CHOP pathway through methods that tonify Qi and nourish Yin, strengthen the spleen and benefit the kidneys, promote diuresis and reduce edema, clear heat and detoxify, as well as invigorate blood and eliminate stasis. These interventions protect the glomerular filtration barrier, reduce capillary basement membrane thickening, enhance protein reabsorption in urine, and delay renal interstitial fibrosis. The mechanistic role of the PERK-eIF2α-ATF4-CHOP signaling pathway in diabetic nephropathy was elucidated, the theoretical basis for traditional Chinese medicine interventions in this pathway was summarized, and recent advances were reviewed in the mechanisms of action of effective components of traditional Chinese medicine targeting this pathway, aiming to provide new ideas and methods for the prevention and treatment of diabetic nephropathy through traditional Chinese medicine.

[**Keywords**] traditional Chinese medicine; diabetic nephropathy; endoplasmic reticulum stress; protein kinase RNA-like endoplasmic reticulum kinase-C/EBP-homologous protein (PERK-CHOP) signaling pathway

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糖尿病肾病(diabetic nephropathy, DN)作为糖尿病常见微血管并发症之一[1],以持续蛋白尿、进行性肾功能减退为主要临床表现,是肾功能衰竭的主要原因[2]。研究表明,糖尿病肾病发病机制复杂,涉及血流动力学异常、糖代谢异常、炎症、氧化应激、内质网应激、自噬等多种病理过程[3]。目前血管紧张素受体阻滞剂/血管紧张素转换酶抑制剂、钠-葡萄糖转运蛋白2抑制剂和非甾体盐皮质激素受体拮抗剂是治疗糖尿病肾病的主要药物。虽有一定疗效,仍不能有效阻止DN的发展[4]。研究表明,内质网应激(endoplasmic reticulum stress, ERS)介导的肾细胞损伤是DN的关键病理环节,调节内质网应激是抑制DN肾功能进行性下降的重要机制[5],蛋白激酶R样内质网激酶(protein kinase RNA-like endoplasmic reticulum kinase, PERK)-真核翻译起始因子2α激酶(eukaryotic initiation factor-2α, eIF2α)-转录激活因子4(activating transcription factor 4, ATF4)- C/EBP同源蛋白(C/EBP-homologous protein, CHOP)信号通路是内质网应激的关键通路。目前西医尚无针对此通路的有效治疗方法,使用中医药调控PERK-eIF2α-ATF4-CHOP信号通路防治糖尿病肾病成为目前的研究热点。基于此通路阐述中医药在糖尿病肾病中的作用机制,为探索糖尿病肾病的防治提供新思路。

1 PERK-eIF2α-ATF4-CHOP通路的生物学特性

细胞中约1/3蛋白质的折叠和结构成熟需要内质网参与[6]。多种刺激因素导致未折叠和错误折叠蛋白质积聚在内质网腔的过程,称为内质网应激[7]。为缓解内质网网腔压力,下游未折叠蛋白反应(unfolded protein response, UPR)被激活,以帮助未折叠蛋白折叠、加速未折叠蛋白降解。内质网应激持续激活,促发细胞过度凋亡,引起组织损伤[8]。PERK具有丝氨酸/苏氨酸激酶活性,是重要的跨膜蛋白[9]。正常情况下,PERK与分子伴侣免疫球蛋白重链集合蛋白(glucose regulated protein 78kD, GRP78)结合,以非活性单体形式存在。在缺氧及氧化应激等病理条件下,PERK与GRP78分离,磷酸化和激活的PERK能够磷酸化下游的eIF2α,导致内质网mRNA翻译和蛋白内流降低[10]。磷酸化的eIF2α促进转录因子ATF4的转录,ATF4通过氨基酸反应元件AARE1(amino acid response element 1)和AARE2(amino acid response element 2)与CHOP结合,激活CHOP的表达[11]。在内源性途径诱导的细胞凋亡中,CHOP能抑制B细胞淋巴瘤/白血病-2(B cell lymphoma/lewkmia-2, BCL-2)、抗凋亡蛋白髓系白血病序列-1(myeloid cell leukemia 1, MCL-1)表达,上调促凋亡基因BIM(Bcl-2 interacting mediator of cell death)表达[12],从而调控BCL-2相关X蛋白(Bcl-2-associated X protein, BAX)-BCL-2拮抗物(BCL2 antagonist/killer, BAK)介导的线粒体外膜通透性,释放细胞色素C(cytochrome C, Cyt-C)和细胞凋亡诱导因子(apoptosis inducing factor, AIF)等凋亡因子,导致细胞凋亡[13]。CHOP还可通过上调Tribble3相关蛋白3(Tribbles homolog 3, TRB3)基因的表达,阻止蛋白激酶B(protein kinase B, Akt)磷酸化,从而调节含半胱氨酸的天冬氨酸蛋白水解酶-3/7(cysteinyl aspartate specific proteinase, caspase-3/7)活性及BAX和BAK表达,调控细胞凋亡[14]。在外源性途径诱导的细胞凋亡中,CHOP通过上调死亡受体4(death receptor 4, DR4)和死亡受体5(death receptor 5, DR5)触发外源性凋亡通路,激活含半胱氨酸的天冬氨酸蛋白水解酶-3/6/7/8/10(caspase-3/6/7/8/10)导致细胞凋亡。Caspase-8将重组人BH3结构域凋亡诱导蛋白(recombinant human BH3-interacting domain death agonist, Bid)被拆分为截短型Bid,调节BAX-BAK介导的线粒体凋亡途径[15]。

