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Exploring the beneficial effect of gut microbiota metabolites on diabetic nephropathy via network pharmacology study

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Diabetic nephropathy (DN) is one of the severe complications of diabetes, current treatment against DN is still limited. It is suggested that gut microbiota metabolites will be a promising alternative therapy against DN. In this study, we explore the beneficial effect of gut microbiota metabolites on DN via employing network pharmacology study. The targets of metabolites were screen from Similarity Ensemble Approach (SEA) and Swiss Target Prediction (STP). The DN targets were acquired from disease database. The intersecting targets of metabolites and DN were considered crucial targets. The Protein–Protein Interaction (PPI) networks, GO function and KEGG analysis were conducted to identify core target and key signaling pathway. A "Microbiota-Substrate-Metabolites-Targets" network was built to screen the core metabolites. Molecular docking was employed to assess the binding affinity between metabolites and targets. GO functional results indicated that the metabolites were mainly enriched in oxidative stress and inflammation. PPARG, AKT1, IL6 and JUN were the top 4 targets of gut microbiota metabolites regulating DN. Butyrate, Acetate, Indole and 3-Indolepropionic acid were the core gut microbiota metabolites that had beneficial effects on attenuating DN. Molecular docking results indicated that 3-Indolepropionic acid displayed a good binding affinity toward targets of PPARG, AKT1, IL6 and JUN. Our study revealed that the gut microbiota metabolites might exert beneficial effect on attenuating DN by regulating multi-signaling pathway and multi-targets. This work offers us a novel insight into the mechanism of DN from the perspective of beneficial benefits of gut microbiota metabolites.

Keywords Diabetic nephropathy, Gut microbiota metabolites, Gut microbiota, Network pharmacology

Abbreviations

DN	Diabetic nephropathy
GM	Gut microbiota
GO	Gene ontology
KEGG	Kyoto Encyclopedia of Genes and Genomes
SCFAs	Short-chain fatty acids
PPI	Protein–protein interaction
VEGF	Vascular endothelial growth factor
NF-κB	Nuclear factor kappa-B
HIF-1	Hypoxia inducible factor-1
IL-6	Interleukin-6
PPARG	Peroxisome proliferator-activated receptor gamma
BP	Biological process
CC	Cellular component
MF	Molecular function
LPS	Lipopolysaccharide
PI3K	Phosphoinositide 3-kinase
mTOR	Mammalian target of rapamycin

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Currently, the high prevalence of diabetes is a global public health challenge facing human community. The epidemiology report pointed out that the diabetes would affected a population of 700 million[1]. Diabetes could cause damages to a variety of organs, including heart, eye, kidney and brain. Diabetic nephropathy (DN) is a chronic kidney disease (CKD) caused by diabetes[2]. Metabolism abnormalities (hyperglycemia and dyslipidemia) and hemodynamic abnormalities (glomerular hypertension) are well-recognized major driving forces in the initiation and progression of DN[3]. Hyperglycemia induces endothelial cell injury by subjecting these cells to mitochondrial oxidative stress[4]. Elevated glucose levels abnormally activate or inhibit downstream signaling pathways such as the hexosamine pathway, advanced glycation end-product (AGEs) pathway, sorbitol pathway, and protein kinase C pathway[5–7]. Ultimately, these alterations lead to endothelial cell damage through activating inflammation and oxidative stress. Although drugs inhibiting SGL2 or RAS are used to ameliorate DN, its long term administration could bring about some side effects[8,9]. Thus, seeking an effective therapeutic approach is an urgent need.

The gut microbiota (GM) is a complicated ecosystem with a large number of microbiota residing in this community, so gut microbiota is also called "human second organ"[10]. Extensive literatures suggested that gut microbiota plays a vital role in maintaining the homeostasis of metabolism[11,12]. The disorder in the composition of gut microbial community participate in the occurrence of various diseases, including colitis, diabetes, obesity and fatty liver[13]. The short chain fatty acids (SCFAs) is a type of beneficial byproducts from GM[14]. The low abundance of SCFAs was found in animal model with DN, the supplement of SCFAs can reduce glucose level[15,16]. Studies reported that fiber diet promoted the generation of SCFAs[17]. Notably, a whole grain food harbors a large quantity of soluble fiber, with β-glucan being a prominent component, which display significant hypoglycemic properties[18]. Additionally, fiber diet owning a property of low glycemic index (GI) facilitates effective blood glucose level management and provides particular advantages for individuals with diabetes[19,20].

Network pharmacology is a powerful tool. It integrates the knowledge of computer science, systems biology and pharmacology that could help us decipher the mystery of interaction among diseases, targets and drugs[21]. In this study, we are going to employ network pharmacology to decipher the regulatory mechanism of gut microbiota metabolites on DN. As shown in Fig. 1, firstly, we will screen the potential targets of gut microbiota metabolites and DN from open public databases. Secondly, VENN diagram is employed to identify hub targets. Third, GO and KEGG are used to identify potential biological function and signaling pathway. Finally, a GM-DN-Pathway network is built for identifying core targets and metabolites, and molecular docking is used to assess the binding capacity of gut microbiota metabolites with targets.

Methods and materials

Data source and tool

The detailed information of data source and tool was available in Table 1.

The identification of metabolites and targets from GM

The metabolites of GM were acquired from gutMGene database. The SMILE of metabolites were submitted to Similarity Ensemble Approach (SEA) and Swiss Target Prediction (STP) respectively for targets obtaining. The overlapping targets of SEA and STP were the core targets of GM metabolites.

