

The Gut-Liver-Pancreas Axis in Metabolic Disease:Emerging Therapeutic Opportunities - A Review

Lovejit Kaur

M Pharmacy (Pharmacology)

Abstract-- Gut-Liver-Pancreas axis is a kind of communication network which includes digestive system, liver and pancreas. This axis depends upon nerve pathways, blood flow and chemical signals. The gut-liver-pancreas axis is in charge of metabolism, chemical release, and energy cycle regulation, including energy storage and utilization. The gut's functions are intimately linked to those of numerous other human organs. In fact, the gut microbiota (GM) metabolizes a number of nutrients and substances that, once released in the bloodstream, can travel to distant organs and affect the host's inflammatory and metabolic tone. Humans harbor more than 10^{14} microorganisms in their bodies, most of which reside in the gastrointestinal tract, while others inhabit different anatomical sites such as the respiratory tract, skin, mammary gland, mucosa, and urogenital tract. Advanced metabolomics techniques, like tandem mass spectrometry and ultra-performance liquid chromatography, have been used to successfully identify a variety of metabolites that may cause physiological and pathological processes in hosts and other microorganisms.

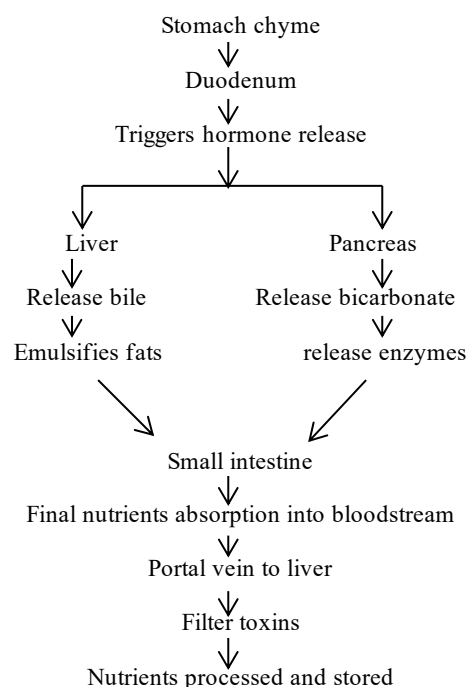
The gut-liver-pancreas metabolic diseases generally caused due to over-nutrition and triggers- MASLD, T2DM, Metabolic pancreatitis, and Severe intestinal dysbiosis and metabolic endotoxemia. Followed by the treatment and therapeutic strategies such as- Incretin Therapies, Microbiome restructuring, and targeted weight loss strategies. In this review, we discussed functions of gut-liver-pancreas axis, along with metabolic diseases and treatment of gut-liver-pancreas metabolic diseases.

I. INTRODUCTION

The liver, pancreas, and the gut play a major role in the metabolism and absorption of nutrients[1]. The human body's greatest mucosal surface is the gastrointestinal system, which is constantly threatened by microorganisms and food antigens. The entire gastrointestinal tract (from mouth to anus) is inhabited by an astounding number of commensals with a variety of roles in health and disease, as recent research has persuasively shown. Our body is able to do this delicate duty because the gastrointestinal barrier is lined with a complex mixture of different cell types of epithelial and endothelial origin as well as innate and adaptive immunity (and its mediators)[2].

A group of risk factors known as the metabolic syndrome—central obesity, hyperglycemia, dyslipidemia, and arterial hypertension—indicate a higher risk of diabetes, cardiovascular disease, and early death [3]. The prevalence of metabolic disorders is rapidly rising, making them a big global health concern. One important player that can interact with the host is the gut microbiota, which can produce a variety of metabolites from endogenous host chemicals or exogenous food substrates. Changes in the gut microbiota's composition and activity are linked to metabolic diseases [4]. The complex and dynamic collection of bacteria known as the gut microbiota is crucial to preserving the health of the host. It has a major role in controlling the immune system, preventing infections, and regulating a number of physiological functions. Microbiota composition can affect inflammation, which is a prevalent component of chronic conditions like metabolic syndrome and type 2 diabetes (T2DM) [5].

II. NORMAL PATHOPHYSIOLOGY IN AXIS



Tightly controlled processes link the physiological functions of the gut with the liver. Bile acids, which are essential for the digestion of fats and also control the makeup of the gut microbiota, are secreted by the liver into the intestine. The gut, in turn, controls the production of bile acids through a feedback loop that is based on the FXR/FGF-19 axis. It also secretes many incretins into the bloodstream that are involved in the metabolism of glucose and fats, at least partially through the modulation of hepatic activities [6,7].

III. FUNCTIONS OF GUT-LIVER-PANCREAS AXIS

Short-chain fatty acids (SCFAs), bile acids, and glucagon-like peptide 1 (GLP-1) are the primary metabolites generated from microbiota that regulate endocrine responses. These molecules have the ability to: (i) promote the production of glycogen in the liver; (ii) control the pancreatic hormones insulin and glucagon; and (iii) increase energy expenditure, particularly in skeletal muscles and brown adipose tissue. To put it another way, they are essential for preserving lipid and glucose balance [8].

