微生物学通报
Microbiology China
http://journals.im.ac.cn/wswxtbcn

Aug. 20, 2023, 50(8): 3659−3670
DOI: 10.13344/j.microbiol.china.221106

专论与综述

肠道微生物群在糖尿病肾病防治中的研究进展

胡颖俊[1]，陈思敏[1,2]，闫文睿[1]，冀乐[1]，郑红星[1,3]，祁珊珊*[1,4]

1 陕西理工大学生物科学与工程学院，陕西 汉中 723000
2 陕西省资源生物重点实验室，陕西 汉中 723000
3 陕西理工大学秦巴生物资源与生态环境省部共建国家重点实验室，陕西 汉中 723000
4 陕西秦巴山区资源综合开发协同创新中心，陕西 汉中 723000

胡颖俊, 陈思敏, 闫文睿, 冀乐, 郑红星, 祁珊珊. 肠道微生物群在糖尿病肾病防治中的研究进展[J]. 微生物学通报, 2023, 50(8): 3659-3670.
HU Yingjun, CHEN Simin, YAN Wenrui, JI Le, ZHENG Hongxing, QI Shanshan. Intestinal microbiome in the prevention and treatment of diabetic kidney disease[J]. Microbiology China, 2023, 50(8): 3659-3670.

摘　要：糖尿病肾病(diabetic kidney disease, DKD)是由糖尿病引起的严重的代谢性疾病，在高糖情况下，引起肾脏慢性炎症和氧化应激，破坏肾脏生理结构并导致肾脏间质纤维化。大量研究表明，肠道微生物群能够影响机体代谢和健康。本文通过梳理肠道微生物群与DKD相关性的最新研究成果，以期阐明肠道微生物群在DKD的发生和防治过程中的作用。首先，阐明了肠道屏障和肠道微生物群代谢物与DKD的联系；其次，总结近几年抗DKD研究中的作用机制；最后，对补充益生元、益生菌和粪便移植在DKD治疗中的可行性进行了讨论。通过梳理相关内容，本文可为DKD的防治提供一定的理论参考与数据支持。

关键词：肠道微生物；糖尿病肾病；机制；预防和治疗

资助项目：秦巴生物资源与生态环境国家重点实验室项目(SXC-2103)；中国富硒产业研究院富硒专项研发项目(2021FXZX06)；陕西省科技厅农业类一般项目(2023-YBNY-185)

This work was supported by the Qinba State Key Laboratory of Biological Resources and Eco-environment (SXC-2103), the China Selenium Rich Industry Research Institute Selenium Rich Special Research and Development Project (2021FXZX06), and the Shaanxi Science and Technology Department General Project of Agriculture (2023-YBNY-185).

*Corresponding author. E-mail: qishanshan@snut.edu.cn

Received: 2022-11-10; Accepted: 2022-12-09; Published online: 2023-01-03

Intestinal microbiome in the prevention and treatment of diabetic kidney disease

HU Yingjun[1], CHEN Simin[1,2], YAN Wenrui[1], JI Le[1], ZHENG Hongxing[1,3], QI Shanshan[*1,4]

1 School of Biological Science and Engineering, Shaanxi University of Technology, Hanzhong 723000, Shaanxi, China
2 Shaanxi Key Laboratory Bio-resources, Hanzhong 723000, Shaanxi, China
3 State Key Laboratory of Biological Resources and Ecological Environment of Qinba Areas, Shaanxi University of Technology, Hanzhong 723000, Shaanxi, China
4 Qinba Mountain Area Collaborative Innovation Center of Bioresources Comprehensive Development, Hanzhong 723000, Shaanxi, China

Abstract: Diabetic kidney disease (DKD) is a serious metabolic disease caused by diabetes mellitus. In high glucose, DKD causes chronic inflammation and oxidative stress in the kidney, destroys the physiological structure of the kidney, and leads to renal interstitial fibrosis. Numerous studies have shown that intestinal microbiome influences the body's metabolism and health. This review summarized the latest research findings on the relevance of the intestinal microbiota to DKD, which aimed to elucidate the effects of the intestinal microbiota on the prevention and treatment of DKD. In addition, the association between intestinal barrier and intestinal microbiome metabolism with DKD was established, and the related mechanisms of the intestinal microbiome against DKD in recent studies were summarized. What's more, the feasibility of supplementing prebiotics and probiotics as well as fecal transplantation in the treatment of DKD was discussed. By combing relevant content, this review provides certain theoretical references and data support for the treatment of DKD.

Keywords: intestinal microbiome; diabetic kidney disease; mechanism; prevention and treatment

糖尿病肾病(diabetic kidney disease, DKD)是由糖尿病引起的最严重的并发症之一，也是引起终末期肾病和肾衰竭的主要原因之一[1]。在高糖情况下，由于体内代谢紊乱和机体处于慢性炎症的状态导致肾小球肥大、系膜基质扩张、有孔内皮细胞丢失和足细胞损伤[2-3]。肾小球滤过屏障的变化伴随结节硬化、肾小球硬化、免疫细胞浸润、最后是肾小管间质纤维化，这是 DKD 的标志性特征[4]。近年来，肠道微生物群的研究引起了人们广泛的关注；研究发现，肠道微生物群在 DKD 中起着关键作用[5]。

生活在宿主肠胃系统里的微生物主要依靠消化宿主体内食物的残渣给自身供给能量，这些微生物与其生存的环境构成了肠道微生态系统[6]。肠道微生物群不仅在营养物质的吸收、代谢和毒素降解中起着重要作用，还能够维持宿主肠道内稳态并促进肠道免疫的成熟[7]。在肠道菌群中占主导地位的有拟杆菌门(*Bacteroidetes*)、厚壁菌门(*Firmicutes*)、变形菌门(*Proteobacteria*)、放线菌门(*Actinobacteria*)和梭杆菌门(*Fusobacteria*)[8-9]。肠道的健康状态与肾脏的健康状态相互影响、相互作用。当肠道内的有害菌增多时会引起机体不适，有的更能引起严重的炎症反应和免疫反应，破坏机体健康。当肾脏损伤或功能障碍时，容易导致肠道中具有保护作用的细菌丧失，会引起肠道内微生物组成发生改变，有害物质泄露，破坏肠道屏障[10]。

