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Review 综 述

中药活性成分通过调控肠道菌群改善 2 型糖尿病的作用研究进展

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摘　要：2 型糖尿病(type 2 diabetes mellitus, T2DM)是慢性代谢疾病之一，因高患病率成为当今全球性公共健康难题。肠道菌群在 T2DM 的发生和发展中发挥重要作用，通过调节肠道菌群治疗 T2DM 已经成为当前研究的焦点。近年来，已有研究表明中药在改善 T2DM 的同时使肠道菌群发生变化，但中药是否通过调控肠道菌群发挥药理作用尚不明确。中药富含的多种活性成分是中药发挥药理作用的关键。因此，本文系统总结了中药多糖类、生物碱类、黄酮类、皂苷类及其他类活性成分调节肠道菌群干预 T2DM 的研究进展，旨在为中药预防和治疗 T2DM 作用提供更充分的理论依据，这对加速中药现代化具有重要意义。

关键词：2 型糖尿病；肠道菌群；中药活性成分；调控；药理作用

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Research progress in the role of active components of traditional Chinese medicine in ameliorating type 2 diabetes mellitus by regulating gut microbiota

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Abstract: Type 2 diabetes mellitus (T2DM) stands as a chronic metabolic disorder posing a challenge to global public health, owing to its widespread prevalence. The intricate interplay between gut microbiota and the onset and progression of T2DM, along with the potential therapeutic benefits of modulating gut microbiota, has emerged as a focal point in contemporary research. Recent studies have underscored the capacity of traditional Chinese medicine to ameliorate T2DM by inducing alterations in gut microbiota. Nevertheless, the precise mechanisms underlying the pharmacological actions of traditional Chinese medicine *via* gut microbiota regulation remain elusive. The diverse bioactive compounds in traditional Chinese medicine play pivotal roles in eliciting its pharmacological effects. This article systematically reviews the advancements in the research concerning the modulation of gut microbiota for T2DM intervention by a spectrum of bioactive components in traditional Chinese medicine, encompassing polysaccharides, alkaloids, flavonoids, saponins, and other compounds. The objective of this review is to furnish a comprehensive theoretical framework supporting the preventive and therapeutic potential of traditional Chinese medicine in T2DM management, thereby significantly contributing to the modernization of traditional Chinese medicine.

Keywords: type 2 diabetes mellitus (T2DM); gut microbiota; active components of traditional Chinese medicine; regulation; pharmacological effects

糖尿病是以高血糖为标志的慢性疾病，截至2021年，全球患糖尿病人数达到5.366亿，预计到2045年将增至7.832亿[1]。糖尿病主要包括1型糖尿病(type 1 diabetes mellitus, T1DM)、2型糖尿病(type 2 diabetes mellitus, T2DM)和妊娠期糖尿病(gestational diabetes mellitus, GDM)，其中T2DM最常见，约占糖尿病人群比例的90%−95%[2]。在《黄帝内经》中，T2DM属于“消渴”范畴，中医理论将多味中药配伍组成的中药方剂用于治疗消渴，这些方剂一直被沿用至今[3]。常见的消渴方、玉女煎在临床试验中能改善T2DM患者血糖，其疗效优于注射胰岛素和口服二甲双胍[4-6]。在临床上，常见的T2DM治疗药物包括胰岛素促分泌剂(如磺脲类)、胰岛素增敏剂(如双胍类、格列酮类)和葡萄糖苷酶抑制剂(如阿卡波糖、伏格列波糖)，这些药物不仅价格高昂，而且

易造成不良反应和耐药性，这些问题亟待解决[7]。相比之下，中药价格低廉、安全性好，有望为T2DM新药开发提供新的来源。因此，探索中药改善 T2DM 的作用机制对推动糖尿病治疗的新方法和开发糖尿病治疗新药具有重要意义。

流行病学研究表明，与正常人相比，T2DM患者的肠道菌群结构不仅发生显著变化[8-9]，而且这种变化与 T2DM 胰岛素分泌不足、胰岛素抵抗、低度炎症等发病机制存在相关性[10-13]。肠道菌群对 T2DM 的影响已成为当前研究领域的热点。肠道菌群的结构和多样性的改变能直接或间接影响肠道菌群分泌的功能分子和代谢产物水平，如短链脂肪酸(short-chain fatty acid, SCFA)、脂多糖(lipopolysaccharide, LPS)、胆汁酸(bile acid, BA)和支链氨基酸(branched-chain amino acids, BCAAs)等[14-16]。因此，探究如何调节肠道菌群组成和恢复肠道菌群代谢物水平对改善 T2DM 具有至关重要的意义。

中药活性成分是中药发挥药理作用的关键物质，研究发现中药活性成分可改变 T2DM 患者肠道菌群丰度和种类，恢复肠道屏障功能，并间接影响肠菌代谢产物的产生[17-18]。因此，中药活性成分改善 T2DM 的作用与中药调控肠道菌群之间存在一定相关性，但仍有大部分活性成分的作用机制尚不明确，亟须探索。因此本文主要总结了 T2DM 人群肠道微生物群的特征、中药活性成分对肠道菌群的调节作用以及中药活性成分协同肠道菌群改善 T2DM 的效应，这或许能为未来中药活性成分-肠道菌群-T2DM 的防治策略提供理论依据。

1 T2DM 的肠道菌群特征

元基因组研究显示，成人肠道的大部分微生物群属于 5 个门，分别是厚壁菌门(*Firmicutes*)、拟杆菌门(*Bacteroidetes*)、变形菌门(*Proteobacteria*)、放线菌门(*Actinobacteria*)和梭杆菌门(*Fusobacteria*)，其中约 90%的细菌种类属于 *Firmicutes* 和 *Bacteroidetes*[19]。早在2010年就有研究提出患T2DM的人群肠道菌群与正常人群在门水平上存在显著差异[20]。通过对 T2DM 患者肠道菌群分析发现，与正常人相比，T2DM 患者肠道菌群多样性降低，并且 T2DM 的发生与 *Firmicutes*/*Bacteroidetes* 比率升高有关[21]。总结发现，T2DM 肠道菌群结构变化集中在 *Firmicutes*、*Bacteroidetes*、*Proteobacteria*、*Actinobacteria*、*Fusobacteria* 和疣微菌门(*Verrucomicrobia*)。如表 1 所示，T2DM 人群 *Firmicutes* 门中殊异韦荣氏球菌(*Veillonella dispar*)、丁酸梭菌(*Clostridium butyricum*)、栖粪杆菌属(*Faecalibacterium*)、罗斯拜瑞氏菌属(*Roseburia*)、戴阿利斯特菌属(*Dialister*)和韦氏布劳特氏菌(*Blautia wexlerae*)等菌属丰度降低，而 *Firmicutes* 菌门的韦荣氏球菌属(*Veillonella*)、乳杆菌属(*Lactobacillus*)、链球菌属(*Streptococcus*)、人罗斯拜瑞氏菌(*Roseburia hominis*)、黏液真杆菌(*Eubacterium limosum*)、坏齿韦荣氏球菌(*Veillonella denticariosi*)、布劳特氏菌属(*Blautia*)、瘤胃球菌属(*Ruminococcus*)等菌属的丰度升高[22-28]。*Bacteroidetes* 门中辨野氏卟啉单胞菌(*Porphyromonas bennonis*)、普雷沃氏菌属(*Prevotella*)、普通拟杆菌(*Bacteroides vulgatus*)、啮齿拟杆菌(*Bacteroides rodentium*)等菌的丰度显著升高，而别样杆菌属(*Alistipes*)、拟杆菌属(*Bacteroides*)菌属丰度降低[22-24,26,29-30]。*Actinobacteria* 门中双歧杆菌(*Bifidobacterium*)和 *Verrucomicrobia* 门中阿克曼氏菌(*Akkermansia*)有益菌减少[22,24,26]。*Proteobacteria* 门中变化主要为埃希氏菌属(*Escherichia*)、志贺氏菌属(*Shigella*)和幽门螺杆菌(*Helicobacter pylori*)等

表 1　2 型糖尿病患者的肠道菌群特征

Table 1　Characterization of gut microbiota in type 2 diabetes mellitus patients

Types of phylum	Microbiota with increased abundance in T2DM	Microbiota with decreased abundance in T2DM
Firmicutes	*Roseburia hominis*[22], *Eubacterium*[23], *Peptostreptococcus*[23], *Veillonella denticariosi*[24], *Blautia*[24], *Ruminococcus*[24], *Eubacterium limosum*[25], *Veillonella*[26], *Lactobacillus*[26], *Streptococcus*[26]	*Coprobacillus* unclassified[22], *Veillonella dispar*[22], *Clostridium butyricum*[23], *Faecalibacterium*[24], *Enterococcus faecium*[25], *Blautia lineages*[25], *Roseburia*[24,26], *Dialister*[26], *Flavonifractor*[26], *Faecalibacterium prausnitzii*[26], *Clostridium sensu stricto1*[27], *Blautia wexlerae*[28]
Bacteroidetes	*Porphyromonas bennonis*[22], *Paraprevotella* unclassified[22], *Prevotella copri*[29], *Bacteroides vulgatus*[29], *Bacteroides rodentium*[29], *Bacteroides xylanisolvens*[29], *Prevotella*[30]	*Bacteroides*[24], *Alistipes*[26]
Proteobacteria	*Desulfovibrio piger*[23], *Escherichia*[26-27], *Shigella*[26-27], *Enterobacteriaceae*[27], *Helicobacter pylori*[31]	*Haemophilus*[26]
Actinobacteria	*Collinsella*[26]	*Bifidobacterium longum*[22], *Bifidobacterium*[24]
Verrucomicrobiota	–	*Akkermansia*[24], *Akkermansia muciniphila*[26]
Fusobacteria	*Fusobacterium*[24]	–

– indicates no record.

