RESEARCH PAPER

GUT FEELINGS: THE ROLE OF INTESTINAL MICROBIOME IN TYPE 2 DIABETES MELLITUS AND ITS COMPLICATIONS

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Abstract

Diabetes, particularly type 2 diabetes mellitus (T2DM), is a complex metabolic disorder influenced by an interplay of genomic, nutritional, and lifestyle factors, with a significant rise in prevalence linked to modern lifestyles. The increasing burden of T2DM, affecting over 422 million individuals globally, is associated with insulin resistance (IR), chronic inflammation, and various organ dysfunctions, leading to severe complications such as diabetic cardiovascular disease and kidney disease. Recent advances in microbiome research have unveiled the gut microbiome's pivotal role as an endocrine organ, influencing metabolic health through mechanisms related to digestion, immunity, and metabolic regulation. This review synthesizes current knowledge on the shifts in gut microbiome composition throughout the progression of T2DM and associated conditions, examining the causal relationships between intestinal microbiota and metabolic dysregulation. Key findings highlight the role of specific microbial taxa in modulating inflammation and glucose metabolism, as well as the therapeutic potential of microbiome-targeted interventions, including dietary modifications, probiotics, and fecal microbiota transplantation. Additionally, we explore the molecular interactions between host factors and microbiota that contribute to dysbiosis in T2DM, emphasizing the impact of microbial metabolites on systemic inflammation and metabolic pathways. By elucidating these intricate relationships, this review aims to contribute to the understanding of how microbiome modulation may offer novel therapeutic strategies for managing T2DM and its complications.

Keywords: Diabetes mellitus,gut microbiome,gut health,microbiome,inflammation,diabetes complications

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Introduction

Diabetes is an intricate metabolic disorder which depends on many different factors. Genomic characteristics, gender, nutrition, ageing, lifestyle and epigenetic features affect the DM pathogenesis. Occurrence rate of DM elevated drastically as lifestyle standards became higher. T2DM constitutes about ninety percent of all DM cases. More than four hundred twenty-two million individuals suffer from this disorder worldwide. Multiple researches established that adiposity is a major risk factor for T2DM [1-3]. This disease is featured by such properties as IR, high blood sugar and chronic inflammatory process. Such conditions are implicated in metabolic disorders and have detrimental impact on functioning of body organs, including renal function, cardiac function, hepatic function, brain function, cardiovascular system, which leads to development of diabetic CVD, retinopathy, kidney disease, NAFLD [4,5]. Advancements in sequencing methods and data analyses have propelled microbiota studies forward significantly over the past decade. Following the completion of the initial two phases of the HMP, studies on the microbiota and its relationship to metabolic health have garnered increasing interest and yielded numerous valuable findings. The gut microbiome is regarded as an endocrine organ. Its advantages can be summarized in 4 key areas: 1. Aiding in the digestion of food and nutrient absorption, 2. Strengthening the gut barrier and defending against pathogens, 3. Enhancing the functioning of the gut immunity, 4. Regulation of metabolism [6-8]. E.g., Zhang and colleagues discovered that Lactiplantibacillus plantarum and other bacteria are able to stimulate insulin transport and release via ligand binding to nucleotide-binding oligomerization domain-containing protein 1 in islet

beta cells [9]. Emerging data demonstrate differences in the composition of the intestinal microbiome and metabolic traits and a connection between the gut microbiome and organism metabolic processes of subjects with type 2 diabetes and healthy subjects. In this review, we present a comprehensive overview of the alterations in intestinal microbiome during the development of type 2 diabetes and associated conditions [10-12]. We also explore the functional mechanisms by which intestinal microbiome influence the gut barrier and the effects of their metabolites, along with relevant microbiome-based therapeutics, drawing on the latest research findings.

Causal connection between intestinal microbiome and type 2 diabetes

Intestinal microbiome cohort trials highlighter the complicated connection between gut microbiota and type 2 diabetes. Animal trials in germ-free mouse model established that intestinal microbiome is the primary factor for this disorder. Germ-free mice showed reduced IR and reduced lipid levels than regular mice [13-15]. Consequent transplant of intestinal microbiome demonstrated that IR and adiposity were considerably elevated in germ-free mice administered with ob/ob mice intestinal microbiome. Although, these findings do not necessarily prove that such mechanisms occur humans since the genomic backgrounds are not the same. Another trial involved 952 human subjects and took place in Netherlands. That trial has identified a causal link between type 2 diabetes and intestinal flora [16-18]. The authors performed whole genome and gut meta-genome analysis, assessed SCFA level in the colon, and evaluated clinical parameters. Causal connection between microbe propertied and blood sugar levels was assessed by bi-directional MR tests. It was established that butyrate elevation caused by genomic parameters was associated with alleviation of insulin resistance (IR) following OGTT. Levels of Roseburia intestinalis and Eubacterium elevated, and the aberrant generation or absorbing of propionate were associated with higher risk of type 2 diabetes. Consistently, butyrate is able to stimulate post-meal insulin release and synthesis of propionate in the colon, which increases the type 2 diabetes risk. However, further research is necessary to elucidate the underlying processes.

Table 1. Key Findings on Gut Microbiome and T2DM

Aspect	Description	Implications	Examples
Prevalence of T2DM	Affects over 422 million individuals globally.	Increased healthcare burden.	Global statistics highlight public health issue.
Microbiome Functions	1. Digestion & nutrient absorption 2. Gut barrier integrity 3. Immune support 4. Metabolic regulation	Essential for overall metabolic health.	SCFAs like butyrate contribute to gut health.
Risk Factors	Adiposity, insulin resistance (IR), chronic inflammation.	Higher susceptibility to T2DM and associated conditions.	Obesity linked to altered microbiota.
Key Microbial Taxa	Lactiplantibacillus plantarum, Roseburia intestinalis, Akkermansia muciniphila.	Modulate inflammation and glucose metabolism.	Specific taxa shown to lower blood sugar levels.
Complications of T2DM	Diabetic cardiovascular disease (CVD), kidney disease, retinopathy.	Compromises quality of life and increases mortality.	Increased risk for chronic kidney disease.
Therapeutic Strategies	Microbiome-targeted interventions (dietary modifications, probiotics, fecal microbiota transplantation).	Potential for improved metabolic outcomes.	Use of probiotics showing beneficial effects.

Intestinal microbiome, T2DM and its complications

T2DM, like CVD, malignancies and CRDs, is believed to be a chronic non-infectious disorder which accounts for eighty percent of premature

mortality worldwide. In 2019, about 463 million individuals suffered from DM globally, and by 2045 this number is estimated to be seven hundred million, assuming present tendencies go on unaffected by different therapeutical approaches [19,20].

DM is featured by hyperglycemia which is caused by reduced insulin synthesis in the pancreas or reduced tissue susceptibility to insulin. Unmanaged DM and metabolic diseases related to T2DM, e.g., fat metabolism disorders, high blood pressure, oxidative stress (OS), may result in various vascular disorders. There could develop small vessel complications such as diabetic kidney disease, retinopathy and nerve damage [21,22]. There is also a possibility of large vessel complications such as cerebro-vascular disorder, CAD, PVD. Among other complications are CHF, fat metabolism dysfunction, inflammatory processes in organs, increase in body mass, and water-electrolyte imbalance [23-25].

Alterations in inter-dependent pathways of metabolism were detected in relation to T2DM. E.g., CAD induced by insulin metabolism disfunction may result in dyslipidaemia, a major risk factor for CV complications of DM. Other factors such as ROS elevation, chronic high blood sugar, and impaired anti-oxidant status may also account for the DM development. Such complications may result in gradual reduction in life quality and elevate mortality [26-28].

Numerous trials have shown a notable connection between alterations in intestinal flora composition and the T2DM progression. For example, impaired eubiosis of Bacteroidetes/ Bacillota phylum was associated with elevated gut permeability, with bacterial by-products infiltrate via the intestinal barrier which stimulated inflammation, a major property of DM [29-31]. At the same time, some bacteria were proved to be able to protect against this disease by decreasing pro-inflammatory biomarkers and keeping the gut barrier intact. E.g., Lb. Fermentum, Lb. Plantarum, Lb. casei, Roseburia intestinalis, Bacteroides fragilis, and Akkermansia muciniphila were proved to ameliorate sugar metabolism and susceptibility to insulin, as well as inhibit pro-inflammatory cytokines [32-35]. It is noteworthy that some DM medications, e.g., metformin, were proved to change the intestinal flora composition, which implies that this drug interplays with the intestinal flora by modulating inflammatory processes, glucose homeostasis, intestinal permeability, and SCFA-generating bacteria. Moreover, in subjects with dysbiosis related to DM, metformin triggers synthesis of butyrate and propionate, ameliorating the subject's capacity of catabolizing aminoacids [36-39]. These alterations together with elevated Akkermansia muciniphila in the intestine could account for the impact of this drug on sugar metabolism. Metabolic factors related to chronic inflammatory processes and OS, that connect dysbiosis of intestinal flora to T2DM, seems to be the same factors that affect the manifestation and development of DM complications. These findings support the idea that regulation of the intestinal flora could have great potential in treating DM and related complications [40-42].

Table 2. Mechanisms Linking Gut Microbiome and T2DM

Mechanism	Details	Effects on Metabolism	Potential Targets for Therapy
Dysbiosis	Altered microbial composition associated with increased T2DM risk.	Disrupts metabolic homeostasis, leading to IR.	Probiotics to restore healthy flora.
Inflammatory Response	Microbial metabolites (e.g., lipopolysaccharides) trigger inflammation.	Enhances systemic inflammation impacting insulin signaling.	Anti-inflammatory agents or diets rich in anti-inflammatory foods.
Metabolite Production	Short-chain fatty acids (SCFAs) enhance insulin sensitivity.	Improves glucose homeostasis and reduces IR.	Dietary fibers to boost SCFA production.
Host-Microbe Interactions	Host molecules (e.g., SIRT1) regulate microbial profiles impacting metabolism.	Enhances dysbiosis clearance promoting a healthier gut environment.	Lifestyle changes targeting SIRT1 activation.
Immune System Influence	Gut microbiota modulation affects innate immune responses and inflammation.	Contributes to the regulation of metabolic	Immunotherapies targeting specific immune pathways.

Mechanism	Details	Effects on Metabolism	Potential Targets for Therapy
		processes.	
Microbiome as an Endocrine Organ	Communication affecting metabolic homeostasis and systemic health.	Alters nutrient absorption and fat storage.	Hormonal therapies to rebalance gut signaling.

Molecular processes connecting host and the intestinal flora in type 2 diabetes

There is an intricate connection between the intestinal flora and type 2 diabetes. Hereby, it is crucial to elucidate the underlying mechanisms of the interplay between host and microbiome regarding impaired sugar metabolism. In pathology, impaired host molecular regulation may contribute to alterations of the intestinal flora composition. Indeed, the flora is a major player in the progression of type 2 diabetes [43,44].

Host molecules which trigger dysbiosis of intestinal microbiome

Whereas type 2 diabetes in associated with the intestinal flora dysbiosis, the cause of this condition is yet to discover. Notably, intestinal microbe homeostasis is regulated by various host molecules. Numerous trials in high-fat diet mouse model demonstrated that SIRT1 defends against metabolic disorders mostly by controlling the levels of Firmicutes and Bacteroidetes. High-fed diet mice with SIRT1 deficiency showed adipocyte hypertrophy, hepatic steatosis and IR [45-48]. Zn-T8 is a trans-membrane protein rich in pancreas beta cells, implicated in progression of DM. Lack of Zn-T8 promoted lipid aggregation and impaired glucose tolerance partly via regulation of the gut morphology and gut flora composition, which could elevate risk of type 2 diabetes and adiposity. It is noteworthy that db/db mice administered with fexaramine, FXR agonist, demonstrated reduced free FA and cholesterol (C) levels in serum, elevated release of GLP1, ameliorated susceptibility to insulin [49-52]. Trials have established that fexaramine triggers activation of TGR-5/GLP1 signaling pathway via elevation of levels of Acetatifactor and Bacteroides which generated lithocholic acid, thus ameliorating sugar metabolism [53-55]. Mavilio and colleagues reported that in high-fat diet mouse model KO of Timp3 triggered FLD and glucoce intolerance [56]. Lack of tissue inhibitor of metalloproteinase 3 resulted in dysbiosis of intestinal flora, that promoted systemic inflammatory process via IL6 signaling pathway. Antibacterial therapy ameliorated metabolism and decreased inflammatory process, which implies that the intestinal flora is mediating the tissue inhibitor of metalloproteinase 3 role in metabolic regulation [57-59]. Moreover, diabetoprotective activity of host molecules, e.g., interleukin 36, TRIM-31 and NAPEPLD, is also associated with the intestinal microbiome. Generally, these host molecules are able to ameliorate metabolic processes to a certain degree via regulation of intestinal flora, thus protecting against adiposity and type 2 diabetes [60-62].

On the other hand, some host molecules may stimulate progression of type 2 diabetes and associated metabolic disorders by facilitating dysbiosis of the intestinal microbiome. Resveratrol was a specific suppressant of mTORC-1 that could alleviate sugar intolerance and IR in high-fat diet mice, which implies that mTORC-1 is critical in glucose homeostasis. It is worth noting that resveratrol decreased Clostridium cluster XI, Oscillibacter, Hydrogenoanaerobacterium, Flavonifractor, and Lactococcus relative abundance in high-fat diet mice [63-66]. Those bacterial taxons were in direct correlation with fasting blood sugar and homeostatic model assessment for insulin resistance index, which implies that alterations in intestinal flora caused by dysregulated mTORC-1 could be linked to DM phenotype [67,68]. Another trial in high-fat diet MGLL KO mice demonstrated ameliorated glucose tolerance and reduced obesity. The response of the intestinal microbiome of these mice to high-fat diet differed from that of wild-type mice. E.g., high-fat diet elevated the Lactobacillus levels in wild-type mice, but not in monoglyceride lipase KO mice [69]. These findings suggest that monoglyceride lipase could be a target for novel therapeutical approaches for metabolic disorders. Furthermore, lack of ANGPTL-4 ameliorated glucose tolerance and elevated concentrations of insulin in mice with UFA, fruit sugar and C diet. Studies in ANGPTL-4 -/- mouse model showed elevated levels of SMB53, Adlercreutzia and Lactobacillus, and reduced levels of Allobaculum [70]. The intestinal microbiome suppression by antibacterial therapy decreased glucose tolerance in ANGPTL-4 -/- mice, which implies that ANGPTL-4 impact on sugar metabolism could rely on the intestinal flora regulation. Similarly, the intestine-specific deletion of GLUT-2 could ameliorate glucose homeostasis by altering intestinal flora composition. Suppression of monoglyceride lipase, GLUT-2, mechanistic target of rapamycin complex 1 or angiopoietin-like 4 could be promising treatment approaches for type 2 diabetes [70].