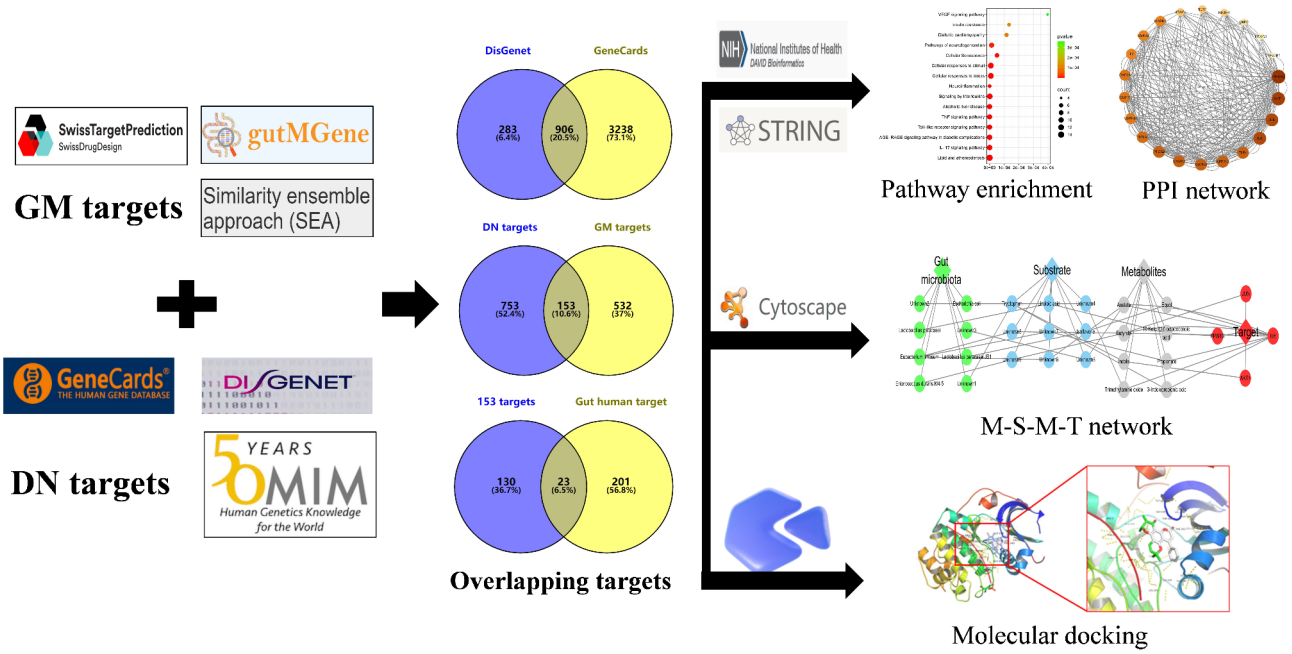

Fig. 1. The flowchart of the study design.

NO	Database, database and analysis platform	Website	Version
1	gutMGene	http://bio-annotation.cn/gutmgene/	\
2	Swiss target prediction	http://www.swisstargetprediction.ch/	\
3	Pubchem	https://pubchem.ncbi.nlm.nih.gov/	\
4	Bioinformatics	http://www.bioinformatics.com.cn/	\
5	STRING	https://string-db.org	V12.0
6	Cytoscape software 3.6	https://cytoscape.org/	3.6
7	OMIM	https://omim.org/	\
8	Genecards	https://www.genecards.org/	\
9	DisgeNet	https://www.disgenet.org/	\
10	DAVID bioinformatics	https://david.ncifcrf.gov/tools.jsp	\
11	Similarity ensemble approach	https://sea.bkslab.org/	\
12	SwissAMDE	http://www.swissadme.ch/index.php	\
13	ADMETlab	https://admetmesh.scbdd.com/	\
14	AutoDock Vina	http://vina.scripps.edu/	V1.1.2

Table 1. Database, software and analysis platform.

The identification of core targets of GM in the treatment of DN

The DN targets were acquired from GeneCards and DisGeNet, and then submitted to VENN diagram for obtaining overlapping targets. The overlapping targets of GM and DN were the core targets that could regulated DN.

The protein–protein interaction (PPI) network

The overlapping targets were submitted to Search Tool for Recurring Instances of Neighbouring Genes (STRING) platform. The PPI visualization was completed by Cytoscape 3.6 (A software platform dedicated to network visualization and analysis) software (https://cytoscape.org/, VERSION:3.6). We used degree centrality (DC) to determine the core targets on PPI network.

GO function and KEGG enrichment analysis

The overlapping targets were submitted to DAVID platform for performing GO and KEGG (Kyoto Encyclopedia of Genes and Genomes) is a comprehensive database designed to integrate information on genomes, metabolic pathways, chemical substances and biological system functions, and it is widely used in biological research, medical education, drug development and other fields[22–24]. GO function contains 3 parts: BP (Biological process), CC (Cellular Component) and MF (Molecular Function). KEGG enrichment analysis is used to identified potential pathways. We used "gene counts, *P* value and FDR" to screen the most related GO terms or pathways that could better understanding the influence of metabolites on DN.

Molecular docking verification

Molecular docking between core components and core targets was performed by AutoDock Vina 1.1.2. The structure files of core components and core targets were obtained from RCSB Protein Data Bank (RCSB PDB) and TCMSP database respectively. The target protein and ligand were separated by the PyMOL (a tool used for visualizing and analyzing protein–protein interaction binding sites) software (https://www.pymol.org/, VERSION: 3.1). The pdbqt formats of target proteins, ligands and ingredients were prepared by AutoDock Tools. For the next step, the active pocket of the receptor was built with Grid plugin. Finally, the binding energy of the target protein and the active component was calculated by Vina. Generally speaking, a binding energy ≤ -5.0 kcal/mol suggested a stable binding ability between component and target.

Results

The identifications of targets of gut microbiota metabolites against DN

A total of 1189 and 4144 DN-related targets were retrieved from the DisGeNET and GeneCards databases (Fig. 2A). The 906 overlapping targets appeared in the VENN diagram were considered the main DN targets (Fig. 2A). A total of 208 GM metabolites were acquired from gutMGene database. The 208 GM metabolites were submitted SEA and STP databases for corresponding targets obtaining. The Fig. 2B indicated that there are 1256 and 992 targets corresponding to GM metabolites from SEA and STP databases respectively. The 685 overlapping targets appeared in the VENN diagram were considered the main targets of GM metabolites (Fig. 2B). Finally, after intersecting the 685 GM targets of metabolites with 906 DN targets, we obtained 153 overlapping targets that were considered the main targets of GM metabolites against DN (Fig. 2C). We also constructed the "disease-targets-GM" network using Cytoscape 3.6 software. As shown in Fig. 2D, the blue rectangle represented targets, the green octagon represented DN and GM.

