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Gut microbiota as the critical correlation of polycystic ovary syndrome and type 2 diabetes mellitus

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ABSTRACT

Gut microbiota forms a symbiotic relationship with the host and maintains the ecological balance of the internal and external environment of the human body. However, dysbiosis of the gut microbiota and immune deficiency, as well as environmental changes, can destroy the host-microbial balance, leading to the occurrence of a variety of diseases, such as polycystic ovary syndrome (PCOS), type 2 diabetes mellitus (T2DM), and obesity. Meanwhile, diseases can also affect gut microbiota, forming a vicious cycle. The role of the intestinal microbiota in different diseases have been proven by several studies; however, as a common target of PCOS and T2DM, there are few reports on the treatment of different diseases through the regulation of intestinal microbiota as the critical correlation. This review analyzed the common mechanisms of intestinal microbiota in PCOS and T2DM, including the dysbiosis of gut microbiota, endotoxemia, short-chain fatty acids, biotransformation of bile acids, and synthesis of amino acid in regulating insulin resistance, obesity, chronic inflammation, and mitochondrial dysfunction. The possible therapeutic effects of probiotics and/or prebiotics, fecal microbiota transplantation, bariatric surgery, dietary intervention, drug treatment, and other treatments targeted at regulating intestinal microbiota were also elucidated.

1. Introduction

The human microbiota consists of bacteria, viruses, fungi, and protozoa, mainly in the gastrointestinal tract, with about 10^{14} microorganisms, and *Firmicutes* and *Bacteroidetes* dominate the intestinal microbiota, accounting for about 90% [1]. Intestinal microbiota forms a symbiotic relationship with the host and maintains the energy balance [2]. It has functions in nutrition, immune regulation, metabolism, elimination of specific toxins, and defense against pathogens [3]. After supplementary feeding, the microbiota remained relatively stable throughout the life cycle when it has reached stable climax community [4]. However, its diversity is influenced by factors such as health, genetics, sex hormones, immunity, ways of birth, nutrition, gastrointestinal tract location, and diseases [5,6]. The diversity of intestinal microbiota mainly comprised of α and β diversity. α diversity measures the diversity of species within a community with Chao1 and Shannon diversity scores as commonly used indicators. β diversity shows the clustering of intestinal microbiota communities, mainly measuring the differences among communities [7]. Diseases can cause changes in intestinal microbiota, affecting its structure, relative abundance, and diversity [8]. Alterations in intestinal microbiota may be reflective of hormonal metabolism, and may expose to a higher risk to develop diseases [9], including metabolic diseases, polycystic ovary syndrome (PCOS), type 2 diabetes mellitus (T2DM), and obesity [10–12].

PCOS and T2DM are common endocrine and metabolic disorders. About 6–20% of women of reproductive age are affected by PCOS, and basic features of PCOS include excess of androgen, ovulatory dysfunction, and/or polycystic ovarian changes [13]. The features can be explained by the Dysbiosis of Gut Microbiota (DOGMA) theory, where the dysbiosis of gut microbiota can increase the gut mucosal permeability and the lipopolysaccharide (LPS) of the systemic circulation, activate the immune system, interfere with insulin receptor function, and increase the levels of serum insulin. Meanwhile, the ovaries produce androgens and interfere with normal follicle development [14]. PCOS

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increased the risk of the development of T2DM. T2DM is caused by insufficient insulin secretion and insulin resistance (IR) [15]. The International Diabetes Federation reported that 463 million adults aged 20–79 years old were living with diabetes in 2019, a number that will likely rise up to 700 million by 2045 [16]. Changes in gut microbiota can contribute to T2DM through different metabolic and immune pathways, including inflammatory status, abnormal glucose metabolism, and IR [17]. PCOS and T2DM interacts with each other, and most patients suffer from both diseases. There are similar mechanisms in IR, chronic inflammation, obesity, and mitochondrial dysfunction [18–20], which increase the incidence of obesity, cardiovascular disease, obstructive apnea syndrome, and other complications [21,22]. Although several dietary supplementations and/or drugs have been used for treating PCOS and T2DM (as shown in Table 1), such as inositol [23], omega-3 [24], vitamin D [25], ketogenic diet (KD) [26], insulin-sensitizer agents [27,28], orlistat [29], and traditional Chinese medicine [30,31], most of them are indicated for a single disease and used as a single target therapy or adjuvant therapy. Moreover, some drugs have side effects, and the clinical efficacy is still unsatisfactory.

Currently, many researches have been conducted on intestinal microbiota, PCOS, and T2DM, respectively [32,33]; however, there are few reports on the simultaneous treatment of PCOS and T2DM by regulating intestinal microbiota as the critical correlation. It may provide new ideas for treating different diseases by understanding the intestinal microbiota as the common targets of PCOS and T2DM.

2. Common pathogenetic mechanisms involved in PCOS and T2DM

The common pathogenesis **mechanisms** of PCOS and T2DM, including IR, obesity, chronic inflammation, mitochondrial dysfunction, and pathogenesis mechanisms, interact with each other. Obesity and IR can cause inflammatory changes and oxidative stress (OS), which might interfere with insulin action by suppressing insulin signal transduction. Obesity can initiate the expression of tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), interleukin-8 (IL-8), C-reactive protein (CRP) by activating Toll-like receptors (TLRs), DNA-PKcs (PKCs), and nuclear factor-kappaB (NF-κB) pathway and induce IR. This might interfere with the anti-inflammatory effect of insulin, which in turn might promote inflammation [34]. Chronic inflammation can lead to apoptosis of cells, which decreases insulin secretion. Obesity can also cause overactivation of mitochondrial β-oxidation. In addition, the decrease of mitochondrial substrate oxidation can induce IR by serine phosphorylation on insulin receptor substrate 1 (IRS-1) and protein kinase B dephosphorylation, leading to obesity [35]. Mitochondrial dysfunction can activate IRS by the MAPK pathway. These factors above can lead to IR. IR can also result in hyperandrogenism and hyperinsulinemia. The mechanisms are shown in Fig. 1.