Immunity and inflammation responses

Crosstalk between intestinal flora and the host was found to control systemic and local immune system and inflammatory processes, that facilitate the progression of type 2 diabetes. The gut barrier has a major role in these mechanisms. The gut barrier defends the organism from gut components. Impairment of its function elevates the flow of

bacteria and their byproducts, hereby facilitating chronic inflammatory process and metabolic disorders [71-73]. Trials in vitro and in vivo support the idea that high blood sugar elevates the gut barrier penetrability by altering the adherens junctions (AJ) and tight junctions (TJ) integral state, which leads to the leakage of bacterial byproducts. It is noteworthy that glucose transporter 2 deficiency in gut epithelium retained the gut barrier by preserving ZO1 and epithelial cadherin, suggesting that glucose transporter 2 could be a promising target for ameliorating inflammatory processes and infections associated with the gut [74,75]. Moreover, the intestinal flora is implicated in the control of gut penetrability in adiposity and DM. E.g., the intestinal flora influences the barrier functioning by controlling the release of glucagon-like peptide-2 in DM. Furthermore, MAM promoted restoration of the injured gut barrier by elevating ZO1 release in db/db mice [76,77]. Akkermansia muciniphila levels were decreased in mice with type 2 diabetes, and Akkermansia muciniphila therapy might ameliorate sugar metabolism and alleviate metabolic endotoxemia via restoration of thickness of the mucous layer. Additionally, EVs obtained from Akkermansia muciniphila decreased gut penetrability by stimulating the TJ proteins release, hereby ameliorating sugar homeostasis in mice with DM. Another study revealed that Akkermansia muciniphila-derived Amuc_1100 retained the integral state of the gut barrier via interplay with TLR-2, thus mitigating adiposity and IR in high-fat diet murine model. These findings suggest that Akkermansia muciniphila is a beneficial intestinal bacterium which is vital for regulation of the gut permeability [78-80]. The innate immune system is known to be present in the body as a quick reaction against infections, whereas PRR and PAMP interplay triggers the response. Foreign pathogens and their byproducts can trigger inflammatory process in the gut by stimulating innate immune system. It is noteworthy that some pattern recognizing receptors, e.g., NLR and toll-like receptors, are closely connected to metabolic disorders [81,82]. Multiple trials in murine models have confirmed that lack of toll-like receptor 5 leads to IR and adiposity, which is associated with alterations in the intestinal flora composition. Interestingly, intestinal flora transplant from mice lacking toll-like receptor 5 to wild-type sterile mice led to a development of metabolic syndrome, which implies that the crosstalk between toll-like receptor 5 and the intestinal flora could be crucial in metabolic disorders [83,84]. Analogously, toll-like receptor 2 KO mice had different intestinal flora composition from that of wild-type mice, they also demonstrated impaired glucose tolerance and IR. Another trial revealed that MyD-88, a toll-like receptor adaptor, is able to control fat and glucose metabolic processes partly be changing the intestinal flora composition. Nucleotide-binding oligomerization domain-containing protein 1 activation facilitated inflammatory process and IR induced by high-fat diet [85-87]. On the contrary, MDP obtained from bacteria walls stimulated the release of IRF-4 via nucleotide-binding oligomerization domain-containing protein 2, hereby alleviating inflammatory process and IR in mice with adiposity. Furthermore, elevated gut penetrability allows bacteria and their byproducts to flow through the barrier and enter the bloodstream [88-90]. Cani and colleagues discovered that high-fat diet mice demonstrated elevated proportion of LPS-containing bacteria in the gut and lipopolysaccharide concentrations in plasma [91]. At the same time, they modeled metabolic dysfunction and inflammatory process caused by high-fat diet in mice by prolonged sub-cutaneous (SQ) administration of lipopolysaccharides, which implies that lipopolysaccharides in bloodstream can facilitate progression of type 2 diabetes. Accordingly, antibacterial therapy alleviated inflammatory processes and endotoxemia, as well as ameliorated metabolic parameters in high-fat diet and ob/ob murine model, suggesting that the intestinal microbiome dysbiosis controlled the gut penetrability and promoted endotoxemia [92].

It is noteworthy that different ICs are implicated in the intestinal flora role in the metabolism. Interleukin-17 receptor deficiency can stimulate gut dysbiosis and lipopolysaccharide transfer to visceral fat tissues by suppressing the neutrophil migrating in the gut mucosa, resulting in the development of sugar intolerance and IR in high-fat diet mice. CR-Ig is released on macrophages and is crucial for immunity responses [93-95]. Luo and colleagues detected aggregation of extracellular vesicles containing intestinal microbe DNA and a reduction in the hepatic CR-Ig+ macrophage count in adiposity [96]. Notably, CR-Ig+ macrophages were able to clear the extracellular vesicles depending on complement C, hereby alleviating inflammatory processes and IR. Moreover, crosstalk between CD-4+ T lymphocytes and the intestinal microbiome is strongly connected to the progression of type 2 diabetes. The intestinal microbiome dysbiosis caused by high-fat diet resulted in a reduction of T helper 17 cells in the LP layer of the small bowel and hereby stimulated the development of type 2 diabetes. At the same time, the T helper 17 cells count was considerably decreased in the gut tissues in mice with adiposity, and further decrease in T helper 17 cells by high-fat diet and vitamin A deficiency exacerbated sugar intolerance and IR [97-99]. Another study revealed that T helper 17 cells can control the Paneth cell functioning and metabolism-associated gut flora via interleukin 17, hereby retaining metabolic homeostasis. Luck and colleagues revealed that high-fat diet mice exhibit a reduction in immunoglobulin A+ IC percentage and levels of secretory immunoglobulin A in the colon, as well as that sugar metabolism diseases were more severe in high-fat diet mice lacking immunoglobulin A [100,101]. Interestingly, immunoglobulin A is able to ameliorate glucose metabolic processes by controlling the gut penetrability and flora composition, which implies that therapeutical approaches targeting immunoglobulin A+ ICs could be useful in type 2 diabetes.

DM and intestinal microbial metabolites

Intestinal microbial metabolites are substances generated by intestinal microbiome during the process of food digestion. Such substances, e.g., short-chain fatty acids, Trp metabolites, trimethylamine N-oxide, lipopolysaccharides and bile acids (BA), were proved to be of great importance in the progression of type 2 diabetes. The majority of metabolites are able to enter the bloodstream and serve as signaling molecules through different receptors, that further control various metabolic pathways [102-105].

Short-chain fatty acids

Short-chain fatty acids are important products that are generated in the process of resistant starch and fiber being anaerobically fermented by the intestinal flora. Just a small portion of short-chain fatty acids in the GI tract is obtained from the food. Propionic acid, butyric acid and acetic acid are the most abundant short-chain fatty acids in the organism. Short-chain fatty acids may be generated by thick-walled microbiome, such as Clostridium perfringens type IV and type XIVa [106-108]. These compounds can penetrate colon epithelial layer through H- or Na-dependent MCTs to supply energy for their genesis. The rest of the short-chain fatty acids are then transferred from the gut to the bloodstream through the hepatic portal venous system and facilitate the progression of various disorders, e.g., adiposity, IR, type 2 diabetes [109-111].

Short-chain fatty acids may serve as substrates for fat generation. It was proved that short-chain fatty acids may trigger activation of AMP activated protein kinase, stimulate expression of PGC1-alpha, and trigger activation of PPAR, thus controlling the FA oxidation. Furthermore, numerous trials emphasized that such major fat metabolic signals as cyclic AMP, ATGL, and UCP are controlled by short-chain fatty acids as well [112-114]. Short-chain fatty acids were proved to take part in HHS via GPCR receptors. The most important short-chain fatty acid receptors are the GPCRs, FFAR-2, FFAR-3, and GPR-109A. ERK-1, ERK-2, activation of Ca^{2+} within cells, cyclic AMP, and G protein (Gq, Gi/o) are downstream signaling molecules indicating that free fatty acid receptor affects the nutrient intake. Free fatty acid receptor 2 is mostly released in white fat cells, islet alpha and beta cells, gut enteroendocrine cells, and ICs [115-118]. Butyrate is able to suppress HDAC release via activation of free fatty acid receptor 2, hereby exerting a suppressive effect on inflammation. Free fatty acid receptor 3 is released in white fat cells, ICs, islet alpha and beta cells, and gut enteroendocrine cells. GPR-109A is a nicotinate GPCR which shows low susceptibility to butyrate [119-121].

Short-chain fatty acids were closely investigated in context of metabolic disorders. Trials have shown that propionate increased expression of PYY peptide and GLP1 in the colon, resulting in a reduction in body mass and considerable decrease in circulating glucose concentrations. Short-chain fatty acids trigger activation of free fatty acid receptor 2 on enteroendocrine L-cells, hereby promoting the expression of glucagon-like peptide-1 and peptide YY [122-124]. Free fatty acid receptor 3 is released in vagus sensory neurons and takes part in a crosstalk with CCK to change nutrient absorption. Via regulation of AMP activated protein kinase, GPR-109A stimulates Nfr-2 nuclear import signaling and triggers autophagy, thus reducing inflammation. It can also control fat metabolism and suppress lipolysis in fat tissues. Recent research revealed that short-chain fatty acids can facilitate the progression of DM via methylation of deoxyribonucleic acid [125,126].

Lipopolysaccharides

LPS is located on the cellular wall of GN bacteria. Lipopolysaccharides are major players in the development of type 2 diabetes. They are able to interact with short-chain fatty acids. Lipopolysaccharides count may be utilized for prediction of inflammation progression. It was proved that HFD-induced ecological regulation impairment increases levels of lipopolysaccharides, leading to the expression of tumor necrosis factor, interleukin 1 and interleukin 5, as well as to systemic inflammatory processes. Endotoxemia progression can promote immunity response, which facilitates pathogenesis of metabolic disorders, e.g., type 2 diabetes [127,128].

TLR4 is considered a crucial receptor of lipopolysaccharides. It is a member of cell surface receptors family. When toll-like receptor 4 is activated, it promotes transcription of tumor necrosis factor alpha, interleukin 1 and interleukin 6 through nuclear factor kappa B and mitogen-activated protein kinase pathways. Concentrations of these cytokines are considerably increased in subjects with type 2 diabetes, leading to development of IR and pancreas beta cells function impairment [129-132].

Bile acids (BA)

Chenodeoxycholic and cholic acids are produced from C by hepatic enzymes. There are 2 pathways of genesis of bile acids, traditional and alternative. Chenodeoxycholic acid undergoes catalysis by Mt CYP-27A1 for oxygenation of CS carbon chain. Cholic acid synthesis relies on CYP-8B1. BSEP releases bile salts bonded to glycine or taurine to the gallbladder or digestion system. Then, bile acids are transformed into secondary bile acids by intestinal flora [133-135]. In the gut, cholic acid and chenodeoxycholic acid may be transformed into DCA and LCA by bacterial BSH and 7 alpha dehydroxylase enzyme. The latter can be produced by Clostridium perfringens. Bile salt hydrolase is an enzyme synthesized by different strains of intestinal microbiome, such as Staphylococcus, Enterococcus, Clostridium perfringens, Neococcus, Bifidobacterium, Parasiticum [136-138]. Bile acids are signalling molecules that control insulin susceptibility and inflammatory processes in type 2 diabetes through FXR and TGR-5. At the same time, bile acids are ligands of VDR receptor, PXR receptor and S1PR-2. They are crucial for management of inflammatory processes and immunity functioning [139-141].

Farnesoid X receptor is released in the gut and liver, and chenodeoxycholic acid is the most endogenous

farnesoid X receptor agonist. When farnesoid X receptor is activated in the gut, it enhances the release of FGF 15/19, that consequently enters liver through EHC. Fibroblast growth factor 15/19 in serum triggers activation of the FGFR-4)/klotho complex in the liver, which suppresses transcription of CYP-7A1 and decreases genesis of BA [142-144]. Moreover, microbiome rich in clostridia was found to stimulate production of bile acids by inhibiting genesis of fibroblast growth factor 19 in the gut. Activated farnesoid X receptor in the liver stimulates transcription of SHP, which inhibits CYP-7A1 expression and decreases genesis of BAs. IRS-1-AKT- PI3K pathway is one of the farnesoid X receptor targets, and it is vital for insulin signalling. Whereas both gut and liver farnesoid X receptor signalling is implicated in regulation of BA homeostasis, they exert different effects in genesis and absorption of fats [145,146]. Semisynthetic BA, e.g., obeticholic acid, was proved to be thirty times more efficient in triggering activation of farnesoid X receptor than chenodeoxycholic acid. Obeticholic acid can suppress BA synthesis, alleviate OS and hepatic fibrosis, reduce C and TG levels in the liver. Sunder and colleagues performed a trial (NCT00501592) and revealed that insulin susceptibility of subjects administered with 25 mg obeticholic acid was elevated by 28 percent, which implies that obeticholic acid could be a promising target in mitigating hepatic inflammatory process and IR [147-149].

Takeda G protein-coupled receptor 5 is a GPCR which is released in multiple body tissues, such as hepatic, fat and gut tissues. This receptor is crucial for regulation of energy metabolism. Activated Takeda G protein-coupled receptor 5 in entero-endocrine L-cells is able to enhance expression of GLP1 resulting in amelioration of insulin susceptibility and sugar homeostasis. Activated Takeda G protein-coupled receptor 5 in fat tissues promotes the DIO-2 hormone release, which transforms not active T4 into active T3, thus increasing energy consumption [150-152].

BA sequestrants, as well as BA chelator, contribute to the regulation of bile acid pathways. BA sequestrants bind to BAs in the gut, averting their re-absorption and stimulating their fecal excretion, resulting in a decrease in the levels of BAs in bloodstream, which drives the liver to produce more BAs from C. A clinical trial was conducted in forty Japanese subjects with type 2 diabetes (NCT038934220) [153-155]. The results showed that colestimide changed BA composition and elevated cholic acids ratio, that stimulated energy metabolism, ameliorated sugar concentrations in blood and mitigated DM through Gpbar-1-cyclic AMP-DIO-2 pathway. BUDCA was proved to ameliorate glycaemic control and decrease concentrations of low-density-Lp-C in serum (NCT03656744). Although, it is noteworthy that BA chelator can reduce the bile acids hydrophoby and elevate risk of gallstones development [156].

Tryptophan (Trp) metabolites

Trp is an important aminoacid which may be converted by intestinal flora into molecules, e.g., indole and indole derivatives, such as ILA, IPA and IAld. Trp metabolites participate in the development of type 2 diabetes. Indole promotes the release of glucagon-like peptide-1 from L-cells in the gut, leading to secretion of insulin and a decrease in blood sugar concentrations. Indole-3-propionic acid was found to have antiseptic characteristics and protect against inflammation via its activity on the AhR [157-159]. In vitro, indole reduced fat deposition and promoted inflammation responses. In vivo, indole reduced fatty liver disease and inflammatory processes in HFD rats. Aryl hydrocarbon receptor activated by Trp metabolites was proved to exert multiple physiologic effects such as management of immunity response, inflammatory processes, cellular differentiating [160-162].

Trimethylamine N-oxide (TMAO)

TMAO takes part in the development of type 2 diabetes and associated conditions. Trials have demonstrated that trimethylamine N-oxide can facilitate progression of type 2 diabetes by stimulating IR, glucose intolerance, and inflammatory processes. Elevated concentrations of trimethylamine N-oxide can be connected to mild cognitive impairment (MCI) and CVD in subjects with type 2 diabetes [163-166].

Trimethylamine N-oxide is synthesized by intestinal flora from food, e.g., meat and eggs. The gut flora breaks down choline, betaine, or carnitine to TMA and DMA, that undergo absorption to circulation and are transferred to the liver, where they undergo oxidation by FMO-3 to synthesize trimethylamine N-oxide. Interestingly, diet rich in animal-based products are connected to higher concentrations of trimethylamine N-oxide [167,168]. The elevation of trimethylamine N-oxide in bloodstream is considered to be associated with such factors as carnitine or choline presence in food, renal function, hepatic function, intestinal flora composition [169,170].

Numerous trials are concentrating on regulation of trimethylamine lytic enzymes to decrease concentrations of trimethylamine N-oxide. E.g., a choline analogue DMB is able to suppress microbial genesis of trimethylamine. It was reported that in murine model of a diet rich in carnitine or choline, 3,3-dimethyl-1-butanol considerably decreases concentrations of trimethylamine N-oxide, hereby suppressing AS induced by diet [171,172]. Metformin was also reported to reduce levels of trimethylamine N-oxide in db/db mice. Moreover, berberine was found to decrease concentrations of trimethylamine N-oxide by controlling trimethylamine lytic enzymes through remodeling intestinal microbiome [173-175]. Trimethylamine N-oxide antagonist, an intestine flora metabolite, was proved to ameliorate glucose homeostasis and metabolic diseases. Taurisolo, a new extract of grape pomace, considerably reduced concentrations of trimethylamine N-oxide in serum of healthy patients, indicating that PPs are able to reduce concentrations of trimethylamine N-oxide, thus mitigating glucose intolerance and inflammatory process in fat tissue in subjects with type 2 diabetes.

Trimethylamine N-oxide is considered a new risk factor for CVD associated with adiposity and type 2 diabetes. Targeting intestinal flora and synthesis of trimethylamine N-oxide can be a promising strategy for type 2 diabetes management [176-178].

Therapeutic options for targeting the intestinal flora in T2DM and associated disorders

Diet

Pre-clinical and clinical trials support the hypothesis that intermittent fasting is able to alleviate various metabolism disorders, such as adiposity, DM, cardiovascular diseases. Animal trials demonstrated that such positive effects can be connected to the amelioration of intestinal microbiome composition. Alternate-day fasting, time-restricted eating and five:two intermittent fasting are 3 of the most popular strategies of fasting to enhance metabolism. Although, it is noteworthy that prolonged fasting can injury the gut immunity [179-181].

In comparison to western diets, conventional diets such as Mediterranean are high in polyphenols (PPs), omega-3 FAs and fibers, that exert positive effects on metabolism and alleviate type 2 diabetes and cardiovascular diseases. Fruits and vegetables are high in PPs, among them ETs, proanthocyanidins, EA and resveratrol are able to alleviate metabolism syndrome via intestinal flora [182,183]. EA is converted to UroA to upregulate expression of the gut TJ proteins via aryl hydrocarbon receptor-Nrf-2 pathway. Intake of PPs from food may stimulate the release of glucagon-like peptide-1 in the gut, thus elevating concentrations of insulin and reducing blood sugar levels. It also protects vessels by promoting the aortic synthesis of NO. Moreover, PPs may facilitate growth of particular bacteria which exert positive effects, e.g., Akkermansia muciniphila, and ameliorate CV metabolism [184-186].