1 肠道屏障

肠道屏障主要由物理、化学、免疫和微生物屏障组成[11]。肠道物理屏障是一种特异性和选择性屏障系统，能够调节营养物质、离子和水的被动运输，并有效阻止有害菌及内毒素等物质透过肠黏膜进入血液[12]。肠道化学屏障主要是由肠上皮细胞分泌各种抗菌化合物和正常寄生菌产生的抑菌物质构成，分为内黏液层和外黏液层[13]。外黏液层是肠道微生物的主要栖息地。内黏液层含有各种抗菌肽和分泌性免疫球蛋白 A (immunoglobulin A, IgA)，它们以化学方式抵抗病原菌的入侵[14]。肠道免疫屏障由肠上皮中具免疫功能的细胞构成，如巨噬细胞、树突状细胞、淋巴细胞和潘氏细胞，可以分泌各种抗菌肽、免疫球蛋白 G 和细胞因子来维持肠道免疫稳态[15-16]。肠道常驻菌群构成肠道微生物屏障，当肠道微生物群稳定性被破坏后，肠道定殖抵抗力下降，导致肠道中潜在性病原体定殖和入侵。在 DKD 中，肠道微生物群的多样性发生改变如表 1 所示，引起肠道菌群失调和肠道通透性增加。例如，在 DKD 中，粪拟杆菌(*Bacteroides caccae*)可以通过分泌大量降解黏液的蛋白酶破坏结肠黏液层[30]；肠道屏障保护细菌嗜黏蛋白阿克曼菌(*Akkermansia muciniphila*)和普氏栖粪杆菌(*Faecalibacterium prausnitzii*)的数量减少，而大肠杆菌(*Escherichia coli*)增加并分泌内切葡糖酶(secreted protease of C1 esterase inhibitor, StcE)来溶解黏蛋白并破坏肠道屏障[31]。当肠道屏障被破坏时，肠道内的细菌、促炎症因子和有害物质进入血液循环，引发全身炎症反应[32]。例如，脂多糖(lipopolysaccharide, LPS)是革兰氏阴性细菌的膜成分，作为共生微生物群和病原体的一部分在肠道中大量存在；LPS 可通过 Toll 样受体 4/髓样分化因子 88 (Toll-like receptor 4/myeloid differentiation factor 88, TLR4/MyD88)依赖性途径激活巨噬细胞，释放炎症因子[33]。

2 肠道微生物群代谢物与 DKD 的联系

2.1 短链脂肪酸

短链脂肪酸(short-chain fatty acids, SCFAs)是由细菌消化膳食多糖发酵的最终产物，作为结肠黏膜上皮的材料，对肠道环境有重大影响[34]。产生 SCFAs 的微生物减少，标志着宿主肠道生态失调。SCFAs 和 G 蛋白偶联受体结合通过血液循环进入肝脏、肾脏、胰腺和脂肪来调节糖脂代谢[35]。SCFAs 能够抑制肠道炎症和氧化应激，通过激活 G 蛋白偶联受体 109A (G-protein-coupled receptor 109A, GPR109A)抑制小鼠核转录因子-κB (nuclear factor-κB, NF-κB)活化和胰腺 β 细胞炎症[36]。补充 SCFAs 可以抑制补体 C5 活化下的肾小球内皮细胞的核信号转导及转录激活蛋白 3 (signal transducer and activator of transcription 3, STAT3)的磷酸化水平上升，通过切断 STAT3 信号途径来减缓小鼠肾脏的炎症反应[37]。Huang 等[38]发现，在高糖或 LPS 诱导下，用 SCFAs 或 G 蛋白偶联受体 43 (G-protein-coupled receptor 43, GPR43)激动剂培养肾小球系膜细胞，可减少活性氧(reactive oxygen species, ROS)的产生和趋化因子(monocyte chemoattractant protein-1, MCP-1)、细胞白介素-1β (Interleukin-1β, IL-1β)的表达。补充 SCFAs 主要通过与代谢物感应受体 GPR43 和 GPR109A 结合，实现减缓由 DKD 所引起的肾小球病变病和炎症反应。

2.2 胆汁酸

胆汁酸(bile acids, BAs)是在肝脏中由胆固醇合成的内源性分子[39]。肠道菌群参与胆汁酸的生成，初级胆汁酸在胆盐水解酶和 7α/β-脱羟

表 1 在 DKD 影响下肠道菌物种相对丰度变化

Table 1 Variation of intestinal bacterial species relative abundance in DKD

肠道菌群 Intestinal microbiome	主要功能 Main function	DKD
拟杆菌门 *Bacteroidetes*		
拟杆菌属 *Bacteroides*	降解多糖，产生短链脂肪酸，抑制炎症，降低脂多糖，改善内毒素血症，参与胆汁酸代谢 Degrade polysaccharide, produce SCFAs, reduce inflammation, reduce LPS, improve endotoxemia, related to bile acid metabolism	↓[17]
另枝菌属 *Alistipes*	产生吲哚，丙酸和乙酸盐，破坏肠道通透性，减少组织纤维化 Produce indole, propionic acid and acetate, destroy intestinal permeability, decrease fibrosis	↑↓[18-19]
普雷沃氏菌属 *Prevotella*	帮助分解碳水化合物和蛋白质，增加肠道通透性 Breaking down carbohydrates and proteins increases intestinal permeability	↓↑[20-21]
厚壁菌门 *Firmicutes*		
乳杆菌属 *Lactobacillus*	逆转炎症反应，减少 DKD 引起的肾组织损伤，与胆汁酸代谢相关 Reverse inflammation and reduce renal tissue injury caused by DKD, related to bile acid metabolism	↓[22-23]
罗氏菌属 *Roseburia*	主要产生丁酸，具有抗炎作用，与血糖呈负相关 Mainly produces butyric acid, anti-inflammatory, negatively correlated with blood glucose	↓[24-25]
颤螺菌属 *Oscillospira*	能产生丁酸盐与 2 型糖尿病和炎症的发展成正相关 Butyrate production, positively associated with the development of type 2 diabetes and inflammation	↓[26]
毛螺菌属 *Lachnospiracea*	产生乙酸，与 DKD 小鼠中牛磺胆酸(TCA)、牛磺 β-鼠胆酸(Tβ-MCA)含量呈正相关 The production of acetic acid, positively correlated with the content of taurocholic acid (TCA) and tauroβ-murine cholic acid (Tβ-MCA) in DKD mice	↓[27]
变形菌门 *Proteobacteria*		
脱硫弧菌属 *Desulforibrioaceae*	能产生短链脂肪酸、H_2S，与体重、甘油三酯的增加呈负相关 Produce short chain fatty acid and H_2S, negatively correlated with the increase of body weight and triglyceride	↑[28]
放线菌门 *Actinobacteria*		
双歧杆菌属 *Bifidobacyerium*	保护肠屏障，产生短链脂肪酸 Protect the intestinal barrier and produce short chain fatty acids	↓[29]

↓表示在糖尿病肾病中该菌属相对丰度减少，↑表示在糖尿病肾病中该菌属相对丰度增加

↓ indicates that the relative abundance of the bacterial community decreases in DKD, while ↑ indicates that the relative abundance of the bacterial community increases in DKD.