2 PERK-eIF2α-ATF4-CHOP通路在DN中的作用

糖尿病肾病发病机制复杂,涉及多种细胞的多样病理学变化,包括足细胞损伤和数量减少、上皮间充质转化、肾小球基底膜增厚、细胞外基质累积、系膜扩张、毛细血管硬化、间质炎症及纤维化等[16-17]。而PERK-eIF2α-ATF4-CHOP通路也与糖尿病肾病中多种肾细胞的病变过程密切相关。足细胞具有高度特化和终末分化的特性,其过度凋亡导致的肾小球基底膜剥离,是糖尿病肾病发生发展的重要机制[18]。足细胞的内质网具有强大的蛋白折叠能力及高水平的合成和分解代谢活性,因而易受内质网应激影响。顾悦等[19]研究发现,与正常葡萄糖环境培养分化小鼠足细胞相比,高糖组足细胞增殖活力显著降低,细胞凋亡率增加,足细胞GRP78、p-PERK/PERK、p-eIF2α/eIF2α、ATF4、CHOP、Bax、Caspase-3蛋白表达显著上升,Bcl-2表达显著下降。表明高糖环境可诱导足细胞的UPR并激活ERS,通过PERK-eIF2α-ATF4-CHOP通路介导足细胞凋亡。肾小球系膜细胞具有支撑毛细血管、调节滤过膜面积和滤过系数、吞噬代谢废物等重要功能。系膜细胞过度凋亡是糖尿病肾病发生

发展的重要机制[20]。Liang 等[21]在同型半胱氨酸诱导的系膜细胞内质网应激中,发现 CHOP 和凋亡相关蛋白 Bax 和 Caspase-3 水平的上调,内质网应激抑制剂 4-苯基丁酸(4-phenylbutyric acid,4-PBA)显著逆转诱导的 CHOP 和凋亡相关蛋白上调,从而显著抑制系膜细胞凋亡。作为肾小球基底膜的主要组成部分,肾小球内皮细胞的凋亡,与肾小球瘢痕形成直接相关,并可加速肾纤维化进程。Guo 等[22]在非对称二甲精氨酸(asymmetric dimethylarginine, ADMA)诱导的肾小球内皮细胞(glomerular endothelial cells, GEnCs)凋亡中发现,ADMA 处理 24 h 后,CHOP 和 ATF4 的诱导达到峰值。即使 GEnCs 暴露于相对低剂量的 ADMA 24 h,CHOP 和 ATF4 的表达也高于对照组。Ju 等[23]研究发现,与正常组比较,高脂肪饮食(high-fat diet, HFD)和低剂量链脲佐菌素(streptozotocin, STZ)诱导的糖尿病肾病大鼠肾小管出现上皮细胞水肿、肾小管扩张、上皮细胞脱落等病理改变。模型组大鼠肾组织 PERK 磷酸化水平明显激活,GRP78、ATF4、CHOP 蛋白表达水平明显升高。提示内质网应激通过影响肾小管上皮细胞,诱导糖尿病肾病的进展。Wang 等[24]研究表明,高糖诱导下的大鼠肾细胞(NRK-52E 细胞)中 p-PERK、p-eIF2α、ATF4 和 CHOP 蛋白的表达水平显著高于对照组细胞。提示糖尿病肾病中通过 PERK-eIF2α-ATF4-CHOP 通路诱导的内质网应激介导肾小管损伤。