致病菌增加[23,26-27,31]。以上研究表明，T2DM 肠道菌群特征表现为菌群组成改变，其中有益菌比例减少而致病菌比例增多。

T2DM 患者肠道菌群的分布特点吸引了大量研究关注，尤其是肠菌分泌的功能分子和代谢物对 T2DM 的作用进行的研究。肠道内有益菌 *Akkermansia muciniphila* 不仅能分泌外囊泡和蛋白质 Amuc_1100 来改善胰岛素抵抗和肠道屏障功能，还能促进 SCFA 的产生来促进胰岛素分泌[32-35]。SCFA 是由肠道菌群将膳食纤维、抗酶解淀粉分解产生的代谢产物之一，SCFA 在体内能增加糖原合成及 SCFA 可能通过胰高血糖素样肽 1 (glucagon-like peptide-1, GLP-1)介导的胰岛素分泌增加来调节血糖浓度[36]。*Bifidobacterium* 属中 *Bifidobacterium longum*、短双歧杆菌(*Bifidobacterium breve*)、青春双歧杆菌(*Bifidobacterium adolescentis*)能促进 SCFA 产生、增强胰岛素敏感性、减少肝脂肪变性、促进肝糖原合成，同时恢复 T2DM 肠道菌群稳态[37-41]。丁酸盐作为 SCFA 之一，能抑制肝脏组蛋白去乙酰化酶(histone deacetylase, HDAC)活性和促进胰岛素受体底物-1 的过度乙酰化，从而改善减少糖异生和胰岛素抵抗[42]。*Faecalibacterium prausnitzii* 是主要的丁酸盐产生菌之一，其代谢产生的微生物抗炎分子和胞外囊泡可以通过调节紧密连接蛋白的表达来恢复 T2DM 的肠道屏障结构和功能[43-44]。研究指出体内高 BCAAs 水平与 T2DM 患病率和胰岛素抵抗有关，*Prevotella copri* 能参与 BCAAs 的生物合成[45-47]。迪氏副拟杆菌(*Parabacteroides distasonis*)产生的代谢物烟酸是一种重要的生物活性分子，它通过激活肠道 G 蛋白偶联受体 109a (G protein coupled receptor, GPR109a)来增强肠道屏障功能，从而改善 T2DM 的胰岛素抵抗[13]。此外，*Parabacteroides distasonis* 的另一种代谢物吲哚丙烯酸，可激活芳烃受体(aryl hydrocarbon receptor, AhR)信号通路，增加白细胞介素-22 (interleukin-22, IL-22)的表达水平和

增强肠道屏障相关蛋白的表达，从而减少肠道菌群紊乱引起的炎症，最终改善胰岛素抵抗[48]。*Blautia wexlerae* 能调节氨基酸相关代谢和碳水化合物代谢，从而改善肥胖诱导的 T2DM 小鼠脂肪堆积、胰岛素抵抗、葡萄糖耐量受损指标[28]。细菌 LPS 又称内毒素，存在于革兰氏阴性细菌的外膜中[49]。研究发现 LPS 能通过激活 Toll 样受体和诱发炎症，从而促进胰岛素抵抗[50-51]。作为已知的产 LPS 菌，*Helicobacter pylori* 在 T2DM 患者中增加可能会通过增加 LPS 加重宿主病情[52-53]。

2 中药活性成分调控肠道菌群改善 T2DM 的作用进展

中药或中药方剂由于成分复杂、作用机制不明确，在 T2DM 药物开发中受到限制。中药活性成分是中药的特征成分，不仅能用于鉴定药材品质好坏，还是中药发挥药理作用的关键[54]。目前已知的具有改善 T2DM 的中药活性成分包括多糖类、生物碱、黄酮类、皂苷类和萜类，它们能降低血糖水平、增加胰岛素敏感性和降低炎症水平[55-56]。如表 2 所示，这些成分会引起肠道

表 2 中药活性成分调控肠道菌群改善 2 型糖尿病及主要作用机制

Table 2 Active ingredients of traditional Chinese medicine (TCM) regulate gut microbiota to improve type 2 diabetes mellitus and their main mechanism

Active components of TCM	Subject investigated	Administration route and dosage	Changes in gut microbiota	Main mechanism
Ganoderma lucidum polysaccharides[57]	Male Sprague-Dawley (SD) rats (HFD+STZ)	400 mg/(kg·d), ig;	*Blautia*, *Dehalobacterium*, *Parabacteroides*, *Bacteroides*↑; *Aerococcus*, *Ruminococcus*, *Corynebactrium*, *Proteus*↓	Restoring amino acid metabolism, carbohydrate metabolism, inflammatory levels, and nucleic acid metabolism in the body
Polygonatum rhizoma polysaccharide[58]	Male db/db mice	1.0 g/(kg·d), ig	*Turicibacter*, *Ruminococcus*↑; *Lachnospiraceae*, *Romboutsia*↓	Regulating the expression of genes involved in liver glucose storage and utilization, and promoting hepatic glycogen formation
Astragalus membranaceus polysaccharides[59-60]	Male C57BL/6J mice (HFD+STZ); Male db/db mice	400 mg/(kg·d) and 600 mg/(kg·d), ig	*Akkermansia*, *Faecalibaculum*, *Bifidobacterium*, *Romboutsia*, *Allobaculum*, *Lactobacillus*, *Prevotellaceae*_UCG-001, *Oscillospiraceae*_UCG-005↑; *Escherichia*, *Shigella*, *Odoribacter*, *Lachnoclostridium*, *Lachnospiraceae*_UCG-006, *Lachnospiraceae*_A2↓	Promoting SCFA production to activate G protein-coupled receptors 41/43 (GPCR41/43), thereby indirectly stimulating GLP-1 secretion and restoring intestinal barrier function
Lycium barbarum Polysaccharide[61-63]	Male C57BL/6J mice (HFD+STZ)	50 mg/(kg·d), 100 mg/(kg·d) and 200 mg/(kg·d), ig	*Bacteroides*, *Ruminococcaceae*_UCG-014, *Intestinimonas*, *Mucispirillum*, *Ruminococcaceae*_UCG-009, *Allobaculum*↑; *Dubosiella*, *Romboutsia*↓	Promoting the production of SCFA to stimulate peptide YY (PYY) and GLP-1 secretion, enhancing the activity of catalase (CAT), superoxide dismutase (SOD), and glutathione peroxidase (GSH-Px), and mitigating inflammation

(待续)

(续表 2)

Active components of TCM	Subject investigated	Administration route and dosage	Changes in gut microbiota	Main mechanism
Coix seed polysaccharides[64-65]	ICR male mice (HFD+STZ)	24 mg/(kg·d), ig	*Lactobacillus*, *Akkermansia*, *Bacteroides*, *Bifidobacterium*↑	Activating the IGF1/PI3K/AKT signaling pathway to decrease blood glucose levels, elevating SCFA levels, and increasing the expression of tight junction proteins for intestinal barrier repair
Cordyceps militaris polysaccharide[66]	Male C57BL/6J mice (HFD+STZ)	400 mg/(kg·d), ig	*Allobaculum*, *Alistipes*, *Lachnospiraceae*_NK4A136_ group, *Muribaculaceae*↑; *Enterococcus*, *Ruminococcus*_ torques_group↓	Inhibiting the TLR4/NF-κB pathway and enhancing the expression of intestinal tight junction proteins
Dendrobium officinale polysaccharide[67-68]	Male C57BL/6J mice (HFD+STZ)	200 mg/(kg·d), ig	*Parabacteroides distasonis*, *Parabacteroides*, *Ruminococcus*, *Dorea*, *Allobaculum*, *Bifidobacterium*, *Lactobacillus*↑; *Helicobacter pylori*↓	Activating intestinal GPR109a and indirectly upregulating the expression of tight junction proteins through the LPS/TLR4/TRIF/NF-κB axis to repair the intestinal barrier
Fructus mori polysaccharide[69]	Male C57BL/6J mice (HFD+STZ)	600 mg/(kg·d), ig	*Allobaculum*, *Bifidobacterium*↑; *Escherichia*, *Shigella*↓	Suppressing the activation of the TLR4/MyD88/NF-κB pathway to alleviate intestinal inflammation and oxidative stress levels, thereby indirectly promoting the expression of tight junction proteins for intestinal barrier restoration
Berberine[54,70-73]	Male SD rats (HFD+STZ); Male GK rats; Male Zucker Diabetic Fatty (ZDF) rats	100 mg/(kg·d) and 200 mg/(kg·d), ig	*Faecalibacterium*, *Roseburia*, *Clostridium*, *Clostridium* XIVa, *Ruminococcus* 2, *Dorea*, *Parabacteroides*, *Paraprevotella*, *Butyricimonas*, *Alistipes*, *Gemmiger*, *Butyricicoccus*, *Coprococcus*, *Bacteroides*, *Oscillospira*, *Akkermansia*, *Aggregatibacter*, *Eubacterium*↑; *Helicobacter pylori*, *Prevotella copri*↓	Promoting the production of SCFA to activate the bile acid receptor Takeda G protein-coupled receptor 5 (TGR5) and stimulating the secretion of GLP1/2, while concurrently suppressing lipopolysaccharide (LPS) production and inflammation
1-deoxynojirimycin[74,75]	Male C57BL/6J mice (HFD+STZ)	20 mg/(kg·d), ig	*Akkermansia*, *Bifidobacterium*, *Lactobacillus*↑; *Enterococcaceae*, *Lachnospiraceae*↓	Inhibiting the expression of suppressor of cytokine signaling 3 (SOCS3) and the activity of the TLR4/NF-κB signaling pathway, while also enhancing the expression of claudin and the ratio of phosphorylated insulin receptor substrate 1 (p-IRS1) to IRS1