基作用下生成次级胆汁酸，胆盐水解酶是某些微生物的代谢物，7α/β-脱羟基作用与梭状芽孢杆菌属(*Clostridium*)有关[40]。BAs 在机体内主要通过与细胞 G 蛋白膜受体和一些核受体结合来调控脂质的代谢，维持机体稳态平衡[38]。有研究发现，BAs 主要通过与肠、胰腺、肝脏中的法尼酯 X 激活受体(farnesoid X recrptor, FXR)和跨膜 G 蛋白偶联受体 5 (takeda G protein-coupled receptor, TGR5)结合来调控糖代谢，FXR 和 TGR5 均在胰岛 β 细胞中表达，并刺激胰高血糖素合成和葡萄糖诱导的胰岛素分泌[41]。在 DKD 模型中，肾脏 FXR 受体的激活能够预防糖尿病，

BAs代谢水平的改变与肾脏中FXR受体的高度表达有关[27]。T2DM 患者血清胆汁酸谱中熊脱氧胆酸、石胆酸水平降低与 DKD 的发生有关，可能是 DKD 防治的一个新靶点[42]。

2.3 H_2S

H_2S 具有多种生物学功能，包括抗凋亡、抗氧化应激、舒张血管、降低血压，以及抗炎和抗纤维化作用[43]。H_2S 的产生主要通过两种途径，一种是依赖于酶的途径，另一种是依赖于肠道细菌的途径[44]。依赖于酶的途径主要是由 D 型或 L 型半胱氨酸通过三种酶催化生成；H_2S 的另一种产生方式主要是肠道细菌，如脱硫菌(*Desulfobacter*)、脱硫弧菌(*Desulfovibrio*)和脱硫肠状菌(*Desulfotomaculum*)还原硫酸盐，某些厌氧细菌菌株，如肠道沙门氏菌(*Salmonella enterica*)、大肠杆菌和产气肠杆菌(*Enterobacter aerogene*)催化半胱氨酸产生 H_2S[45]。ROS 的过度产生导致氧化应激增加，与糖尿病的发生有关，外源性 H_2S 通过 Kelch 样 ECH 相关蛋白 1 (kelch-like ECH-associated protein 1, Keap1)巯基化 Cys151 激活核因子 E2 相关因子(nuclear factor erythroid 2-related, Nrf2)信号传导来抑制氧化应激，从而改善糖尿病加速的动脉粥样硬化[46]。H_2S 通过激活的 ATP 敏感性钾通道(ATP-sensitive potassium channel, KATP)抑制胰岛素分泌，抑制或促进胰岛 β 细胞的凋亡来调节血糖浓度[47]。外源性 H_2S 通过降低糖尿病肾组织中基质金属蛋白酶、V 型胶原和金属蛋白酶组织抑制物的表达水平，以及抑制生长转化因子-β1 (Transforming growth factor, TGF-β1)信号通路激活自噬来改善糖尿病诱导的肾组织纤维化[48]。内源性 H_2S 可抑制糖尿病大鼠肾脏中细胞外基质的过度积聚，延缓 DKD 的病理改变[49]。目前，H_2S 的浓度对机体所造成不同影响的机制尚不完全清楚，而且 H_2S 调节全身糖代谢的分子机制仍需要进一步研究。

3 DKD 相关的药物研究

近年来，很多食药用植物的活性成分和功能被广泛发掘。研究发现，其活性成分具有很大的营养价值和药用功能，我们之前的研究中已经证明黑米中的花青素[50-51] (主要成分：矢车菊素-3-O-葡萄糖苷)、红景天中主要活性成分红景天苷[3]，以及人体必需微量元素铬[52]对 DKD 具有很好的防治作用，它们能够通过抗炎、抗氧化、抑制 TGF-β1/Smad 信号通路来改善 DKD。此外，在另一些研究中发现，中国传统药用植物和中药复方对 DKD 具有很好的治疗效果。它们通过抗炎、抗氧化、改善肠道菌群的相对丰度、保护肠屏障等作用机制来减少高糖条件下的肾功能障碍和肾脏病理损伤及纤维化，如表 2 所示。

从天然产物中提取的多糖成分具有来源广泛、副作用小等特点，被广泛用于治疗 DKD 的研究；它们可以通过调节肠道菌群代谢物来影响肠道生态系统的稳定，减少 DKD 的发生与发展[60]。实验证明，蝉虫草多糖[54]、蜜环菌丝体多糖[55]、柴胡多糖[56]能够恢复肠道微生物群的组成，抑制机体炎症反应，并能减少 LPS 含量，从而减少糖尿病大鼠的肾组织损伤。另外，拟杆菌属、乳杆菌属(*Lactobacillus*)、双歧杆菌属(*Bifidobacterium*)和阿克曼菌属(*Akkermansia*)丰度的增加与肠道屏障的完整性和血浆 LPS 浓度的减弱呈正相关[54]。这些多糖可以通过提高益生菌的相对丰度和减少产生 LPS 的细菌来保护肠道微生物群免受破坏，减轻 DKD 大鼠肾损伤和肾小管间质纤维化[55-56]。