Obesity could activate tumor necrosis factor by activating toll like receptors (TLRs)- α and induced IR. This may interfere with the anti-inflammatory effect of insulin, which in turn may promote inflammation. Chronic inflammation could lead to apoptosis and reduce insulin secretion. Obesity could also lead to mitochondria β- Oxidative overactivation. The reduction of mitochondrial substrate oxidation could induce IR through serine phosphorylation and protein kinase B dephosphorylation on insulin receptor substrate 1, resulting in obesity. Mitochondrial dysfunction could activate IRS through MAPK pathway, and the above factors together lead to IR.

IR, insulin resistance; TNF-α, tumor necrosis factor-α IL-6, interleukin-6; IL-8, interleukin-8; CRP, C-reactive protein; IRS, insulin receptor substrate; DNA-PKcs (PKCs); nuclear factor-kappaB (NF-κB).

Table 1
Dietary supplementations and/or drugs for PCOS and T2DM.

Dietary supplementations and/or drugs	Effects and mechanisms
Inositol	Inositol are present in many foods and dietary supplements, and it can improve IR, regulate glucose intake, decrease serum androgen levels, and improve metabolic parameters in treating PCOS and T2DM.
Omega-3 supplements	Omega-3 supplements can improve IR, dyslipidemia, hyperandrogenism, and regulate metabolic indicators.
Vitamin D	Vitamin D is a steroid hormone. The level and concentration of vitamin D were negatively associated with androgen, IR, and body fat mass. Vitamin D supplements have beneficial effects on IR and lipid metabolism.
Ketogenic diet (KD)	The KD is a high-fat and very low-carb diet which can reduce weight and decrease glucose and improve IR.
Insulin-sensitizer agents	Insulin-sensitizer agents such as metformin and pioglitazone can reduce body mass index (BMI), ameliorate insulin sensitivity, and improve menstrual cycle.
Orlistat	Orlistat can reduce BMI/body weight in PCOS and T2DM.
Traditional Chinese medicine (TCM)	TCM includes monomer components and TCM compounds. Berberine is the main active component of *Rhizoma coptidis*, and it can improve IR. Quercetin can influence insulin sensitivity. Liuwei Dihuang Pills can improve insulin sensitivity, alleviate IR, and regulate sexual hormone levels.

2.1. IR

Insulin regulates glucose homeostasis and lipolysis by stimulating glucose uptake and suppressing hepatic glucose production. If the insulin function decreases, exogenous or endogenous insulin cannot increase glucose uptake and utilization, and an increased amount of insulin is required to achieve metabolic action, eventually leading to IR. IR is an important pathogenesis of metabolic diseases, as it is related to chronic inflammation, obesity, mitochondrial dysfunction [36]. Furthermore, it plays a key role in the development of PCOS and T2DM [37,38]. PCOS is related to IR and defects in insulin secretion, and its mechanisms may be associated with excessive serine phosphorylation of the insulin receptor, intrinsic and acquired defects in insulin signaling, and post-binding defect in insulin signal transduction [39]. These factors together with obesity can lead to an increased risk of T2DM [40].

IR and hyperinsulinemia are common features of patients with PCOS, and about 70% of patients are associated with IR [41]. IR and hyperinsulinemia have a co-gonadotropic effect, stimulating cytochrome P450 17 alpha (P450c17α) enzymatic activity and influencing the activity of 17-hydroxylase and 17,20-lyase [42], promoting androgen secretion, increasing circulating androgen levels, and inhibiting insulin signaling and translocation of glucose transporter 4 (GLUT4), which influences glucose uptake and lipid metabolism [43]. Androgens can produce IR by directly affecting insulin action in skeletal muscle and adipose tissue, changing adipokine secretion and increasing visceral adiposity. Moreover, IR is pathologically relevant with hyper-Ser/Thr phosphorylation of IRS [44]. Regarding the major defect in insulin action, there is a post-binding defect in the insulin signaling receptor which could be caused by the serine hyperphosphorylation of the receptor and IRS-1, which affects metabolism [37]. Almost 90% of diabetes have IR, which precedes the first symptoms of diabetes [45]. The primary cause of IR could be attributed to the presence of obesity and accelerated progression to T2DM accompanied by the propensity for beta-cell failure [46]. IR is a core defect in T2DM, and it can lead to a decrease in glucose uptake and utilization and increase the production of hepatic glucose in the liver. Hyperglycemia occurs when the capacity of insulin to stimulate glucose disposal and transport decreases. Moreover, when insulin sensitivity and insulin secretion are impaired, the individual with IR is unable to secrete sufficient insulin to overcome this defect [15]. Therefore, their affinity for insulin or a defect in the post-receptor signaling leads to T2DM [47].