Fecal microbiome transplant (FMT)

FMT is an efficient therapeutic approach for Clostridium difficile infections treatment. This approach was also applied for treatment of UC and immunity disorders. Fecal microbiota transplantation was found to be effective in lowering the occurrence rate of major detrimental reactions. Trials have demonstrated that transplant of the gut bacteria from thinner donors can elevate insulin susceptibility and the flora diversity in subjects with adiposity and metabolism disorders [187-189]. These results indicate the potential of fecal microbiota transplantation for type 2 diabetes and associated disorders treatment. Although, the safety profile of fecal microbiota transplantation is not good enough yet for clinical use. In 2019, two subjects have received fecal microbiota transplantation and gotten an infection with pathologic Escherichia coli, which led to serious bacteremia and death. This incident slowed down the use of this therapy and showed that more rigorous donor screening was required. To date, it is not fully understood what are the prolonged effects of fecal microbiota transplantation [190-192]. Although, the fecal microbiota transplantation national registry created by the AGA Institute is focused on ten-year observation of subjects following fecal microbiota transplantation in order to assess the safety and efficacy of this approach. Resent research revealed that fecal microbiota transplantation has very good impact on Clostridioides difficile infections for six-month therapy, with ninety percent cure rate. Grave symptoms associated with fecal microbiota transplantation involved stomach ache (2%), diarrhoea (2%), hospital admission (1%) a month after the treatment. After six months, IRS and IBD were found in 1% of subjects. Further follow-up research is required to elucidate the prolonged effects of fecal microbiota transplantation [193-195].

Probiotics and prebiotics

Apart from FMT, application of probiotics and prebiotics seems to be a promising strategy for type 2 diabetes and associated disorders treatment. Studies have revealed that numerous probiotics, e.g., Akkermansia muciniphila, Bifidobacterium and Lacticaseibacillus rhamnosus, are able to alleviate metabolic disorders. L. reuteri ADR1 or L. reuteri ADR3 supplements decreased Hb A1c and C levels in serum of subjects with type 2 diabetes. Furthermore, Bifidobacterium and Akkermansia muciniphila, which are in inverse correlation with inflammatory processes, IR, and type 2 diabetes, were reported to synthesize short-chain fatty acids, defend the gut barrier integrity and decrease concentrations of lipopolysaccharides [196-198]. Whereas Akkermansia muciniphila is considered the next possible probiotic for the market, there are still conflicting evidence on the connection between the amount of Akkermansia muciniphila with type 2 diabetes and MS which imply that more research is required. Some probiotics that were found to have considerable positive impact on metabolism of animals did not show such impact in humans. Some trials have revealed common promotion action of distinct strains of intestinal flora, e.g., Lacticaseibacillus rhamnosus GG and bacteria synthesizing butyrate, and particular strains of Bifidobacterium (Ba-8145) and Akkermansia muciniphila [199,200]. While the effect of some probiotics on amelioration of health condition was proved, the safety profiles and stability are still under investigation. Some probiotics are able to inhabit the gut and influence the flora via competition with local gut flora. Resistance, as well as infections, are the most important safety issues that have to be studied. Trials demonstrated that Lactobacillus rhamnosus supplements are able to promote bacterial transport to the bloodstream and result in bacteremia [201-203]. Lactobacillus and Bifidobacterium can transport the AB resistance genome to other pathogenic microbes in the gut flora and increase their AB resistance. Hereby, it's important to assess the risk and positive effects of probiotics before their application [204,205].

Prebiotics are compounds which are utilized by microbes in a selective manner. Prebiotics of FOSs, galactose (Gal), RS, and inulin were reported to exert positive effect on metabolism disorders. E.g., supplements with resistant starch are able to elevate the number of probiotics in the gut, elevate short-

chain fatty acids levels, thus decreasing concentrations of substances associated with CKD [206-208]. While these findings appear promising, large-scale RCTs are necessary to confirm the effectiveness in clinical settings. Furthermore, the use of prebiotics and probiotics should be conducted under scientific supervision, following established guidelines for proper dosing and tailored treatment plans [209-211].

Moreover, some trials demonstrated that prebiotics and probiotics combined with DM drugs show higher effectiveness than mono therapy. Bifidobacterium milk species DSM-10140 combined with L. paracasei DSM-46331 and oat beta-glucan considerably decreased the gain of body mass, reduced blood sugar levels and fat levels, and improved the gut homeostasis. The combined therapy with prebiotic polycarbohydrates, sitagliptin and metformin considerably decreased adiposity and blood sugar in comparison to hypoglycemic therapy alone. These findings indicate that probiotic, prebiotic and DM medication therapy should be investigated more closely [212-214].

Engineering bacteria and phages

Creation of synthetic bacteria is a promising novel area of micro-ecological treatment with possibly a good safety profile and targeting. E.g., Limosilactobacillus reuteri artificial bacteria are able to generate interleukin 22 to elevate the release of anti-microbial REG-3G in the gut and protect from pathogens. Rats with DM were administered with Synthetic Lactobacillus gasseri that express glucagon-like peptide-1 (1-37), which led to enhancement of hepatocyte nuclear factor-6 expression in endocrine cells in the gut crypt, thus programming the gut cells to sugar-responsive insulin-releasing cells and decreasing blood sugar [215-217]. Escherichia coli, stam Nissle 1917 synthesized to release glucagon-like peptide-1 or PDX1 can promote insulin release as a reaction to glucose in ECs. Trials in murine model of adiposity caused by HFD showed that artificial Escherichia coli, stam Nissle 1917 generating NAPE may decrease obesity, food consumption, IR, and fatty liver disease. Application of genomically altered L. Lactis releasing interleukin 10 and pro-insulin or GAD65 and interleukin 10 may ameliorate T1DM [218-220].

Bacteriophages represent the most common micro-organisms in the intestine. Bacteriophages are prokaryotic viruses which fight bacteria. Bacteriophages may decrease the number of targeted bacteria as well as enrich bacteria with resistance. Moreover, bacteriophages are prevalent in the virus environment of the intestine. Available data indicate that fecal virome transplant (FVT) is able to change the intestinal flora and metabolism, alleviating IBD, adiposity and type 2 diabetes. Alterations in microbial genome in the gut and bacteriophages can be useful for management of the gut microbe composition and for engineering tailored therapeutic approaches [221-223].

Intestinal microbiome and anti-diabetic drugs

Metformin

Since metformin was introduced in the middle of the twentieth century, it is widely used for type 2 diabetes therapy. Metformin is able to suppress hepatic GNG and ameliorate insulin susceptibility. Although, the exact processes underlying the activity of this drug are yet to fully investigate. Multiple trials demonstrated that intestinal flora could mediate the hypoglycaemic mechanisms of this drug. It is known that metformin influences sugar metabolic processes targeting flora in such factors: A. Preventing imbalance of the ecology of the gut micro-organisms, ameliorating the intestinal flora dysbiosis in subjects with type 2 diabetes [224,225].

B. Ameliorating the short-chain fatty acids production capacity, elevating the count of bacteria which generate short-chain fatty acids, e.g., Lactobacillus, Blautia Bifidobacterium, Prevotella, Akkermansia, Shewanella, Megasphaera, Butyrivibrio. Short-chain fatty acids are able to ameliorate insulin susceptibility and exhibit hypoglycaemic effects by elevating expression of glucagon-like peptide-1 and peptide YY. Trials demonstrated that metformin is able to ameliorate the concentrations of glucagon-like peptide-1 in the plasma and in the gut in subjects with type 2 diabetes [226,227].

C. Regulation of sugar metabolism via BA pathways. Sun and colleagues reported that this drug exerts hypoglycaemic effects via the gut B. fragilis-BA-glycoursodeoxycholic acid-gut farnesoid X receptor axis. Metformin suppresses the Bacteroides fragilis growth by altering the Met and folic acid metabolic processes, thus promoting the action of BSH and elevating glycoursodeoxycholic acid concentrations. Glycoursodeoxycholic acid is endogenous gut farnesoid X receptor antagonist. It suppresses the farnesoid X receptor signaling in the gut, which may elevate the expression of glucagon-like peptide-1 and maintain sugar metabolism [228,229].

D. Elevating the probiotics number. In the trial on intestinal microbiome, the elevation of probiotics amount, e.g., Bifidobacteria or Lactobacilli, was observed following the infusion of metformin. Recent research in murine model demonstrated that glucose-induced sodium/glucose cotransporter 1 activation in proximal colon is able to decrease glucose generation. HFD decreased the release of sodium/glucose cotransporter 1 in the ileum and decreased levels of Lactobacilli. Metformin neutralizes these alterations and promotes restoration of glucose sensibility. Although, it is yet to investigate if these mechanisms take place in human body [230,231].

E. Affected by imidazole propionate (ImP). ImP suppresses insulin conductivity via mechanistic target of rapamycin complex 1 pathway and facilitates development of DM. Resent research demonstrated that ImP is responsible for the hypoglycaemic effects of metformin. ImP levels are higher in subjects with type 2 diabetes who receive metformin treatment, but have elevated blood sugar. Trials in murine model supported the theory that ImP blocks metformin

hypoglycaemic effects. Cytological studies discovered that ImP suppresses AMP activated protein kinase activation caused by metformin via suppression of its phosphorylation via p38gamma-Akt signaling pathway [232-234]. The p38gamma kinase suppressant can suppress the metformin inhibition induced by ImP. This led to the development of novel tailored therapeutic approaches for subjects with DM. Moreover, approximately 33% of subjects who receive metformin therapy showed GI adverse side effects, e.g., diarrhoea, distended abdomen, nausea. This drug was proved to considerably elevate the E. coli levels and enhanced associated virulence factors as well as gas metabolic genes [235,236].

Acarbose

Acarbose is alpha-glucosidase suppressant (AGI). It decreases the uptake of CHs in small intestine, thus decreasing the post-meal blood sugar. Acarbose activity takes place entirely in the gut, which can in part influence the intestinal microbiome composition. Another trial demonstrated that intestinal microbiome of pre-diabetes was altered considerably upon administration of acarbose, where levels of Faecalibacteria, Lactobacilli and Dialister were upregulated [237-239]. Dialister was in inverse correlation with glycated hemoglobin in subjects with pre-DM, which implies that it takes part in regulating sugar metabolism. This compound is able to elevate levels of B. longum and E. faecalis in subjects with type 2 diabetes. E. faecalis was in inverse correlation with levels of lipopolysaccharides, and B. longum was in direct correlation with levels of high-density-Lp-C. In newly diagnosed subjects with type 2 diabetes, this compound elevated levels of Lactobacilli and Bifidobacteria and decreased levels of Bacteroides. Plasma and fecal BA metabolic spectrum was altered, indicating that this compound can influence the BA pathway mediated by the intestine and can ameliorate sugar metabolism [240-242]. Moreover, baseline properties of the intestinal microbiome are responsible for the acarbose impact. Metabolic characteristics of subjects with Bacteroides prevalent in the gut microbiome, such as insulin, fasting plasma glucose, C-peptide concentration, IR, were ameliorated more notably in comparison to subjects with Prevotella prevalent in the gut microbiome. Consistently, dividing the subjects with type 2 diabetes into groups based on intestinal microbiome properties prior to therapy is preferred for tailored treatment [243,244].

Conclusion

In conclusion, the intricate relationship between the intestinal microbiome and type 2 diabetes mellitus (T2DM) underscores the significance of microbial influences on metabolic health. The dysbiosis observed in individuals with T2DM highlights the disturbance in microbial composition and function, which can exacerbate insulin resistance and systemic inflammation. Emerging research reveals that specific gut bacteria not only play a role in the regulation of glucose metabolism but also possess the potential to modulate immune responses and inflammatory pathways, further influencing the progression of diabetes and its complications.

Interventions aimed at restoring a healthy microbiome through dietary modifications, probiotics, prebiotics, and fecal microbiota transplantation show promise in improving metabolic outcomes and enhancing insulin sensitivity. These findings suggest that a multifaceted approach that targets gut microbiota could complement traditional diabetes management strategies, potentially leading to better long-term health outcomes for patients with T2DM.

Future research is essential to better understand the causal relationships between gut microbiota, host metabolism, and the pathogenesis of T2DM. Large-scale clinical trials are needed to evaluate the efficacy of microbiome-targeted therapies and to establish guidelines for their clinical application. By further elucidating the mechanisms underlying the microbiome's impact on metabolic health, we can develop innovative strategies for preventing and managing type 2 diabetes and its associated complications, ultimately improving the quality of life for millions affected by this disorder.

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References

1. Ruze, R., Liu, T., Zou, X., Song, J., Chen, Y., Xu, R., Yin, X., & Xu, Q. (2023). Obesity and type 2 diabetes mellitus: connections in epidemiology, pathogenesis, and treatments. *Frontiers in endocrinology*, *14*, 1161521. https://doi.org/10.3389/fendo.2023.1161521

2. Galicia-Garcia, U., Benito-Vicente, A., Jebari, S., Larrea-Sebal, A., Siddiqi, H., Uribe, K. B., Ostolaza, H., & Martín, C. (2020). Pathophysiology of Type 2 Diabetes Mellitus. *International journal of molecular sciences*, *21*(17), 6275. https://doi.org/10.3390/ijms21176275

3. Dilworth L, Facey A, Omoruyi F. Diabetes Mellitus and Its Metabolic Complications: The Role of Adipose Tissues. Int J Mol Sci. 2021 Jul 16;22(14):7644. doi: 10.3390/ijms22147644. PMID: 34299261; PMCID: PMC8305176.

4. Galicia-Garcia, U., Benito-Vicente, A., Jebari, S., Larrea-Sebal, A., Siddiqi, H., Uribe, K. B., Ostolaza, H., & Martín, C. (2020). Pathophysiology of Type 2 Diabetes Mellitus. *International journal of molecular sciences*, *21*(17), 6275. https://doi.org/10.3390/ijms21176275

5. Antar SA, Ashour NA, Sharaky M, Khattab M, Ashour NA, Zaid RT, Roh EJ, Elkamhawy A, Al-

Karmalawy AA. Diabetes mellitus: Classification, mediators, and complications; A gate to identify potential targets for the development of new effective treatments. Biomed Pharmacother. 2023 Dec;168:115734. doi: 10.1016/j.biopha.2023.115734. Epub 2023 Oct 17. PMID: 37857245.

6. Wensel, C. R., Pluznick, J. L., Salzberg, S. L., & Sears, C. L. (2022). Next-generation sequencing: insights to advance clinical investigations of the microbiome. *The Journal of clinical investigation*, *132*(7), e154944. https://doi.org/10.1172/JCI154944

7. Bai, X., Narayanan, A., Nowak, P., Ray, S., Neogi, U., & Sönnerborg, A. (2021). Whole-Genome Metagenomic Analysis of the Gut Microbiome in HIV-1-Infected Individuals on Antiretroviral Therapy. *Frontiers in microbiology*, *12*, 667718. https://doi.org/10.3389/fmicb.2021.667718

8. Carter, M. M., Olm, M. R., Merrill, B. D., Dahan, D., Tripathi, S., Spencer, S. P., Yu, F. B., Jain, S., Neff, N., Jha, A. R., Sonnenburg, E. D., & Sonnenburg, J. L. (2023). Ultra-deep sequencing of Hadza hunter-gatherers recovers vanishing gut microbes. *Cell*, *186*(14), 3111–3124.e13. https://doi.org/10.1016/j.cell.2023.05.046

9. Zhang Q, Zhao Q, Li T, Lu L, Wang F, Zhang H, Liu Z, Ma H, Zhu Q, Wang J, Zhang X, Pei Y, Liu Q, Xu Y, Qie J, Luan X, Hu Z, Liu X. Lactobacillus plantarum-derived indole-3-lactic acid ameliorates colorectal tumorigenesis via epigenetic regulation of $CD8^+$ T cell immunity. Cell Metab. 2023 Jun 6;35(6):943-960.e9. doi: 10.1016/j.cmet.2023.04.015. Epub 2023 May 15. PMID: 37192617.

10. Wu, J., Wang, K., Wang, X., Pang, Y., & Jiang, C. (2021). The role of the gut microbiome and its metabolites in metabolic diseases. *Protein & cell*, *12*(5), 360–373. https://doi.org/10.1007/s13238-020-00814-7

11. Fu, Y., Li, S., Xiao, Y., Liu, G., & Fang, J. (2023). A Metabolite Perspective on the Involvement of the Gut Microbiota in Type 2 Diabetes. *International journal of molecular sciences*, *24*(19), 14991. https://doi.org/10.3390/ijms241914991

12. Zhou Z, Sun B, Yu D, Zhu C. Gut Microbiota: An Important Player in Type 2 Diabetes Mellitus. Front Cell Infect Microbiol. 2022 Feb 15;12:834485. doi: 10.3389/fcimb.2022.834485. PMID: 35242721; PMCID: PMC8886906.