肾炎康复片[57-58]、芪地糖肾颗粒[27]、糖肾方[59]对 DKD 的治疗有重要的影响，能通过调节肾脏炎症信号级联和肠道微生物群来减轻糖

表 2　在一些研究中药物对 DKD 的治疗机制

Table 2　Therapeutic mechanisms of drugs on DKD in some studies

药物 Medicine	简介 Introduce	作用机制 Mechanism
矢车菊素-3-O-葡萄糖苷[50-51] Cyanidin-3-glucoside (C3G)[50-51]	黑米提取物 Black rice extract	C3G 抗炎、抗氧化，调节 TGFβ1/Smad 通路 C3G suppressing oxidative stress and inflammation, and regulating TGFβ1/Smad expression
紫草酸镁 B[53] Magnesium lithospermate B (MLB)[53]	丹参水提物的主要成分 The major component of danshen water extracts	MLB 改善肠道菌群和胆汁酸代谢状况 MLB can improve intestinal flora and bile acid metabolism
蝉虫草多糖[54] Cordyceps cicadae polysaccharides (CCP)[54]	药用寄生真菌中的活性成分 Active ingredients of natural medicinal fungi	CCP 抑制 TLR4/NF-κB 和 TGF-β1/Smad 信号通路，改善炎症反应和肠道菌群失调 CCP improve inflammation, intestinal flora dysregulation, inhibiting TLR4/NF-κB and TGF-β1/Smad signaling pathways
烟草蜜环菌菌丝体多糖[55] Armillariella tabescens polysaccharides (AT)[55]	天然药用菌类活性成分 Active ingredients of natural medicinal fungi	HAT 调节肠道微生物群组成、改善肠道屏障功能、降低 LPS 含量和全身炎症 HAT regulates gut microbiota composition, improves intestinal barrier function, reduces LPS and systemic inflammation
柴胡多糖[56] Bupleurum polysaccharides (BP)[56]	柴胡中提取的多糖成分 Bupleurum polysaccharides	BP 调节肠道菌群和炎症反应 BP regulates gut microbiota and inflammation
肾炎康复片[57-58] Shenyan Kangfu tablet (SYKFT)[57-58]	传统中草药 Traditional Chinese herbal medicine	SYKFT 调节肾脏炎症信号级联和肠道微生物群 SYKFT regulates renal inflammatory signaling cascades and gut microbiota
芪地糖肾颗粒[27] QiDiTangshen granules (QDTS)[27]	传统中草药 Traditional Chinese herbal medicine	QDTS 调节肠道微生物群，改善胆汁酸谱 QDTS regulate gut microbiota and improve bile acid profile
糖肾方[59] Tangshen formula (TSF) [59]	传统中草药 Traditional Chinese herbal medicine	TSF 调节肠道菌群组成，降低 LPS 和硫酸吲哚氧基的水平 TSF regulates the composition of intestinal flora, reduces the levels of LPS and indoleoxyl sulfate

尿病肾病小鼠的肾脏炎症反应及纤维化，改善肾功能。其中，糖肾方抑制糖尿病肾组织损伤和炎症反应与肠道微生物群组成的改变有重要联系；在门水平上，观察到拟杆菌门和迷踪菌门(*Elusimicrobia*)均与尿白蛋白肌酐比值(urinary albumin to creatinine ratio, UACR)和肾小管损伤指数呈正相关；迷踪菌门与肾小球硬化症、血清 MCP-1 和肿瘤坏死因子-α (tumor necrosis factor-α, TNF-α)呈正相关；而厚壁菌门和放线菌门与 UACR 和肾小管损伤指数呈负相关；放线菌门和广古菌门(*Euryarchaeota*)与肾功能参数呈负相关[59]。

4　治疗和展望

4.1　益生元和益生菌

益生菌是通过定殖在人体内改变宿主某一部位菌群组成的一类对宿主有益的活性微生物。益生元是含有可发酵纤维的膳食补充剂，

对宿主的健康有益[61]。益生菌和益生元的补充对代谢性疾病有重要的影响。有研究表明，口服葡萄糖丸后接受益生菌小鼠的葡萄糖水平更快地恢复正常[62]。罗伊氏乳杆菌(*Lactobacillus reuteri*)可降低 2 型糖尿病患者的糖化血红蛋白和血清胆固醇[63]。嗜粘蛋白-阿克曼氏菌和双歧杆菌与低炎症、胰岛素抵抗和 2 型糖尿病呈负相关，可以产生 SCFAs，保护肠道屏障，降低体内 LPS 水平[64]。槲皮素可以作为益生元，在链脲佐菌素诱导的糖尿病周围神经病变大鼠上进行研究，结果表明槲皮素具有良好的抗氧化作用，通过调节与活性氧产生和糖尿病周围神经病变表型相关肠道微生物的组成，来减少氧化应激并改善糖尿病大鼠的周围神经病变[65]。

4.2 粪菌移植

粪菌移植(fecal microbiota transplantation, FMT)是最早被用于治疗艰难梭菌感染的主要方法，并且对高龄虚弱患者有效且耐受性良好[66]。另外，还有研究发现 FMT 在炎症性肠炎中有积极的作用。Xiao 等[67]诱导构建结肠炎诱发心脏病的 IL-10 缺陷型小鼠模型，将野生型 C57BL/6J 小鼠当作供体进行 FMT，发现 FMT 能降低模型组小鼠的脑钠肽水平，提高模型组左心室射血分数，减轻模型组小鼠的心损伤。Bastos 等[68]的研究揭示了 FMT 可以改善糖尿病小鼠的临床前功能和形态学参数，降低体重，降低回肠、升结肠内蛋白尿和 TNF-α 水平，保护肠道结构完整性，改善糖尿病小鼠的胰岛素抵抗。Cai 等[69]发现，将健康小鼠的粪便作为供源移植给肾组织损伤的糖尿病小鼠配合给药白黎芦醇，经过 6 周治疗后，发现 FMT 能够减少糖尿病小鼠肾组织损伤和炎症，并改善肠道通透性。综上所述，FMT 临床前模型实验中有较高的安全性和有效性，但 DKD 是多机制调控的疾病，FMT 并不能直接降低血糖并减缓肾组织损伤，在 FMT 的方法上还需要配合其他药物的使用。

5 小结

肠道菌群对 DKD 的影响主要有两方面，一方面是肠道屏障的破坏使得肠道内的细菌、促炎症因子和有害物质进入血液循环，引发肾脏炎症反应；另一方面是肠道微生物平衡被打破，使得对人体有害菌群增加，益生菌相对丰度下降，肠道微生物通过调节短链脂肪酸、胆汁酸代谢和硫化氢的产生等来影响 DKD 的发生。补充益生菌和益生元可以改善 DKD 患者肠道菌的物种组成，修复肠屏障。FMT 临床前模型实验中有较高的安全性和有效性，还需要进一步研究来证明其在临床上的可行性。