PPI network cluster analysis

We uploaded the 153 overlapping targets to STRING platform for PPI network analysis (Fig. 3A), and the PPI network was visualized by Cytoscape 3.6 software (Fig. 3B). The PPI network contained 153 nodes and 4374

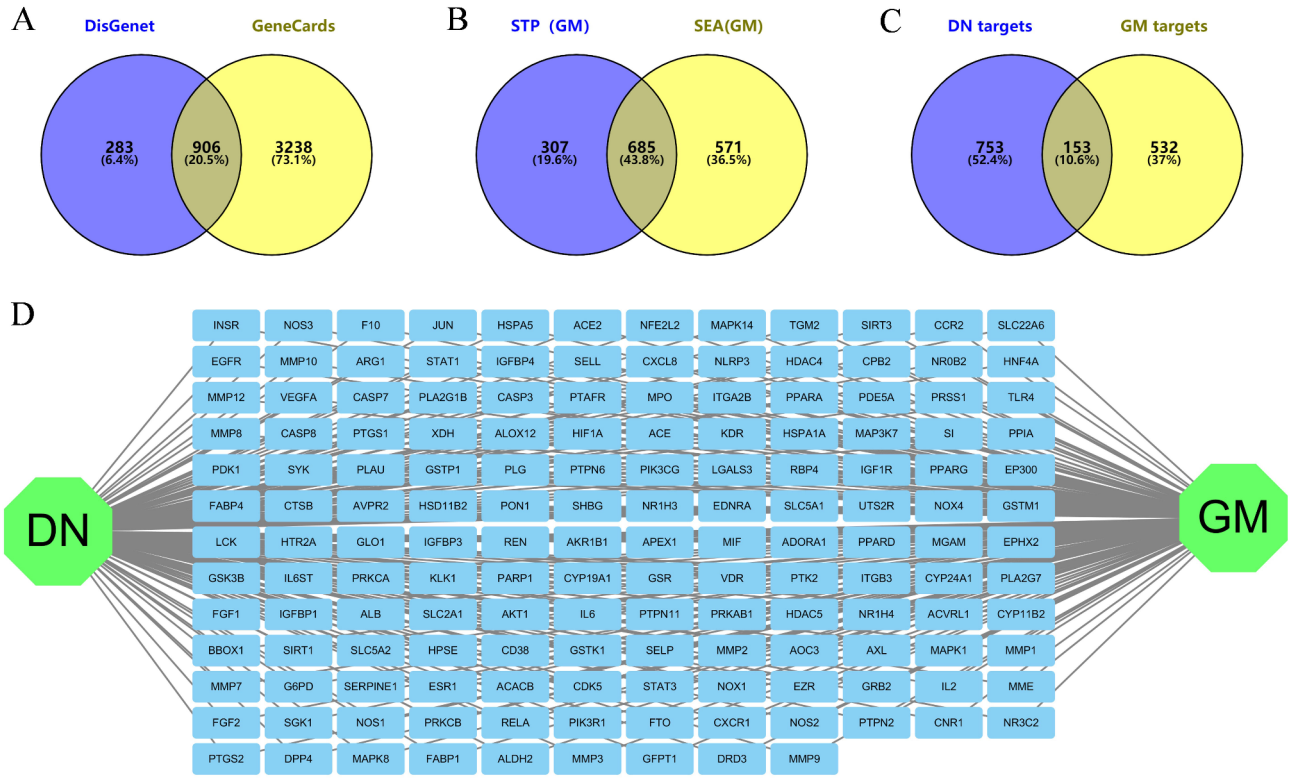

Fig. 2. The identifications of targets of gut microbiota metabolites against DN. (**A**) The overlapping targets corresponding to DN between DisGenet and GeneCards. (**B**) The overlapping targets corresponding to gut microbiota metabolites between SEA and STP. (**C**) The overlapping targets corresponding between gut microbiota metabolites and DN. (**D**) The network of Gut-Target-DN. Note: SEA stands for Similarity Ensemble Approach; STP stands for Swiss Target Prediction; DN stands for Diabetic Nephropathy.

edges. We used MCODE plug-in to interpret the feature of PPI network. The PPI network could be divided into 4 clusters. We select the top 2 cluster for further analysis based on their score. The cluster 1 contains 38 nodes and 1085 edges with a score of 28.59 (Fig. 3C), and The cluster 2 contains 25 nodes and 218 edges with a score of 9.08 (Fig. 3E). In order to gain a better understanding of the cluster 1 and cluster 2, we uploaded targets of cluster 1 and cluster 2 were uploaded to DAVID platform for GO function analysis. The GO function results revealed that the targets in cluster 1 were mainly enriched in cellular response to reactive oxygen species, inflammatory response, negative regulation of IL-1 production and extracellular matrix disassembly, etc. (Fig. 3D). The targets in cluster 2 were mainly enriched in negative regulation of IL-6 production, inflammatory response, epidermal growth factor receptor signaling pathway, negative regulation of smooth muscle cell proliferation and positive regulation of reactive oxygen species metabolic process, etc. (Fig. 3F). The results implied that the clusters of PPI network were mainly related to negative regulation of oxidative stress as well as inflammatory response, which played a promoted role in the development of diabetes.

Biological analysis of targets of gut microbiota metabolites in DN treatment

In order to gain a better understanding of the molecular mechanism of GM-DN targets, we uploaded the 153 targets to DAVID platform for GO function and KEGG pathway analysis. The Fig. 4A showed that the BPs were mainly enriched in the negative regulation of apoptotic process, response to hypoxia, inflammatory response, positive regulation of angiogenesis and extracellular matrix disassembly. The Fig. 4B showed that the CCs were mainly enriched in cytosol, cytoplasm, extracellular matrix, extracellular space and extracellular exosome. The Fig. 4C showed that the CCs were mainly enriched in insulin-like growth factor I binding, protein phosphatase binding serine-type endopeptidase activity, peptidase activity, enzyme binding, nuclear receptor activity. The Fig. 4D showed that the KEGG pathways were mainly enriched in IL10 signaling pathway, TNF signaling pathway, NF-kappa B signaling pathway, KEAP1-NFE2L2 pathway and HIF-1 signaling pathway. Further KEGG functional annotation analysis could be divided into 3 parts: Metabolism (Energy metabolism), Organismal system (Longevity), Human disease (Alzheimer disease, Type II diabetes mellitus and Nonalcoholic fatty liver disease) (Fig. 4E).