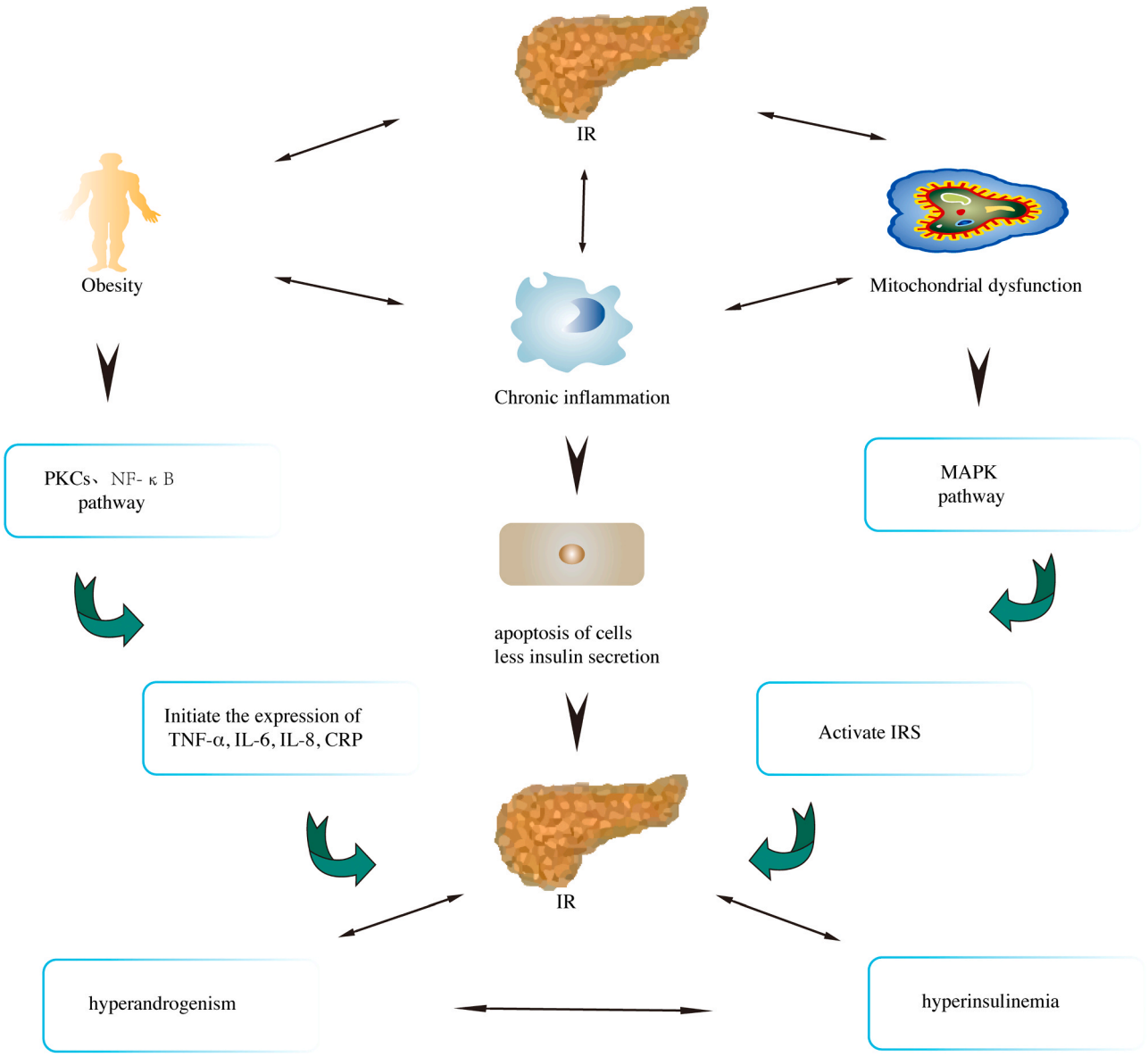

Fig. 1. The common pathogenesis of PCOS and T2DM.

2.2. Obesity

Adipose tissue can secrete hormones, adipokines, and cytokines and participates in the endocrine processes of regulating glucose and fatty metabolism, immunity, and inflammatory response [48]. Obesity results in adipocyte hypertrophy and hypoxia-induced necrosis of adipocytes, which can promote pro-inflammatory cytokine production [49], including TNF-α and IL-6 [50]. Low-grade inflammation can impair the action of insulin and lead to IR [51]. Free fatty acids (FFA) induce lipid accumulation in skeletal muscle, and it is a source of proinflammatory cytokines [52], which aggravate IR by downregulating the expression and inducing the reduction of total insulin receptor number [53]. Excess fat stimulates the TLRs on the resident macrophages of adipose tissue that secretes TNF-α, which leads to the activation of NFκB-mediated cellular toxicity by stimulating various PKCs and downregulating tyrosine phosphorylation of insulin receptors and compromises insulin signaling, promoting IR [54]. Obesity exacerbates hormonal and clinical features of PCOS, which increase the risk of obesity [55]. Obesity is the principal factor in hyperglycemia and hyperinsulinemia, which result in IR. Importantly, it is an significant risk factor for the development of T2DM [53].

About 30–60% of patients with PCOS exhibit obesity [56]. Obesity and hyperandrogenism interact, since androgens can induce abdominal fat accumulation and may cause adipose tissue dysfunction, leading to obesity and IR [57]. Increased IR is a primary feature of obesity in PCOS [55]. The adipose tissue, liver, muscle, and pancreas are inflammatory sites in obesity. The production of pro-inflammatory cytokines interferes with insulin signaling in peripheral tissues or induces β-cell dysfunction and insulin deficiency [58]. Nearly 90% of individuals with T2DM are overweight or obese, and IR in T2DM can lead to obesity [59]. Obesity is related to IR by increasing the production of leptin and TNF-α in adipose tissue. TNF-α and leptin can mediate the serine phosphorylation of IRS-1, which then interferes with insulin action by inhibiting insulin receptor and type 1 insulin growth factor (IGF) receptor tyrosine kinases and stimulating IGF binding protein production [55]. Visceral adipocytes are thought to express defects in insulin intracellular signaling. This defect decreases the activity of the PI3K (phosphoinositide-3 kinase) enzyme, which can reduce GLUT-4 and decrease the insulin-dependent cellular glucose uptake with an increased risk of T2DM [60].

2.3. Chronic inflammation

Chronic inflammation is the basis of a variety of physiological and pathological processes. It is associated with IR, obesity, and hyperandrogenism [61], and it may induce IR by stimulating major inflammatory NF-κB and JNK pathways to inhibit insulin action [52]. Obesity itself is an inflammatory site that promotes pro-inflammatory cytokines. Chronic inflammation can induce apoptosis of cells and abnormal function of endothelial cells, decrease insulin secretion, and lead to IR. Chronic inflammation is a significant pathogenetic factor in PCOS and T2DM [45,62].