3　中医药对 DN 中 PERK-eIF2α-ATF4-CHOP 通路的干预

糖尿病肾病在中医古籍中无具体名称,《外台秘要方》[25]中描述:“其久病变,或发痈疽,或为水病”,《圣济总录》[26]明确提出“肾消”病名。张仲景在《伤寒论》中描述关格和癃闭等均属糖尿病肾病的晚期症状。结合糖尿病肾病早期的水肿、蛋白尿,晚期肾衰竭出现恶心、呕吐、少尿等症状。中医多将糖尿病肾病归于“水肿”“尿浊”“肾消”“关格”“癃闭”等范畴,现多称为消渴病肾病。

消渴病因分为外感和内伤两端。外感多由六淫内侵、邪气伏内、日久入里,化燥伤阴。内伤病因则多种多样,一则禀赋不足、五脏柔弱;二则嗜食肥甘、饮酒过度、纵欲过度;三则情志化火、内伤气阴。消渴病形成,日久耗气伤阴、瘀血痰浊内停、气血运行阻滞,自上而下,伤及肾阴,阴损及阳,继而阴阳俱虚。消渴以阴虚为本、燥热为标,消渴病肾病则为消渴日久不愈发展而成,实为本虚标实之证。中医治疗糖尿病肾病,历史悠久、疗效显著,不仅可明显减轻患者水肿,降低蛋白尿,更能保护患者肾功能,延缓疾病进展。越来越多的实验证据证明,中医药可以基于调控 PERK-eIF2α-ATF4-CHOP 通路,达到防治糖尿病肾病的目的。根据目前研究,现将基于此通路的中医药分为活血通络、补气利水、补益肝肾、清热利湿、综合辨治五类。

3.1　益气养阴、生津止渴

消渴病以阴虚为本,燥热为标,日久则耗气伤津,渐累下焦肾脏,肾气虚则气化不利,水湿内停,发为水肿。肾水不足,上行无力,难以制心火,以致心火上扰,出现烦躁、口渴。气阴两虚为消渴病肾病之基本病机。初期当以益气养阴、生津止渴为治法。黄芪为益气生津,利水消肿之要药,其有效成分黄芪甲苷属于三萜皂苷类化合物[27],有抗炎、抗氧化、抗细胞凋亡的药理作用[28]。Ju 等[29]研究表明,黄芪甲苷显著降低 HFD 和 STZ 诱导的糖尿病大鼠肾组织 GRP78、ATF4、CHOP、Bax、Caspase-3 表达水平,降低 Bax 与 Bcl-2 比值。表明黄芪甲苷通过抑制 PERK-eIF2α-ATF4-CHOP 通路,减少糖尿病肾小管上皮细胞凋亡。蜂胶能补虚弱、止消渴、化浊脂,是治疗消渴病肾病的常用药物[30]。白杨素作为其主要活性成分之一,属于黄酮类化合物[31],具有抗炎、抗氧化、抗细胞凋亡、抗癌等诸多药理作用[32]。Kang 等[33]研究表明,白杨素通过抑制糖尿病 db/db 小鼠肾组织和高糖诱导的小鼠足细胞中 PERK-eIF2α-ATF4-CHOP 通路的表达,增强 Bcl-2、肾病蛋白(Nephrin)、肾小球足细胞跨膜蛋白(Podocin)的表达,抑制 Bax 和凋亡酶激活因子-1(apoptotic protease activating factor-1, Apaf-1)的表达,最终减轻因足细胞凋亡导致的肾小球滤过功能障碍。白芍可敛阴止汗、养血调经,有抗氧化、抗炎、抗血栓、调节免疫等药理作用[34]。白芍的主要有效成分白芍总苷,属于糖苷类化合物[35],能通过抑制 STZ 诱导糖尿病大鼠肾组织 PERK-eIF2α-ATF4-CHOP 通路,减轻内质网应激,并通过减少硫氧还蛋白互作蛋(thioredoxin-interacting protein, TXNIP)的表达,以减少白细胞介素-1β(interleukin-1beta, IL-1β)表达,达到抑制细胞炎性因子,减少糖尿病肾病细胞凋亡的作用[36]。酸枣仁有养心安神,敛汗生津之功效,具有扩张血管、抗氧化、抗炎、调节神经递质等药理作用[37]。酸枣仁皂苷 A 作为酸枣仁的主要有效成分,属于皂苷类化合物[38]。Zhong 等[39]研究发现,酸枣仁皂苷 A 通过抑制 HFD + STZ 诱导糖尿病肾病 SD 大鼠肾组织 p-PERK、ATF4、p-CHOP、Bax、CytC、Caspase 9、Caspase-12 的表达,减