Identification and biological analysis of core targets against DN

In order to further identify the core GM targets in the treatment of DN, we obtain 224 human gut targets from gutMGene database (Fig. 5A). The 23 overlapping targets appeared in Fig. 5A were considered the core targets of human gut targets against DN. The 23 targets were submitted to STRING platform for PPI analysis (Fig. 5B)

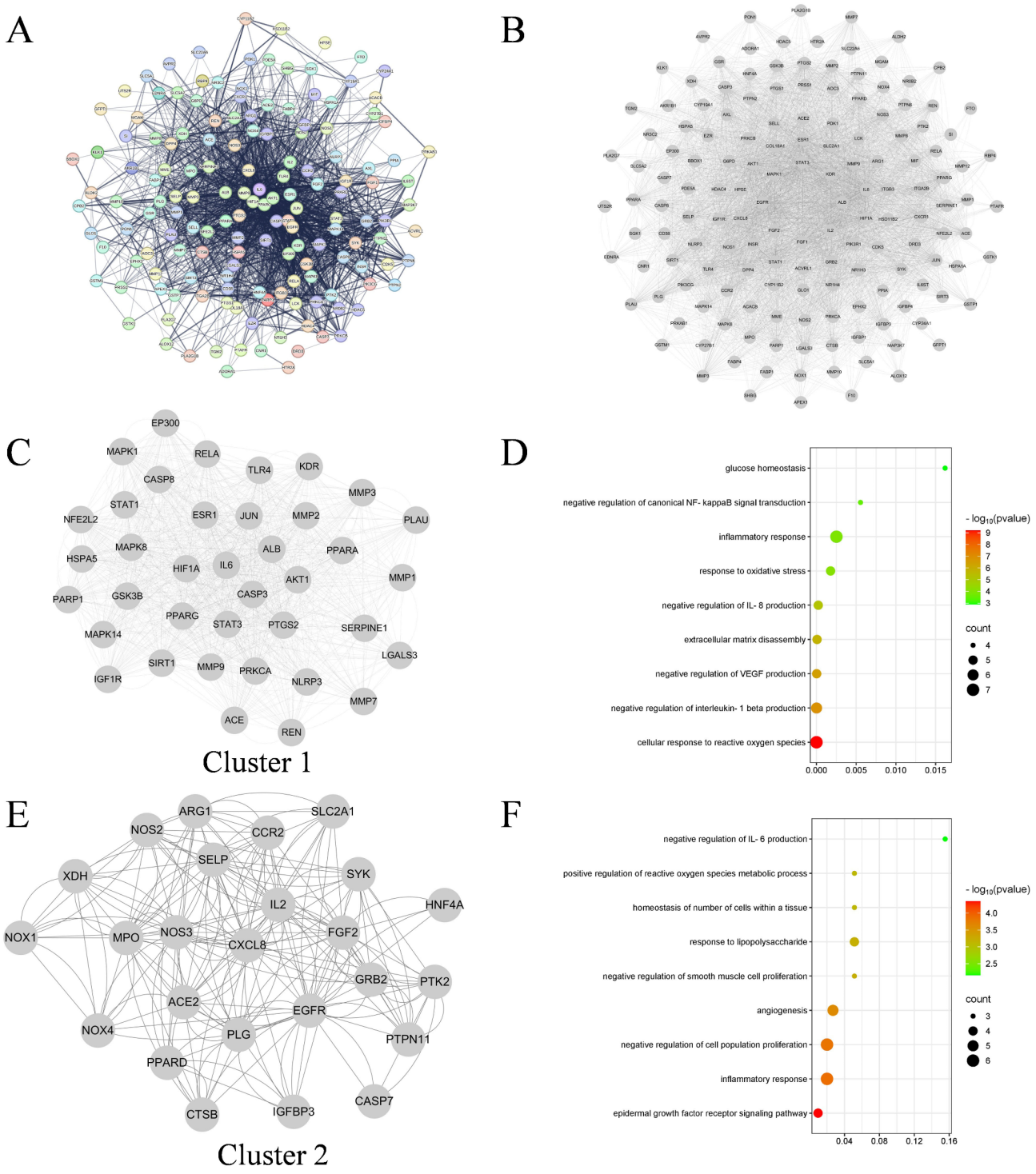

Fig. 3. The PPI network cluster analysis. (**A**) The PPI network from STRING platform. (**B**) The visualization of PPI network. (**C**) The Cluster1 of PPI network. (**D**) The GO-BP function analysis of Cluster1. (**E**) The Cluster2 of PPI network. (**F**) The GO-BP function analysis of Cluster2.

and visualized by Cytoscape 3.6 software (Fig. 5C). We employed Degree Centrality (DC) to describe the feature of PPI network (Fig. 5C). The size and shape of nodes reflected the significance of the targets in the PPI network. As shown in Fig. 5D, we obtained the top 4 targets based on their DC value: PPARG (DC: 42), AKT1(DC: 40), IL6(DC: 38) and JUN (DC: 38). The GO function results indicated that the 23 targets were mainly enriched in regulation of apoptotic process, cellular response to reactive oxygen species and inflammatory response (Fig. 5E). The KEGG pathway results indicated that the 23 targets were mainly enriched in VEGF signaling pathway, TNF signaling pathway, IL-17 signaling pathway (Fig. 5F). Further KEGG functional annotation analysis could be