Multiple inflammatory markers such as TNF-α, IL-6, IL-8, and CRP are elevated in patients with PCOS. It is also associated with proinflammatory states [63,64]. In PCOS, chronic inflammation is connected with the hypertrophy of adipocytes, which cause compression phenomena in the stromal vessels, resulting in adipose tissue hypoperfusion and hypoxia, leading to chronic inflammation [61]. In addition, glucose induces inflammation and promotes the production of androgens in the ovaries, whereas hyperandrogenism results in mononuclear cell (MNC) activation and increases MNC sensitivity of glucose ingestion, thereby inducing inflammation [65]. The serum levels of CRP and IL-6 are increased in T2DM, and the magnitude of increase is related to the degree of hyperglycemia [45]. Visceral adipose tissue can induce adipocyte inflammation by increasing the production of inflammatory cytokines, monocyte chemotactic proteins, and recruitment of immune cells [66].

2.4. Mitochondrial dysfunction

Mitochondria as organelles which govern fundamental cellular functions and are important structures that regulate OS, it is important in reactive oxygen species (ROS) clearance, stress response, and maintenance of redox homeostasis [67]. Balance of mitochondrial quality is key to maintaining cellular energy and metabolic homeostasis as a decrease in mitochondrial function results in excess generation of ROS from mitochondria [68]. Dysfunctional mitochondria can activate inflammasomes, dysregulate immune signal transduction, and release mitochondrial damage-associated molecular patterns, leading to chronic inflammatory which can trigger numerous chronic diseases [69]. OS is associated with inflammation, and it can impair insulin signaling, which leads to IR. mtDNA copy number reduction, OS induced by mitochondrial dysfunction, and mitochondrial DNA (mtDNA) mutations contribute to IR and lipid metabolism [70]. Mitochondrial dysfunction is an important factor in PCOS and T2DM, and it is associated with IR, inflammation, obesity, lipolysis, and hyperandrogenemia. Mitochondrial dysfunction can influence the MAPK pathway; activate P38, JNK, and IKK bypass; decrease Ser/Thr phosphorylation of IRS and expression of IRS1 and IRS2 and uncoupling of upstream receptors and downstream effectors attenuating insulin signaling; and finally lead to IR [71].

PCOS presents with increased OS and decreased antioxidant capacity [71]. Obesity is correlated with mitochondrial dysfunction and elevated OS, which may aggravate IR and hyperandrogenism [71]. Glucose and lipid metabolism are largely dependent on mitochondria to generate energy in cells, and mitochondrial dysfunction can halt energy production and induce OS and chronic inflammation due to oxidative damage [72]. The formation of ROS may result in maladaptive consequences, increasing the rate of mutagenesis and stimulating proinflammatory processes [73]. OS leads to the activation of p38 and JNK MAPKs stimulating the secretion of TNF-α and IL-6 [74]. Type 2 diabetes has the characteristics of mitochondrial dysfunction and high ROS [75]. Persistent hyperglycemia lead to increased ROS production by mitochondria, which is the major source of OS [76]. Mitochondrial dysfunction is a main cause of β-cell failure in the evolution of T2DM. ROS influences the structure and function of the mitochondria, and it results in β-cell failure. ROS activates uncoupling protein 2 (UCP2), which leads to reduced β-cell adenosine-triphosphate (ATP) synthesis and impacts insulin secretion [77]. The production of superoxide anion is facilitated during hyperglycemia by the proton electrochemical gradient of the mitochondrial electron transport, and heme oxygenase (HO)−1 has a low expression. Superoxide anion is a precursor of most ROS, and it is related to OS [78]. HO-1 is one of the major defenses against OS, and the decrease of HO-1 contributes to mitochondrial OS, which is associated with IR, IR can lead to hyperglycemia [74].

3. Physiological role of intestinal microorganisms in the host

Intestinal microorganisms play a physiological role in nutrition, immune regulation, and host defense [79]. Intestinal microorganisms feed on food and intestinal secretions, promote food re-decomposition and absorption, and synthesize essential amino acids, vitamin, and short-chain fatty acids (SCFAs), such as acetic, propionic, and butyric acids, which contribute to lipid and amino metabolism and protein digestion and provide nutrients and energy for the host [80]. Butyric acid contributes to intestinal epithelial barrier integrity, anti-inflammation, and immune homeostasis [81]. Intestinal microorganisms are associated with the largest population of immune cells in the body, promoting the maturation of the immune system during infancy, such as the maturation of intestinal CD4+ and CD8+T cells and dendritic cells, and maintaining the integrity and homeostasis of the immune system [82]. The normal arrangement of intestinal microorganisms contributes to the integrity of the gut mucosal barrier and prevents the establishment of food-borne pathogens and the reproduction of pathogenic microorganisms. Intestinal microorganisms stimulate the immune system and have the ability to recognize gram-negative bacteria and induce IgG antibodies to defend against pathogen invasion [83]. Therefore, the host's intestinal microorganisms are important.

4. Mechanisms of gut microbiota in the pathogenesis of PCOS and T2DM

PCOS and T2DM can result in dysbiosis of gut microbiota, which can increase intestinal permeability and release of LPS, and abnormal expression of SCFAs, bile acids, and amino acid. This leads to the activation of the immune system, inflammation, and OS thereby inducing obesity by activating the TLR pathway, fat-insulin signaling pathway, bile acid receptors, and a decrease in glucose transport. The mechanism of gut microorganisms was shown in Fig. 2.

PCOS and T2DM could lead to intestinal microbial imbalance, thereby increasing intestinal permeability and LPS release, as well as abnormal expression of SCFAs, bile acids and amino acids, which leads to the activation of immune system, inflammation and OS, which induces obesity by activating TLR pathway, fat insulin signaling pathway, bile acid receptor and reduced glucose transport.

LPS, lipopolysaccharide; SCFAs, short-chain fatty acids; TLR, Toll-like receptor, OS, oxidative stress; IR, insulin resistance.

4.1. Clinical correlation of intestinal microorganisms in PCOS and T2DM

Intestinal microorganisms and their metabolites are closely related to PCOS, T2DM, and obesity [84]. Compared with the control group, PCOS and T2DM revealed significant variations in the number of species and metabolites produced, mainly represented by the decrease in α and β diversity, which was represented by the reduction of beneficial bacteria and the augmentation of pathogenic bacteria [12,85].