轻内质网应激介导的细胞凋亡,起到保护肾脏的作用。药食两用的番茄具有生津止渴之效。番茄红素属于异丙二烯类化合物[40],具有增强免疫、抗炎、抗氧化等功效[41]。刘艳峰等[42]研究表明,番茄红素通过抑制高糖高脂+STZ诱导的糖尿病肾病SD大鼠肾组织中GRP78、CHOP和Caspase-12的表达,减少细胞凋亡,并诱导减少核因子-κB(nuclear factor kappa-B, NF-κB)的表达,降低C反应蛋白(C-reactive protein, CRP)、肿瘤坏死因子-α(tumor necrosis factor-α, TNF-α)、IL-1β含量等炎症因子的释放,减轻肾组织炎症反应。

3.2 健脾益肾、利水消肿

肾为先天之本,脾胃为后天之本。壮火食气,累及中焦,而致脾气不足。阴液亏损,脏腑失养,肾阴亏虚,肾阳化生无源,而至脾肾两虚。脾肾气化失司,水液运化无力,泛溢全身,以致水肿。治当健脾益肾,利水消肿。山药又称薯蓣,有益气养阴之功,可补肺脾肾三脏。薯蓣皂苷作为山药的主要活性成分之一,属于皂苷类化合物[43],具有抗氧化、抗炎、抗凋亡等药理作用[44]。薯蓣皂苷可以抑制高糖诱导的肾近端小管上皮细胞中PERK、p-PERK、ATF4、p-CHOP表达,并能减少Caspase-12表达,调节其内质网应激状态,减少细胞凋亡[45]。桑葚可补益肝肾、滋阴生津。作为桑葚主要有效成分,白黎芦醇属于多酚类化合物[46],有抗氧化,抗血小板聚集,改善微循环,调节脂质代谢等药理作用[47]。白黎芦醇通过抑制STZ诱导的糖尿病肾病大鼠肾组织p-PERK、GRP78、ATF4、CHOP的表达,减少肾组织细胞凋亡,从而改善肾小球、小管细胞肥大、肿胀,肾小球系膜增厚等病理变化。白黎芦醇处理前后,正常大鼠的PERK、GRP78、ATF4、CHOP表达水平及肾脏细胞形态学未见明显变化,体现白黎芦醇的安全性[48]。黄蜀葵花有利尿通淋,消肿解毒之效。作为黄蜀葵花的主要活性成分之一,黄蜀葵花总黄酮属于黄酮类化合物[49],通过抑制HFD+单侧肾切除+STZ腹腔注射诱导的糖尿病肾小管病大鼠肾组织p-PERK、p-eIF2α、ATF4、CHOP、Bax、Caspase-12表达水平,升高Bcl-2蛋白表达水平,减少肾小管上皮细胞细胞凋亡,以减轻肾小管及肾间质纤维化[50]。