(待续)

(续表 2)

Active components of TCM	Subject investigated	Administration route and dosage	Changes in gut microbiota	Main mechanism
Myricetin[76]	Male C57BL/6J mice (HFD+STZ)	75 mg/(kg·d), ig	*Alistipes*, *Lachnospiraceae* UCG-006, *Odoribacter*, *Alloprevotella*, *Bacteroidales* S24-7, *Bacteroides*, *Delftia*, *Faecalibaculum*, *Lachnospiraceae*_NK4A136 group, *Ruminiclostridium* 9↑; *Corynebacterium* 1, *Erysipelotrichaceae*_ uncultured, *Lactobacillus*↓	Elevating the levels of superoxide dismutase (SOD)
Luteolin[77]	Male Kunming mice (HFD+STZ)	100 mg/(kg·d), ig	*Lactobacillus*, *Alloprevotella*, *Alistipes*, *Bacteroides*, *Ruminiclostridium*, *Brevundimonas*, *Pseudomonas*↑	Regulating aberrant glucose metabolism *via* the peroxisome proliferator-activated receptor (PPAR) signaling pathway
licochalcone A[78]	Male C57BL/6J mice (HFD+STZ)	35 mg/(kg·d), ig	*Bifidobacterium*, *Turicibacter*, *Blautia*, *Faecococcus*↑; *Enterococcus*, *Dorea*, *Arachnococcus*↓	–
Pelargonidin-3-*O*-glucoside[79]	Male db/db mice	150 mg/(kg·d), ig	*Bacteroidales*, *Prevotella*↑; *Firmicutes*↓	Enhancing SCFA levels and safeguarding intestinal barrier integrity
Lycium barbarum flavonoids[80]	Male C57BL/6J mice (HFD+STZ)	100 mg/(kg·d) and 200 mg/(kg·d), ig	*Bacteroidales*_S24−7_group, *Lachnospiraceae*, *Ruminococcaceae*, *Clostridiales*_vadinBB60_ group, *Allobaculum*, *Turicibacter*, *Coriobacteriaeceae*, *Enterococcus*↓	Enhancing overall organismal glucose and lipid metabolic functions
Epigallocatechin-3-Gallate[81]	Male db/db mice	100 mg/(kg·d), ig	*Lactobacillus gasseri*, *Lactobacillus intestinalis*, *Lactobacillus reuteri*, *Christensenellaceae*↑; *Enterobacteriaceae*, *Proteobacteria*↓	–
Polygonatum sibiricum saponin[82-83]	ICR male mice (HFD+STZ)	1.0, 1.5, and 2.0 g/(kg·d), ig	*Lactobacillus*, *Lachnospiraceae*_NK4A136 _group, *Intestinimonas*, *Bifidobacterium*↑; *Firmicutes*, *Enterococcus*, *Enterobacteriaceae*, *Clostridium perfringens*↓	Regulating both carbohydrate and amino acid metabolism
Ginsenoside compound K[84-85]	Male db/db mice diabetic patients and healthy subjects	40 mg/(kg·d), ig	*Lactobacillaceae*, *Akkermansiaceae*, *Lachnospirace*, *Ruminococcaceae*, *Alistipes*, *Parabacteroides*↑; *Bacteroidaceae*, *Enterococcaceae*↓	Activating the gut microbiota-bile acid-TGR5 pathway to enhance GLP-1 secretion

(待续)

(续表 2)

Active components of TCM	Subject investigated	Administration route and dosage	Changes in gut microbiota	Main mechanism
Ginsenoside Rb1[86]	Male KKAy rats (HFD)	200 mg/(kg·d), ig	*Bacteroides*, *Parasutterella*, *Marvinbryantia*, *Erysipelatoclostridium*↑; *Firmicutes*/*Bacteroidetes*, *Helicobacter*, *Alistipes*, *Prevotellaceae*_unclassified, *Odoribacter*, *Roseburia*, *Mucispirillum*, *Coprococcus*, *Anaeroplasma*↓	Reducing the levels of metabolites such as alpha-linolenic acid, oleic acid, arachidonic acid, palmitic acid, stearic acid, and others
Ginsenoside Rd[87]	Male SD rats (HFD+STZ)	300 mg/(kg·d), ig	*Enterococcus*, *SMB*53, *rc*4-4, *Turicibacters*, *Ruminococcus*↑; *Lactobacillus helveticus*, *Clostridium celatum*↓	Activating the Akt pathway to enhance glycogen synthesis and suppress hepatic gluconeogenesis
Ginsenoside Rg1[88]	Male SD rats (HFD+STZ)	100 mg/(kg·d), ig	*Lachnospiraceae*_NK4A136_ group, *Lachnoclostridium*↑; *Lactobacillus*↓	–
Ginsenoside Rg5[89]	Male db/db mice	90 mg/(kg·d), ig	*Bacteroidales*↑; *Firmicutes*, *Proteobacteria*↓	Restoring the intestinal barrier and reducing systemic levels of LPS
Ginsenoside T19[90]	Male C57BL/6J mice (HFD+STZ)	30 mg/(kg·d) and 60 mg/(kg·d), ig	*Probacillus*, *Streptococcus*, *Lactobacillus*, *Ruminococcus*, *Anaerotruncus*, *Roseburia*, *Coprococcus*, *Lachnospiraceae*↑; *Firmicutes*/*Bacteroidetes*↓	Activating the AMP-activated protein kinase (AMPK) and phosphoinositide 3-kinase (PI3K) signaling pathways
Astragalus saponins[91]	Male SD rats (HFD+STZ)	80 mg/(kg·d), ig	*Bifidobacterium*, *Ruminococcaceae*_UCG-014↑; *Lactobacillus*, *Turicibacter*↓	Elevating the expression levels of hepatic IRS-1, PI3K, PDK1, and phosphorylated AKT (p-AKT), while diminishing the protein expression levels of phosphorylated glycogen synthase kinase 3 beta (p-GSK-3β), thereby ameliorating glucose and lipid metabolism associated with T2DM and insulin resistance
Astragaloside IV[92]	Male Kunming mice (HFSD+STZ)	25, 50, and 100 mg/(kg·d), ig	*Anaerobacter*, *Romboutsia*, *Alkalibacteria*, *Canadidatus stoquefichus*, *Oligobacterium*, *Brautella*, *Erysipelatoclostridum*↑; *Bacteroides*, *Oscillibacter*, *Parabacteroides*, *Roseburia*, *Muribaculum*↓	Elevating butyrate levels and activating the PI3K/Akt signaling pathway to diminish hepatic gluconeogenesis and glycogenolysis, while enhancing glycogen synthesis and fatty acid synthesis

(待续)

(续表 2)

Active components of TCM	Subject investigated	Administration route and dosage	Changes in gut microbiota	Main mechanism
Andrographolide[93]	Male db/db mice	150 mg/(kg·d), ig	*Akkermansia*, *Prevotella*, *Adlercreutzia*↑; *Odoribacter*, *Alistipes*, *Dehalobacterium*, *Defluviitalae*, *Oscillospira*, *Parabacteroides*↓	Restoring the intestinal barrier and lowering systemic levels of LPS
Curcumin[94]	Male SD rats (HFD+STZ)	200 mg/(kg·d), ig	*Bacteroidea*, *Bifidobacterium*↑; *Firmicutes*, *Enterobacterales*↓	Increasing Occludin and ZO-1 expression levels to preserve intestinal barrier integrity, thereby reducing LPS production and ameliorating insulin resistance

HFD: High fat die; HFSD: High fat/high sugar diet; STZ: Streptozotocin; ig: Intragastric gavage; − indicates no record; ↑ indicates increase; ↓ indicates decrease.