13. Kamareddine, L., Najjar, H., Sohail, M. U., Abdulkader, H., & Al-Asmakh, M. (2020). The Microbiota and Gut-Related Disorders: Insights from Animal Models. *Cells*, *9*(11), 2401. https://doi.org/10.3390/cells9112401

14. Xia, F., Wen, L. P., Ge, B. C., Li, Y. X., Li, F. P., & Zhou, B. J. (2021). Gut microbiota as a target for prevention and treatment of type 2 diabetes: Mechanisms and dietary natural products. *World journal of diabetes*, *12*(8), 1146–1163. https://doi.org/10.4239/wjd.v12.i8.1146

15. Crudele L, Gadaleta RM, Cariello M, Moschetta A. Gut microbiota in the pathogenesis and therapeutic approaches of diabetes. EBioMedicine. 2023 Nov;97:104821. doi: 10.1016/j.ebiom.2023.104821. Epub 2023 Oct 5. PMID: 37804567; PMCID: PMC10570704.

16. Manca, C., Boubertakh, B., Leblanc, N., Deschênes, T., Lacroix, S., Martin, C., Houde, A., Veilleux, A., Flamand, N., Muccioli, G. G., Raymond, F., Cani, P. D., Di Marzo, V., & Silvestri, C. (2020). Germ-free mice exhibit profound gut microbiota-dependent alterations of intestinal endocannabinoidome signaling. *Journal of lipid research*, *61*(1), 70–85. https://doi.org/10.1194/jlr.RA119000424

17. Harsch, I. A., & Konturek, P. C. (2018). The Role of Gut Microbiota in Obesity and Type 2 and Type 1 Diabetes Mellitus: New Insights into "Old" Diseases. *Medical sciences (Basel, Switzerland)*, *6*(2), 32. https://doi.org/10.3390/medsci6020032

18. Guzzardi MA, La Rosa F, Iozzo P. Trust the gut: Outcomes of gut microbiota transplant in metabolic and cognitive disorders. Neurosci Biobehav Rev. 2023 Jun;149:105143. doi: 10.1016/j.neubiorev.2023.105143. Epub 2023 Mar 27. PMID: 36990372.

19. Hossain, M. J., Al-Mamun, M., & Islam, M. R. (2024). Diabetes mellitus, the fastest growing global public health concern: Early detection should be focused. *Health science reports*, *7*(3), e2004. https://doi.org/10.1002/hsr2.2004

20. Jyotsna, F., Ahmed, A., Kumar, K., Kaur, P., Chaudhary, M. H., Kumar, S., Khan, E., Khanam, B., Shah, S. U., Varrassi, G., Khatri, M., Kumar, S., & Kakadiya, K. A. (2023). Exploring the Complex Connection Between Diabetes and Cardiovascular Disease: Analyzing Approaches to Mitigate Cardiovascular Risk in Patients With Diabetes. *Cureus*, *15*(8), e43882. https://doi.org/10.7759/cureus.43882

21. Galicia-Garcia, U., Benito-Vicente, A., Jebari, S., Larrea-Sebal, A., Siddiqi, H., Uribe, K. B., Ostolaza, H., & Martín, C. (2020). Pathophysiology of Type 2 Diabetes Mellitus. *International journal of molecular sciences*, *21*(17), 6275. https://doi.org/10.3390/ijms21176275

22. Daryabor, G., Atashzar, M. R., Kabelitz, D., Meri, S., & Kalantar, K. (2020). The Effects of Type 2 Diabetes Mellitus on Organ Metabolism and the Immune System. *Frontiers in immunology*, *11*, 1582. https://doi.org/10.3389/fimmu.2020.01582

23. Benjamin, E. J., Blaha, M. J., Chiuve, S. E., Cushman, M., Das, S. R., Deo, R., de Ferranti, S. D., Floyd, J., Fornage, M., Gillespie, C., Isasi, C. R., Jiménez, M. C., Jordan, L. C., Judd, S. E., Lackland, D., Lichtman, J. H., Lisabeth, L., Liu, S., Longenecker, C. T., Mackey, R. H., … American Heart Association Statistics Committee and Stroke

Statistics Subcommittee (2017). Heart Disease and Stroke Statistics-2017 Update: A Report From the American Heart Association. *Circulation*, *135*(10), e146–e603. https://doi.org/10.1161/CIR.0000000000000485

24. Echefu, G., Stowe, I., Burka, S., Basu-Ray, I., & Kumbala, D. (2023). Pathophysiological concepts and screening of cardiovascular disease in dialysis patients. *Frontiers in nephrology*, *3*, 1198560. https://doi.org/10.3389/fneph.2023.1198560

25. Poznyak AV, Orekhova VA, Sukhorukov VN, Khotina VA, Popov MA, Orekhov AN. Atheroprotective Aspects of Heat Shock Proteins. Int J Mol Sci. 2023 Jul 21;24(14):11750. doi: 10.3390/ijms241411750. PMID: 37511509; PMCID: PMC10380699.

26. De Rosa, S., Arcidiacono, B., Chiefari, E., Brunetti, A., Indolfi, C., & Foti, D. P. (2018). Type 2 Diabetes Mellitus and Cardiovascular Disease: Genetic and Epigenetic Links. *Frontiers in endocrinology*, *9*, 2. https://doi.org/10.3389/fendo.2018.00002

27. Giri B, Dey S, Das T, Sarkar M, Banerjee J, Dash SK. Chronic hyperglycemia mediated physiological alteration and metabolic distortion leads to organ dysfunction, infection, cancer progression and other pathophysiological consequences: An update on glucose toxicity. Biomed Pharmacother. 2018 Nov;107:306-328. doi: 10.1016/j.biopha.2018.07.157. Epub 2018 Aug 8. PMID: 30098549.

28. Ye J, Li L, Wang M, Ma Q, Tian Y, Zhang Q, Liu J, Li B, Zhang B, Liu H, Sun G. Diabetes Mellitus Promotes the Development of Atherosclerosis: The Role of NLRP3. Front Immunol. 2022 Jun 29;13:900254. doi: 10.3389/fimmu.2022.900254. PMID: 35844498; PMCID: PMC9277049.

29. Slouha, E., Rezazadah, A., Farahbod, K., Gerts, A., Clunes, L. A., & Kollias, T. F. (2023). Type-2 Diabetes Mellitus and the Gut Microbiota: Systematic Review. *Cureus*, *15*(11), e49740. https://doi.org/10.7759/cureus.49740

30. López-Villodres, J. A., Escamilla, A., Mercado-Sáenz, S., Alba-Tercedor, C., Rodriguez-Perez, L. M., Arranz-Salas, I., Sanchez-Varo, R., & Bermúdez, D. (2023). Microbiome Alterations and Alzheimer's Disease: Modeling Strategies with Transgenic Mice. *Biomedicines*, *11*(7), 1846. https://doi.org/10.3390/biomedicines11071846

31. Zhang, F., Lau, R.I., Liu, Q. *et al.* Gut microbiota in COVID-19: key microbial changes, potential mechanisms and clinical applications. *Nat Rev Gastroenterol Hepatol* **20**, 323–337 (2023). https://doi.org/10.1038/s41575-022-00698-4

32. Guo, M., Lu, M., Chen, K., Xu, R., Xia, Y., Liu, X., Liu, Z., & Liu, Q. (2023). *Akkermansia muciniphila* and *Lactobacillus plantarum* ameliorate systemic lupus erythematosus by possibly regulating immune response and remodeling gut microbiota. *mSphere*, *8*(4), e0007023. https://doi.org/10.1128/msphere.00070-23

33. Gurung, M., Li, Z., You, H., Rodrigues, R., Jump, D. B., Morgun, A., & Shulzhenko, N. (2020). Role of gut microbiota in type 2 diabetes pathophysiology. *EBioMedicine*, *51*, 102590. https://doi.org/10.1016/j.ebiom.2019.11.051

34. Dutta, D., Lim, S.H. Bidirectional interaction between intestinal microbiome and cancer: opportunities for therapeutic interventions. *Biomark Res* **8**, 31 (2020). https://doi.org/10.1186/s40364-020-00211-6

35. Rastogi S, Singh A. Gut microbiome and human health: Exploring how the probiotic genus *Lactobacillus* modulate immune responses. Front Pharmacol. 2022 Oct 24;13:1042189. doi: 10.3389/fphar.2022.1042189. PMID: 36353491; PMCID: PMC9638459.

36. Lee, C. B., Chae, S. U., Jo, S. J., Jerng, U. M., & Bae, S. K. (2021). The Relationship between the Gut Microbiome and Metformin as a Key for Treating Type 2 Diabetes Mellitus. *International journal of molecular sciences*, *22*(7), 3566. https://doi.org/10.3390/ijms22073566

37. Pavlo Petakh, Kamyshna, I., & Kamyshnyi, A. (2023). Effects of metformin on the gut microbiota: A systematic review. *Molecular metabolism*, *77*, 101805. https://doi.org/10.1016/j.molmet.2023.101805

38. Garg K, Mohajeri MH. Potential effects of the most prescribed drugs on the microbiota-gut-brain-axis: A review. Brain Res Bull. 2024 Feb;207:110883. doi: 10.1016/j.brainresbull.2024.110883. Epub 2024 Jan 18. PMID: 38244807.

39. Liu W, Luo Z, Zhou J, Sun B. Gut Microbiota and Antidiabetic Drugs: Perspectives of Personalized Treatment in Type 2 Diabetes Mellitus. Front Cell Infect Microbiol. 2022 May 31;12:853771. doi: 10.3389/fcimb.2022.853771. PMID: 35711668; PMCID: PMC9194476.

40. Wu J, Yang K, Fan H, Wei M, Xiong Q. Targeting the gut microbiota and its metabolites for type 2 diabetes mellitus. Front Endocrinol (Lausanne). 2023 May 9;14:1114424. doi: 10.3389/fendo.2023.1114424. PMID: 37229456; PMCID: PMC10204722.

41. Duan L, An X, Zhang Y, Jin D, Zhao S, Zhou R, Duan Y, Zhang Y, Liu X, Lian F. Gut microbiota as the critical correlation of polycystic ovary syndrome and type 2 diabetes mellitus. Biomed Pharmacother. 2021 Oct;142:112094. doi: 10.1016/j.biopha.2021.112094. Epub 2021 Aug 26. PMID: 34449321.

42. Nikiforov NG, Kirichenko TV, Kubekina MV, Chegodaev YS, Zhuravlev AD, Ilchuk LA, Nikolaeva MA, Arefieva AS, Popov MA, Verkhova SS, Bagheri Ekta M, Orekhov AN. Macrophages derived from LPS-stimulated monocytes from individuals with subclinical atherosclerosis were

characterized by increased pro-inflammatory activity. Cytokine. 2023 Dec;172:156411. doi: 10.1016/j.cyto.2023.156411. Epub 2023 Oct 31. PMID: 37918051.

43. Sadagopan, A., Mahmoud, A., Begg, M., Tarhuni, M., Fotso, M., Gonzalez, N. A., Sanivarapu, R. R., Osman, U., Latha Kumar, A., & Mohammed, L. (2023). Understanding the Role of the Gut Microbiome in Diabetes and Therapeutics Targeting Leaky Gut: A Systematic Review. *Cureus*, *15*(7), e41559. https://doi.org/10.7759/cureus.41559

44. Sharma BR, Jaiswal S, Ravindra PV. Modulation of gut microbiota by bioactive compounds for prevention and management of type 2 diabetes. Biomed Pharmacother. 2022 Aug;152:113148. doi: 10.1016/j.biopha.2022.113148. Epub 2022 Jun 2. PMID: 35665671.

45. Loh, J.S., Mak, W.Q., Tan, L.K.S. *et al.* Microbiota–gut–brain axis and its therapeutic applications in neurodegenerative diseases. *Sig Transduct Target Ther* **9**, 37 (2024). https://doi.org/10.1038/s41392-024-01743-1

46. Momen YS, Mishra J, Kumar N. Brain-Gut and Microbiota-Gut-Brain Communication in Type-2 Diabetes Linked Alzheimer's Disease. Nutrients. 2024 Aug 3;16(15):2558. doi: 10.3390/nu16152558. PMID: 39125436; PMCID: PMC11313915.

47. Fernandes R, Viana SD, Nunes S, Reis F. Diabetic gut microbiota dysbiosis as an inflammaging and immunosenescence condition that fosters progression of retinopathy and nephropathy. Biochim Biophys Acta Mol Basis Dis. 2019 Jul 1;1865(7):1876-1897. doi: 10.1016/j.bbadis.2018.09.032. Epub 2018 Oct 1. PMID: 30287404.

48. He L, Yang FQ, Tang P, Gao TH, Yang CX, Tan L, Yue P, Hua YN, Liu SJ, Guo JL. Regulation of the intestinal flora: A potential mechanism of natural medicines in the treatment of type 2 diabetes mellitus. Biomed Pharmacother. 2022 Jul;151:113091. doi: 10.1016/j.biopha.2022.113091. Epub 2022 May 13. PMID: 35576662.

49. Williams, C. L., & Long, A. E. (2019). What has zinc transporter 8 autoimmunity taught us about type 1 diabetes?. *Diabetologia*, *62*(11), 1969–1976. https://doi.org/10.1007/s00125-019-04975-x

50. Chen, B., Yu, P., Chan, W.N. *et al.* Cellular zinc metabolism and zinc signaling: from biological functions to diseases and therapeutic targets. *Sig Transduct Target Ther* **9**, 6 (2024). https://doi.org/10.1038/s41392-023-01679-y

51. Sui, L., Du, Q., Romer, A., Su, Q., Chabosseau, P. L., Xin, Y., Kim, J., Kleiner, S., Rutter, G. A., & Egli, D. (2023). ZnT8 Loss of Function Mutation Increases Resistance of Human Embryonic Stem Cell-Derived Beta Cells to Apoptosis in Low Zinc Condition. *Cells*, *12*(6), 903. https://doi.org/10.3390/cells12060903

52. Firth, G., Georgiadou, E., Griffiths, A., Amrahli, M., Kim, J., Yu, Z., Hu, M., Stewart, T. J., Leclerc, I., Okamoto, H., Gomez, D., Blower, P. J., & Rutter, G. A. (2023). Impact of an *SLC30A8* loss-of-function variant on the pancreatic distribution of zinc and manganese: laser ablation-ICP-MS and positron emission tomography studies in mice. *Frontiers in endocrinology*, *14*, 1171933. https://doi.org/10.3389/fendo.2023.1171933

53. Li, Z., Yuan, H., Chu, H., & Yang, L. (2023). The Crosstalk between Gut Microbiota and Bile Acids Promotes the Development of Non-Alcoholic Fatty Liver Disease. *Microorganisms*, *11*(8), 2059. https://doi.org/10.3390/microorganisms11082059

54. Cai J, Rimal B, Jiang C, Chiang JYL, Patterson AD. Bile acid metabolism and signaling, the microbiota, and metabolic disease. Pharmacol Ther. 2022 Sep;237:108238. doi: 10.1016/j.pharmthera.2022.108238. Epub 2022 Jul 2. PMID: 35792223.

55. Liu, L., Zhang, J., Cheng, Y., Zhu, M., Xiao, Z., Ruan, G., & Wei, Y. (2022). Gut microbiota: A new target for T2DM prevention and treatment. *Frontiers in endocrinology*, *13*, 958218. https://doi.org/10.3389/fendo.2022.958218

56. Mavilio M, Marchetti V, Fabrizi M, Stöhr R, Marino A, Casagrande V, Fiorentino L, Cardellini M, Kappel B, Monteleone I, Garret C, Mauriello A, Monteleone G, Farcomeni A, Burcelin R, Menghini R, Federici M. A Role for Timp3 in Microbiota-Driven Hepatic Steatosis and Metabolic Dysfunction. Cell Rep. 2016 Jul 19;16(3):731-43. doi: 10.1016/j.celrep.2016.06.027. Epub 2016 Jun 30. Erratum in: Cell Rep. 2016 Aug 23;16(8):2269. doi: 10.1016/j.celrep.2016.07.078. PMID: 27373162.

57. Shahini, A., & Shahini, A. (2023). Role of interleukin-6-mediated inflammation in the pathogenesis of inflammatory bowel disease: focus on the available therapeutic approaches and gut microbiome. *Journal of cell communication and signaling*, *17*(1), 55–74. https://doi.org/10.1007/s12079-022-00695-x

58. Zhai, Z., Dong, W., Sun, Y., Gu, Y., Ma, J., Wang, B., & Cao, H. (2022). Vitamin-Microbiota Crosstalk in Intestinal Inflammation and Carcinogenesis. *Nutrients*, *14*(16), 3383. https://doi.org/10.3390/nu14163383

59. Poznyak AV, Sukhorukov VN, Popov MA, Chegodaev YS, Postnov AY, Orekhov AN. Mechanisms of the Wnt Pathways as a Potential Target Pathway in Atherosclerosis. J Lipid Atheroscler. 2023 Sep;12(3):223-236. doi: 10.12997/jla.2023.12.3.223. Epub 2023 Sep 7. PMID: 37800111; PMCID: PMC10548192.