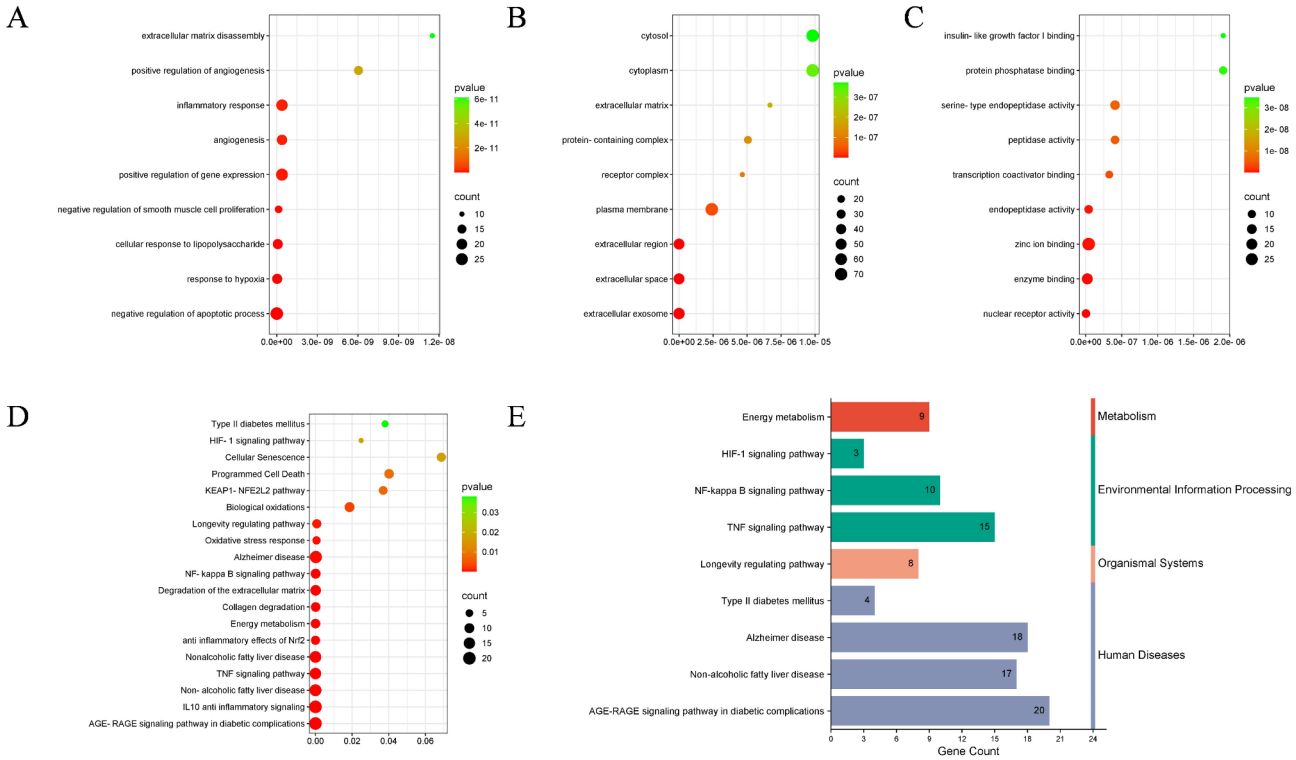

Fig. 4. Biological analysis of targets of GM against DN. (**A**–**C**) The GO function analysis of hub targets, including Biological Process (BP), Cellular Component (CC) and Molecular Function (MF). (**D**) The KEGG pathway analysis of hub targets. (**E**) The KEGG functional annotation analysis of hub targets.

divided into 3 parts: Environmental Information Processing (VEGF signaling pathway, TNF signaling pathway), Organismal system (IL-17 signaling pathway), Human disease (Alzheimer disease, Diabetic cardiomyopathy, alcoholic fatty liver disease, lipid and atherosclerosis) (Fig. 5G). Interestingly, the GO function and KEGG pathway results of human gut targets were consistent with prediction results of the gut microbiota metabolites. Taken together, these results indicated the targets of gut microbiota metabolites were mainly associated with the inflammation, oxidative stress and the regulation of TNF signaling pathway.

Identification of core metabolites against DN

In order to obtain the core gut microbiota metabolites in the treatment of DN, we built a "Microbiota-Substrate-Metabolites-Targets" (M-S-M-T) network to elucidate their intricate relationship. The results showed that the top 4 core targets (PPARG, AKT1, IL6 and JUN) corresponding to 8 metabolites, 9 substrates and 8 gut microbiotas regulating DN (Fig. 6). As shown in Fig. 6, the red color represented the targets, the gray color represented the metabolites, the blue color represented Substrate, the green color represented gut microbiota. The IL-6 had the most connection with metabolites, while PPARG, AKT1 and JUN were corresponding to 1 metabolite respectively. After analyzing the network, we found that Butyrate, Acetate, Indole and 3-Indolepropionic acid were the top 4 metabolites based on their degree value, which could have a positive regulatory effect on DN.

Molecular docking of core metabolites with core targets

Through the simulation of molecular interactions, molecular docking is capable of predicting the affinity of drugs in the binding sites of target binding sites as well as their interactions with specific metabolic enzymes, ultimately facilitating a deeper understanding of the intricate nature of biological systems. Each core target was corresponding to the core 4 targets, and we employed molecular docking methodology to assess the binding affinity between core metabolites and core targets. The heatmap reflected the affinity of core 4 metabolites toward each target (Fig. 7A). The binding affinity < -5.0 kcal mol^{-1} indicates that the ligand possesses the good binding ability toward target. The smaller the value of binding affinity is, the greater the binding ability is. The binding affinity results showed that 3-Indolepropionic acid owning a good binding ability toward targets of PPARG (-5.9 kcal mol^{-1}), AKT1(-7.3 kcal mol^{-1}), IL6(-5.3 kcal mol^{-1}) and JUN (-7.4 kcal mol^{-1}), and we visualized the molecular docking results (Fig. 7B–E). Taken together, 3-Indolepropionic acid can be considered as a potential candidate agent for DN management.