3.3 活血祛瘀、通经活络

消渴日久,气阴两伤,虚热内生,气虚则血行无力,阴虚内热则津亏血燥,血行不畅则瘀血内生。《金匮要略》[51]提到:“血不利则为水”。下焦气机为瘀血所阻,水津不布,而成水肿,当以活血祛瘀通络为法。丹参有活血祛瘀,通经止痛之功效,有抗凝血,抗氧化、抗炎、改善血液循环等药理作用[52]。其主要成分丹参酮IIa属于二萜醌类化合物[53],通过抑制STZ诱导糖尿病大鼠肾组织p-PERK、p-eIF2α、ATF-4、GRP78和CHOP的表达,抑制转化生长因子-β1(transforming growth factor beta 1, TGF-β1)和凝血酶敏感蛋白-1(thrombospondin-1, TSP-1)的表达水平,减轻胶原蛋白沉积和肾小球滤过膜增厚,抑制肾组织纤维化[54]。红花有活血通经,散瘀止痛之效。现代药理研究表明,红花具有抗凝血、抗血栓、调节免疫改善缺血再灌注血流量的作用[55]。红花黄色素作为红花的主要提取物,属于醌式查尔酮类化合物[56],可通过抑制高糖诱导的小鼠足细胞(MPC5)中GRP78、eIF2α、CHOP的表达,抑制caspase-12、裂解的聚ADP核糖聚合酶(cleaved-poly ADP-ribose polymerase, Cleaved-PARP)表达,从而减轻内质网应激引起的足细胞凋亡[57]。葛根可通经活络,生津止渴,具有抗血小板聚集、扩张外周血管、改善微循环等药理作用[58]。葛根的主要活性成分葛根素属于异黄酮类化合物[59],可以激活STZ诱导的DN小鼠PERK-eIF2α-ATF4-CHOP通路,并进一步激活苄氯素1(Beclin1)、微管相关蛋白1轻链3-Ⅱ(microtubule-associated protein light chain 3II, LC3II)和自噬相关蛋白5(autophagy related 5, Atg5)水平升高,和螯合体1(SQSTM1/p62)水平下调,从而调节糖尿病肾病细胞自噬的程度,最终减轻肾小球的塌陷和肾小管扩张[60]。姜黄可活血行气、通经止痛。药理学研究表明,姜黄素属于多酚类化合物[61],具有抗炎、抗氧化、抗纤维化等作用[62]。可以通过抑制过氧化氢诱导的胰腺β细胞(MIN6细胞)GRP78、p-PERK、p-eIF2α、ATF4和CHOP表达,减轻氧化应激导致的胰岛细胞内质网应激程度,通过保护胰岛细胞功能,延缓早期糖尿病肾病的进展[63]。

3.4 清热泻火、凉血解毒

消渴病肾病有上中下三消,热邪贯穿始终。初期肺阴亏虚,热伏于肺。中期阳明热盛,上灼肺阴,下煎肾水。后期热伏于肾,损伤肾络,更与湿邪交蒸,弥漫三焦,发为水肿。晚期肾元衰败,湿热浊毒、痰饮瘀血内停,而至三焦壅塞,气机逆乱,形成关格。热邪常贯穿于糖尿病肾病全过程,而湿邪与热邪交蒸,使热邪难解。当以清热泻火,凉血解毒为治法。大黄有清热泻火,凉血解毒之功效,具有抗炎、利尿、护肾、改善血流的药理作用[64]。大黄的主要成分大黄素属于蒽醌类化合物[65],通过抑制KK-Ay小鼠DN模型肾组织和足细胞p-PERK、p-eIF2α、ATF4、CHOP表达,显著提高Bcl-2表达,降