60. Frühbeck, G., Gómez-Ambrosi, J., Ramírez, B., Mentxaka, A., Rodríguez, A., Becerril, S., Reina, G., Valentí, V., Moncada, R., Silva, C., & Catalán, V. (2022). Increased Levels of Interleukin-36 in Obesity and Type 2 Diabetes Fuel Adipose Tissue Inflammation by Inducing Its Own Expression and Release by Adipocytes and Macrophages. *Frontiers*

in immunology, *13*, 832185. https://doi.org/10.3389/fimmu.2022.832185

61. Giannoudaki E, Hernandez-Santana YE, Mulfaul K, Doyle SL, Hams E, Fallon PG, Mat A, O'Shea D, Kopf M, Hogan AE, Walsh PT. Interleukin-36 cytokines alter the intestinal microbiome and can protect against obesity and metabolic dysfunction. Nat Commun. 2019 Sep 5;10(1):4003. doi: 10.1038/s41467-019-11944-w. PMID: 31488830; PMCID: PMC6728358.

62. Vals-Delgado C, Alcala-Diaz JF, Molina-Abril H, Roncero-Ramos I, Caspers MPM, Schuren FHJ, Van den Broek TJ, Luque R, Perez-Martinez P, Katsiki N, Delgado-Lista J, Ordovas JM, van Ommen B, Camargo A, Lopez-Miranda J. An altered microbiota pattern precedes Type 2 diabetes mellitus development: From the CORDIOPREV study. J Adv Res. 2021 May 13;35:99-108. doi: 10.1016/j.jare.2021.05.001. PMID: 35024196; PMCID: PMC8721255.

63. Huda, M. N., Kim, M., & Bennett, B. J. (2021). Modulating the Microbiota as a Therapeutic Intervention for Type 2 Diabetes. *Frontiers in endocrinology*, *12*, 632335. https://doi.org/10.3389/fendo.2021.632335

64. Guney, C., Bal, N. B., & Akar, F. (2023). The impact of dietary fructose on gut permeability, microbiota, abdominal adiposity, insulin signaling and reproductive function. *Heliyon*, *9*(8), e18896. https://doi.org/10.1016/j.heliyon.2023.e18896

65. Zhang Y, Chen R, Zhang D, Qi S, Liu Y. Metabolite interactions between host and microbiota during health and disease: Which feeds the other? Biomed Pharmacother. 2023 Apr;160:114295. doi: 10.1016/j.biopha.2023.114295. Epub 2023 Jan 27. PMID: 36709600.

66. Bui TPN. The Human Microbiome as a Therapeutic Target for Metabolic Diseases. Nutrients. 2024 Jul 19;16(14):2322. doi: 10.3390/nu16142322. PMID: 39064765; PMCID: PMC11280041.

67. Yan, M., Guo, X., Ji, G., Huang, R., Huang, D., Li, Z., Zhang, D., Chen, S., Cao, R., Yang, X., & Wu, W. (2023). Mechanismbased role of the intestinal microbiota in gestational diabetes mellitus: A systematic review and meta-analysis. *Frontiers in immunology*, *13*, 1097853. https://doi.org/10.3389/fimmu.2022.1097853

68. Młynarska, E., Wasiak, J., Gajewska, A., Steć, G., Jasińska, J., Rysz, J., & Franczyk, B. (2024). Exploring the Significance of Gut Microbiota in Diabetes Pathogenesis and Management-A Narrative Review. *Nutrients*, *16*(12), 1938. https://doi.org/10.3390/nu16121938

69. Dione, N., Lacroix, S., Taschler, U., Deschênes, T., Abolghasemi, A., Leblanc, N., Di Marzo, V., & Silvestri, C. (2020). *Mgll* Knockout Mouse Resistance to Diet-Induced Dysmetabolism Is Associated with Altered Gut Microbiota. *Cells*, *9*(12), 2705. https://doi.org/10.3390/cells9122705

70. Janssen, A. W. F., Katiraei, S., Bartosinska, B., Eberhard, D., Willems van Dijk, K., & Kersten, S. (2018). Loss of angiopoietin-like 4 (ANGPTL4) in mice with diet-induced obesity uncouples visceral obesity from glucose intolerance partly via the gut microbiota. *Diabetologia*, *61*(6), 1447–1458. https://doi.org/10.1007/s00125-018-4583-5

71. Li, K., Ly, K., Mehta, S., & Braithwaite, A. (2022). Importance of crosstalk between the microbiota and the neuroimmune system for tissue homeostasis. *Clinical & translational immunology*, *11*(5), e1394. https://doi.org/10.1002/cti2.1394

72. Ullah, H., Arbab, S., Tian, Y., Chen, Y., Liu, C. Q., Li, Q., & Li, K. (2024). Crosstalk between gut microbiota and host immune system and its response to traumatic injury. *Frontiers in immunology*, *15*, 1413485. https://doi.org/10.3389/fimmu.2024.1413485

73. Kim, S., Seo, SU. & Kweon, MN. Gut microbiota-derived metabolites tune host homeostasis fate. *Semin Immunopathol* **46**, 2 (2024). https://doi.org/10.1007/s00281-024-01012-x

74. Lee, J. S., Wang, R. X., Alexeev, E. E., & Colgan, S. P. (2021). Intestinal Inflammation as a Dysbiosis of Energy Procurement: New Insights into an Old Topic. *Gut microbes*, *13*(1), 1–20. https://doi.org/10.1080/19490976.2021.1880241

75. Savytska, M., Kyriienko, D., Zaychenko, G., Ostapchenko, D., Falalyeyeva, T., & Kobyliak, N. (2024). Probiotic co-supplementation with absorbent smectite for pancreatic beta-cell function in type 2 diabetes: a secondary-data analysis of a randomized double-blind controlled trials. *Frontiers in endocrinology*, *15*, 1276642. https://doi.org/10.3389/fendo.2024.1276642

76. Zeng, Y., Wu, Y., Zhang, Q., & Xiao, X. (2024). Crosstalk between glucagon-like peptide 1 and gut microbiota in metabolic diseases. *mBio*, *15*(1), e0203223. https://doi.org/10.1128/mbio.02032-23

77. Fu Y, Li S, Xiao Y, Liu G, Fang J. A Metabolite Perspective on the Involvement of the Gut Microbiota in Type 2 Diabetes. Int J Mol Sci. 2023 Oct 8;24(19):14991. doi: 10.3390/ijms241914991. PMID: 37834439; PMCID: PMC10573635.

78. Li, J., Yang, G., Zhang, Q., Liu, Z., Jiang, X., & Xin, Y. (2023). Function of *Akkermansia muciniphila* in type 2 diabetes and related diseases. *Frontiers in microbiology*, *14*, 1172400. https://doi.org/10.3389/fmicb.2023.1172400

79. Si, J., Kang, H., You, H. J., & Ko, G. (2022). Revisiting the role of *Akkermansia muciniphila* as a therapeutic bacterium. *Gut microbes*, *14*(1), 2078619. https://doi.org/10.1080/19490976.2022.2078619

80. Lei, W., Cheng, Y., Gao, J., Liu, X., Shao, L., Kong, Q., Zheng, N., Ling, Z., & Hu, W. (2023). *Akkermansia muciniphila* in neuropsychiatric disorders: friend or foe?. *Frontiers in cellular and*

infection microbiology, *13*, 1224155. https://doi.org/10.3389/fcimb.2023.1224155

81. Thompson, M. R., Kaminski, J. J., Kurt-Jones, E. A., & Fitzgerald, K. A. (2011). Pattern recognition receptors and the innate immune response to viral infection. *Viruses*, *3*(6), 920–940. https://doi.org/10.3390/v3060920

82. Hu, A., Sun, L., Lin, H. *et al.* Harnessing innate immune pathways for therapeutic advancement in cancer. *Sig Transduct Target Ther* **9**, 68 (2024). https://doi.org/10.1038/s41392-024-01765-9

83. Lundberg, R., Toft, M.F., Metzdorff, S.B. *et al.* Human microbiota-transplanted C57BL/6 mice and offspring display reduced establishment of key bacteria and reduced immune stimulation compared to mouse microbiota-transplantation. *Sci Rep* **10**, 7805 (2020). https://doi.org/10.1038/s41598-020-64703-z

84. Pearson JA, Hu Y, Peng J, Wong FS, Wen L. TLR5-deficiency controls dendritic cell subset development in an autoimmune diabetes-susceptible model. Front Immunol. 2024 Feb 28;15:1333967. doi: 10.3389/fimmu.2024.1333967. PMID: 38482010; PMCID: PMC10935730.

85. Li, J. H., Chen, Y., Ye, Z. H., Chen, L. P., Xu, J. X., Han, J., Xie, L., Xing, S., Tian, D. A., Seidler, U., Liao, J. Z., & Xiao, F. (2024). Suppression of MyD88 disturbs gut microbiota and activates the NLR pathway and hence fails to ameliorate DSS-induced colitis. *Precision clinical medicine*, *7*(2), pbae013. https://doi.org/10.1093/pcmedi/pbae013

86. Hasain Z, Mokhtar NM, Kamaruddin NA, Mohamed Ismail NA, Razalli NH, Gnanou JV, Raja Ali RA. Gut Microbiota and Gestational Diabetes Mellitus: A Review of Host-Gut Microbiota Interactions and Their Therapeutic Potential. Front Cell Infect Microbiol. 2020 May 15;10:188. doi: 10.3389/fcimb.2020.00188. PMID: 32500037; PMCID: PMC7243459.

87. Brandt A, Kromm F, Hernández-Arriaga A, Martínez Sánchez I, Bozkir HÖ, Staltner R, Baumann A, Camarinha-Silva A, Heijtz RD, Bergheim I. Cognitive Alterations in Old Mice Are Associated with Intestinal Barrier Dysfunction and Induced Toll-like Receptor 2 and 4 Signaling in Different Brain Regions. Cells. 2023 Aug 27;12(17):2153. doi: 10.3390/cells12172153. PMID: 37681885; PMCID: PMC10486476.

88. Balasubramanian, I., & Gao, N. (2017). From sensing to shaping microbiota: insights into the role of NOD2 in intestinal homeostasis and progression of Crohn's disease. *American journal of physiology. Gastrointestinal and liver physiology*, *313*(1), G7–G13. https://doi.org/10.1152/ajpgi.00330.2016

89. Trindade, B. C., & Chen, G. Y. (2020). NOD1 and NOD2 in inflammatory and infectious diseases. *Immunological reviews*, *297*(1), 139–161. https://doi.org/10.1111/imr.12902

90. Zangara, M. T., Johnston, I., Johnson, E. E., & McDonald, C. (2021). Mediators of Metabolism: An Unconventional Role for NOD1 and NOD2. *International journal of molecular sciences*, *22*(3), 1156. https://doi.org/10.3390/ijms22031156

91. Cani PD, Osto M, Geurts L, Everard A. Involvement of gut microbiota in the development of low-grade inflammation and type 2 diabetes associated with obesity. Gut Microbes. 2012 Jul-Aug;3(4):279-88. doi: 10.4161/gmic.19625. Epub 2012 May 14. PMID: 22572877; PMCID: PMC3463487.

92. Cani PD, Bibiloni R, Knauf C, Waget A, Neyrinck AM, Delzenne NM, Burcelin R. Changes in gut microbiota control metabolic endotoxemia-induced inflammation in high-fat diet-induced obesity and diabetes in mice. Diabetes. 2008 Jun;57(6):1470-81. doi: 10.2337/db07-1403. Epub 2008 Feb 27. PMID: 18305141.

93. Pérez MM, Martins LMS, Dias MS, Pereira CA, Leite JA, Gonçalves ECS, de Almeida PZ, de Freitas EN, Tostes RC, Ramos SG, de Zoete MR, Ryffel B, Silva JS, Carlos D. Interleukin-17/interleukin-17 receptor axis elicits intestinal neutrophil migration, restrains gut dysbiosis and lipopolysaccharide translocation in high-fat diet-induced metabolic syndrome model. Immunology. 2019 Apr;156(4):339-355. doi: 10.1111/imm.13028. Epub 2018 Dec 27. PMID: 30472727; PMCID: PMC6418416.

94. Stolfi C, Maresca C, Monteleone G, Laudisi F. Implication of Intestinal Barrier Dysfunction in Gut Dysbiosis and Diseases. Biomedicines. 2022 Jan 27;10(2):289. doi: 10.3390/biomedicines10020289. PMID: 35203499; PMCID: PMC8869546.

95. Poznyak AV, Kashirskikh DA, Postnov AY, Popov MA, Sukhorukov VN, Orekhov AN. Sialic acid as the potential link between lipid metabolism and inflammation in the pathogenesis of atherosclerosis. Braz J Med Biol Res. 2023 Dec 11;56:e12972. doi: 10.1590/1414-431X2023e12972. PMID: 38088673; PMCID: PMC10712282.

96. Luo Z, Ji Y, Gao H, Gomes Dos Reis FC, Bandyopadhyay G, Jin Z, Ly C, Chang YJ, Zhang D, Kumar D, Ying W. CRIg^{+} Macrophages Prevent Gut Microbial DNA-Containing Extracellular Vesicle-Induced Tissue Inflammation and Insulin Resistance. Gastroenterology. 2021 Feb;160(3):863-874. doi: 10.1053/j.gastro.2020.10.042. Epub 2020 Nov 2. PMID: 33152356; PMCID: PMC7878308.

97. Tanase, D. M., Gosav, E. M., Neculae, E., Costea, C. F., Ciocoiu, M., Hurjui, L. L., Tarniceriu, C. C., Maranduca, M. A., Lacatusu, C. M., Floria, M., & Serban, I. L. (2020). Role of Gut Microbiota on Onset and Progression of Microvascular Complications of Type 2 Diabetes (T2DM). *Nutrients*, *12*(12), 3719. https://doi.org/10.3390/nu12123719

98. Li, X., Watanabe, K., & Kimura, I. (2017). Gut Microbiota Dysbiosis Drives and Implies Novel

Therapeutic Strategies for Diabetes Mellitus and Related Metabolic Diseases. *Frontiers in immunology*, *8*, 1882. https://doi.org/10.3389/fimmu.2017.01882

99. Fakharian, F., Thirugnanam, S., Welsh, D. A., Kim, W. K., Rappaport, J., Bittinger, K., & Rout, N. (2023). The Role of Gut Dysbiosis in the Loss of Intestinal Immune Cell Functions and Viral Pathogenesis. *Microorganisms*, *11*(7), 1849. https://doi.org/10.3390/microorganisms11071849

100. Hong CP, Park A, Yang BG, Yun CH, Kwak MJ, Lee GW, Kim JH, Jang MS, Lee EJ, Jeun EJ, You G, Kim KS, Choi Y, Park JH, Hwang D, Im SH, Kim JF, Kim YK, Seoh JY, Surh CD, Kim YM, Jang MH. Gut-Specific Delivery of T-Helper 17 Cells Reduces Obesity and Insulin Resistance in Mice. Gastroenterology. 2017 Jun;152(8):1998-2010. doi: 10.1053/j.gastro.2017.02.016. Epub 2017 Feb 27. PMID: 28246016.

101. Zi C, Wang D, Gao Y, He L. The role of Th17 cells in endocrine organs: Involvement of the gut, adipose tissue, liver and bone. Front Immunol. 2023 Jan 16;13:1104943. doi: 10.3389/fimmu.2022.1104943. PMID: 36726994; PMCID: PMC9884980.

102. Wang, L., Cao, Z. M., Zhang, L. L., Li, J. M., & Lv, W. L. (2022). The Role of Gut Microbiota in Some Liver Diseases: From an Immunological Perspective. *Frontiers in immunology*, *13*, 923599. https://doi.org/10.3389/fimmu.2022.923599

103. Blagov AV, Sukhorukov VN, Guo S, Zhang D, Popov MA, Orekhov AN. Impaired Mitochondrial Function in T-Lymphocytes as a Result of Exposure to HIV and ART. Cells. 2023 Apr 2;12(7):1072. doi: 10.3390/cells12071072. PMID: 37048145; PMCID: PMC10093108.