随着药食同源的推进，很多食用植物的药用价值被开发，它们来源更加广泛，而且更加安全、毒性更小。在我们之前的研究中，通过给健康的 SD 大鼠注射链脲佐菌素来构建糖尿病大鼠模型，并用黑米花青苷、红景天苷等天然食品提取物处理一段时间，结果表明黑米花青苷、红景天苷能够改善糖尿病肾功能障碍和减少肾病病理损伤[3,51]。在另一些研究中，食药用植物提取物和中药复方也能改善糖尿病肾组织损伤和肾功能障碍，并调节肠道微生物群的组成，保护肠屏障[53-59]。

截至目前，DKD 与肠道微生物群两者之间的联系被广泛研究，但由于 DKD 发病机制的复杂性，以及 DKD 发展过程的漫长和连续性，肠道微生物群及其代谢物在 DKD 的不同阶段会发生变化。然而，目前的研究大多未对其动态进行持续监测。因此，未来的研究不仅应关注肠道菌群与代谢性疾病之间的分子相互作用机制，还应根据个体的不同需求和 DKD 发展的不同阶段进行动态检测，以便后续更有针对性地治疗。

REFERENCES

[1] 祁珊珊, 何佳, 孙泽, 邵梦丽, 郑红星. 糖尿病肾病SD大鼠模型的建立和评价[J]. 中国临床药理学杂志, 2021, 37(9): 1114-1116, 1125.
QI SS, HE J, SUN Z, SHAO ML, ZHENG HX. Establishment and evaluation of SD rat model of diabetic nephropathy[J]. The Chinese Journal of Clinical Pharmacology, 2021, 37(9): 1114-1116, 1125 (in Chinese).

[2] PICCOLI GB, GRASSI G, CABIDDU G, NAZHA M, ROGGERO S, CAPIZZI I, DE PASCALE A, PRIOLA AM, DI VICO C, MAXIA S, LOI V, ASUNIS AM, PANI A, VELTRI A. Diabetic kidney disease: a syndrome rather than a single disease[J]. The Review of Diabetic Studies: RDS, 2015, 12(1-2): 87-109.

[3] QI SS, ZHENG HX, JIANG H, YUAN LP, DONG LC. Protective effects of chromium picolinate against diabetic-induced renal dysfunction and renal fibrosis in streptozotocin-induced diabetic rats[J]. Biomolecules, 2020, 10(3): 398.

[4] MOSTERD CM, KANBAY M, van den BORN BJH, van RAALTE DH, RAMPANELLI E. Intestinal microbiota and diabetic kidney diseases: the role of microbiota and derived metabolites inmodulation of renal inflammation and disease progression[J]. Best Practice & Research Clinical Endocrinology & Metabolism, 2021, 35(3): 101484.

[5] WANG PP, WANG T, ZHENG XJ, CUI W, SHANG J, ZHAO ZZ. Gut microbiota, key to unlocking the door of diabetic kidney disease[J]. Nephrology, 2021, 26(8): 641-649.

[6] 郭慧玲, 邵玉宇, 孟和毕力格, 张和平. 肠道菌群与疾病关系的研究进展[J]. 微生物学通报, 2015, 42(2): 400-410.
GUO HL, SHAO YY, MENG H, ZHANG HP. Research on the relation between gastrointestinal microbiota and disease[J]. Microbiology China, 2015, 42(2): 400-410 (in Chinese).

[7] CHI MX, MA K, WANG J, DING ZL, LI YL, ZHU SM, LIANG X, ZHANG QX, SONG LJ, LIU C. The immunomodulatory effect of the gut microbiota in kidney disease[J]. Journal of Immunology Research, 2021, 2021: 5516035.

[8] LÜ QL, LI ZY, SUI AH, YANG XM, HAN YF, YAO RY. The role and mechanisms of gut microbiota in diabetic nephropathy, diabetic retinopathy and cardiovascular diseases[J]. Frontiers in Microbiology, 2022, 13: 977187.

[9] RINNINELLA E, RAOUL P, CINTONI M, FRANCESCHI F, MIGGIANO GAD, GASBARRINI A, MELE MC. What is the healthy gut microbiota composition? A changing ecosystem across age, environment, diet, and diseases[J]. Microorganisms, 2019, 7(1): 14.

[10] 张萌萌, 姜宁, 张爱忠. 肠道微生物对肠道屏障功能完整性的维护机制研究概况[J]. 微生物学通报, 2020, 47(3): 933-940.
ZHANG MM, JIANG N, ZHANG AZ. Maintenance mechanism of intestinal barrier function integrity by intestinal microbes[J]. Microbiology China, 2020, 47(3): 933-940 (in Chinese).

[11] LIU YP, XU Z, HUANG HY, ZHANG DD, ZHANG YJ, LI WJ, LI X. Fucoidan ameliorates glucose metabolism by the improvement of intestinal barrier and inflammatory damage in type 2 diabetic rats[J]. International Journal of Biological Macromolecules, 2022, 201: 616-629.

[12] WEICKERT MO. What dietary modification best improves insulin sensitivity and why?[J]. Clinical Endocrinology, 2012, 77(4): 508-512.

[13] RIEDEL S, PHEIFFER C, JOHNSON R, LOUW J, MULLER CJF. Intestinal barrier function and immune homeostasis are missing links in obesity and type 2 diabetes development[J]. Frontiers in Endocrinology, 2022, 12: 833544.

[14] 祁珊珊, 郑红星. 肠道SIgA及其调节机制研究进展[J]. 中国兽医杂志, 2015, 51(6): 76-79.
QI SS, ZHENG HX. Research progress of intestinal *SIgA* and its regulatory mechanism[J]. Chinese Journal of Veterinary Medicine, 2015, 51(6): 76-79 (in Chinese).

[15] JOHANSSON MEV, SJÖVALL H, HANSSON GC. The gastrointestinal mucus system in health and disease[J]. Nature Reviews Gastroenterology & Hepatology, 2013, 10(6): 352-361.

[16] OLIVARES-VILLAGÓMEZ D, van KAER L. Intestinal intraepithelial lymphocytes: sentinels of the mucosal barrier[J]. Trends in Immunology, 2018, 39(4): 264-275.

[17] ZHANG M, YANG LC, ZHU MM, YANG B, YANG YJ, JIA XB, FENG L. Moutan cortex polysaccharide ameliorates diabetic kidney disease via modulating gut microbiota dynamically in rats[J]. International Journal of Biological Macromolecules, 2022, 206: 849-860.