Discussion

DN is one of the main complications of diabetes and the main cause of end-stage renal disease[25]. DN is closely associated multiple disease, such as dementia, cancer and cerebrovascular diseases that leads to high mortality

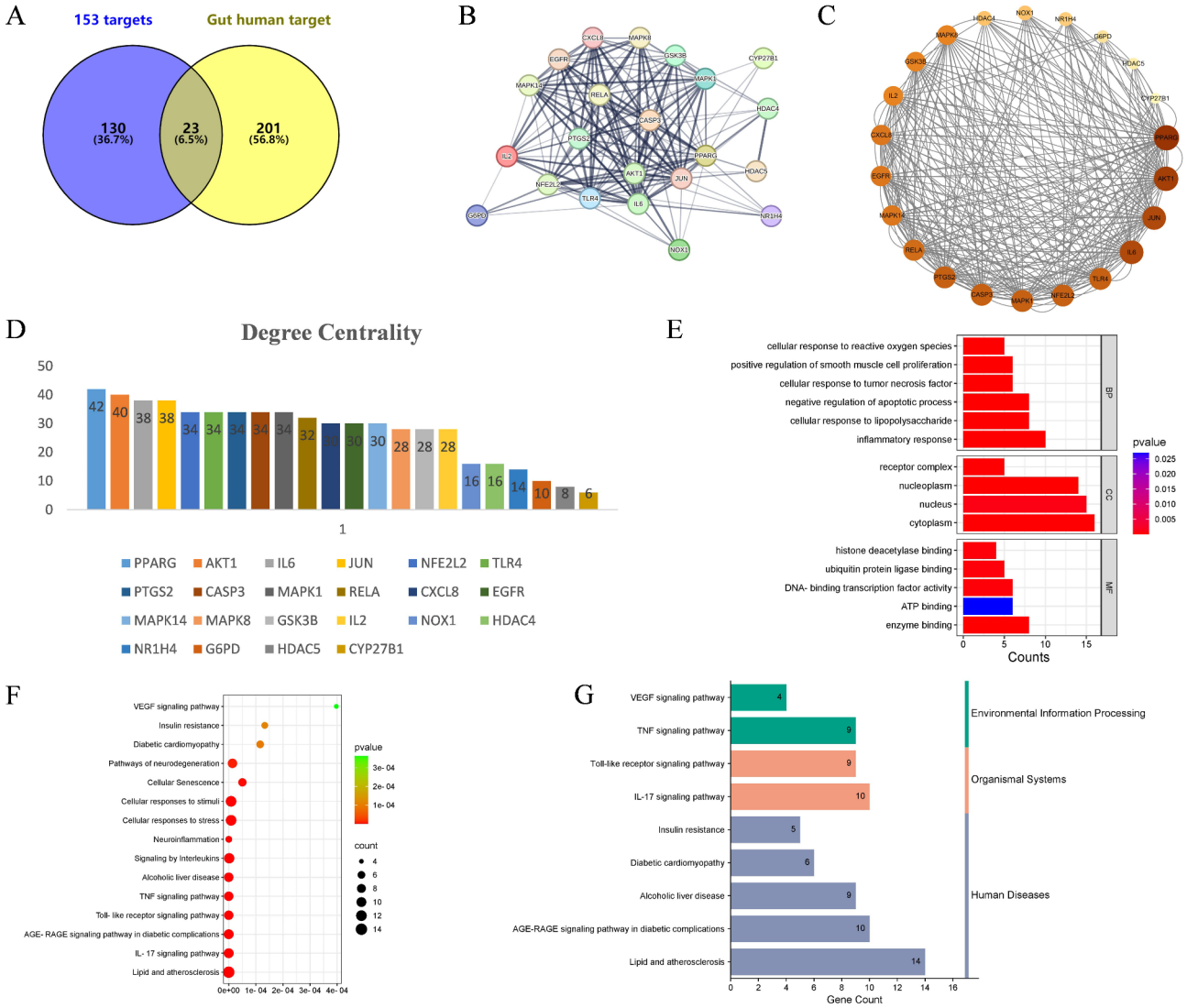

Fig. 5. The identification of core targets against DN. (**A**) The hub targets of 153 targets and human gut targets. (**B**) PPI network from STRING platform. (**C**) The visualization of PPI network. (**D**) The Degree Centrality of hub targets. (**E**) The GO function analysis of hub targets. (**F**) The KEGG pathway analysis of hub targets. (**G**) The KEGG functional annotation analysis of hub targets. Note: We have got permission to use the KEGG software from the Kanehisa laboratory on 2025/1/28.

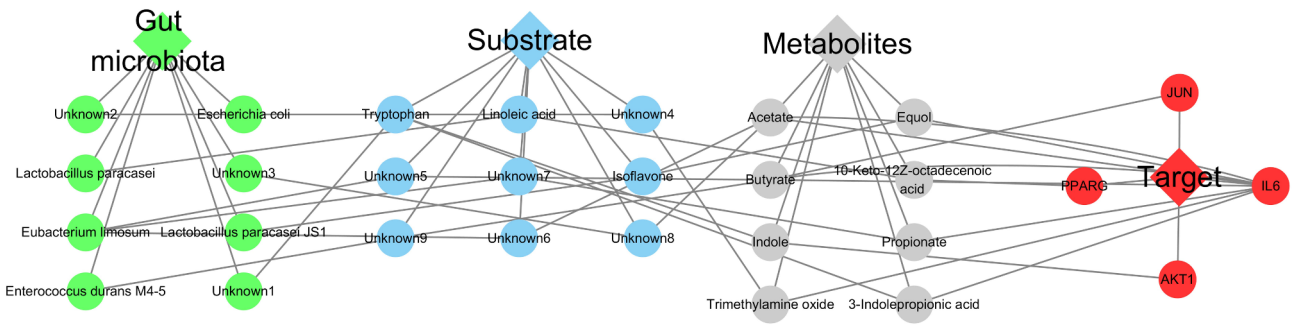

Fig. 6. The identification of core metabolites. Note: The red color represented the targets, the gray color represented the metabolites, the blue color represented Substrate, the green color represented gut microbiota.