104. Rahman, S., O'Connor, A. L., Becker, S. L., Patel, R. K., Martindale, R. G., & Tsikitis, V. L. (2023). Gut microbial metabolites and its impact on human health. *Annals of gastroenterology*, *36*(4), 360–368. https://doi.org/10.20524/aog.2023.0809

105. Facchin, S., Bertin, L., Bonazzi, E., Lorenzon, G., De Barba, C., Barberio, B., Zingone, F., Maniero, D., Scarpa, M., Ruffolo, C., Angriman, I., & Savarino, E. V. (2024). Short-Chain Fatty Acids and Human Health: From Metabolic Pathways to Current Therapeutic Implications. *Life (Basel, Switzerland)*, *14*(5), 559. https://doi.org/10.3390/life14050559

106. Portincasa, P., Bonfrate, L., Vacca, M., De Angelis, M., Farella, I., Lanza, E., Khalil, M., Wang, D. Q., Sperandio, M., & Di Ciaula, A. (2022). Gut Microbiota and Short Chain Fatty Acids: Implications in Glucose Homeostasis. *International journal of molecular sciences*, *23*(3), 1105. https://doi.org/10.3390/ijms23031105

107. den Besten, G., van Eunen, K., Groen, A. K., Venema, K., Reijngoud, D. J., & Bakker, B. M. (2013). The role of short-chain fatty acids in the interplay between diet, gut microbiota, and host energy metabolism. *Journal of lipid research*, *54*(9), 2325–2340. https://doi.org/10.1194/jlr.R036012

108. Mazhar, M., Zhu, Y., & Qin, L. (2023). The Interplay of Dietary Fibers and Intestinal Microbiota Affects Type 2 Diabetes by Generating Short-Chain Fatty Acids. *Foods (Basel, Switzerland)*, *12*(5), 1023. https://doi.org/10.3390/foods12051023

109. Schönfeld, P., & Wojtczak, L. (2016). Short- and medium-chain fatty acids in energy metabolism: the cellular perspective. *Journal of lipid research*, *57*(6), 943–954. https://doi.org/10.1194/jlr.R067629

110. van der Beek, C. M. (2017). The gut in control of health and disease: unraveling the role of short-chain fatty acids in human metabolism. [Doctoral Thesis, Maastricht University]. Datawyse / Universitaire Pers Maastricht. https://doi.org/10.26481/dis.20171004cvdb

111. LeBlanc, J.G., Chain, F., Martín, R. *et al.* Beneficial effects on host energy metabolism of short-chain fatty acids and vitamins produced by commensal and probiotic bacteria.*Microb Cell Fact* **16**, 79 (2017). https://doi.org/10.1186/s12934-017-0691-z

112. He, J., Zhang, P., Shen, L., Niu, L., Tan, Y., Chen, L., Zhao, Y., Bai, L., Hao, X., Li, X., Zhang, S., & Zhu, L. (2020). Short-Chain Fatty Acids and Their Association with Signalling Pathways in Inflammation, Glucose and Lipid Metabolism. *International journal of molecular sciences*, *21*(17), 6356. https://doi.org/10.3390/ijms21176356

113. González-Bosch, C., Boorman, E., Zunszain, P. A., & Mann, G. E. (2021). Short-chain fatty acids as modulators of redox signaling in health and disease. *Redox biology*, *47*, 102165. https://doi.org/10.1016/j.redox.2021.102165

114. Du Y, He C, An Y, Huang Y, Zhang H, Fu W, Wang M, Shan Z, Xie J, Yang Y, Zhao B. The Role of Short Chain Fatty Acids in Inflammation and Body Health. Int J Mol Sci. 2024 Jul 5;25(13):7379. doi: 10.3390/ijms25137379. PMID: 39000498; PMCID: PMC11242198.

115. Priyadarshini, M., Kotlo, K. U., Dudeja, P. K., & Layden, B. T. (2018). Role of Short Chain Fatty Acid Receptors in Intestinal Physiology and Pathophysiology. *Comprehensive Physiology*, *8*(3), 1091–1115. https://doi.org/10.1002/cphy.c170050

116. Alexander N. Orekhov1,* , Volha I. Summerhill1,* , Victoria A. Khotina2, Mikhail A. Popov3, Jamol K. Uzokov4 and Vasily N. Sukhorukov1. Role of Mitochondria in the Chronification of Inflammation: Focus on Dysfunctional Mitophagy and Mitochondrial DNA Mutations. Gene Expression 2023;22(4):329-344. doi: 10.14218/GE.2023.00061

117. Carretta, M. D., Quiroga, J., López, R., Hidalgo, M. A., & Burgos, R. A. (2021). Participation of Short-Chain Fatty Acids and Their Receptors in Gut Inflammation and Colon Cancer. *Frontiers in*

physiology, *12*, 662739. https://doi.org/10.3389/fphys.2021.662739

118. He, J., Zhang, P., Shen, L., Niu, L., Tan, Y., Chen, L., Zhao, Y., Bai, L., Hao, X., Li, X., Zhang, S., & Zhu, L. (2020). Short-Chain Fatty Acids and Their Association with Signalling Pathways in Inflammation, Glucose and Lipid Metabolism. *International journal of molecular sciences*, *21*(17), 6356. https://doi.org/10.3390/ijms21176356

119. Peng, K., Dong, W., Luo, T., Tang, H., Zhu, W., Huang, Y., & Yang, X. (2023). Butyrate and obesity: Current research status and future prospect. *Frontiers in endocrinology*, *14*, 1098881. https://doi.org/10.3389/fendo.2023.1098881

120. Bridgeman, S., Ellison, G., Newsholme, P., & Mamotte, C. (2021). The HDAC Inhibitor Butyrate Impairs β Cell Function and Activates the Disallowed Gene Hexokinase I. *International journal of molecular sciences*, *22*(24), 13330. https://doi.org/10.3390/ijms222413330

121. Zhang, D., Jian, Y. P., Zhang, Y. N., Li, Y., Gu, L. T., Sun, H. H., Liu, M. D., Zhou, H. L., Wang, Y. S., & Xu, Z. X. (2023). Short-chain fatty acids in diseases. *Cell communication and signaling : CCS*, *21*(1), 212. https://doi.org/10.1186/s12964-023-01219-9

122. May, K. S., & den Hartigh, L. J. (2021). Modulation of Adipocyte Metabolism by Microbial Short-Chain Fatty Acids. *Nutrients*, *13*(10), 3666. https://doi.org/10.3390/nu13103666

123. Psichas, A., Sleeth, M. L., Murphy, K. G., Brooks, L., Bewick, G. A., Hanyaloglu, A. C., Ghatei, M. A., Bloom, S. R., & Frost, G. (2015). The short chain fatty acid propionate stimulates GLP-1 and PYY secretion via free fatty acid receptor 2 in rodents. *International journal of obesity (2005)*, *39*(3), 424–429. https://doi.org/10.1038/ijo.2014.153

124. Müller, M., Hernández, M.A.G., Goossens, G.H. *et al.* Circulating but not faecal short-chain fatty acids are related to insulin sensitivity, lipolysis and GLP-1 concentrations in humans. *Sci Rep* **9**, 12515 (2019). https://doi.org/10.1038/s41598-019-48775-0

125. Cook, T. M., Gavini, C. K., Jesse, J., Aubert, G., Gornick, E., Bonomo, R., Gautron, L., Layden, B. T., & Mansuy-Aubert, V. (2021). Vagal neuron expression of the microbiota-derived metabolite receptor, free fatty acid receptor (FFAR3), is necessary for normal feeding behavior. *Molecular metabolism*, *54*, 101350. https://doi.org/10.1016/j.molmet.2021.101350

126. Carbone, A. M., Borges, J. I., Suster, M. S., Sizova, A., Cora, N., Desimine, V. L., & Lymperopoulos, A. (2022). Regulator of G-Protein Signaling-4 Attenuates Cardiac Adverse Remodeling and Neuronal Norepinephrine Release-Promoting Free Fatty Acid Receptor FFAR3 Signaling. *International journal of molecular sciences*, *23*(10), 5803. https://doi.org/10.3390/ijms23105803

127. Crudele L, Gadaleta RM, Cariello M, Moschetta A. Gut microbiota in the pathogenesis and therapeutic approaches of diabetes. EBioMedicine. 2023 Nov;97:104821. doi: 10.1016/j.ebiom.2023.104821. Epub 2023 Oct 5. PMID: 37804567; PMCID: PMC10570704.

128. Fan H, Liu X, Ren Z, Fei X, Luo J, Yang X, Xue Y, Zhang F, Liang B. Gut microbiota and cardiac arrhythmia. Front Cell Infect Microbiol. 2023 Apr 25;13:1147687. doi: 10.3389/fcimb.2023.1147687. PMID: 37180433; PMCID: PMC10167053.

129. Kim, H. J., Kim, H., Lee, J. H., & Hwangbo, C. (2023). Toll-like receptor 4 (TLR4): new insight immune and aging. *Immunity & ageing : I & A*, *20*(1), 67. https://doi.org/10.1186/s12979-023-00383-3

130. Kuzmich, N. N., Sivak, K. V., Chubarev, V. N., Porozov, Y. B., Savateeva-Lyubimova, T. N., & Peri, F. (2017). TLR4 Signaling Pathway Modulators as Potential Therapeutics in Inflammation and Sepsis. *Vaccines*, *5*(4), 34. https://doi.org/10.3390/vaccines5040034

131. Wei J, Zhang Y, Li H, Wang F, Yao S. Toll-like receptor 4: A potential therapeutic target for multiple human diseases. Biomed Pharmacother. 2023 Oct;166:115338. doi: 10.1016/j.biopha.2023.115338. Epub 2023 Aug 16. PMID: 37595428.

132. Tam, J. S. Y., Coller, J. K., Hughes, P. A., Prestidge, C. A., & Bowen, J. M. (2021). Toll-like receptor 4 (TLR4) antagonists as potential therapeutics for intestinal inflammation. *Indian journal of gastroenterology : official journal of the Indian Society of Gastroenterology*, *40*(1), 5–21. https://doi.org/10.1007/s12664-020-01114-y

133. Li, J., & Dawson, P. A. (2019). Animal models to study bile acid metabolism. *Biochimica et biophysica acta. Molecular basis of disease*, *1865*(5), 895–911. https://doi.org/10.1016/j.bbadis.2018.05.011

134. Liu, J., Carlson, H. A., & Scott, E. E. (2022). The structure and characterization of human cytochrome P450 8B1 supports future drug design for nonalcoholic fatty liver disease and diabetes. *The Journal of biological chemistry*, *298*(9), 102344. https://doi.org/10.1016/j.jbc.2022.102344

135. Šarenac TM, Mikov M. Bile Acid Synthesis: From Nature to the Chemical Modification and Synthesis and Their Applications as Drugs and Nutrients. Front Pharmacol. 2018 Sep 25;9:939. doi: 10.3389/fphar.2018.00939. PMID: 30319399; PMCID: PMC6168039.

136. Majait, S., Nieuwdorp, M., Kemper, M., & Soeters, M. (2023). The Black Box Orchestra of Gut Bacteria and Bile Acids: Who Is the Conductor?. *International journal of molecular sciences*, *24*(3), 1816. https://doi.org/10.3390/ijms24031816

137. Staley, C., Weingarden, A. R., Khoruts, A., & Sadowsky, M. J. (2017). Interaction of gut microbiota with bile acid metabolism and its

influence on disease states. *Applied microbiology and biotechnology*, *101*(1), 47–64. https://doi.org/10.1007/s00253-016-8006-6

138. Guzior, D.V., Quinn, R.A. Review: microbial transformations of human bile acids.*Microbiome* **9**, 140 (2021). https://doi.org/10.1186/s40168-021-01101-1

139. Ahmad, T. R., & Haeusler, R. A. (2019). Bile acids in glucose metabolism and insulin signalling - mechanisms and research needs. *Nature reviews. Endocrinology*, *15*(12), 701–712. https://doi.org/10.1038/s41574-019-0266-7

140. Fleishman, J.S., Kumar, S. Bile acid metabolism and signaling in health and disease: molecular mechanisms and therapeutic targets. *Sig Transduct Target Ther* **9**, 97 (2024). https://doi.org/10.1038/s41392-024-01811-6

141. Chen, S., Shao, Q., Chen, J., Lv, X., Ji, J., Liu, Y., & Song, Y. (2023). Bile acid signalling and its role in anxiety disorders. *Frontiers in endocrinology*, *14*, 1268865. https://doi.org/10.3389/fendo.2023.1268865

142. Mori, H., Svegliati Baroni, G., Marzioni, M., Di Nicola, F., Santori, P., Maroni, L., Abenavoli, L., & Scarpellini, E. (2022). Farnesoid X Receptor, Bile Acid Metabolism, and Gut Microbiota. *Metabolites*, *12*(7), 647. https://doi.org/10.3390/metabo12070647

143. Fallon, C. M., Smyth, J. S., Quach, A., Lajczak-McGinley, N., O'Toole, A., Barrett, K. E., Sheridan, H., & Keely, S. J. (2022). Pentacyclic triterpenes modulate farnesoid X receptor expression in colonic epithelial cells: Implications for colonic secretory function. *The Journal of biological chemistry*, *298*(11), 102569. https://doi.org/10.1016/j.jbc.2022.102569

144. Di Ciaula A, Bonfrate L, Baj J, Khalil M, Garruti G, Stellaard F, Wang HH, Wang DQ, Portincasa P. Recent Advances in the Digestive, Metabolic and Therapeutic Effects of Farnesoid X Receptor and Fibroblast Growth Factor 19: From Cholesterol to Bile Acid Signaling. Nutrients. 2022 Nov 22;14(23):4950. doi: 10.3390/nu14234950. PMID: 36500979; PMCID: PMC9738051.

145. Zhao, L., Yang, W., Chen, Y., Huang, F., Lu, L., Lin, C., Huang, T., Ning, Z., Zhai, L., Zhong, L. L., Lam, W., Yang, Z., Zhang, X., Cheng, C., Han, L., Qiu, Q., Shang, X., Huang, R., Xiao, H., Ren, Z., … Bian, Z. (2020). A Clostridia-rich microbiota enhances bile acid excretion in diarrhea-predominant irritable bowel syndrome. *The Journal of clinical investigation*, *130*(1), 438–450. https://doi.org/10.1172/JCI130976

146. Chiang, J. Y. L., & Ferrell, J. M. (2020). Bile acid receptors FXR and TGR5 signaling in fatty liver diseases and therapy. *American journal of physiology. Gastrointestinal and liver physiology*, *318*(3), G554–G573. https://doi.org/10.1152/ajpgi.00223.2019

147. Ho PP, Steinman L. Obeticholic acid, a synthetic bile acid agonist of the farnesoid X receptor, attenuates experimental autoimmune encephalomyelitis. Proc Natl Acad Sci U S A. 2016 Feb 9;113(6):1600-5. doi: 10.1073/pnas.1524890113. Epub 2016 Jan 25. PMID: 26811456; PMCID: PMC4760777.

148. Papazyan, R., Liu, X., Liu, J., Dong, B., Plummer, E. M., Lewis, R. D., 2nd, Roth, J. D., & Young, M. A. (2018). FXR activation by obeticholic acid or nonsteroidal agonists induces a human-like lipoprotein cholesterol change in mice with humanized chimeric liver. *Journal of lipid research*, *59*(6), 982–993. https://doi.org/10.1194/jlr.M081935

149. Lee, S.M., Jun, D.W., Yoon, E.L. *et al.* Discovery biomarker to optimize obeticholic acid treatment for non-alcoholic fatty liver disease. *Biol Direct* **18**, 50 (2023). https://doi.org/10.1186/s13062-023-00407-4

150. Yang, M., & Zhang, C. Y. (2021). G protein-coupled receptors as potential targets for nonalcoholic fatty liver disease treatment. *World journal of gastroenterology*, *27*(8), 677–691. https://doi.org/10.3748/wjg.v27.i8.677

151. Oteng, A. B., & Liu, L. (2023). GPCR-mediated effects of fatty acids and bile acids on glucose homeostasis. *Frontiers in endocrinology*, *14*, 1206063. https://doi.org/10.3389/fendo.2023.1206063

152. Lun W, Yan Q, Guo X, Zhou M, Bai Y, He J, Cao H, Che Q, Guo J, Su Z. Mechanism of action of the bile acid receptor TGR5 in obesity. Acta Pharm Sin B. 2024 Feb;14(2):468-491. doi: 10.1016/j.apsb.2023.11.011. Epub 2023 Nov 10. PMID: 38322325; PMCID: PMC10840437.