[18] PARKER BJ, WEARSCH PA, VELOO ACM, RODRIGUEZ-PALACIOS A. The genus *Alistipes*: gut bacteria with emerging implications to inflammation, cancer, and mental health[J]. Frontiers in Immunology, 2020, 11: 906.

[19] RAU M, REHMAN A, DITTRICH M, GROEN AK, HERMANNS HM, SEYFRIED F, BEYERSDORF N, DANDEKAR T, ROSENSTIEL P, GEIER A. Fecal SCFAs and SCFA-producing bacteria in gut microbiome of human NAFLD as a putative link to systemic T-cell activation and advanced disease[J]. United European Gastroenterology Journal, 2018, 6(10): 1496-1507.

[20] ILJAZOVIC A, ROY U, GÁLVEZ EJC, LESKER TR, ZHAO B, GRONOW A, AMEND L, WILL SE, HOFMANN JD, PILS MC, SCHMIDT-HOHAGEN K, NEUMANN-SCHAAL M, STROWIG T. Perturbation of the gut microbiome by *Prevotella* spp. enhances host susceptibility to mucosal inflammation[J]. Mucosal Immunology, 2021, 14(1): 113-124.

[21] LEY RE. *Prevotella* in the gut: choose carefully[J]. Nature Reviews Gastroenterology & Hepatology, 2016, 13(2): 69-70.

[22] XU H, WANG JQ, CAI J, FENG WK, WANG YG, LIU Q, CAI L. Protective effect of *Lactobacillus rhamnosus* GG and its supernatant against myocardial dysfunction in obese mice exposed to intermittent hypoxia is associated with the activation of Nrf2 pathway[J]. International Journal of Biological Sciences, 2019, 15(11): 2471-2483.

[23] WEI HL, WANG L, AN ZC, XIE HD, LIU WJ, DU Q, GUO Y, WU X, LI SC, SHI Y, ZHANG XH, LIU HF. QiDiTangShen granules modulated the gut microbiome composition and improved bile acid profiles in a mouse model of diabetic nephropathy[J]. Biomedicine & Pharmacotherapy, 2021, 133: 111061.

[24] VRIEZE A, van NOOD E, HOLLEMAN F, SALOJÄRVI J, KOOTTE RS, BARTELSMAN JFWM, DALLINGA-THIE GM, ACKERMANS MT, SERLIE MJ, OOZEER R, DERRIEN M, DRUESNE A, van HYLCKAMA VLIEG JET, BLOKS VW, GROEN AK, HEILIG HGHJ, ZOETENDAL EG, STROES ES, de VOS WM, HOEKSTRA JBL, NIEUWDORP M. Transfer of intestinal microbiota from lean donors increases insulin sensitivity in individuals with metabolic syndrome[J]. Gastroenterology, 2012, 143(4): 913-916.e7

[25] KONIKOFF T, GOPHNA U. *Oscillospira*: a central, enigmatic component of the human gut microbiota[J]. Trends in Microbiology, 2016, 24(7): 523-524.

[26] FENG WW, LIU J, AO H, YUE SJ, PENG C. Targeting gut microbiota for precision medicine: focusing on the efficacy and toxicity of drugs[J]. Theranostics, 2020, 10(24): 11278-11301.

[27] CHEN YR, JING QL, CHEN FL, ZHENG HM, CHEN LD, YANG ZC. *Desulfovibrio* is not always associated with adverse health effects in the Guangdong Gut Microbiome Project[J]. Peer-Reviewed Science Mega Journal, 2021, 9: e12033.

[28] WANG XF, YANG ST, LI SH, ZHAO L, HAO YL, QIN JJ, ZHANG L, ZHANG CY, BIAN WJ, ZUO L, GAO X, ZHU BL, LEI XG, GU ZL, CUI W, XU XP, LI ZM, ZHU BZ, LI Y, CHEN SW, et al. Aberrant gut microbiota alters host metabolome and impacts renal failure in humans and rodents[J]. Gut, 2020, 69(12): 2131-2142.

[29] VAZIRI ND, WONG J, PAHL M, PICENO YM, YUAN J, DE SANTIS TZ, NI ZM, NGUYEN TH, ANDERSEN GL. Chronic kidney disease alters intestinal microbial flora[J]. Kidney International, 2013, 83(2): 308-315.

[30] DESAI MS, SEEKATZ AM, KOROPATKIN NM, KAMADA N, HICKEY CA, WOLTER M, PUDLO NA, KITAMOTO S, TERRAPON N, MULLER A, YOUNG VB, HENRISSAT B, WILMES P, STAPPENBECK TS, NÚÑEZ G, MARTENS EC. A dietary fiber-deprived gut microbiota degrades the colonic mucus barrier and enhances pathogen susceptibility[J]. Cell, 2016, 167(5): 1339-1353.e21.

[31] GRYS TE, SIEGEL MB, LATHEM WW, WELCH RA. The StcE protease contributes to intimate adherence of enterohemorrhagic *Escherichia coli* O157: H7 to host cells[J]. Infection and Immunity, 2005, 73(3): 1295-1303.

[32] THAISS CA, LEVY M, GROSHEVA I, ZHENG DP, SOFFER E, BLACHER E, BRAVERMAN S, TENGELER AC, BARAK O, ELAZAR M, BEN-ZEEV R, LEHAVI-REGEV D, KATZ MN, PEVSNER-

FISCHER M, GERTLER A, HALPERN Z, HARMELIN A, AAMAR S, SERRADAS P, GROSFELD A, SHAPIRO H, GEIGER B, ELINAV E. Hyperglycemia drives intestinal barrier dysfunction and risk for enteric infection[J]. Science, 2018, 359(6382): 1376-1383.

[33] HU NH, WANG C, DAI XY, ZHOU MT, GONG LH, YU LY, PENG C, LI YX . Phillygenin inhibits LPS-induced activation and inflammation of LX2 cells by TLR4/MyD88/NF-κB signaling pathway[J]. Journal of Ethnopharmacology, 2020, 248: 112361.

[34] TANASE DM, GOSAV EM, NECULAE E, COSTEA CF, CIOCOIU M, HURJUI LL, TARNICERIU CC, MARANDUCA MA, LACATUSU CM, FLORIA M, SERBAN IL. Role of gut microbiota on onset and progression of microvascular complications of type 2 diabetes (T2DM)[J]. Nutrients, 2020, 12(12): 3719.