微生物变化、增加有益菌和减少有害菌，所以肠道菌群在中药活性成分改善 T2DM 中发挥的作用值得探索。

2.1 多糖类

多项动物试验表明，中药多糖作为肠道菌群的营养源，可促进有益菌的生长、抑制有害菌的生长和改变肠道菌群组成。如灵芝多糖能上调 T2DM 大鼠肠道副拟杆菌属(*Parabacteroides*)和拟杆菌属(*Bacteroides*)丰度，下调 *Ruminococcus* 和 *Corynebactrium* 丰度，并调节宿主-微生物共代谢，以改善 T2DM[57]。Chen 等[58]也发现黄精多糖能调节 db/db 小鼠肝脏中有关葡萄糖代谢基因的表达，并下调肠道菌群丰富度至正常水平。多项动物试验揭示多糖对 T2DM 的积极影响与促进 SCFA 产生有关，同时还能抑制 LPS 的生成，修复肠道屏障受损，改善 T2DM 胰岛素抵抗。如黄芪多糖、枸杞多糖和薏苡仁多糖能上调 T2DM 小鼠肠道粪小杆菌属(*Faecalibaculum*)、别样棒菌属(*Allobaculum*)、*Akkermansia*、*Bifidobacterium* 和 *Lactobacillus* 等有益菌丰度，促进 SCFA 产生以间接促进 GLP-1 分泌和修复肠道屏障[59-65]；而冬虫夏草多糖、铁皮石斛多糖和桑葚多糖能上调 T2DM 小鼠中 *Allobaculum*、*Alistipes*、*Bifidobacterium* 等有益菌，下调 *Helicobacter pylori*、*Escherichia* 和 *Shigella* 等致病菌的丰度，并抑制 LPS/Toll 样受体 4 (Toll-like receptor 4, TLR4)/核转录因子 (nuclear transcription factor, NF-κB)途径间接改善胰岛素抵抗和修复肠道屏障[66-69]。中药多糖对 T2DM 的改善作用与肠道菌群密切相关。铁皮石斛多糖和桑葚多糖能显著降低 T2DM 小鼠血糖水平，而干预伪无菌 T2DM 小鼠时，几乎无治疗效果，这表明肠道菌群是二者改善 T2DM 中重要的参与者[68-69]。因此，肠道菌群的存在对中药多糖的干预效果起着重要的调节作用，这一发现为中药多糖在治疗 T2DM 方面的应用提供了更加科学的依据。

2.2 生物碱类

小檗碱、1-脱氧野尻霉素是具有改善 T2DM 活性的代表性生物碱类成分，均能调节肠道菌群结构和修复肠道屏障。曾有研究发现，小檗碱对伪无菌 T2DM 小鼠的治疗效果弱于普通 T2DM 小鼠，这个结果揭示肠道菌群是小檗碱发挥药理作用的重要部位[70-71]。研究发现小檗碱能增加 T2DM 大鼠体中丁酸盐水平、降低 LPS 水平、改善肠道炎症并保护肠道屏障，这与肠道中 *Helicobacter pylori*、*Prevotella copri* 等产 LPS 致病菌丰度降低，*Roseburia*、*Akkermansia* 和

Bifidobacterium 产丁酸菌丰度增加有关[54,72]。此外，小檗碱促进次级胆汁酸产生，增加 *Bacteroides* 和颤螺菌属(*Oscillospira*)丰度，并激活结肠 L 细胞 G 蛋白偶联胆汁酸受体 5 (takeda G protein-coupled receptor 5, TGR5)受体以促进 GLP-1/2 的分泌[73]。1-脱氧野尻霉素是桑叶、桑白皮的主要成分，可增加 T2DM 小鼠中 *Akkermansia*、*Bifidobacterium* 和 *Lactobacillus* 等有益菌的丰度，降低肠球菌科(*Enterococcaceae*)和毛螺菌科(*Lachnospiraceae*)的丰度[74-75]。

2.3 黄酮类

黄酮类化合物是中药中广泛存在的一类物质且对肠道菌群具有调控作用，如杨梅素、木犀草素可增加有益菌丰度，降低致病菌丰度，从而降低血糖水平并抑制 T2DM 小鼠的炎症反应[76-77]。甘草的黄酮类成分之一甘草查尔酮 A 可降低 T2DM 小鼠胰岛素抵抗指数以及血糖和血脂水平，这可能与促进 *Bifidobacterium*、*Turicibacter*、*Blautia* 和 *Faecococcus* 等有益菌生长，抑制 *Enterococcus*、*Arachnococcus* 等有害菌生长有关[78]。覆盆子中的天竺葵素-3-*O*-葡萄糖苷具有改善 T2DM 作用，并显著上调 *Bacteroidales* 丰度，降低 *Firmicutes* 门丰度，促进 SCFA 产生并增强肠道屏障的完整性[79]。枸杞总黄酮可降低 T2DM 小鼠肠道中瘤胃球菌科(*Ruminococcaceae*)、苏黎世杆菌属(*Turicibacter*)、*Lachnospiraceae*、*Allobaculum* 和 *Enterococcus* 的丰度以改善糖脂质代谢和抑制促炎因子的产生[80]。表没食子儿茶素没食子酸酯是广泛存在于自然界的黄酮类成分，其维持 T2DM 小鼠葡萄糖稳态的效应与肠道 *Lactobacillus* 丰度呈正相关[81]。

2.4 皂苷类

据报道，皂苷是治疗 T2DM 的有效生物活性化合物，调控肠道菌群和调节肠菌-宿主共代谢水平可能是其发挥作用的关键途径。黄精皂苷能调节 T2DM 小鼠碳水化合物和氨基酸代谢，增加肠道中 *Lactobacillus*、*Lachnospiraceae*_NK4A136_group 和鼠肠单胞菌属(*Intestinimonas*)的丰度[82-83]。目前已知，具有改善 T2DM 功效的人参皂苷中，人参皂苷 K、人参皂苷 Rb、人参皂苷 Rb1、人参皂苷 Rg1 和人参皂苷 Rg5 能调节肠道菌群[84-89]。人参皂苷 Rb1 能上调 T2DM 小鼠 *Bacteroides* 和副萨特氏菌属(*Parasutterella*)丰度，下调臭气杆菌属(*Odoribacter*)、粪球菌属(*Coprococcus*)和 *Helicobacter pylori* 等菌丰度，以及调节脂肪酸代谢，而对伪无菌 T2DM 小鼠的改善作用减弱[86]。人参皂苷 Rg5 能改善 T2DM 小鼠高血糖和恢复 T2DM 小鼠肠道菌群组成，但对于伪无菌 T2DM 小鼠，其对高血糖、内毒素血症、炎症的改善作用则会减弱[89]。这 2 项结果揭示人参皂苷 Rb1 和人参皂苷 Rg5 在一定程度上能通过调控肠道微生物群来改善 T2DM。人参皂苷 T19 能改善 T2DM 小鼠的肠道菌群紊乱情况，并提高 *Lachnospiraceae*、*Lactobacillus*、*Ruminococcus* 等菌属的相对丰度，其中 *Lachnospiraceae* 丰度与葡萄糖和脂质水平呈负相关[90]。此外，黄芪皂苷均能调节肠道微生物群落结构，并激活磷脂酰肌醇-3-激酶/蛋白激酶 B (phosphatidylinositol-3-kinase/protein kinase B, PI3K/Akt)信号通路以减少肝葡萄糖的产生和糖原分解，并增加糖原合成和脂肪酸合成，从而控制 T2DM 葡萄糖和脂质稳态[91]。

2.5 其他活性成分

其他类别的中药活性成分方面，萜类成分黄芪甲苷可以调节 T2DM 小鼠肠道菌群组成，例如增加厌氧杆菌属(*Anaerobacter*)、龙包茨氏菌属(*Romboutsia*)、*Alkalibacteria* 的丰度，降低 *Odoribacter*、*Parabacteroides*、*Roseburia* 和鼠杆状菌属(*Muribaculum*)的丰度[92]。穿心莲内酯是

穿心莲的特征萜类成分，能调节 T2DM 小鼠肠道微生物群组成，增加有益菌 *Akkermansia* 的丰度，以及增加 SCFA 水平[93]。姜黄素是存在于姜黄、莪术等植物中的二酮类化合物，可以修复糖尿病大鼠肠黏膜屏障、降低血清炎症因子水平、改善内毒素血症，并增加 *Bacteroidetes*/*Firmicutes* 比值和 *Bifidobacterium* 的丰度[94]。

3 中药活性成分与肠道有益菌联合改善 T2DM 的协同效应

现有研究发现，益生菌与抗糖尿病药物具有协同改善 T2DM 病理指标的作用[95]。T2DM 患者连续 16 周服用小檗碱联合 *Bifidobacterium* 后，空腹血糖和糖化血红蛋白水平降低，表明 *Bifidobacterium* 具有增强小檗碱降血糖作用的潜力[96]。芒果苷联合 *Lactobacillus reuteri* 1-12 使用可增加 *Lactobacillus acidophilus*、*Lactobacillus murinus* 等有益菌丰度，这与肠道中的自诱导因子-2 (autoinducer-2, AI-2)表达增加有关[97]。此外，甘草酸联合 *Lactobacillus* 能显著提高甘草酸在体内的口服生物利用度，从而增强甘草酸对 T2DM 的改善作用[98-99]。在 T2DM 患者肠道中有益菌往往减少，因此探索合适的益生菌与中药活性成分联合补充方案，对增强中药活性成分对 T2DM 的疗效具有重要意义。这些研究结果为中药与益生菌联合应用改善 T2DM 方面提供了更为科学的依据。

4 总结与展望

T2DM 的发生发展与肠道菌群之间有重要联系，因此从调节肠道菌群的角度出发对于防治 T2DM 具有重要意义。中药活性成分能调节肠道菌群结构，恢复菌群平衡，以达到改善 T2DM 的目的。同时，部分中药活性成分生物利用度低却仍能发挥一定的功效，这可能与肠道菌群代谢作用有关。因此靶向肠道菌群的中药给药方式可能会成为一个未来的研究热点。