153. Palmiotti, A., de Vries, H. D., Hovingh, M. V., Koehorst, M., Mulder, N. L., Verkade, E., Veentjer, M. K., van Dijk, T. H., Bloks, V. W., Havinga, R., Verkade, H. J., de Boer, J. F., & Kuipers, F. (2023). Bile Acid Sequestration via Colesevelam Reduces Bile Acid Hydrophobicity and Improves Liver Pathology in *Cyp2c70*$^{-/-}$ Mice with a Human-like Bile Acid Composition. *Biomedicines*, *11*(9), 2495. https://doi.org/10.3390/biomedicines11092495

154. Maurer, A., Ward, J. L., Dean, K., Billinger, S. A., Lin, H., Mercer, K. E., Adams, S. H., & Thyfault, J. P. (2020). Divergence in aerobic capacity impacts bile acid metabolism in young women. *Journal of applied physiology (Bethesda, Md. : 1985)*, *129*(4), 768–778. https://doi.org/10.1152/japplphysiol.00577.2020

155. Hou, Y., Zhai, X., Wang, X. *et al.* Research progress on the relationship between bile acid metabolism and type 2 diabetes mellitus. *Diabetol Metab Syndr* **15**, 235 (2023). https://doi.org/10.1186/s13098-023-01207-6

156. Gao R, Meng X, Xue Y, Mao M, Liu Y, Tian X, Sui B, Li X, Zhang P. Bile acids-gut microbiota crosstalk contributes to the improvement of type 2

diabetes mellitus. Front Pharmacol. 2022 Oct 25;13:1027212. doi: 10.3389/fphar.2022.1027212. PMID: 36386219; PMCID: PMC9640995.

157. Su, X., Gao, Y., & Yang, R. (2022). Gut Microbiota-Derived Tryptophan Metabolites Maintain Gut and Systemic Homeostasis. *Cells*, *11*(15), 2296. https://doi.org/10.3390/cells11152296

158. Ye, X., Li, H., Anjum, K., Zhong, X., Miao, S., Zheng, G., Liu, W., & Li, L. (2022). Dual Role of Indoles Derived From Intestinal Microbiota on Human Health. *Frontiers in immunology*, *13*, 903526. https://doi.org/10.3389/fimmu.2022.903526

159. Roager, H.M., Licht, T.R. Microbial tryptophan catabolites in health and disease. *Nat Commun* **9**, 3294 (2018). https://doi.org/10.1038/s41467-018-05470-4

160. Konopelski, P., & Mogilnicka, I. (2022). Biological Effects of Indole-3-Propionic Acid, a Gut Microbiota-Derived Metabolite, and Its Precursor Tryptophan in Mammals' Health and Disease. *International journal of molecular sciences*, *23*(3), 1222. https://doi.org/10.3390/ijms23031222

161. Li S. (2023). Modulation of immunity by tryptophan microbial metabolites. *Frontiers in nutrition*, *10*, 1209613. https://doi.org/10.3389/fnut.2023.1209613

162. Zhang, B., Jiang, M., Zhao, J., Song, Y., Du, W., & Shi, J. (2022). The Mechanism Underlying the Influence of Indole-3-Propionic Acid: A Relevance to Metabolic Disorders. *Frontiers in endocrinology*, *13*, 841703. https://doi.org/10.3389/fendo.2022.841703

163. Li, S. Y., Chen, S., Lu, X. T., Fang, A. P., Chen, Y. M., Huang, R. Z., Lin, X. L., Huang, Z. H., Ma, J. F., Huang, B. X., & Zhu, H. L. (2022). Serum trimethylamine-N-oxide is associated with incident type 2 diabetes in middle-aged and older adults: a prospective cohort study. *Journal of translational medicine*, *20*(1), 374. https://doi.org/10.1186/s12967-022-03581-7

164. Papandreou, C., Moré, M., & Bellamine, A. (2020). Trimethylamine N-Oxide in Relation to Cardiometabolic Health-Cause or Effect?. *Nutrients*, *12*(5), 1330. https://doi.org/10.3390/nu12051330

165. Zhou Y, Zhang Y, Jin S, Lv J, Li M, Feng N. The gut microbiota derived metabolite trimethylamine N-oxide: Its important role in cancer and other diseases. Biomed Pharmacother. 2024 Aug;177:117031. doi: 10.1016/j.biopha.2024.117031. Epub 2024 Jun 25. PMID: 38925016.

166. Shanmugham M, Bellanger S, Leo CH. Gut-Derived Metabolite, Trimethylamine-N-oxide (TMAO) in Cardio-Metabolic Diseases: Detection, Mechanism, and Potential Therapeutics. Pharmaceuticals (Basel). 2023 Mar 28;16(4):504. doi: 10.3390/ph16040504. PMID: 37111261; PMCID: PMC10142468.

167. Gatarek, P., & Kaluzna-Czaplinska, J. (2021). Trimethylamine N-oxide (TMAO) in human health. *EXCLI journal*, *20*, 301–319. https://doi.org/10.17179/excli2020-3239

168. Hoyles, L., Jiménez-Pranteda, M.L., Chilloux, J. *et al.* Metabolic retroconversion of trimethylamine *N*-oxide and the gut microbiota. *Microbiome* **6**, 73 (2018). https://doi.org/10.1186/s40168-018-0461-0

169. Zhen, J., Zhou, Z., He, M., Han, H. X., Lv, E. H., Wen, P. B., Liu, X., Wang, Y. T., Cai, X. C., Tian, J. Q., Zhang, M. Y., Xiao, L., & Kang, X. X. (2023). The gut microbial metabolite trimethylamine N-oxide and cardiovascular diseases. *Frontiers in endocrinology*, *14*, 1085041. https://doi.org/10.3389/fendo.2023.1085041

170. Evans, M., Dai, L., Avesani, C. M., Kublickiene, K., & Stenvinkel, P. (2023). The dietary source of trimethylamine N-oxide and clinical outcomes: an unexpected liaison. *Clinical kidney journal*, *16*(11), 1804–1812. https://doi.org/10.1093/ckj/sfad095

171. Fechtner, S., Allen, B. E., Chriswell, M. E., Jubair, W. K., Robertson, C. E., Kofonow, J. N., Frank, D. N., Holers, V. M., & Kuhn, K. A. (2023). 3,3-dimethyl-1-butanol and its metabolite 3,3-dimethylbutyrate ameliorate collagen-induced arthritis independent of choline trimethylamine lyase activity. *Research square*, rs.3.rs-3297018. https://doi.org/10.21203/rs.3.rs-3297018/v1

172. Tacconi, E., Palma, G., De Biase, D., Luciano, A., Barbieri, M., de Nigris, F., & Bruzzese, F. (2023). Microbiota Effect on Trimethylamine N-Oxide Production: From Cancer to Fitness-A Practical Preventing Recommendation and Therapies. *Nutrients*, *15*(3), 563. https://doi.org/10.3390/nu15030563

173. Kuka J, Videja M, Makrecka-Kuka M, Liepins J, Grinberga S, Sevostjanovs E, Vilks K, Liepinsh E, Dambrova M. Metformin decreases bacterial trimethylamine production and trimethylamine N-oxide levels in db/db mice. Sci Rep. 2020 Sep 3;10(1):14555. doi: 10.1038/s41598-020-71470-4. PMID: 32884086; PMCID: PMC7471276.

174. Guo HH, Shen HR, Wang LL, Luo ZG, Zhang JL, Zhang HJ, Gao TL, Han YX, Jiang JD. Berberine is a potential alternative for metformin with good regulatory effect on lipids in treating metabolic diseases. Biomed Pharmacother. 2023 Jul;163:114754. doi: 10.1016/j.biopha.2023.114754. Epub 2023 Apr 23. PMID: 37094549.

175. Wang Z, Wu F, Zhou Q, Qiu Y, Zhang J, Tu Q, Zhou Z, Shao Y, Xu S, Wang Y, Tao J. Berberine Improves Vascular Dysfunction by Inhibiting Trimethylamine-N-oxide *via* Regulating the Gut Microbiota in Angiotensin II-Induced Hypertensive Mice. Front Microbiol. 2022 Mar 8;13:814855. doi: 10.3389/fmicb.2022.814855. PMID: 35350612; PMCID: PMC8957906.

176. Annunziata, G., Maisto, M., Schisano, C., Ciampaglia, R., Narciso, V., Tenore, G. C., & Novellino, E. (2019). Effects of Grape Pomace Polyphenolic Extract (Taurisolo®) in Reducing TMAO Serum Levels in Humans: Preliminary Results from a Randomized, Placebo-Controlled, Cross-Over Study. *Nutrients*, *11*(1), 139. https://doi.org/10.3390/nu11010139

177. Annunziata, G., Ciampaglia, R., Maisto, M., D'Avino, M., Caruso, D., Tenore, G. C., & Novellino, E. (2021). Taurisolo®, a Grape Pomace Polyphenol Nutraceutical Reducing the Levels of Serum Biomarkers Associated With Atherosclerosis. *Frontiers in cardiovascular medicine*, *8*, 697272. https://doi.org/10.3389/fcvm.2021.697272

178. Li X, Hong J, Wang Y, Pei M, Wang L, Gong Z. Trimethylamine-N-Oxide Pathway: A Potential Target for the Treatment of MAFLD. Front Mol Biosci. 2021 Oct 1;8:733507. doi: 10.3389/fmolb.2021.733507. PMID: 34660695; PMCID: PMC8517136.

179. Zang, B. Y., He, L. X., & Xue, L. (2022). Intermittent Fasting: Potential Bridge of Obesity and Diabetes to Health?. *Nutrients*, *14*(5), 981. https://doi.org/10.3390/nu14050981

180. Frank, J., Gupta, A., Osadchiy, V., & Mayer, E. A. (2021). Brain-Gut-Microbiome Interactions and Intermittent Fasting in Obesity. *Nutrients*, *13*(2), 584. https://doi.org/10.3390/nu13020584

181. Cheung, K., Chan, V., Chan, S., Wong, M. M. H., Chung, G. K., Cheng, W. Y., Lo, K., & Zeng, F. (2024). Effect of Intermittent Fasting on Cardiometabolic Health in the Chinese Population: A Meta-Analysis of Randomized Controlled Trials. *Nutrients*, *16*(3), 357. https://doi.org/10.3390/nu16030357

182. Guasch-Ferré, M., Merino, J., Sun, Q., Fitó, M., & Salas-Salvadó, J. (2017). Dietary Polyphenols, Mediterranean Diet, Prediabetes, and Type 2 Diabetes: A Narrative Review of the Evidence. *Oxidative medicine and cellular longevity*, *2017*, 6723931. https://doi.org/10.1155/2017/6723931

183. Pant, A., Chew, D. P., Mamas, M. A., & Zaman, S. (2024). Cardiovascular Disease and the Mediterranean Diet: Insights into Sex-Specific Responses. *Nutrients*, *16*(4), 570. https://doi.org/10.3390/nu16040570

184. Xu, X., Sun, S., Liang, L., Lou, C., He, Q., Ran, M., Zhang, L., Zhang, J., Yan, C., Yuan, H., Zhou, L., Chen, X., Dai, X., Wang, B., Zhang, J., & Zhao, J. (2021). Role of the Aryl Hydrocarbon Receptor and Gut Microbiota-Derived Metabolites Indole-3-Acetic Acid in Sulforaphane Alleviates Hepatic Steatosis in Mice. *Frontiers in nutrition*, *8*, 756565. https://doi.org/10.3389/fnut.2021.756565

185. Pinto, C. J. G., Ávila-Gálvez, M. Á., Lian, Y., Moura-Alves, P., & Nunes Dos Santos, C. (2023). Targeting the aryl hydrocarbon receptor by gut phenolic metabolites: A strategy towards gut inflammation. *Redox biology*, *61*, 102622. https://doi.org/10.1016/j.redox.2023.102622

186. Sayed, T.S., Maayah, Z.H., Zeidan, H.A. *et al.* Insight into the physiological and pathological roles of the aryl hydrocarbon receptor pathway in glucose homeostasis, insulin resistance, and diabetes development. *Cell Mol Biol Lett* **27**, 103 (2022). https://doi.org/10.1186/s11658-022-00397-7

187. Soveral, L. F., Korczaguin, G. G., Schmidt, P. S., Nunes, I. S., Fernandes, C., & Zárate-Bladés, C. R. (2022). Immunological mechanisms of fecal microbiota transplantation in recurrent *Clostridioides difficile* infection. *World journal of gastroenterology*, *28*(33), 4762–4772. https://doi.org/10.3748/wjg.v28.i33.4762

188. Yang R, Chen Z, Cai J. Fecal microbiota transplantation: Emerging applications in autoimmune diseases. J Autoimmun. 2023 Dec;141:103038. doi: 10.1016/j.jaut.2023.103038. Epub 2023 Apr 26. PMID: 37117118.

189. Yadegar A, Pakpoor S, Ibrahim FF, Nabavi-Rad A, Cook L, Walter J, Seekatz AM, Wong K, Monaghan TM, Kao D. Beneficial effects of fecal microbiota transplantation in recurrent Clostridioides difficile infection. Cell Host Microbe. 2023 May 10;31(5):695-711. doi: 10.1016/j.chom.2023.03.019. PMID: 37167952; PMCID: PMC10966711.

190. Jaramillo, A. P., Awosusi, B. L., Ayyub, J., Dabhi, K. N., Gohil, N. V., Tanveer, N., Hussein, S., Pingili, S., & Makkena, V. K. (2023). Effectiveness of Fecal Microbiota Transplantation Treatment in Patients With Recurrent Clostridium difficile Infection, Ulcerative Colitis, and Crohn's Disease: A Systematic Review. *Cureus*, *15*(7), e42120. https://doi.org/10.7759/cureus.42120

191. Wu, Z., Zhang, B., Chen, F., Xia, R., Zhu, D., Chen, B., Lin, A., Zheng, C., Hou, D., Li, X., Zhang, S., Chen, Y., & Hou, K. (2023). Fecal microbiota transplantation reverses insulin resistance in type 2 diabetes: A randomized, controlled, prospective study. *Frontiers in cellular and infection microbiology*, *12*, 1089991. https://doi.org/10.3389/fcimb.2022.1089991

192. Boicean A, Ichim C, Todor SB, Anderco P, Popa ML. The Importance of Microbiota and Fecal Microbiota Transplantation in Pancreatic Disorders. Diagnostics (Basel). 2024 Apr 23;14(9):861. doi: 10.3390/diagnostics14090861. PMID: 38732276; PMCID: PMC11082979.

193. Kelly CR, Kim AM, Laine L, Wu GD. The AGA's Fecal Microbiota Transplantation National Registry: An Important Step Toward Understanding Risks and Benefits of Microbiota Therapeutics. Gastroenterology. 2017 Mar;152(4):681-684. doi: 10.1053/j.gastro.2017.01.028. Epub 2017 Jan 29. PMID: 28143773.

194. Peery AF, Kelly CR, Kao D, Vaughn BP, Lebwohl B, Singh S, Imdad A, Altayar O; AGA Clinical Guidelines Committee. Electronic address: clinicalpractice@gastro.org. AGA Clinical Practice

Guideline on Fecal Microbiota-Based Therapies for Select Gastrointestinal Diseases. Gastroenterology. 2024 Mar;166(3):409-434. doi: 10.1053/j.gastro.2024.01.008. PMID: 38395525.

195. Michailidis, L., Currier, A. C., Le, M., & Flomenhoft, D. R. (2021). Adverse events of fecal microbiota transplantation: a meta-analysis of high-quality studies. *Annals of gastroenterology*, *34*(6), 802–814. https://doi.org/10.20524/aog.2021.0655

196. Corb Aron, R. A., Abid, A., Vesa, C. M., Nechifor, A. C., Behl, T., Ghitea, T. C., Munteanu, M. A., Fratila, O., Andronie-Cioara, F. L., Toma, M. M., & Bungau, S. (2021). Recognizing the Benefits of Pre-/Probiotics in Metabolic Syndrome and Type 2 Diabetes Mellitus Considering the Influence of *Akkermansia muciniphila* as a Key Gut Bacterium. *Microorganisms*, *9*(3), 618. https://doi.org/10.3390/microorganisms9030618

197. Zhao, Y., Yang, H., Wu, P., Yang, S., Xue, W., Xu, B., Zhang, S., Tang, B., & Xu, D. (2024). *Akkermansia muciniphila*: A promising probiotic against inflammation and metabolic disorders. *Virulence*, *15*(1), 2375555. https://doi.org/10.1080/21505594.2024.2375555

198. Horvath A, Zukauskaite K, Hazia O, Balazs I, Stadlbauer V. Human gut microbiome: Therapeutic opportunities for metabolic syndrome-Hype or hope? Endocrinol Diabetes Metab. 2024 Jan;7(1):e436. doi: 10.1002/edm2.436. Epub 2023 Sep 28. PMID: 37771199; PMCID: PMC10781898.