[35] HUANG W, GUO HL, DENG X, ZHU TT, XIONG JF, XU YH, XU Y. Short-chain fatty acids inhibit oxidative stress and inflammation in mesangial cells induced by high glucose and lipopolysaccharide[J]. Experimental and clinical endocrinology & diabetes: official journal, German Society of Endocrinology [and] German Diabetes Association, 2017, 125(2): 98-105.

[36] LI YJ, CHEN XC, KWAN TK, LOH YW, SINGER J, LIU YZ, MA J, TAN J, MACIA L, MACKAY CR, CHADBAN SJ, WU HL. Dietary fiber protects against diabetic nephropathy through short-chain fatty acid-mediated activation of G protein-coupled receptors GPR43 and GPR109A[J]. Journal of the American Society of Nephrology, 2020, 31(6): 1267-1281.

[37] LI L, WEI TT, LIU SY, WANG CS, ZHAO M, FENG YH, MA L, LU YR, FU P, LIU JP. Complement C5 activation promotes type 2 diabetic kidney disease via activating STAT3 pathway and disrupting the gut-kidney axis[J]. Journal of Cellular and Molecular Medicine, 2021, 25(2): 960-974.

[38] HUANG W, MAN Y, GAO CL, ZHOU LP, GU JL, XU HW, WAN Q, LONG Y, CHAI L, XU YH, XU Y. Short-chain fatty acids ameliorate diabetic nephropathy via GPR43-mediated inhibition of oxidative stress and NF-κB signaling[J]. Oxidative Medicine and Cellular Longevity, 2020, 2020: 4074832.

[39] WAHLSTRÖM A, SANYIN SI, MARSHALL HU, BÄCKHED F. Intestinal crosstalk between bile acids and microbiota and its impact on host metabolism[J]. Cell Metabolism, 2016, 24(1): 41-50.

[40] DAWSON PA, KARPEN SJ. Intestinal transport and metabolism of bile acids[J]. Journal of Lipid Research, 2015, 56(6): 1085-1099.

[41] CHÁVEZ-TALAVERA O. Bile acid control of metabolism and inflammation in obesity, type 2 diabetes, dyslipidemia, and nonalcoholic fatty liver disease[J]. Gastroenterology, 2017, 152(7): 1679-1694.e3

[42] 徐亚南, 温洪华, 骆宴施, 郭茂君, 张少坤, 祝群. 2型糖尿病患者血清熊脱氧胆酸、石胆酸水平与糖尿病肾脏病的相关性研究[J]. 临床内科杂志, 2022, 39(10): 679-682.
XU YN, WEN HH, LUO YS, GUO MJ, ZHANG SK, ZHU Q. Correlation of serum ursodeoxycholic acid and lithocholic acid levels with diabetic kidney disease in type 2 diabetic patients[J]. Journal of Clinical Internal Medicine, 2022, 39(10): 679-682 (in Chinese).

[43] ZHANG H, ZHAO HT, GUO NN. Protective effect of hydrogen sulfide on the kidney (Review)[J]. Molecular Medicine Reports, 2021, 24(4): 696.

[44] SINGH S, PADOVANI D, LESLIE RA, CHIKU T, BANERJEE R. Relative contributions of cystathionine beta-synthase and gamma-cystathionase to H_2S biogenesis via alternative trans-sulfuration reactions[J]. The Journal of Biological Chemistry, 2009, 284(33): 22457-22466.

[45] TOMASOVA L, KONOPELSKI P, UFNAL M. Gut bacteria and hydrogen sulfide: the new old players in circulatory system homeostasis[J]. Molecules (Basel, Switzerland), 2016, 21(11): 1558.

[46] XIE LP, GU Y, WEN ML, ZHAO S, WANG W, MA Y, MENG GL, HAN Y, WANG YH, LIU G, MOORE PK, WANG X, WANG H, ZHANG ZR, YU Y, FERRO A, HUANG ZR, JI Y. Hydrogen sulfide induces Keap1 S-sulfhydration and suppresses diabetes-accelerated atherosclerosis via Nrf2 activation[J]. Diabetes, 2016, 65(10): 3171-3184.

[47] LIU YY, LIU JY, LI X, WANG FT, XU X, WANG CL. Exogenous H_2S prevents high glucose-induced damage to osteoblasts through regulation of KATP channels[J]. Biochimie, 2017, 137: 151-157.

[48] LU MM, LI H, LIU WL, ZHANG XM, LI LL, ZHOU HL. Curcumin attenuates renal interstitial fibrosis by regulating autophagy and retaining mitochondrial

function in unilateral ureteral obstruction rats[J]. Basic & Clinical Pharmacology & Toxicology, 2021, 128(4): 594-604.

[49] 黄雯, 李晓璐, 陈燊, 张红, 杨敏. 内源性 H_2S 对糖尿病肾病细胞外基质积聚的作用[J]. 首都医科大学学报, 2009, 30(2): 133-136.
HUANG W, LI XL, CHEN S, ZHANG H, YANG M. Role of endogenous H_2S in the accumulation of extracellular matrix of the diabetic nephropathy[J]. Journal of Capital Medical University, 2009, 30(2): 133-136 (in Chinese).

[50] ZHENG HX, QI SS, HE J, HU CY, HAN H, JIANG H, LI XS. Cyanidin-3-glucoside from black rice ameliorates diabetic nephropathy via reducing blood glucose, suppressing oxidative stress and inflammation, and regulating transforming growth factor β1/smad expression[J]. Journal of Agricultural and Food Chemistry, 2020, 68(15): 4399-4410.

[51] QI SS, HE J, DONG LC, YUAN LP, WU JL, ZU YX, ZHENG HX. Cyanidin-3-glucoside from black rice prevents renal dysfunction and renal fibrosis in streptozotocin-diabetic rats[J]. Journal of Functional Foods, 2020, 72: 104062.

[52] QI SS, SHAO ML, SUN Z, ZHENG HX. Salidroside from *Rhodiola rosea* L. attenuates diabetic nephropathy in STZ induced diabetic rats via anti-oxidative stress, anti-inflammation, and inhibiting TGF-β1/Smad pathway[J]. Journal of Functional Foods, 2021, 77: 104329.

[53] ZHAO J, ZHANG QL, SHEN JH, WANG K, LIU J. Magnesium lithospermate B improves the gut microbiome and bile acid metabolic profiles in a mouse model of diabetic nephropathy[J]. Acta Pharmacologica Sinica, 2019, 40(4): 507-513.