In PCOS, the genus levels of *Lactobacillus*, *Escherichia/Shigella*, and *Bacteroides* increased in patients with PCOS [86]. The relative abundances of *Porphyromonas* spp., *Bacteroides coprophilus,* and *Blautia* spp. were consistently higher, while *Odoribacter* spp., *Roseburia* spp., *Anaerococcus* spp., *and Ruminococcus bromii* were lower [87]. *Parabacteroides* and *Clostridium* were enriched in PCOS [88]. In PCOS rats induced by letrozole, *Lactobacillus*, *Ruminococcus*, and *Clostridium* were lower; however, *Prevotella* was higher, and the abundance of *Prevotella* was

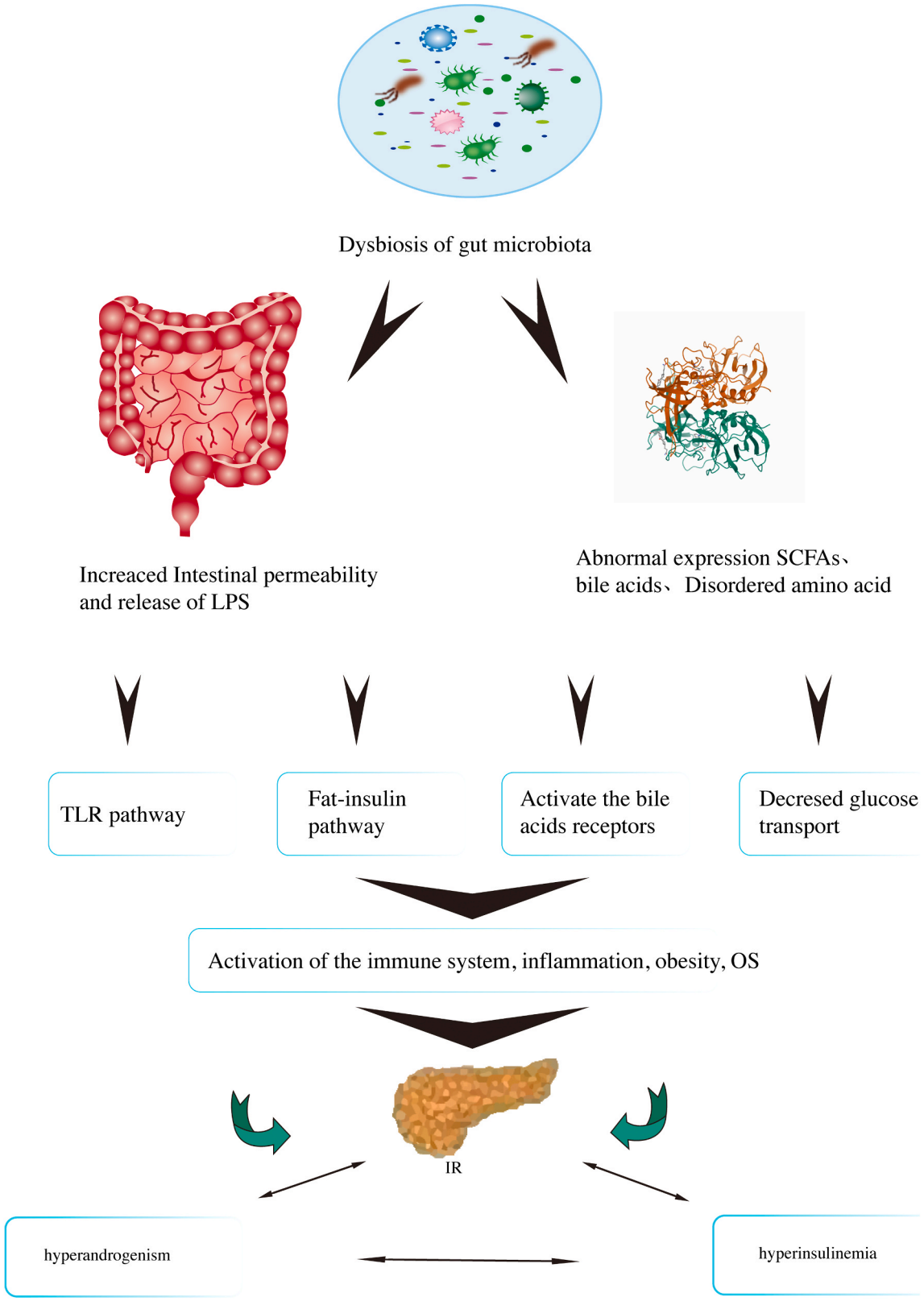

Fig. 2. The mechanism of gut microorganisms in the pathogenesis of PCOS and T2DM.

associated with inflammation, positively related to androgen, and negatively related to estradiol [89]. *Bacteroides vulgatus* was significantly increased in patients with PCOS, and the transplantation of *B. vulgatus*-colonized recipient mice lead to the disruption of ovarian functions and IR [90]. *Bifidobacterium lactis* V9 regulates the levels of sex hormones by regulating the gut microbiome in PCOS patients [88]. There is a potential interaction between sex hormones and gut microbiota. Administration of probiotics including *Lactobacillus*, *Bifidobacterium*, and selenium can decrease total levels of testosterone and hirsutism [91]. The pro-inflammatory bacteria, containing *Bacteroides*,

play a key role in IR, hormonal disturbance, and inflammation [92]. Gram-negative bacteria, which belong to the phyla *Bacteroidetes* and *Proteobacteria*, were relatively enriched in T2DM [11]. *Lactobacilli* dominate the gut of T2DM patients [93]. The abundance of some butyrate-producing bacteria decreases, including *Roseburia intestinalis* and *Faecalibacterium prausnitzii*, and various opportunistic pathogens increase, including *Lactobacillus gasseri* and *Streptococcus mutans*, *Proteobacteria*, and certain *Clostridiales* [94]. Butyrate-producing bacteria are negatively correlated with glycemic parameters. Moreover, the number of *Blautia* increases [95]. Regarding *Bacteroides* and *Prevotella* species, the *P. copri* and *B. vulgatus* species were related to the development of IR and T2DM [96]. The genera of *Bifidobacterium*, *Bacteroides*, *Faecalibacterium*, *Akkermansia*, and *Roseburia* were negatively related to T2DM; however, the genera of *Ruminococcus*, *Fusobacterium*, and *Blautia* were positively relevant to T2DM [97]. *Firmicutes* is related to inflammation. Obese patients have a reduced proportion of *Akkermancia muciniphila*, which can improve insulin action, glucose tolerance, and metabolic endotoxemia [98].