199. Li, L., Li, M., Chen, Y., Yu, Z., Cheng, P., Yu, Z., Cheng, W., Zhang, W., Wang, Z., Gao, X., Sun, H., & Wang, X. (2024). Function and therapeutic prospects of next-generation probiotic *Akkermansia muciniphila* in infectious diseases. *Frontiers in microbiology*, *15*, 1354447. https://doi.org/10.3389/fmicb.2024.1354447

200. Chiantera V, Laganà AS, Basciani S, Nordio M, Bizzarri M. A Critical Perspective on the Supplementation of *Akkermansia muciniphila*: Benefits and Harms. Life (Basel). 2023 May 24;13(6):1247. doi: 10.3390/life13061247. PMID: 37374030; PMCID: PMC10301191.

201. Maftei, N. M., Raileanu, C. R., Balta, A. A., Ambrose, L., Boev, M., Marin, D. B., & Lisa, E. L. (2024). The Potential Impact of Probiotics on Human Health: An Update on Their Health-Promoting Properties. *Microorganisms*, *12*(2), 234. https://doi.org/10.3390/microorganisms12020234

202. Mazziotta, C., Tognon, M., Martini, F., Torreggiani, E., & Rotondo, J. C. (2023). Probiotics Mechanism of Action on Immune Cells and Beneficial Effects on Human Health. *Cells*, *12*(1), 184. https://doi.org/10.3390/cells12010184

203. Petrariu, O. A., Barbu, I. C., Niculescu, A. G., Constantin, M., Grigore, G. A., Cristian, R. E., Mihaescu, G., & Vrancianu, C. O. (2024). Role of probiotics in managing various human diseases, from oral pathology to cancer and gastrointestinal diseases. *Frontiers in microbiology*, *14*, 1296447. https://doi.org/10.3389/fmicb.2023.1296447

204. Plaza-Diaz, J., Ruiz-Ojeda, F. J., Gil-Campos, M., & Gil, A. (2019). Mechanisms of Action of Probiotics. *Advances in nutrition (Bethesda, Md.)*, *10*(suppl_1), S49–S66. https://doi.org/10.1093/advances/nmy063

205. Barzegari, A., Kheyrolahzadeh, K., Hosseiniyan Khatibi, S. M., Sharifi, S., Memar, M. Y., & Zununi Vahed, S. (2020). The Battle of Probiotics and Their Derivatives Against Biofilms. *Infection and drug resistance*, *13*, 659–672. https://doi.org/10.2147/IDR.S232982

206. Davani-Davari, D., Negahdaripour, M., Karimzadeh, I., Seifan, M., Mohkam, M., Masoumi, S. J., Berenjian, A., & Ghasemi, Y. (2019). Prebiotics: Definition, Types, Sources, Mechanisms, and Clinical Applications. *Foods (Basel, Switzerland)*, *8*(3), 92. https://doi.org/10.3390/foods8030092

207. Kaur, A. P., Bhardwaj, S., Dhanjal, D. S., Nepovimova, E., Cruz-Martins, N., Kuča, K., Chopra, C., Singh, R., Kumar, H., Şen, F., Kumar, V., Verma, R., & Kumar, D. (2021). Plant Prebiotics and Their Role in the Amelioration of Diseases. *Biomolecules*, *11*(3), 440. https://doi.org/10.3390/biom11030440

208. Ballini, A., Charitos, I. A., Cantore, S., Topi, S., Bottalico, L., & Santacroce, L. (2023). About Functional Foods: The Probiotics and Prebiotics State of Art. *Antibiotics (Basel, Switzerland)*, *12*(4), 635. https://doi.org/10.3390/antibiotics12040635

209. Chieng, W. K., Abdul Jalal, M. I., Bedi, J. S., Zainuddin, A. A., Mokhtar, M. H., Abu, M. A., Chew, K. T., & Nur Azurah, A. G. (2022). Probiotics, a promising therapy to reduce the recurrence of bacterial vaginosis in women? a systematic review and meta-analysis of randomized controlled trials. *Frontiers in nutrition*, *9*, 938838. https://doi.org/10.3389/fnut.2022.938838

210. Mohr, A. E., Pugh, J., O'Sullivan, O., Black, K., Townsend, J. R., Pyne, D. B., Wardenaar, F. C., West, N. P., Whisner, C. M., & McFarland, L. V. (2022). Best Practices for Probiotic Research in Athletic and Physically Active Populations: Guidance for Future Randomized Controlled Trials. *Frontiers in nutrition*, *9*, 809983. https://doi.org/10.3389/fnut.2022.809983

211. Zhang, Q., Chen, B., Zhang, J. *et al.* Effect of prebiotics, probiotics, synbiotics on depression: results from a meta-analysis. *BMC Psychiatry* **23**, 477 (2023). https://doi.org/10.1186/s12888-023-04963-x

212. Chen, Y., Shen, X., Ma, T., Yu, X., Kwok, L. Y., Li, Y., Sun, Z., Li, D., & Zhang, H. (2023). Adjunctive Probio-X Treatment Enhances the Therapeutic Effect of a Conventional Drug in Managing Type 2 Diabetes Mellitus by Promoting Short-Chain Fatty Acid-Producing Bacteria and Bile Acid Pathways. *mSystems*, *8*(1), e0130022. https://doi.org/10.1128/msystems.01300-22

213. Ayesha, I. E., Monson, N. R., Klair, N., Patel, U., Saxena, A., Patel, D., & Venugopal, S. (2023). Probiotics and Their Role in the Management of Type 2 Diabetes Mellitus (Short-Term Versus Long-Term Effect): A Systematic Review and Meta-Analysis. *Cureus*, *15*(10), e46741. https://doi.org/10.7759/cureus.46741

214. Barthow, C., Hood, F., McKinlay, E. *et al.* Food 4 Health - He Oranga Kai: Assessing the efficacy, acceptability and economic implications of *Lactobacillus rhamnosus* HN001 and β-glucan to improve glycated haemoglobin, metabolic health, and general well-being in adults with pre-diabetes: study protocol for a 2 × 2 factorial design, parallel group, placebo-controlled randomized controlled trial, with embedded qualitative study and economic analysis. *Trials* **20**, 464 (2019). https://doi.org/10.1186/s13063-019-3553-7

215. Yadav, M., & Chauhan, N. S. (2021). Microbiome therapeutics: exploring the present scenario and challenges. *Gastroenterology report*, *10*, goab046. https://doi.org/10.1093/gastro/goab046

216. Ananda, N., Suniarti, D. F., & Bachtiar, E. W. (2024). The antimicrobial effect of *Limosilactobacillus reuteri* as probiotic on oral bacteria: A scoping review. *F1000Research*, *12*, 1495. https://doi.org/10.12688/f1000research.139697.1

217. Peng Y, Ma Y, Luo Z, Jiang Y, Xu Z, Yu R. *Lactobacillus reuteri* in digestive system diseases: focus on clinical trials and mechanisms. Front Cell Infect Microbiol. 2023 Aug 18;13:1254198. doi: 10.3389/fcimb.2023.1254198. PMID: 37662007; PMCID: PMC10471993.

218. Ma J, Li C, Wang J, Gu J. Genetically Engineered Escherichia coli Nissle 1917 Secreting GLP-1 Analog Exhibits Potential Antiobesity Effect in High-Fat Diet-Induced Obesity Mice. Obesity (Silver Spring). 2020 Feb;28(2):315-322. doi: 10.1002/oby.22700. PMID: 31970910.

219. Chavkin, T. A., Pham, L. D., & Kostic, A. (2021). E. coli Nissle 1917 modulates host glucose metabolism without directly acting on glucose. *Scientific reports*, *11*(1), 23230. https://doi.org/10.1038/s41598-021-02431-8

220. Shi, J., Ma, D., Gao, S., Long, F., Wang, X., Pu, X., Cannon, R. D., & Han, T. L. (2023). Probiotic *Escherichia coli* Nissle 1917-derived outer membrane vesicles modulate the intestinal microbiome and host gut-liver metabolome in obese and diabetic mice. *Frontiers in microbiology*, *14*, 1219763. https://doi.org/10.3389/fmicb.2023.1219763

221. Emencheta, S. C., Olovo, C. V., Eze, O. C., Kalu, C. F., Berebon, D. P., Onuigbo, E. B., Vila, M. M. D. C., Balcão, V. M., & Attama, A. A. (2023). The Role of Bacteriophages in the Gut Microbiota: Implications for Human Health. *Pharmaceutics*, *15*(10), 2416. https://doi.org/10.3390/pharmaceutics15102416

222. Shuwen, H., & Kefeng, D. (2022). Intestinal phages interact with bacteria and are involved in human diseases. *Gut microbes*, *14*(1), 2113717. https://doi.org/10.1080/19490976.2022.2113717

223. Kirk D, Costeira R, Visconti A, Khan Mirzaei M, Deng L, Valdes AM, Menni C. Bacteriophages, gut bacteria, and microbial pathways interplay in cardiometabolic health. Cell Rep. 2024 Feb 27;43(2):113728. doi: 10.1016/j.celrep.2024.113728. Epub 2024 Jan 31. PMID: 38300802.

224. Baker, C., Retzik-Stahr, C., Singh, V., Plomondon, R., Anderson, V., & Rasouli, N. (2021). Should metformin remain the first-line therapy for treatment of type 2 diabetes?. *Therapeutic advances in endocrinology and metabolism*, *12*, 2042018820980225. https://doi.org/10.1177/2042018820980225

225. Amengual-Cladera, E., Morla-Barcelo, P. M., Morán-Costoya, A., Sastre-Serra, J., Pons, D. G., Valle, A., Roca, P., & Nadal-Serrano, M. (2024). Metformin: From Diabetes to Cancer-Unveiling Molecular Mechanisms and Therapeutic Strategies. *Biology*, *13*(5), 302. https://doi.org/10.3390/biology13050302

226. Fusco, W., Lorenzo, M. B., Cintoni, M., Porcari, S., Rinninella, E., Kaitsas, F., Lener, E., Mele, M. C., Gasbarrini, A., Collado, M. C., Cammarota, G., & Ianiro, G. (2023). Short-Chain Fatty-Acid-Producing Bacteria: Key Components of the Human Gut Microbiota. *Nutrients*, *15*(9), 2211. https://doi.org/10.3390/nu15092211

227. Zhang, L., Chu, J., Hao, W., Zhang, J., Li, H., Yang, C., Yang, J., Chen, X., & Wang, H. (2021). Gut Microbiota and Type 2 Diabetes Mellitus: Association, Mechanism, and Translational Applications. *Mediators of inflammation*, *2021*, 5110276. https://doi.org/10.1155/2021/5110276

228. Jiang, P., Di, Z., Huang, W., & Xie, L. (2024). Modulating the Gut Microbiota and Metabolites with Traditional Chinese Medicines: An Emerging Therapy for Type 2 Diabetes Mellitus and Its Complications. *Molecules (Basel, Switzerland)*, *29*(12), 2747. https://doi.org/10.3390/molecules29122747

229. LaMoia TE, Shulman GI. Cellular and Molecular Mechanisms of Metformin Action. Endocr Rev. 2021 Jan 28;42(1):77-96. doi: 10.1210/endrev/bnaa023. PMID: 32897388; PMCID: PMC7846086.

230. Nesci, A., Carnuccio, C., Ruggieri, V., D'Alessandro, A., Di Giorgio, A., Santoro, L., Gasbarrini, A., Santoliquido, A., & Ponziani, F. R. (2023). Gut Microbiota and Cardiovascular Disease: Evidence on the Metabolic and Inflammatory Background of a Complex Relationship. *International journal of molecular sciences*, *24*(10), 9087. https://doi.org/10.3390/ijms24109087

231. Palacios, T., Vitetta, L., Coulson, S., Madigan, C. D., Lam, Y. Y., Manuel, R., Briskey, D., Hendy, C., Kim, J. N., Ishoey, T., Soto-Giron, M. J., Schott, E. M., Toledo, G., & Caterson, I. D. (2020). Targeting the Intestinal Microbiota to Prevent Type 2 Diabetes and Enhance the Effect of Metformin on Glycaemia: A Randomised Controlled Pilot Study. *Nutrients*, *12*(7), 2041. https://doi.org/10.3390/nu12072041

232. Koh A, Molinaro A, Ståhlman M, Khan MT, Schmidt C, Mannerås-Holm L, Wu H, Carreras A, Jeong H, Olofsson LE, Bergh PO, Gerdes V, Hartstra A, de Brauw M, Perkins R, Nieuwdorp M, Bergström G, Bäckhed F. Microbially Produced Imidazole Propionate Impairs Insulin Signaling through mTORC1. Cell. 2018 Nov 1;175(4):947-961.e17. doi: 10.1016/j.cell.2018.09.055. Epub 2018 Oct 25. PMID: 30401435.

233. Koh, A., Mannerås-Holm, L., Yunn, N. O., Nilsson, P. M., Ryu, S. H., Molinaro, A., Perkins, R., Smith, J. G., & Bäckhed, F. (2020). Microbial Imidazole Propionate Affects Responses to Metformin through p38γ-Dependent Inhibitory AMPK Phosphorylation. *Cell metabolism*, *32*(4), 643–653.e4. https://doi.org/10.1016/j.cmet.2020.07.012

234. Kim, H. E., Lee, J. Y., Yoo, D. H., Park, H. H., Choi, E. J., Nam, K. H., Park, J., & Choi, J. K. (2024). Imidazole propionate ameliorates atopic dermatitis-like skin lesions by inhibiting mitochondrial ROS and mTORC2. *Frontiers in immunology*, *15*, 1324026. https://doi.org/10.3389/fimmu.2024.1324026

235. Sanit, J., Prompunt, E., Adulyaritthikul, P., Nokkaew, N., Mongkolpathumrat, P., Kongpol, K., Kijtawornrat, A., Petchdee, S., Barrère-Lemaire, S., & Kumphune, S. (2019). Combination of metformin and p38 MAPK inhibitor, SB203580, reduced myocardial ischemia/reperfusion injury in non-obese type 2 diabetic Goto-Kakizaki rats. *Experimental and therapeutic medicine*, *18*(3), 1701–1714. https://doi.org/10.3892/etm.2019.7763

236. Chen, S. C., Brooks, R., Houskeeper, J., Bremner, S. K., Dunlop, J., Viollet, B., Logan, P. J., Salt, I. P., Ahmed, S. F., & Yarwood, S. J. (2017). Metformin suppresses adipogenesis through both AMP-activated protein kinase (AMPK)-dependent and AMPK-independent mechanisms. *Molecular and cellular endocrinology*, *440*, 57–68. https://doi.org/10.1016/j.mce.2016.11.011

237. Altay M. (2022). Acarbose is again on the stage. *World journal of diabetes*, *13*(1), 1–4. https://doi.org/10.4239/wjd.v13.i1.1

238. McIver LA, Preuss CV, Tripp J. Acarbose. [Updated 2024 Feb 12]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK493214/

239. Kashtoh H, Baek KH. Recent Updates on Phytoconstituent Alpha-Glucosidase Inhibitors: An Approach towards the Treatment of Type Two Diabetes. Plants (Basel). 2022 Oct 14;11(20):2722. doi: 10.3390/plants11202722. PMID: 36297746; PMCID: PMC9612090.

240. Megur, A., Daliri, E. B., Baltriukienė, D., & Burokas, A. (2022). Prebiotics as a Tool for the Prevention and Treatment of Obesity and Diabetes: Classification and Ability to Modulate the Gut Microbiota. *International journal of molecular sciences*, *23*(11), 6097. https://doi.org/10.3390/ijms23116097

241. Portincasa P, Khalil M, Graziani A, Frühbeck G, Baffy G, Garruti G, Di Ciaula A, Bonfrate L. Gut microbes in metabolic disturbances. Promising role for therapeutic manipulations? Eur J Intern Med. 2024 Jan;119:13-30. doi: 10.1016/j.ejim.2023.10.002. Epub 2023 Oct 4. PMID: 37802720.

242. Kaplina, A., Kononova, S., Zaikova, E., Pervunina, T., Petrova, N., & Sitkin, S. (2023). Necrotizing Enterocolitis: The Role of Hypoxia, Gut Microbiome, and Microbial Metabolites. *International journal of molecular sciences*, *24*(3), 2471. https://doi.org/10.3390/ijms24032471

243. Crudele, L., Gadaleta, R. M., Cariello, M., & Moschetta, A. (2023). Gut microbiota in the pathogenesis and therapeutic approaches of diabetes. *EBioMedicine*, *97*, 104821. https://doi.org/10.1016/j.ebiom.2023.104821

244. Zhang, X., Ren, H., Zhao, C., Shi, Z., Qiu, L., Yang, F., Zhou, X., Han, X., Wu, K., Zhong, H., Li, Y., Li, J., & Ji, L. (2022). Metagenomic analysis reveals crosstalk between gut microbiota and glucose-lowering drugs targeting the gastrointestinal tract in Chinese patients with type 2 diabetes: a 6 month, two-arm randomised trial. *Diabetologia*, *65*(10), 1613–1626. https://doi.org/10.1007/s00125-022-05768-5