然而，肠道菌群是一个复杂的、动态平衡的微生物群体，在体内的分布和生存状态受多种因素的影响，如饮食习惯、精神状态、生活环境。然而中药调节菌群紊乱防治糖尿病的相关研究尚存有空白和局限性。具体表现在以下方面：(1) 随着肠道菌群与 T2DM 关系研究的不断深入，肠道菌群研究开始转向多组学技术，如 16S rRNA 基因测序联合代谢组学、16S rRNA 基因测序联合蛋白组学等，而大量中药活性成分涉及肠道菌群运用多组学技术的研究仍然很少。(2) 中药活性成分多种多样，其对 T2DM 的调控作用可能与一些特异菌有关，而这些特异菌是否与中药活性成分干预 T2DM 作用有关还待确认。(3) 动物和人类的代谢系统之间存在各种差异，然而目前大量中药活性成分对 T2DM 的肠道微生物群和粪便代谢物的变化研究仍然局限在动物模型中，针对 T2DM 人群研究相对较少。(4) 大部分中药活性成分对 T2DM 肠道菌群的机制研究不够深入，仍局限在肠道局部，而有关肠-肝轴、脑-肠轴的机制研究较少。

因此，未来应加强有关中药活性成分在肠道菌群方面的多组学研究和中药活性成分临床研究，深入理解中药改善 T2DM 的作用机制，以及加强对糖尿病人群中特定肠道微生物群及其分子功能的探索，以期为开发新的治疗策略提供科学依据和丰富中医药现代化研究的内容，并提升中医药在现代医学领域中的地位和应用价值。

参考文献

[1] SUN H, SAEEDI P, KARURANGA S, PINKEPANK M, OGURTSOVA K, DUNCAN BB, STEIN C, BASIT A, CHAN JCN, MBANYA JC, PAVKOV ME, RAMACHANDARAN A, WILD SH, JAMES S, HERMAN WH, ZHANG P, BOMMER C, KUO S,

BOYKO EJ, MAGLIANO DJ. IDF diabetes atlas: global, regional and country-level diabetes prevalence estimates for 2021 and projections for 2045[J]. Diabetes Research and Clinical Practice, 2022, 183: 109119.

[2] BALLAN R, SAAD SMI. Characteristics of the gut microbiota and potential effects of probiotic supplements in individuals with type 2 diabetes mellitus[J]. Foods, 2021, 10(11): 2528.

[3] 任威铭, 战丽彬. 从《黄帝内经》“移热”理论探讨消渴病病机演变规律[J]. 中国中医基础医学杂志, 2024, 30(2): 181-184.
REN WM, ZHAN LB. Discussion of the evolution law of Xiaoke disease pathogenesis from the theory of “heat transfer” in Inner Canon of Huangdi[J]. Journal of Basic Chinese Medicine, 2024, 30(2): 181-184 (in Chinese).

[4] 谢书俊. 消渴方加减治疗2型糖尿病患者的疗效观察[J]. 中西医结合心血管病电子杂志, 2016, 4(16): 169, 171.
XIE SJ. Observation on the therapeutic effect of Xiaoke recipe on patients with type 2 diabetes[J]. Cardiovascular Disease Journal of Integrated Traditional Chinese and Western Medicine, 2016, 4(16): 169, 171 (in Chinese).

[5] 李淑兵, 张太阳, 梁嘉朗. 消渴方加减联合二甲双胍片对2型糖尿病患者HOMA-IR及血液流变学的影响[J]. 中国当代医药, 2017, 24(35): 138-140.
LI SB, ZHANG TY, LIANG JL. Influence of addition and subtraction of Xiaoke prescription combined with metformin tablets on HOMA-IR and hemorheology in patients with type 2 diabetes mellitus[J]. China Modern Medicine, 2017, 24(35): 138-140 (in Chinese).

[6] 郭婷婷. 玉女煎加减治疗消渴病中消证的临床分析[J]. 糖尿病新世界, 2020, 23(4): 38-39.
GUO TT. Clinical analysis of modified Yunv decoction in treating diabetes and eliminating syndrome[J]. Diabetes New World, 2020, 23(4): 38-39 (in Chinese).

[7] XIAO E, LUO LG. Alternative therapies for diabetes: a comparison of western and traditional Chinese medicine (TCM) approaches[J]. Current Diabetes Reviews, 2018, 14(6): 487-496.

[8] HE Q, WANG LS, ZHAO RX, YAN F, SHA S, CUI C, SONG J, HU HQ, GUO XH, YANG MM, CUI YX, SUN YJ, SUN Z, LIU FQ, DONG M, HOU XG, CHEN L. Mesenchymal stem cell-derived exosomes exert ameliorative effects in type 2 diabetes by improving hepatic glucose and lipid metabolism *via* enhancing autophagy[J]. Stem Cell Research & Therapy, 2020, 11(1): 223.

[9] NAH G, PARK SC, KIM K, KIM S, PARK J, LEE SH, WON S. Type-2 diabetics reduces spatial variation of microbiome based on extracellur vesicles from gut microbes across human body[J]. Scientific Reports, 2019, 9(1): 20136.

[10] YANG G, WEI JL, LIU PY, ZHANG QH, TIAN Y, HOU GW, MENG LB, XIN Y, JIANG X. Role of the gut microbiota in type 2 diabetes and related diseases[J]. Metabolism: Clinical and Experimental, 2021, 117: 154712.

[11] LIU J, LIU JY, ZHANG JY, LIU CY, QU CB, NA LX. Vitamin D deficiency in early life regulates gut microbiome composition and leads to impaired glucose tolerance in adult and offspring rats[J]. Food & Function, 2023, 14(12): 5768-5786.

[12] SCHEITHAUER TPM, RAMPANELLI E, NIEUWDORP M, VALLANCE BA, VERCHERE CB, van RAALTE DH, HERREMA H. Gut microbiota as a trigger for metabolic inflammation in obesity and type 2 diabetes[J]. Frontiers in Immunology, 2020, 11: 571731.

[13] SUN YG, NIE QX, ZHANG SS, HE HJ, ZUO S, CHEN CH, YANG JR, CHEN HH, HU JL, LI S, CHENG JB, ZHANG BJ, ZHENG ZT, PAN SJ, HUANG P, LIAN L, NIE SP. *Parabacteroides distasonis* ameliorates insulin resistance *via* activation of intestinal GPR109a[J]. Nature Communications, 2023, 14: 7740.

[14] ZHANG LL, CHU JJ, HAO WH, ZHANG JJ, LI HB, YANG CJ, YANG JH, CHEN XH, WANG HG. Gut microbiota and type 2 diabetes mellitus: association, mechanism, and translational applications[J]. Mediators of Inflammation, 2021, 2021: 5110276.

[15] SUN Y, QU H, NIU XH, LI T, WANG LJ, PENG HR. Carvacrol improves blood lipid and glucose in rats with type 2 diabetes mellitus by regulating short-chain fatty acids and the GPR41/43 pathway[J]. The Korean Journal of Physiology & Pharmacology: Official Journal of the Korean Physiological Society and the Korean Society of Pharmacology, 2024, 28(1): 1-10.

[16] HOU YS, ZHAI XZ, WANG XT, WU Y, WANG HY, QIN YX, HAN JL, MENG Y. Research progress on the relationship between bile acid metabolism and type 2 diabetes mellitus[J]. Diabetology & Metabolic Syndrome, 2023, 15(1): 235.

[17] HE QY, DONG H, GUO YJ, GONG MM, XIA QS, LU FE, WANG DK. Multi-target regulation of intestinal microbiota by berberine to improve type 2 diabetes mellitus[J]. Frontiers in Endocrinology, 2022, 13: 1074348.

[18] NIE QX, CHEN HH, HU JL, FAN ST, NIE SP. Dietary compounds and traditional Chinese medicine ameliorate type 2 diabetes by modulating gut microbiota[J]. Critical Reviews in Food Science and Nutrition, 2019, 59(6): 848-863.

[19] LI W, MA ZS. FBA ecological guild: trio of firmicutes-bacteroidetes alliance against *Actinobacteria* in human oral microbiome[J]. Scientific Reports, 2020, 10: 287.

[20] LARSEN N, VOGENSEN FK, van den BERG FWJ, NIELSEN DS, ANDREASEN AS, PEDERSEN BK, AL-SOUD WA, SØRENSEN SJ, HANSEN LH, JAKOBSEN M. Gut microbiota in human adults with type 2 diabetes differs from non-diabetic adults[J]. PLoS One, 2010, 5(2): e9085.

[21] AL-MUHANNA FA, DOWDELL AK, AL ELEQ AH, ALBAKER WI, BROOKS AW, AL-SULTAN AI, AL-RUBAISH AM, ALKHARSAH KR, SULAIMAN RM, AL-QUORAIN AA, CYRUS C, ALALI RA, VATTE C, ROBINSON FL, ZHOU X, SNYDER MP, ALMUHANNA AF, KEATING BJ, PIENING BD, AL-ALI AK. Gut microbiota analyses of Saudi populations for type 2 diabetes-related phenotypes reveals significant association[J]. BMC Microbiology, 2022, 22(1): 301.