低 Bax 表达,减少足细胞的凋亡。大黄素对 DN 小鼠肾组织中激活转录因子 6(activating transcription factor 6, ATF6)和肌醇需求酶 1(immunoglobulin regulated enhancer 1, IRE1)水平无明显改变,提示大黄素通过 PERK-eIF2α-ATF4-CHOP 通路减轻 DN 的内质网应激。免疫组化结果显示肾组织中 Nephrin 的表达呈剂量依赖性上调[66]。黄连可清热燥湿,泻火解毒。药理研究表明,小檗碱(黄连素)属于季铵生物碱类化合物[67],具有抗炎、抗氧化、降血糖、调脂等功效[68]。小檗碱通过抑制 DN 大鼠肾组织 PERK、CHOP 表达,从而减少细胞凋亡。另一方面,小檗碱还可以通过抑制 DN 大鼠肾组织中 UPR 的另外两条通路 IRE1 和 ATF6 的相关内质网应激通路,共同减少 CHOP、Caspase-12、Caspase-3 的表达[69]。积雪草可清热利湿、解毒消肿。积雪草酸属于三萜类化合物[70],能通过抑制高糖诱导的肾小球系膜细胞(HBZY-1 细胞)中 P-PERK、CHOP 的表达,并减少 Caspase-12 的表达,减少细胞凋亡[71]。金银花具有清热解毒之效,有抗菌、抗炎、抗氧化、降血糖等药理作用[72-73]。作为金银花的有效成分之一,绿原酸属于苯丙素类化合物[74],通过抑制 STZ 诱导 DN 大鼠肾组织 p-PERK、p-eIF2α、CHOP 和 ATF6 表达,同时抑制两条关键内质网应激通路,从而改善 DN 大鼠肾小球形态变化和基底膜扩张程度。此外,绿原酸通过升高超氧化物歧化酶(superoxide dismutase, SOD)、过氧化氢酶(catalase, CAT)和谷胱甘肽过氧化物酶(glutathione peroxidase, GSH-Px)水平,降低丙二醛(malondialdehyde, MDA)水平,减轻 DN 大鼠肾组织的氧化应激反应[75]。

3.5　综合辨治

糖尿病肾病为本虚标实、虚实夹杂之证。本虚多由气阴两虚渐致阴阳俱虚,标实多属消渴日久湿、浊、瘀、热互相交结于肾。单味中药或单体效果单一,难于兼顾复杂病机。中药复方多药配合,结合病机辨证论治,疗效更佳。补肾活血方为《中国 2 型糖尿病防治指南(2020 年版)》[76]中糖尿病肾病气阴两虚兼血瘀证的推荐方,具有滋补肝肾、益气养阴、化瘀通络的功效,补肾活血方含药血清通过抑制人肾小管上皮细胞中 PERK、eIF2α、ATF4、CHOP 的蛋白表达水平,降低 Bax、Caspase-3、Caspase-9 蛋白表达水平,并升高 Bcl-2 蛋白表达水平,减少肾小管上皮细胞凋亡,从而减轻肾间质纤维化及肾小管吸收功能障碍[77]。黄芪汤出自《仁斋直指方论》[78],有益气补肾、养阴生津之功效。黄芪汤能抑制 PERK-eIF2α-ATF4-CHOP 通路,降低高糖诱导下足细胞中 GRP78、PERK、eIF2α、CHOP 蛋白表达水平,增加 Podocin 和 Bcl-2 的表达,从而抑制足细胞内质网应激,减少足细胞凋亡率,以缓解高糖对糖尿病肾病的足细胞损伤[79]。肾康注射液是慢性肾功能不全湿浊血瘀证的常用中成药,具有降逆泄浊、益气活血、通腑利湿之功效。肾康注射液可以通过抑制 PERK-eIF2α-ATF4-CHOP 通路,分别降低糖尿病肾病大鼠肾组织和肾小管上皮细胞中 PERK、GRP78、eIF2α、ATF4 和 CHOP 蛋白表达水平,继而显著降低 Bax 蛋白表达水平,增加 Bcl-2 的蛋白表达水平。表明肾康注射液在体内和体外均可通过抑制内质网应激,减少糖尿病肾小管上皮细胞的凋亡[80]。丹蛭降糖胶囊为安徽中医药大学第一附属医院院内制剂,有益气养阴,温肾健脾之效。研究表明,丹蛭降糖胶囊可通过抑制 STZ 诱导 DN 大鼠肾组织晚期糖基化终末产物/糖基化终产物受体(advanced glycation end products/the receptor of advanced glycation end products, AGEs/RAGE)的生成来抑制 PERK-eIF2α-ATF4-CHOP 通路,减少 GRP78、PERK 及 CHOP 的表达,抑制糖尿病肾病的内质网应激和细胞凋亡,减轻 DN 大鼠肾组织的肾小球空泡、肾小管损伤和肾间质增宽,延缓糖尿病肾病的发生发展[81-82]。