PCOS and T2DM can affect the diversity and composition of intestinal microbiota, and there are similarities between PCOS and T2DM. Therefore, understanding the changes of intestinal microbiota may be helpful for the early diagnosis of PCOS and T2DM and may become a new strategy for the prevention and treatment in the future.

4.2. Dysbiosis of gut microbiota

Dysbiosis of gut microbiota is vital for the pathogenesis of PCOS and T2DM, and it is closely relevant with chronic inflammation-related diseases. Disorders of gut microbiota result in the decrease of beneficial bacteria and the augmentation of harmful bacteria. Dysbiosis of gut microbiota leads to impairment of gut mucosal barrier function and increases intestinal permeability, which results in LPS from visceral gram-negative bacteria entering the systemic circulation through the leaky intestinal wall and activating the TLR4 immune system leading to chronic inflammation [92,99]. Long-term chronic inflammation interferes with insulin receptors, impairs insulin secretion and insulin sensitivity, and results in IR, while IR and chronic inflammation can lead to obesity [100]. Excess fat storage in obese patients increases insulin levels in the blood, triggering and aggravating IR [101]. IR, chronic inflammation, obesity, and other mechanisms interact to promote the development of PCOS and T2DM. Gut microbiota alters inflammation and oxidative stress, which influence each other. Gut microbiota sends signals to the mitochondria, and the dysbiosis of the gut microbiota can change the mitochondrial metabolism, activate immune cells, and alter the function of the epithelial barrier [102]. Changes in gut microbiota may contribute to diseases through a variety of mechanisms [103]. Therefore, understanding the mechanisms of dysbiosis of the intestinal microbiota may provide new methods for the simultaneous treatment of PCOS and T2DM.

4.3. Endotoxemia

Endotoxemia is associated with intestinal dysbiosis and increased intestinal permeability which is related to malabsorption of nutrients and micronutrients. It has been found that vitamin D signaling promotes innate immunity and maintains tight intestinal connections, and the deficiency of vitamin D may impair the intestinal innate immunity, leading to bacterial translocation and endotoxemia [104]. Vitamin D deficiency is found both in PCOS and T2DM. Endotoxemia is involved in the development of PCOS and T2DM which are associated with IR and chronic inflammation. Endotoxemia, which is produced by the gut microbiota, could be an essential factor in promoting IR, chronic inflammation, lipid storage, and other metabolic disorders through the upregulation of pro-inflammatory signaling which is involved in the development of PCOS and T2DM [105]. LPS constitutes the outermost layer of the cell wall of gram-negative bacteria, and can trigger a low-grade inflammatory response. The dysbiosis of gut microbiota can lead to an increase of serum LPS concentration which acts as an endotoxin, destroys the intestinal barrier, increases intestinal permeability, and leads to the change in mucosal immune response [106]. LPS binds to TLR-4 found on immune cells, which activate the immune system and induce pro-inflammatory cascades and IR [107]. In addition, intestinal permeability disorders lead to infiltration of macrophages, produce and activate inflammatory cytokines, and result in local inflammation, such as serum TNF-α, IL-6, and other inflammatory cytokines [108]. Endotoxemia causes a decrease in *Bifidobacterium* spp., resulting in impaired glucose tolerance and inflammatory status [109].

4.4. SCFAs

SCFAs are microbial metabolites that have obvious physiological effects on the host, and it can be utilized as an energy source by the colonocytes, promote the absorption of energy, and influence obesity, insulin sensitivity, and the levels of lipid and glucose [110]. Gut microbiota produces SCFAs such as acetic, propionic, and butyric acids. SCFAs are microbial metabolites, the proportion of commensal intestinal bacteria affect the level of SCFAs. SCFAs are regarded as mediators between intestinal microbiome and immune system, influence the intestinal immune cells and inflammatory balance [111]. The production of SCFAs can be affected by intestinal microorganisms through the fermentation process, which varies depending on the bacteria. Intestinal microorganisms can produce acetic acid through the fermentation of indigestible carbohydrates and the Wood–Ljungdahl pathway [112]. The hexoses and pentoses are the most used substrates in the fermentation process, and the main substrates of propionic acid fermentation are glucose and lactate [113]. Butyric acid is vital in anti-inflammatory activity and improving insulin activity. SCFAs are important in protecting the gut. It lines up around epithelial cells, helps form tight connections between cells, and maintains the integrity of the gut barrier [114]. The microbial production of SCFAs influence glucose and energy metabolism, and butyrate is a major source of energy for the intestinal epithelium and also influences insulin sensitivity. Dietary supplementation of butyrate can prevent and treat diet-induced IR in mouse [115]. Furthermore, butyrate plays a key role in immune metabolism [116]. Intensive dysbacteriosis reduces butyric acid, which influences the function of macrophages, colon-regulated T cells, and pancreatic cells. Dysbacteriosis can decrease insulin secretion and thereby increase blood glucose. Dysbacteriosis reduces acetic acid, propionic acid, and butyric acid, inhibiting the actions of receptors of free fatty acids (FFAR), Gpr41 (FFAR3) and Gpr43 (FFAR2), decreasing insulin secretion and insulin sensitivity, which leads to IR [117]. The inhibition of Gpr43 decreased the regulation of fat-insulin signaling and energy consumption, hence increasing fat. In addition, intensive dysbacteriosis can also decrease intestinal anti-inflammatory response, increasing NF-kB, TNF-α, and IL-8, leading to intestinal inflammation. The reduction of SCFAs can result in IR by affecting the gut anti-inflammatory response capacity and weakening the ability of SCFAs receptor activation [118]. SCFAs can modulate satiety, and acetate can increase fatty acid oxidation and energy expenditure. Butyrate can increase brown adipose tissue mass and UCP1 expression, and acetate and butyrate can reduce body weight [119]. SCFAs can also decrease IR, promote pancreatic β-cell proliferation and insulin secretion, and improve metabolism.