[22] WANG L, YU XW, XU XQ, MING J, WANG ZF, GAO B, XING Y, ZHOU J, FU JF, LIU T, LIU XY, GARSTKA MA, WANG XK, JI QH. The fecal microbiota is already altered in normoglycemic individuals who go on to have type 2 diabetes[J]. Frontiers in Cellular and Infection Microbiology, 2021, 11: 598672.

[23] DOUMATEY AP, ADEYEMO A, ZHOU J, LEI L, ADEBAMOWO SN, ADEBAMOWO C, ROTIMI CN. Gut microbiome profiles are associated with type 2 diabetes in urban africans[J]. Frontiers in Cellular and Infection Microbiology, 2020, 10: 63.

[24] GURUNG M, LI ZP, YOU H, RODRIGUES R, JUMP DB, MORGUN A, SHULZHENKO N. Role of gut microbiota in type 2 diabetes pathophysiology[J]. EBioMedicine, 2020, 51: 102590.

[25] DASH NR, AL BATAINEH MT, ALILI R, AL SAFAR H, ALKHAYYAL N, PRIFTI E, ZUCKER JD, BELDA E, CLÉMENT K. Functional alterations and predictive capacity of gut microbiome in type 2 diabetes[J]. Scientific Reports, 2023, 13(1): 22386.

[26] LETCHUMANAN G, ABDULLAH N, MARLINI M, BAHAROM N, LAWLEY B, OMAR MR, MOHIDEEN FBS, ADDNAN FH, NUR FARIHA MM, ISMAIL Z, PATHMANATHAN SG. Gut microbiota composition in prediabetes and newly diagnosed type 2 diabetes: a systematic review of observational studies[J]. Frontiers in Cellular and Infection Microbiology, 2022, 12: 943427.

[27] KWAN SY, SABOTTA CM, JOON A, WEI P, PETTY LE, BELOW JE, WU XG, ZHANG JH, JENQ RR, HAWK ET, McCORMICK JB, FISHER-HOCH SP, BERETTA L. Gut microbiome alterations associated with diabetes in Mexican Americans in south Texas[J]. mSystems, 2022, 7(3): e0003322.

[28] HOSOMI K, SAITO M, PARK J, MURAKAMI H, SHIBATA N, ANDO M, NAGATAKE T, KONISHI K, OHNO H, TANISAWA K, MOHSEN A, CHEN YA, KAWASHIMA H, NATSUME-KITATANI Y, OKA Y, SHIMIZU H, FURUTA M, TOJIMA Y, SAWANE K, SAIKA A, et al. Oral administration of *Blautia wexlerae* ameliorates obesity and type 2 diabetes *via* metabolic remodeling of the gut microbiota[J]. Nature Communications, 2022, 13: 4477.

[29] LEITE AZ, RODRIGUES NC, GONZAGA MI, PAIOLO JCC, de SOUZA CA, STEFANUTTO NAV, OMORI WP, PINHEIRO DG, BRISOTTI JL, MATHEUCCI JUNIOR E, MARIANO VS, de OLIVEIRA GLV. Detection of increased plasma interleukin-6 levels and prevalence of *Prevotella copri* and *Bacteroides vulgatus* in the feces of type 2 diabetes patients[J]. Frontiers in Immunology, 2017, 8: 1107.

[30] MEDINA-VERA I, SANCHEZ-TAPIA M, NORIEGA-LÓPEZ L, GRANADOS-PORTILLO O, GUEVARA-CRUZ M, FLORES-LÓPEZ A, AVILA-NAVA A, FERNÁNDEZ ML, TOVAR AR, TORRES N. A dietary intervention with functional foods reduces metabolic endotoxaemia and attenuates biochemical abnormalities by modifying faecal microbiota in people with type 2 diabetes[J]. Diabetes & Metabolism, 2019, 45(2): 122-131.

[31] BENER A, AĞAN AF, AL-HAMAQ AOAA, BARISIK CC, ÖZTÜRK M, ÖMER A. Prevalence of *Helicobacter pylori* infection among type 2 diabetes mellitus[J]. Advanced Biomedical Research, 2020, 9: 27.

[32] PLOVIER H, EVERARD A, DRUART C, DEPOMMIER C, van HUL M, GEURTS L, CHILLOUX J, OTTMAN N, DUPARC T, LICHTENSTEIN L, MYRIDAKIS A, DELZENNE NM, KLIEVINK J, BHATTACHARJEE A, van der ARK KCH, AALVINK S, MARTINEZ LO, DUMAS ME, MAITER D, LOUMAYE A, et al. A purified membrane protein from *Akkermansia muciniphila* or the pasteurized bacterium improves metabolism in obese and diabetic mice[J]. Nature Medicine, 2017, 23: 107-113.

[33] CHELAKKOT C, CHOI Y, KIM DK, PARK HT, GHIM J, KWON Y, JEON J, KIM MS, JEE YK, GHO YS, PARK HS, KIM YK, RYU SH. *Akkermansia muciniphila*-derived extracellular vesicles influence gut

permeability through the regulation of tight junctions[J]. Experimental & Molecular Medicine, 2018, 50(2): e450.

[34] WANG Z, CUI SY, ZHANG TT, WANG W, LI JY, CHEN YQ, ZHU SL. *Akkermansia muciniphila* supplementation improves glucose tolerance in intestinal *Ffar4* knockout mice during the daily light to dark transition[J]. mSystems, 2023, 8(5): e0057323.

[35] HE KY, LEI XY, WU DH, ZHANG L, LI JQ, LI QT, YIN WT, ZHAO ZL, LIU H, XIANG XY, ZHU LJ, CUI CY, WANG KK, WANG JH, LV L, SUN QH, LIU GL, XU ZX, JIAN YP. *Akkermansia muciniphila* protects the intestine from irradiation-induced injury by secretion of propionic acid[J]. Gut Microbes, 2023, 15(2): 2293312.

[36] SALAMONE D, RIVELLESE AA, VETRANI C. The relationship between gut microbiota, short-chain fatty acids and type 2 diabetes mellitus: the possible role of dietary fibre[J]. Acta Diabetologica, 2021, 58(9): 1131-1138.

[37] KIM WJ, RYU R, DOO EH, CHOI Y, KIM K, KIM BK, KIM H, KIM M, HUH CS. Supplementation with the probiotic strains *Bifidobacterium longum* and *Lactiplantibacillus rhamnosus* alleviates glucose intolerance by restoring the IL-22 response and pancreatic beta cell dysfunction in type 2 diabetic mice[J]. Probiotics and Antimicrobial Proteins, 2023. DOI: 10.1007/s12602-023-10156-5.

[38] GAO K, REN XL, CHEN CL, FAN QL, LI YJ, WANG HF, CHEN S. Oral administration of *Bifidobacterium longum* WHH2270 ameliorates type 2 diabetes in rats[J]. Journal of Food Science, 2023, 88(9): 3967-3983.

[39] HAO JY, ZHANG YL, WU T, LIU R, SUI WJ, ZHU JG, FANG SG, GENG JT, ZHANG M. The antidiabetic effects of *Bifidobacterium longum* subsp. *longum* BL21 through regulating gut microbiota structure in type 2 diabetic mice[J]. Food & Function, 2022, 13(19): 9947-9958.

[40] QIAN X, SI Q, LIN GP, ZHU MM, LU JY, ZHANG H, WANG G, CHEN W. *Bifidobacterium adolescentis* is effective in relieving type 2 diabetes and may be related to its dominant core genome and gut microbiota modulation capacity[J]. Nutrients, 2022, 14(12): 2479.

[41] CHAIYASUT C, SIVAMARUTHI BS, LAILERD N, SIRILUN S, THANGALEELA S, KHONGTAN S, BHARATHI M, KESIKA P, SAELEE M, CHOEISOONGNERN T, FUKNGOEN P, PEERAJAN S, SITTIPRAPAPORN P. Influence of *Bifidobacterium breve* on the glycaemic control, lipid profile and microbiome of type 2 diabetic subjects: a preliminary randomized clinical trial[J]. Pharmaceuticals, 2023, 16(5): 695.

[42] ARORA T, TREMAROLI V. Therapeutic potential of butyrate for treatment of type 2 diabetes[J]. Frontiers in Endocrinology, 2021, 12: 761834.

[43] XU JH, LIANG RR, ZHANG W, TIAN KY, LI JY, CHEN XM, YU T, CHEN QK. *Faecalibacterium prausnitzii*-derived microbial anti-inflammatory molecule regulates intestinal integrity in diabetes mellitus mice *via* modulating tight junction protein expression[J]. Journal of Diabetes, 2020, 12(3): 224-236.

[44] MOOSAVI SM, AKHAVAN SEPAHI A, MOUSAVI SF, VAZIRI F, SIADAT SD. The effect of *Faecalibacterium prausnitzii* and its extracellular vesicles on the permeability of intestinal epithelial cells and expression of PPARs and ANGPTL4 in the Caco-2 cell culture model[J]. Journal of Diabetes & Metabolic Disorders, 2020, 19(2): 1061-1069.