4　讨论

随着对糖尿病肾病机制的不断深入,肾脏组织内质网应激介导的细胞凋亡成为探索糖尿病肾病发生发展的重要方向。PERK-eIF2α-ATF4-CHOP 通路作为内质网应激的重要通路,目前多项临床与基础实验研究均证明该通路的上调导致糖尿病肾病的多种组织形态改变。现代医学防治糖尿病肾病的方法有限,而中医药在减轻肾组织损伤,保护肾脏功能,延缓糖尿病肾病进展等方面,疗效显著。总结通过干预 PERK-eIF2α-ATF4-CHOP 通路防治糖尿病肾病的中医药相关研究,发现多种中药单体及中药复方作用于该通路的相关靶点,并可作用于肾脏组织的不同部位。这些中药单体及复方,可分类为活血祛瘀、通经活络,益气养阴、生津止渴,健脾益肾、利水消肿,清热泻火、凉血解毒及综合辨治等治法,基本与糖尿病肾病的中医病机相一致。中药单体中,目前主要以三萜类、苷类、黄酮类、多酚类、醌类、生物碱类、烯类、苯丙素类为主,如表 1[26,30,34,37,39,42,45,48,52,55,58,64,66,69,73]所示。中药复方能通过辨证,明晰病机,灵活组方,通过多种有效药物共同作用,达到更好的疗效,但活性成分复杂,难以明确主要的药物成分,如表 2[76,78-80]所示。

表 1 中药单药对 PERK-eIF2α-ATF4-CHOP 信号通路干预作用[26,30,34,37,39,42,45,48,52,55,58,64,66,69,73]

Table 1 Intervention effectsof single Chinese medicine on PERK-eIF2α-ATF4-CHOP signaling pathway[26,30,34,37,39,42,45,48,52,55,58,64,66,69,73]

治法	药物成分	成分类型	作用机制
益气养阴、生津止渴	黄芪甲苷	三萜皂苷类[26]	抑制 PERK-eIF2α-ATF4-CHOP 信号通路,减少 Bax、Cleave Caspase-3 表达,降低 Bax/Bcl-2 比例
	白杨素	黄酮类[30]	抑制 PERK-eIF2α-ATF4-CHOP 信号通路,减少 Bax 和 Apaf-1 表达,增强 Bcl-2、nephrin、podocin 表达
	白芍总苷	糖苷类[34]	抑制 PERK-eIF2α-ATF4-CHOP 信号通路,减少 GRP78、CHOP 表达,减少 TXNIP、IL-1β表达
	酸枣仁皂苷 A	皂苷类[37]	抑制 PERK-eIF2α-ATF4-CHOP 信号通路,减少 GRP78、CHOP 表达,抑制 Caspase-12 表达
	番茄红素	异戊二烯类[39]	抑制 PERK-eIF2α-ATF4-CHOP 信号通路,减少 CHOP 和 Caspase-12 表达,诱导减少 NF-κB 表达,抑制 CRP、TNF-α、IL-1β 释放
健脾益肾、利水消肿	薯蓣皂苷	皂苷类[42]	抑制 PERK-eIF2α-ATF4-CHOP 信号通路,减少 GRP78、CHOP 表达,抑制 Caspase-12 表达
	白黎芦醇	多酚类[45]	抑制 PERK-eIF2α-ATF4-CHOP 信号通路,减少 PERK、GRP78、ATF4、CHOP 表达
	黄蜀葵花总黄酮	黄酮类[48]	抑制 PERK-eIF2α-ATF4-CHOP 信号通路,降低 Bax 和 Caspase-12 蛋白表达,升高 Bcl-2 蛋白表达
活血祛瘀、通经活络	丹参酮 IIa	二萜醌类[52]	抑制 PERK-eIF2α-ATF4-CHOP 信号通路,减少 GRP78、CHOP 表达,抑制 TGF-β1 和 TSP-1 的表达
	红花黄色素	醌式查尔酮类[55]	抑制 PERK-eIF2α-ATF4-CHOP 信号通路,抑制 Cleaved Caspase-12、Cleaved-PARP 的表达
	葛根素	异黄酮类[58]	抑制 PERK-eIF2α-ATF4-CHOP 信号通路,减少 GRP78、CHOP 表达,调节自噬,升高 Beclin-1、LC3II 和 Atg5 水平,下调 p62 水平
	姜黄素	多酚类[60]	抑制 PERK-eIF2α-ATF4-CHOP 信号通路,减少 GRP78、ATF4、CHOP 表达
清热泻火、凉血解毒	大黄素	蒽醌类[64]	抑制 PERK-eIF2α-ATF4-CHOP 信号通路,提高 Bcl-2 表达,降低 Bax 表达,对 ARF6 和 IRE1 水平无明显改变
	小檗碱	季铵生物碱类[66]	抑制 PERK-eIF2α-ATF4-CHOP 信号通路,减少 CHOP,Caspase-3 表达,抑制 IRE1、ATF6 通路,减少 Caspase-12 表达
	积雪草酸	三萜类[69]	抑制 PERK-eIF2α-ATF4-CHOP 信号通路,减少 CHOP 和 Caspase-12 表达
	绿原酸	苯丙素类[73]	抑制 PERK-eIF2α-ATF4-CHOP 和 ATF6 信号通路,减少 GRP78、CHOP 表达,升高 SOD、CAT、GSH-Px 水平,降低 MDA 水平