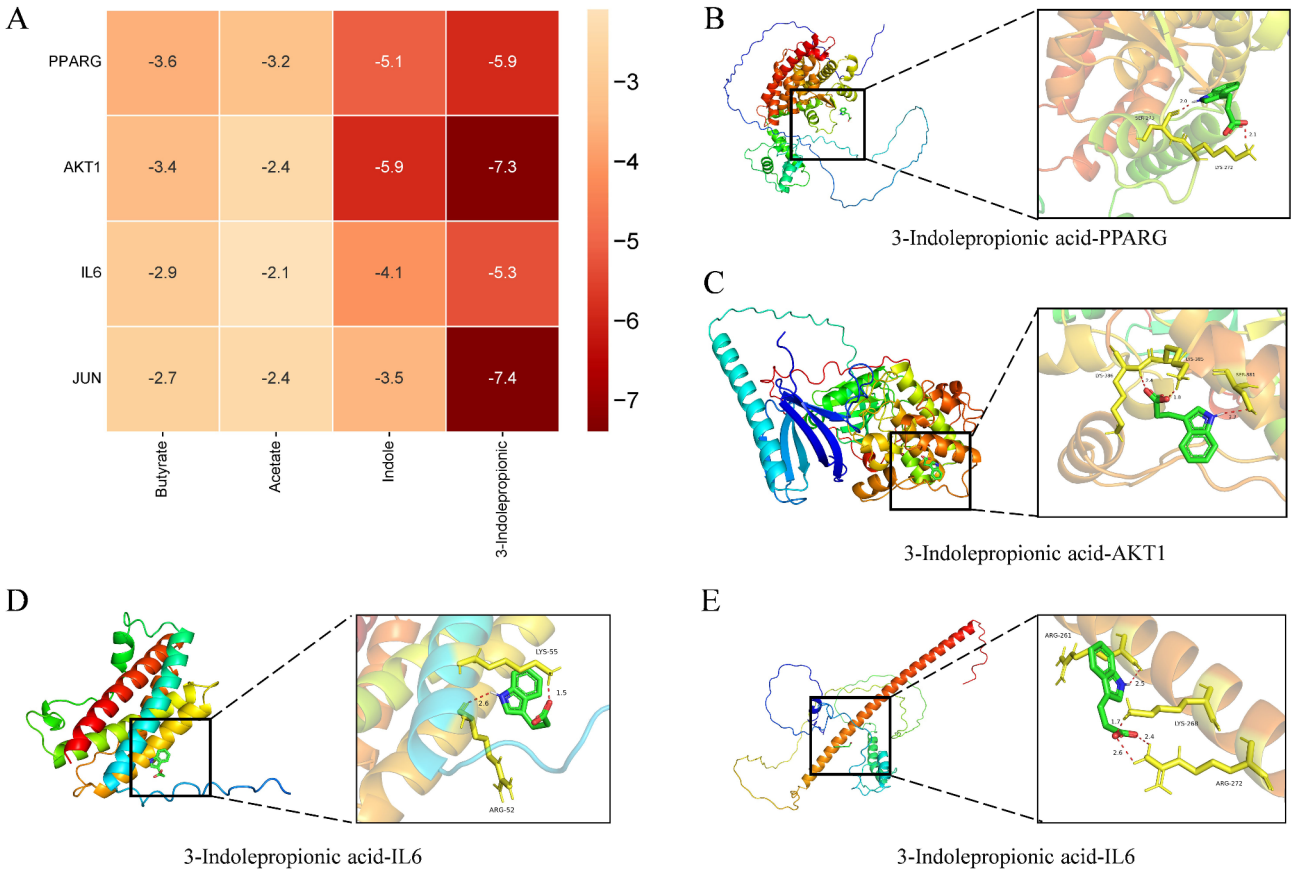

Fig. 7. Molecular docking of core metabolites with core targets. (**A**) The heatmap reflected the binding energy between metabolites and targets. (**B**) 3-Indolepropionic acid-PPARG. (C) 3-Indolepropionic acid-AKT1. (**D**) 3-Indolepropionic acid-IL6. (**E**) 3-Indolepropionic acid-JUN.

and morbidity, which seriously affects the life quality of patients[26]. How to combat and prevent the progression of DN is top challenge. Recently, the concept of gut microbiota on the risk of developing DN was widely accepted by science community. Numerous studies indicated that the composition of gut microbiota living in body of those DN diagnosed are different from that of healthy individuals[27]. The features of gut microbiota in DN was manifested by shortage of SCFAs producing bacteria, the decreased beneficial bacterial abundance and reduced gut microbiota community stability[28].

Recent studies discovered that fiber dietary therapy could regulate glucose and lipid metabolism by enhancing the production of prebiotics and altering the composition of gut microbiota[29,30]. Prebiotics are considered important nutrients that produce multiple beneficial effect on health, such as anti-oxidation and anti-inflammatory reaction by selectively fostering the growth and proliferation of beneficial bacteria[31]. Consumption of Prebiotics can enhance the diversity of intestinal microbiota, particularly by increasing the abundance of certain beneficial bacteria in the gut, such as *Akkermansia muciniphila*, *Roseburia*, *Lactobacillus*, *Bifidobacterium*, and *Faecalibacterium prausnitzii*[32]. The proliferation of beneficial gut microbiota can protect the intestinal environment by inhibiting the growth of harmful bacteria. The consumption of Prebiotics boosts the production of metabolites from beneficial gut microbiota, particularly the synthesis of SCFAs such as acetic acid, propionic acid, and butyric acid[32]. SCFAs play a pivotal role in maintaining metabolic homeostasis. The beneficial effects of SCFAs were associated with their impact on metabolic processes such as fatty acid synthesis and catabolism, as well as glucose absorption and utilization by activating specific receptors or signaling pathways[33,34]. SCFAs also possessed the function of anti-inflammation and immune-regulation, which was capable of inhibiting the expression of inflammatory cytokines and reducing the recruitment of macrophages and neutrophils, thereby alleviating intestinal inflammatory response[20]. Furthermore, the supplementation of SCFAs helps strengthen gut barrier, decrease intestinal permeability and prevent harmful substances from entering the bloodstream. This may be related to the regulatory effect of SCFAs on promoting the production of beneficial gut microbiota that contributes to maintain the integrity of gut barrier.