[45] KIVELÄ J, MEINILÄ J, UUSITUPA M, TUOMILEHTO J, LINDSTRÖM J. Longitudinal branched-chain amino acids, lifestyle intervention, and type 2 diabetes in the finnish diabetes prevention study[J]. The Journal of Clinical Endocrinology and Metabolism, 2022, 107(10): 2844-2853.

[46] GOJDA J, CAHOVA M. Gut microbiota as the link between elevated BCAA serum levels and insulin resistance[J]. Biomolecules, 2021, 11(10): 1414.

[47] deLa RUBIA ORTÍ JE, MONETI C, SERRANO-BALLESTEROS P, CASTELLANO G, BAYONA-BABILONI R, CARRIQUÍ-SUÁREZ AB, MOTOS-MUÑOZ M, PROAÑO B, BENLLOCH M. Liposomal epigallocatechin-3-gallate for the treatment of intestinal dysbiosis in children with autism spectrum disorder: a comprehensive review[J]. Nutrients, 2023, 15(14): 3265.

[48] LIU DL, ZHANG SB, LI SJ, ZHANG Q, CAI Y, LI P, LI H, SHEN BC, LIAO QF, HONG YJ, XIE ZY. Indoleacrylic acid produced by *Parabacteroides distasonis* alleviates type 2 diabetes *via* activation of AhR to repair intestinal barrier[J]. BMC Biology, 2023, 21(1): 90.

[49] RAETZ CRH, WHITFIELD C. Lipopolysaccharide endotoxins[J]. Annual Review of Biochemistry, 2002, 71: 635-700.

[50] CAMARGO A, JIMENEZ-LUCENA R, ALCALA-DIAZ JF, RANGEL-ZUÑIGA OA, GARCIA-CARPINTERO S, LOPEZ-MORENO J, BLANCO-ROJO R, DELGADO-LISTA J, PEREZ-MARTINEZ P, van OMMEN B, MALAGON MM, ORDOVAS JM, PEREZ-JIMENEZ F, LOPEZ-MIRANDA J. Postprandial endotoxemia may

influence the development of type 2 diabetes mellitus: from the CORDIOPREV study[J]. Clinical Nutrition, 2019, 38(2): 529-538.

[51] KHONDKARYAN L, MARGARYAN S, POGHOSYAN D, MANUKYAN G. Impaired inflammatory response to LPS in type 2 diabetes mellitus[J]. International Journal of Inflammation, 2018, 2018: 2157434.

[52] XU SY, WANG YP, WANG JJ, GENG WT. Kombucha reduces hyperglycemia in type 2 diabetes of mice by regulating gut microbiota and its metabolites[J]. Foods, 2022, 11(5): 754.

[53] LI H, LIAO TT, DEBOWSKI AW, TANG H, NILSSON HO, STUBBS KA, MARSHALL BJ, BENGHEZAL M. Lipopolysaccharide structure and biosynthesis in *Helicobacter pylori*[J]. Helicobacter, 2016, 21(6): 445-461.

[54] XU XZ, GAO ZZ, YANG FQ, YANG YY, CHEN L, HAN L, ZHAO N, XU JY, WANG XM, MA Y, SHU L, HU XX, LYU N, PAN YL, ZHU BL, ZHAO LH, TONG XL, WANG J. Antidiabetic effects of Gegen Qinlian decoction *via* the gut microbiota are attributable to its key ingredient berberine[J]. Genomics, Proteomics & Bioinformatics, 2020, 18(6): 721-736.

[55] PAN JM, XU YJ, CHEN S, TU YF, MO YF, GAO F, ZHOU J, HU C, JIA WP. The effectiveness of traditional Chinese medicine jinlida granules on glycemic variability in newly diagnosed type 2 diabetes: a double-blinded, randomized trial[J]. Journal of Diabetes Research, 2021, 2021: 6303063.

[56] SHARMA BR, JAISWAL S, RAVINDRA PV. Modulation of gut microbiota by bioactive compounds for prevention and management of type 2 diabetes[J]. Biomedicine & Pharmacotherapy, 2022, 152: 113148.

[57] CHEN MY, XIAO D, LIU W, SONG YF, ZOU BR, LI L, LI P, CAI Y, LIU DL, LIAO QF, XIE ZY. Intake of *Ganoderma lucidum* polysaccharides reverses the disturbed gut microbiota and metabolism in type 2 diabetic rats[J]. International Journal of Biological Macromolecules, 2020, 155: 890-902.

[58] CHEN X, TONG YL, REN ZM, CHEN SS, MEI XY, ZHOU QY, DAI GH. Hypoglycemic mechanisms of *Polygonatum sibiricum* polysaccharide in db/db mice *via* regulation of glycolysis/gluconeogenesis pathway and alteration of gut microbiota[J]. Heliyon, 2023, 9(4): e15484.

[59] SONG QB, CHENG SW, LI D, CHENG HY, LAI YS, HAN QB, WU HY, SHAW PC, ZUO Z. Gut microbiota mediated hypoglycemic effect of *Astragalus membranaceus* polysaccharides in db/db mice[J]. Frontiers in Pharmacology, 2022, 13: 1043527.

[60] CHEN XX, CHEN C, FU X. Hypoglycemic effect of the polysaccharides from *Astragalus membranaceus* on type 2 diabetic mice based on the gut microbiota-mucosal barrier[J]. Food & Function, 2022, 13(19): 10121-10133.

[61] MA QY, ZHAI RH, XIE XQ, CHEN T, ZHANG ZQ, LIU HC, NIE CX, YUAN XJ, TU AB, TIAN BM, ZHANG M, CHEN ZF, LI JX. Hypoglycemic effects of *Lycium barbarum* polysaccharide in type 2 diabetes mellitus mice *via* modulating gut microbiota[J]. Frontiers in Nutrition, 2022, 9: 916271.

[62] YANG Y, CHANG YF, WU Y, LIU HR, LIU QS, KANG ZZ, WU M, YIN H, DUAN JY. A homogeneous polysaccharide from *Lycium barbarum*: structural characterizations, anti-obesity effects and impacts on gut microbiota[J]. International Journal of Biological Macromolecules, 2021, 183: 2074-2087.

[63] ZHOU WT, YANG TT, XU WQ, HUANG YJ, RAN LW, YAN YM, MI J, LU L, SUN Y, ZENG XX, CAO YL. The polysaccharides from the fruits of *Lycium barbarum* L. confer anti-diabetic effect by regulating gut microbiota and intestinal barrier[J]. Carbohydrate Polymers, 2022, 291: 119626.

[64] CHEN LC, FAN ZY, WANG HY, WEN DC, ZHANG SY. Effect of polysaccharides from adlay seed on anti-diabetic and gut microbiota[J]. Food & Function, 2019, 10(7): 4372-4380.

[65] XIA T, LIU CS, HU YN, LUO ZY, CHEN FL, YUAN LX, TAN XM. *Coix* seed polysaccharides alleviate type 2 diabetes mellitus *via* gut microbiota-derived short-chain fatty acids activation of IGF1/PI3K/AKT signaling[J]. Food Research International, 2021, 150(Pt A): 110717.

[66] ZHAO HJ, LI M, LIU L, LI D, ZHAO LJ, WU Z, ZHOU MX, JIA L, YANG F. *Cordyceps militaris* polysaccharide alleviates diabetic symptoms by regulating gut microbiota against TLR4/NF-κB pathway[J]. International Journal of Biological Macromolecules, 2023, 230: 123241.

[67] LIU HD, XING Y, WANG YB, REN XX, ZHANG DY, DAI JY, XIU ZL, YU SQ, DONG YS. *Dendrobium officinale* polysaccharide prevents diabetes *via* the regulation of gut microbiota in prediabetic mice[J]. Foods, 2023, 12(12): 2310.

[68] CHEN XX, CHEN C, FU X. *Dendrobium officinale* polysaccharide alleviates type 2 diabetes mellitus by restoring gut microbiota and repairing intestinal barrier *via* the LPS/TLR4/TRIF/NF-κB axis[J]. Journal of Agricultural and Food Chemistry, 2023, 71(31): 11929-11940.

[69] CHEN XX, WU JL, FU X, WANG PP, CHEN C. *Fructus mori* polysaccharide alleviates diabetic symptoms by regulating intestinal microbiota and intestinal barrier against TLR4/NF-κB pathway[J]. International Journal of Biological Macromolecules, 2023, 249: 126038.

[70] 张明发, 沈雅琴. 非处方药小檗碱抗腹泻作用的再评价[J]. 中国医院用药评价与分析, 2003, 3(3): 148-153.
ZHANG MF, SHEN YQ. Re-evaluation of the effect of non-prescription drug berberine on antidiarrhea[J]. Evaluation and Analysis of Drug-Use in Hospital of China, 2003, 3(3): 148-153 (in Chinese).

[71] YAO Y, CHEN H, YAN LJ, WANG WB, WANG DS. Berberine alleviates type 2 diabetic symptoms by altering gut microbiota and reducing aromatic amino acids[J]. Biomedicine & Pharmacotherapy, 2020, 131: 110669.

[72] WANG Y, LIU HY, ZHENG MY, YANG YH, REN HZ, KONG Y, WANG SS, WANG JY, JIANG YY, YANG JH, SHAN CY. Berberine slows the progression of prediabetes to diabetes in zucker diabetic fatty rats by enhancing intestinal secretion of glucagon-like peptide-2 and improving the gut microbiota[J]. Frontiers in Endocrinology, 2021, 12: 609134.