4.5. Biotransformation of bile acids

Bile acids maintain the functions of the intestinal barrier and prevent the excessive growth and migration of gut bacteria. Changes in the co-metabolism of bile acids, branched fatty acids, and choline have been relevant with the obese or diabetes phenotype [120]. Bile acids may regulate glucose tolerance and influence insulin sensitivity and energy metabolism [121]. Bile acids are endocrine signaling molecules, and they can affect host physiology by the activation of bile acid receptors

such as farnesoid X receptor (FXR) and transmembrane G-coupled receptor 5 (TGR5). Changes in bile acid homeostasis are often related to metabolic disease [122]. The increase in circulating conjugated primary bile acids is positively related to hyperandrogenism in PCOS [123]. Ursodeoxycholic acid (UDCA) is a steroid bile acid with antioxidant, anti-inflammatory, and immunomodulating effects and has been shown to improve IR [124]. UDCA therapy improves ovarian morphology and decreases the levels of total testosterone and insulin of PCOS rat [125]. Glycodeoxycholic acid and tauroursodeoxycholic acid were markedly reduced in the PCOS group [90]. There are strong interactions between bile acids and the microbiota. Gut microbiota is able to manipulate intestinal barrier function, modulate the immune system, and regulate the expression of CYP7A1 and CYP7B1, which is associated with the formation of bile acids [126]. Bile acids can influence gut microbiota by promoting the growth of bile acid-metabolizing bacteria [127]. Primary bile acids (PBAs) are transformed into secondary bile acids through the intestinal microbiota. The dysregulation of microbiota results in the reduction of the production of secondary bile acids and inhibits the activation of bile acid receptors such as FXR, TGR5, and pregnancy X receptor [128]. PBAs can promote the activation of FXR/TGR5 and the secretion of GLP-1, and promote insulin secretion, reduce gluconeogenesis. *Lactobacillus* species *and Firmicutes which related to T2DM* can promote the produce and metabolism of bile acids [129].

4.6. Synthesis of amino acid

Branched-chain amino acids (BCAAs), including leucine, isoleucine, and valine, are vital nutrients, which are the necessary substrates for protein biosynthesis. BCAAs can regulate metabolism of glucose, lipids, gut microbiota, immunity, and diseases in humans by the PI3K/AKT/mTOR signal pathway [130]. Myocytes and adipocytes activate mitochondrial BCAA catabolic enzymes to promote the production of ATP in normal physiology; however, disordered amino acid metabolism can reduce the production of ATP and glucose transport [131]. Disordered amino acid metabolism may exacerbate IR by altering glucose metabolism or inducing inflammation. Obesity and IR are potential factors for PCOS and T2DM and influence the synthesis and catabolism of BCAAs [132]. Defective BCAA oxidative metabolism might occur in obesity, resulting in further accumulation of BCAAs and toxic intermediates [133]. BCAA can stimulate the secretion of insulin and glucagon [134]. The increase of circulating BCAAs and related metabolites are relevant in IR and can predict the development of diabetes [135]. Essential BCAAs are derived from gut microbial biosynthesis, and it is related to the activated mucosal immunity and the maintenance of intestinal integrity. Emerging evidence has proved that BCAAs are involved in maintaining gut barrier function, and BCAAs hold vital roles in promoting gut development and health and improving immune defenses [136]. BCAAs serve as promoters for AMP expression and regulate immunity via crosstalk with their receptors or ligands. BCAAs can upregulate the expression of defensins in enterocytes, activate alexins, and prevent the colonization of exogenous pathogenic bacteria [137].

5. Gut microbiota in the treatment of PCOS and T2DM

Although the potential role of gut microbiota in the treatment of PCOS and T2DM has attracted increasing attention, its therapeutic role is still under clinical investigation. Considering the multifactorial factors of PCOS and T2DM, they share common characteristics in pathogenesis and clinical manifestations, among other aspects, and are related to the intestinal microbiota. Therefore, it is necessary to restore the composition of microbiota, because they may act on different mechanisms to achieve the purpose of treating different diseases with the same treatment. Probiotics and/or prebiotics, fecal microbiota transplantation (FMT), bariatric surgery, dietary intervention, drug treatment, and other treatments may provide new ways for the prevention and treatment of PCOS and T2DM.

5.1. Probiotics and/or prebiotics

Probiotics and/or prebiotics are dietary supplements that contain live microbes [138]. They can shape the intestinal microbiota and promote overall wellness [139]. Probiotics and/or prebiotics can improve insulin sensitivity, reduce intestinal endotoxin concentrations, and reduce pro-inflammation. They can also reduce intestinal permeability and OS [140]. Probiotics can decrease blood glucose [141]. Prebiotics such as α-lactalbumin can regulate beneficial microorganisms, including *Bifidobacterium* and *Lactobacillus* spp. *which* have been shown to have anti-obesity effects, increase the production of SCFAs, and improve gut mucosal barrier [142]. *Lactobacillus acidophilus*, *Streptococcus thermophilus*, and/or *Bifidobacterium lactis* can improve glycemic control in adults with T2DM [143]. *Lactic acid bacteria* can increase SCFAs levels and alleviate PCOS in rat models by regulating sex hormones associated with gut microbiota [144]. Inulin can alleviate PCOS by increasing *Bifidobacterium* and decreasing *Proteobacteria* and *Helicobacter* [145]. *Bifidobacterium lactis V9* regulates the levels of sex hormones by regulating the gut microbiota in patients with PCOS [88]. Moreover, α-lactalbumin can reduce glucose and chronic inflammation. The combination of myo-inositol and α-lactalbumin can improve IR and re-establish ovulation in PCOS [146].