[54] YANG JL, DONG HB, WANG Y, ZHANG WN, LU YM, CHEN Y, CHEN L. *Cordyceps cicadae* polysaccharides ameliorated renal interstitial fibrosis in diabetic nephropathy rats by repressing inflammation and modulating gut microbiota dysbiosis[J]. International Journal of Biological Macromolecules, 2020, 163: 442-456.

[55] YANG R, LI YD, MEHMOOD S, YAN CC, HUANG YZ, CAI JJ, JI JQ, PAN WJ, ZHANG WN, CHEN Y. Polysaccharides from *Armillariella tabescens* mycelia ameliorate renal damage in type 2 diabetic mice[J]. International Journal of Biological Macromolecules, 2020, 162: 1682-1691.

[56] FENG YC, WENG HB, LING LJ, ZENG T, ZHANG YY, CHEN DF, LI H. Modulating the gut microbiota and inflammation is involved in the effect of *Bupleurum* polysaccharides against diabetic nephropathy in mice[J]. International Journal of Biological Macromolecules, 2019, 132: 1001-1011.

[57] CHEN Q, REN DW, WU JQ, YU HY, CHEN XP, WANG J, ZHANG Y, LIU MY, WANG T. Shenyan Kangfu tablet alleviates diabetic kidney disease through attenuating inflammation and modulating the gut microbiota[J]. Journal of Natural Medicines, 2021, 75(1): 84-98.

[58] 王晓丽, 李春霞, 陈倩, 王佳, 王涛, 陈晓鹏. 肾炎康复片对糖尿病肾病小鼠粪便中短链脂肪酸的调节作用[J]. 天津中医药, 2021, 38(10): 1324-1329.
WANG XL, LI CX, CHEN Q, WANG J, WANG T, CHEN XP. Regulatory effect of Shenyan Kangfu Tablet on short-chain fatty acids in feces of diabetic nephropathy mice[J]. Tianjin Journal of Traditional Chinese Medicine, 2021, 38(10): 1324-1329 (in Chinese).

[59] ZHAO TT, ZHANG HJ, YIN XB, ZHAO HL, MA L, YAN MH, PENG L, WANG Q, DONG X, LI P. Tangshen formula modulates gut microbiota and reduces gut-derived toxins in diabetic nephropathy rats[J]. Biomedicine & Pharmacotherapy, 2020, 129: 110325.

[60] 黄媛媛, 陈华国, 谢文, 唐婷, 赵超, 龚小见, 周欣. 多糖与肠道菌群相互作用及其构效关系研究进展[J]. 微生物学通报, 2022, 49(6): 2325-2346.
HUANG YY, CHEN HG, XIE W, TANG T, ZHAO C, GONG XJ, ZHOU X. Interaction between polysaccharide and intestinal flora and its structure-effect relationship: a review[J]. Microbiology China, 2022, 49(6): 2325-2346 (in Chinese).

[61] LI HY, ZHOU DD, GAN RY, HUANG SY, ZHAO CN, SHANG A, XU XY, LI HB. Effects and mechanisms of probiotics, prebiotics, synbiotics, and postbiotics on metabolic diseases targeting gut microbiota: a narrative review[J]. Nutrients, 2021, 13(9): 3211.

[62] WANG JJ, TANG H, ZHANG CH, ZHAO YF, DERRIEN M, ROCHER E, VAN-HYLCKAMA VLIEG JE, STRISSEL K, ZHAO LP, OBIN M, SHEN J. Modulation of gut microbiota during probiotic-mediated attenuation of metabolic syndrome in high fat diet-fed

mice[J]. The ISME Journal, 2015, 9(1): 1-15.

[63] HSIEH MC, TSAI WH, JHENG YP, SU SL, WANG SY, LIN CC, CHEN YH, CHANG WW. The beneficial effects of *Lactobacillus reuteri* ADR-1 or ADR-3 consumption on type 2 diabetes mellitus: a randomized, double-blinded, placebo-controlled trial[J]. Scientific Reports, 2018, 8: 16791.

[64] DAO MC, EVERARD A, ARON-WISNEWSKY J, SOKOLOVSKA N, PRIFTI E, VERGER EO, KAYSER BD, LEVENEZ F, CHILLOUX J, HOYLES L, CONSORTIUM MO, DUMAS ME, RIZKALLA SW, DORÉ J, CANI PD, CLÉMENT K. *Akkermansia muciniphila* and improved metabolic health during a dietary intervention in obesity: relationship with gut microbiome richness and ecology[J]. Gut, 2016, 65(3): 426-436.

[65] XIE J, SONG W, LIANG XC, ZHANG Q, SHI Y, LIU W, SHI XH. Protective effect of quercetin on streptozotocin-induced diabetic peripheral neuropathy rats through modulating gut microbiota and reactive oxygen species level[J]. Biomedicine & Pharmacotherapy, 2020, 127: 110147.

[66] NIVET C, DUHALDE V, BEAURAIN M, DELOBEL P, QUELVEN I, ALRIC L. Fecal microbiota transplantation for refractory *Clostridioides* difficile infection is effective and well tolerated even in very old subjects: a real-life study[J]. The Journal of Nutrition, Health & Aging, 2022, 26(3): 290-296.

[67] XIAO Y, ZHONG XS, LIU XW, LI QJ. Therapeutic evaluation of fecal microbiota transplantation in an interleukin 10-deficient mouse model[J]. Journal of Visualized Experiments, 2022(182): e63350.

[68] BASTOS RMC, SIMPLÍCIO-FILHO A, SÁVIO-SILVA C, OLIVEIRA LFV, CRUZ GNF, SOUSA EH, NORONHA IL, MANGUEIRA CLP, QUAGLIERINI-RIBEIRO H, JOSEFI-ROCHA GR, RANGEL ÉB. Fecal microbiota transplant in a pre-clinical model of type 2 diabetes mellitus, obesity and diabetic kidney disease[J]. International Journal of Molecular Sciences, 2022, 23(7): 3842.

[69] CAI TT, YE XL, LI RR, CHEN H, WANG YY, YONG HJ, PAN ML, LU W, TANG Y, MIAO H, SNIJDERS AM, MAO JH, LIU XY, LU YB, DING DF. Resveratrol modulates the gut microbiota and inflammation to protect against diabetic nephropathy in mice[J]. Frontiers in Pharmacology, 2020, 11: 1249.