[73] LI M, ZHOU WJ, DANG YQ, LI CL, JI G, ZHANG L. Berberine compounds improves hyperglycemia *via* microbiome mediated colonic TGR5-GLP pathway in db/db mice[J]. Biomedicine & Pharmacotherapy, 2020, 132: 110953.

[74] HU TG, WEN P, SHEN WZ, LIU F, LI Q, LI EN, LIAO ST, WU H, ZOU YX. Effect of 1-deoxynojirimycin isolated from mulberry leaves on glucose metabolism and gut microbiota in a streptozotocin-induced diabetic mouse model[J]. Journal of Natural Products, 2019, 82(8): 2189-2200.

[75] REN XX, XING Y, HE LY, XIU ZL, YANG L, HAN AZ, JIA QH, DONG YS. Effect of 1-deoxynojirimycin on insulin resistance in prediabetic mice based on next-generation sequencing and intestinal microbiota study[J]. Journal of Ethnopharmacology, 2022, 289: 115029.

[76] ZHAO ZQ, CHEN YZ, LI XQ, ZHU LY, WANG X, LI L, SUN HB, HAN XQ, LI JJ. Myricetin relieves the symptoms of type 2 diabetes mice and regulates intestinal microflora[J]. Biomedicine & Pharmacotherapy, 2022, 153: 113530.

[77] GE XD, HE XY, LIU JW, ZENG F, CHEN LG, XU W, SHAO R, HUANG Y, FARAG MA, CAPANOGLU E, EL-SEEDI HR, ZHAO C, LIU B. Amelioration of type 2 diabetes by the novel 6,8-guanidyl luteolin quinone-chromium coordination *via* biochemical mechanisms and gut microbiota interaction[J]. Journal of Advanced Research, 2023, 46: 173-188.

[78] LUO ZH, XU J, GAO QQ, WANG ZF, HOU MX, LIU YN. Study on the effect of licochalcone A on intestinal flora in type 2 diabetes mellitus mice based on 16S rRNA technology[J]. Food & Function, 2023, 14(19): 8903-8921.

[79] SU HM, XIE LH, XU Y, KE HH, BAO T, LI YT, CHEN W. Pelargonidin-3-*O*-glucoside derived from wild raspberry exerts antihyperglycemic effect by inducing autophagy and modulating gut microbiota[J]. Journal of Agricultural and Food Chemistry, 2020, 68(46): 13025-13037.

[80] YANG TT, ZHOU WT, XU WQ, RAN LW, YAN YM, LU L, MI J, ZENG XX, CAO YL. Modulation of gut microbiota and hypoglycemic/hypolipidemic activity of flavonoids from the fruits of *Lycium barbarum* on high-fat diet/streptozotocin-induced type 2 diabetic mice[J]. Food & Function, 2022, 13(21): 11169-11184.

[81] PARK JM, SHIN Y, KIM SH, JIN M, CHOI JJ. Dietary epigallocatechin-3-gallate alters the gut microbiota of obese diabetic db/db mice: *Lactobacillus* is a putative target[J]. Journal of Medicinal Food, 2020, 23(10): 1033-1042.

[82] CHAI YY, LUO JY, BAO YH. Effects of *Polygonatum sibiricum* saponin on hyperglycemia, gut microbiota composition and metabolic profiles in type 2 diabetes mice[J]. Biomedicine & Pharmacotherapy, 2021, 143: 112155.

[83] LUO JY, CHAI YY, ZHAO M, GUO QQ, BAO YH. Hypoglycemic effects and modulation of gut microbiota of diabetic mice by saponin from *Polygonatum sibiricum*[J]. Food & Function, 2020, 11(5): 4327-4338.

[84] TIAN FY, HUANG S, XU WD, CHEN L, SU JM, NI HX, FENG XH, CHEN J, WANG X, HUANG Q. Compound K attenuates hyperglycemia by enhancing glucagon-like peptide-1 secretion through activating TGR5 *via* the remodeling of gut microbiota and bile acid metabolism[J]. Journal of Ginseng Research, 2022, 46(6): 780-789.

[85] HUANG S, SHAO L, CHEN MY, WANG L, LIU J, ZHANG W, HUANG WH. Biotransformation differences of ginsenoside compound K mediated by the gut microbiota from diabetic patients and healthy subjects[J]. Chinese Journal of Natural Medicines, 2023, 21(10): 723-729.

[86] ZHOU RR, HE D, ZHANG HC, XIE J, ZHANG SH, TIAN XF, ZENG HL, QIN YH, HUANG LQ. Ginsenoside Rb1 protects against diabetes-associated

metabolic disorders in Kkay mice by reshaping gut microbiota and fecal metabolic profiles[J]. Journal of Ethnopharmacology, 2023, 303: 115997.

[87] WANG W, GUAN FT, SAGRATINI G, YAN J, XIE JH, JIN ZB, LIU MH, LIU HM, LIU JS. Ginsenoside Rd attenuated hyperglycemia *via* Akt pathway and modulated gut microbiota in streptozotocin-induced diabetic rats[J]. Current Research in Food Science, 2023, 6: 100491.

[88] PENG M, WANG LM, SU H, ZHANG L, YANG Y, SUN L, WU Y, RAN L, LIU SD, YIN M, LI SD, CHUNYU WX. Ginsenoside Rg1 improved diabetes through regulating the intestinal microbiota in high-fat diet and streptozotocin-induced type 2 diabetes rats[J]. Journal of Food Biochemistry, 2022, 46(10): e14321.

[89] WEI YG, YANG HX, ZHU CH, DENG JJ, FAN DD. Hypoglycemic effect of ginsenoside Rg5 mediated partly by modulating gut microbiota dysbiosis in diabetic db/db mice[J]. Journal of Agricultural and Food Chemistry, 2020, 68(18): 5107-5117.

[90] XU J, LI T, XIA XY, FU CF, WANG XD, ZHAO YQ. Dietary ginsenoside T19 supplementation regulates glucose and lipid metabolism *via* AMPK and PI3K pathways and its effect on intestinal microbiota[J]. Journal of Agricultural and Food Chemistry, 2020, 68(49): 14452-14462.

[91] MA LL, LA XJ, ZHANG BW, XU WX, TIAN CY, FU QR, WANG M, WU CX, CHEN Z, CHANG H, LI J. Total *Astragalus saponins* can reverse type 2 diabetes mellitus-related intestinal dysbiosis and hepatic insulin resistance *in vivo*[J]. Frontiers in Endocrinology, 2023, 14: 1190827.

[92] GONG P, XIAO XY, WANG S, SHI FX, LIU N, CHEN XF, YANG WJ, WANG L, CHEN FX. Hypoglycemic effect of astragaloside IV *via* modulating gut microbiota and regulating AMPK/SIRT1 and PI3K/AKT pathway[J]. Journal of Ethnopharmacology, 2021, 281: 114558.

[93] SU HM, MO JL, NI JD, KE HH, BAO T, XIE JH, XU Y, XIE LH, CHEN W. Andrographolide exerts antihyperglycemic effect through strengthening intestinal barrier function and increasing microbial composition of *Akkermansia muciniphila*[J]. Oxidative Medicine and Cellular Longevity, 2020, 2020: 6538930.

[94] HUANG JZ, GUAN BB, LIN LJ, WANG YP. Improvement of intestinal barrier function, gut microbiota, and metabolic endotoxemia in type 2 diabetes rats by curcumin[J]. Bioengineered, 2021, 12(2): 11947-11958.

[95] KATTAR SA, JURJUS R, PINON A, LEGER DY, JURJUS A, BOUKARIM C, DIAB-ASSAF M, LIAGRE B. Metformin and probiotics in the crosstalk between colitis-associated colorectal cancer and diabetes in mice[J]. Cancers, 2020, 12(7): 1857.

[96] MING J, YU XW, XU XQ, WANG L, DING C, WANG ZF, XIE X, LI SL, YANG WJ, LUO S, HE QZ, DU YF, TIAN ZF, GAO XL, MA KY, FANG YJ, LI C, ZHAO JJ, WANG XK, JI QH. Effectiveness and safety of *Bifidobacterium* and berberine in human hyperglycemia and their regulatory effect on the gut microbiota: a multi-center, double-blind, randomized, parallel-controlled study[J]. Genome Medicine, 2021, 13(1): 125.

[97] MENG FY, ZHANG F, MENG M, CHEN QD, YANG YQ, WANG WB, XIE HN, LI X, GU W, YU J. Effects of the synbiotic composed of mangiferin and *Lactobacillus reuteri* 1-12 on type 2 diabetes mellitus rats[J]. Frontiers in Microbiology, 2023, 14: 1158652.

[98] TAN DC, TSENG HHL, ZHONG ZF, WANG SP, VONG CT, WANG YT. Glycyrrhizic acid and its derivatives: promising candidates for the management of type 2 diabetes mellitus and its complications[J]. International Journal of Molecular Sciences, 2022, 23(19): 10988.

[99] YUAN TJ, WANG J, CHEN LT, SHAN JJ, DI LQ. *Lactobacillus murinus* improved the bioavailability of orally administered glycyrrhizic acid in rats[J]. Frontiers in Microbiology, 2020, 11: 597.