5.2. FMT

FMT has become an effective strategy to treat metabolic diseases. FMT can decrease intestinal permeability by increasing the production of SCFAs, particularly butyrate, which maintains the integrity of the epithelial barrier. FMT stimulates the intestinal adaptive immune response via the TLR pathway to accelerate the synthesis of immunoglobulins, thereby protecting the intestinal mucosa [147]. FMT can regulate the composition of intestinal microbiota, mediate inflammatory cytokine secretion, and regulate blood glucose and insulin sensitivity [148]. FMT and *Lactobacillus* transplantation can improve androgenism and affect insulin function in PCOS rat models [89]. Treatment of PCOS rat models with FMT in comparison to healthy rats showed an improved female cycle and reduced androgen biosynthesis [149]. High-fat-diet-induced T2DM can be treated via FMT by improving the IR and alleviating hyperglycemia [150]. The diversity of gut microbiota increased after FMT. FMT has been shown to regulate the intestinal microbiota of T2DM. It can improve glucose metabolism, increase insulin sensitivity, and decrease systemic inflammation. Fecal bacteria from normal glucose tolerance may be used to treat diabetic patients [151]. However, more researches are needed to examine the role of FMT in the treatment of T2DM [152].

5.3. Bariatric surgery

Bariatric surgery, for instance, Roux-en-Y gastric bypass and sleeve gastrectomy, has been widely used to treat obesity and its related metabolic diseases. Bariatric surgery can reduce weight and inflammation and improve glucose metabolism and IR. It can also modulate immunity and lead to changes in adaptive immune cells [153]. Weight loss can improve PCOS and T2DM phenotype, which is still one of the first-line treatment methods. During obesity, the gut microbiota has the following features: low microbial gene richness and alterations of composition and function. Bariatric surgery has been shown to change intestinal microbiota and increase the richness and diversity of gut microbiota [154]. Bile acids and the FXR signaling are vital for the metabolic benefits of bariatric surgery [155]. Bariatric surgery changes the gastrointestinal anatomy which could influence enterohepatic recirculation of bile acids. After bariatric surgery, serum bile acid levels were significantly increased, and glucose and lipid metabolism was improved [156]. Bariatric surgery is beneficial for obesity associated with PCOS and T2DM. The study found that sleeve gastrectomy (SG) restored the microbiome to healthy levels and increased the abundance

of *B. thetaiotaomicron*, which was associated with a decrease in body mass index, and its gut microbiota were similar to lean individuals [157]. SG can increase the Bacteroidetes phyla and Roseburia species which can improve diabetes [158].

5.4. Dietary intervention

Diet can modify the intestinal microbiota and affect health. Low dietary fiber intake may lead to chronic inflammatory diseases. Dietary fiber helps maintain a healthy gut microbiota, promotes the production of SCFAs, and reduces body weight and chronic inflammation [159]. High-fat diet reduces *Lactobacillus*, which is related to healthy metabolic states [160]. Western diet (high in animal protein and fat, low in fiber) results in reductions of *Bifidobacterium* and *Eubacterium species* [161]. The Mediterranean diet (high fiber/antioxidants/unsaturated fatty acid) can improve obesity, lipid profile levels, and the inflammatory state. It can increase *Bifidobacterium*, *Lactobacillus*, and *Prevotella* and decrease *Clostridium* [162].

5.5. Drug treatment

Metformin is used to treat T2DM and PCOS-related symptoms, as it can alter the composition of gut microbiota and promote the production of butyrate and propionate, reduce blood glucose and weight, and improve IR [163]. Vitamin D maintains the gut tight junctions, and the deficiency of vitamin D may result in bacterial translocation, endotoxemia, systemic inflammation, and IR [104], which is relevant with PCOS and T2DM. Adequacy of vitamin D can improve IR, obesity, T2DM, and metabolic syndrome [164]. TCM offers a multi-component, multi-target compound that can treat PCOS and T2DM by regulating gut microbiota, such as quercetin which can modulate intestinal dysbiosis and reduce IR to treat obesity [165].

5.6. Other treatments

Acupuncture and moxibustion stimulate the sensation of specific parts to prevent and cure diseases. It can enhance the cellular immune function and have positive roles in regulating intestinal microbiota and immune inflammation [166]. Electroacupuncture can regulate the composition and function of gut microbiota in obese mice [167]. In addition, lack of exercise is a major contributor to chronic diseases, as it disrupts metabolic homeostasis in the body, reduces insulin sensitivity, and increases lipid accumulation. Proper exercise can reduce circulating lipid levels and increase glucose uptake in muscles during exercise [168]. Physical exercise has beneficial effects on gastrointestinal tract health and microbial composition. It can affect immunity, inflammation, and OS and improve energy homeostasis and metabolic disorders [169]. Physical exercise can increase the diversity of gut microbiota, modulate its distribution, and promote formation of SCFAs [170].

6. Conclusion

Similarities in the pathogenesis, clinical manifestations, and treatments between PCOS and T2DM exist. It has been proven that gut microbiota alterations play a central role in PCOS and T2DM. Dysbiosis of gut microbiota participates in the occurrence and development of diseases. Understanding intestinal microbiota as a common target of PCOS and T2DM treatment may provide new perspectives for the simultaneous treatment of different diseases. Therefore, therapies aiming to restore microbiota composition can be used as a strategy to counteract the progression of both conditions. Probiotics and/or prebiotics, FMT, bariatric surgery, dietary intervention, drug treatment, and other treatments in gut microbiota may be a new strategy for the prevention and therapy of PCOS and T2DM. Certainly, it is necessary to further study that gut microbiota alterations can open new possibilities to counteract other metabolic and chronic conditions, and consider the gut microbiota as the critical correlation in achieving the goal of treating different diseases concurrently.

CRediT authorship contribution statement

Fengmei Lian and Xinmin Liu designed the study. **De Jin, Shenghui Zhao, Rongrong Zhou, Yingying Duan, and Yuqing Zhang** searched the related literature. **Fengmei Lian, Liyun Duan, Xuedong An, and Yuehong Zhang** drafted the manuscript and figures. All authors approved the final version of the manuscript.

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