表 2 中药复方/中成药对 PERK-eIF2α-ATF4-CHOP 信号通路干预作用[76,78-80]

Table 2 Intervention effect of TCM compound/proprietary Chinese medicine on PERK-eIF2α-ATF4-CHOP signaling pathway[76,78-80]

中药复方	治法	药物组方	作用机制
补肾活血方	滋补肝肾、益气养阴、化瘀通络	黄芪、女贞子、水蛭、大黄、太子参、枸杞子	抑制 PERK-eIF2α-ATF4-CHOP 信号通路,降低 Bax、Caspase-3、Caspase-9 表达,增加 Bcl-2 蛋白表达
黄芪汤	益气补肾、养阴生津	生黄芪、生地黄、茯苓、麦冬、北五味子、瓜蒌根、炙甘草	抑制 PERK-eIF2α-ATF4-CHOP 信号通路,增加足细胞 Podocin 和 Bcl-2 表达
肾康注射液	降逆泄浊、益气活血、通腑利湿	大黄、黄芪、红花、丹参提取物	抑制 PERK-eIF2α-ATF4-CHOP 信号通路,降低 Bax、Caspase-12 表达水平,增加 Bcl-2 表达水平
丹蛭降糖胶囊	益气养阴、温肾健脾	太子参、生地黄、牡丹皮、菟丝子、泽泻、水蛭	抑制 PERK-eIF2α-ATF4-CHOP 信号通路,减少 GRP78、PERK、CHOP 表达

5 结论与展望

目前中医药干预 PERK-eIF2α-ATF4-CHOP 信号通路防治 DN 的病理机制主要体现在以下几个方面:①通过内源性细胞凋亡,调控 BCL-2、BAX,减少各类肾细胞的过度凋亡;②通过外源性细胞凋亡途径,调控 Caspase-3、Caspase-12,减少各类肾细胞的过度凋亡;③通过调节自噬,调控 Beclin-1、LC3II、Atg5、p62 水平,减少各类肾细胞的过度凋亡。

中医药干预 PERK-eIF2α-ATF4-CHOP 信号通路防治糖尿病作用的肾细胞主要有:①足细胞:通过抑制足细胞的内质网应激和凋亡,防止裂孔膜间隙破坏,维持肾小球滤过屏障稳定,延缓蛋白尿的发生;②肾小球系膜细胞:通过抑制肾小球系膜细胞的内质网应激和凋亡,维持细胞基质和细胞因子分泌,保持肾小球毛细血管网完整性,延缓肾小球

硬化的发生;③肾小管上皮细胞:通过抑制肾小管上皮细胞的内质网应激和凋亡,延缓肾间质纤维化的进展,增加尿液中蛋白质的重吸收。

中医药防治糖尿病肾病有多靶点多途径调节的优势,并且在临床上取得了显著疗效。但中医药复方成分复杂,有效成分难以界定,单味中药及其提取物疗效有限,需要更加广泛而深入的研究。目前基因工程和多组学研究不断深入,使从更微观的角度分析中医药的作用机制成为可能。这将为系统阐释糖尿病肾病的中医机理,寻找糖尿病肾病更有效的治疗手段,提供更多方法和思路。

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