Network pharmacology combines knowledge from fields such as computer science, systems biology, and pharmacology. By utilizing technologies such as big data, network analysis, and model construction, it explores the relationship between guts and diseases, providing new methods and perspectives for the research of gut microbiota. The PPI network revealed that PPARG, AKT1, IL6 and JUN were the top 4 targets. From the M-S-

M-T network, we identified Butyrate, Acetate, Indole and 3-Indolepropionic acid as the top 4 metabolites based on their degree value. These core metabolites and core targets play vital roles in the regulation of DN.

Peroxisome Proliferator-activated Receptor Gamma (PPARG) is a nuclear transcription factor that serves a vital role in the regulation of lipid metabolism and inflammation. Inflammation is one of the most important factors in the development of DN and results in renal injury and renal fibrosis. A study revealed that activation of PPARG could exert renal protection against inflammation via reducing the production of pro-inflammatory cytokines, such as IL-1β and TNF-α[35]. Another study revealed that natural product like ombuin could inhibit inflammation and pro-fibrogenetic factor in DN animals via enhancing the expression PPARG[36]. AKT, also known as protein kinase B (PKB), serves as a pivotal molecule within the canonical PI3K-AKT-mTOR signaling pathway. This pathway exerts a multitude of effects on cellular metabolic processes by regulating cellular responsiveness and survival in response to exogenous growth stimuli[37]. The activation of PI3K-AKT-mTOR signaling pathway induced by Butyrate could attenuated oxidative stress and muscle atrophy in DN animals[38]. JUN (c-Jun N-terminal kinase, JNK) is also known as stress-activated protein kinase (SAPK). Under hyperglycemia condition, the excessive generation of reactive oxygen species (ROS) led to an upregulation of JUN expression, causes the phosphorylation of insulin protein substrate and facilitated the degradation of insulin receptor substrates, ultimately contributing to insulin resistance[39].

DN is characterized by increased proteinuria excretion, and podocyte injury plays a pivotal role in mediating urinary albumin excretion, glomerulosclerosis and renal function decline[40]. High glucose stimulation leads to podocyte damage, which contributes to the loss integrity of the glomerular filtration barrier, glomerulosclerosis and renal fibrosis[41]. Therefore, mitigating podocyte injury could help delay the progression of DN. Numerous studies indicated that Butyrate could reduce the excretion of proteinuria through alleviating podocyte apoptosis via inhibiting the AMPK/Sirt1/PGC-1α signaling pathway[42]. Furthermore, high glucose condition induced the generation of oxygen species (ROS) and inflammatory responses. Acetate could ameliorate the accumulation of ROS, reduce the level of inflammatory factors and inhibit renal fibrosis by blocking the activation of ROS/NLRP3 pathway[43,44].

An increase in gut microbial diversity is generally correlated with improved glucose metabolism and enhanced insulin sensitivity[45]. The supplementation of butyrate and acetate promote the diversity of beneficial gut microbiota that exert a positive influence on DN[46,47]. Additionally, butyrate could repair intestinal barrier injury in diabetic mice[38]. The disruption of the intestinal barrier allows harmful substances, such as lipopolysaccharide (LPS), to enter the bloodstream leading to inflammation and insulin resistance. By reducing the levels of monocyte chemoattractant protein-1 (MCP-1) and LPS in the serum, acetate improves intestinal permeability and alleviates inflammatory responses[48]. Metabolic dysfunction-associated steatotic liver disease (MASLD) is closely related to diabetes[49]. Literatures revealed that decreased levels of Indole was found in patients MASLD compared to healthy ones. Notably, oral administration of the probiotic (*Bifidobacterium bifidum*) can effectively prevent hepatic steatosis and inflammation. The mechanism underlying this effect is attributed to Indole's ability to inhibit the NF-κB signaling pathway, reduce endotoxin levels and suppress macrophage activation[50]. 3-Indolepropionic acid (IPA), a derivative of indole, possesses potent antioxidant that can protect neurons from damage[51]. High concentrations of IPA is associated with a lower risk of Type 2 diabetes, suggesting its significant role in preventing metabolism diseases[52]. Intermittent Fasting therapy can markedly improve diabetes-related insulin resistance and cognitive impairments by altering the composition and diversity of the gut microbiota in diabetic mice, enhancing the abundance of *Lactobacillus* bacteria and the concentration of 3-Indolepropionic acid (IPA)[41,53]. These results suggested that butyrate, acetate, indole and 3-Indolepropionic acid could serve as potential therapeutic agent for mitigating the damage associated with DN by reducing the abundance of harmful bacteria, increasing gut microbiota diversity and repairing the intestinal barrier.

Although this study highlights the beneficial effect of gut microbiota metabolites on DN, some limitations are still needed to be addressed. On one hand, the prediction results regarding GM against DN is only dependent on open databases instead of real-time sequencing data. On the other hand, the prediction results are needed to be validated through preclinical or clinical experiments to confirm authenticity. Therefore, it is necessary for us to improve the accuracy of our study, for example, by consistently incorporating latest datasets.

Conclusion

Our study further confirmed the pivotal role of gut microbiota metabolites in the pathogenesis of DN. Notably, Butyrate, Acetate, Indole and 3-Indolepropionic acid were 4 key metabolites derived from GM, which exerted regulatory effects on DN through regulating oxidative stress and inflammation. These findings offer novel therapeutic strategies for DN. Future research should further investigate the precise mechanisms of gut microbiota metabolites in clinical treatment. Meanwhile, the development of effective therapies based on beneficial gut microbiota may also emerge as a new pathway for the prevention and treatment of DN.

Data availability

The data generated in this study are available online repositories. The data could be found below: gutMGene (http://bio-computing.hrbmu.edu.cn/gutmgene/#/home).

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Author contributions

Pengyu Tao, Weiguo Yao and Jinlin Huo concepted the experiment. Weiguo Yao, Kun Liu and Jinlin Huo obtained data from the dataset. Pengyu Tao, Weiguo Yao and Jinlin Huo analyzed the data. Weiguo Yao and Kun Liu provided funding resources. Pengyu Tao and Weiguo Yao wrote the manuscript. All the listed authors had read and approved the manuscript publication.

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Declarations

Competing interests

The authors declare no conflicts of interest related to this study.

Ethical approval and consent to participate

This study does not involve any human or animal experiment. The ethical statement is not applicable.

Additional information

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