IV. METABOLIC DISEASES

The primary theories on the genesis and progression of multiple sclerosis are discussed in connection with type 2 diabetes, obesity, and hepatic steatosis, although they cover the majority of metabolic syndrome components that have been identified thus far [9]. Millions of people are affected by type 2 diabetes (T2D) and nonalcoholic fatty liver disease (NAFLD), both of which have a high correlation with rising body mass index. [10]

4.1 T2DM (Type 2 Diabetes Mellitus) – a metabolic disease

Tissue-specific insulin resistance and pancreatic β -cell dysfunction are hallmarks of type 2 diabetes mellitus (T2DM), which is caused by a combination of systemic dysregulation of tissue crosstalk and local abnormalities within various tissues.

The primary local processes include endoplasmic reticulum stress, altered mitochondrial metabolism with oxidative stress, metabolic (lipid) signaling, and local inflammation [11,12]. One of the main components of metabolic syndrome is type 2 diabetes mellitus, a condition that is common around the world. [13,14]

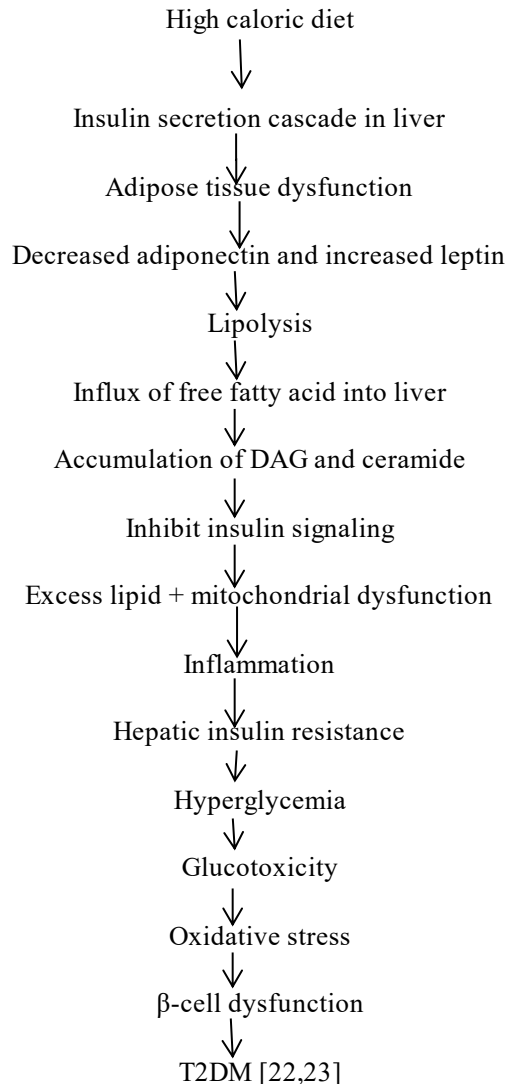
Pathophysiology

a) Impaired glucose homeostasis and hepatic insulin resistance

The liver plays a key role in keeping the body's blood glucose levels balanced. The liver-pancreas axis' metabolic regulation is initially upset at the liver level when hepatocytes misinterpret insulin signals, which then has a cascading effect on the islets. Hepatic insulin resistance has thus emerged as one of the most significant and early abnormalities in the pathophysiology of type 2 diabetes mellitus [15,16]. Chronic hyperglycemia is a hallmark of type 2 diabetes, a prevalent metabolic disease characterized by decreased insulin production and action [17].

b) The Effect of MASLD on β -Function of Cells

Persistent hyperglycemia brought on by peripheral tissue insulin resistance combined with insufficient compensatory insulin production by pancreatic β -cells is the hallmark of type 2 diabetes mellitus (T2DM), a chronic metabolic disease [18]. A hallmark of metabolic dysfunction-associated steatotic liver disease (MASLD) is the buildup of lipid droplets within the cells. MASLD is intimately linked to metabolic illnesses, including obesity and β -Function of Cells [19]. Beyond just coexisting, MASLD and T2DM are linked by shared pathophysiological processes, mainly insulin resistance and compensatory hyperinsulinemia, which cause metabolic dysfunction and β -cell failure [20]. A significant contributor to the worldwide burden of non-communicable diseases (NCDs) is metabolic dysfunction-associated steatotic liver disease (MASLD), formerly known as nonalcoholic fatty liver disease and metabolic dysfunction-associated fatty liver disease. MASLD is pathophysiologically linked to more general metabolic dysfunction, such as insulin resistance, obesity, type 2 diabetes, and cardiovascular issues, in addition to its hepatic symptoms [21].



c) Hyperglucagonemia and glucagon resistance

Numerous metabolic signals, including variations in blood glucose levels, certain amino acids, possibly free fatty acids, and stress, cause the release of glucagon [24]. Clinical trials utilizing glucagon receptor antagonists (GRAs) have been carried out in individuals with type 2 diabetes since hyperglucagonemia is now recognized to be at least partially responsible for diabetic hyperglycemia [25].

d) Intestinal Dysbiosis and the Gut–Liver–Pancreas Axis

There is growing evidence that the dysregulation of the liver-pancreas axis in metabolic disorders is mostly caused by intestinal dysbiosis.

The severity of MASLD is correlated with both compositional changes in the gut microbiota and small intestinal bacterial overgrowth (SIBO). Mechanistically, when the integrity of the gut barrier is compromised, bacterial components like lipopolysaccharide (LPS) are more likely to translocate into the portal circulation and cause hepatic inflammation through TLR4 activation [26]

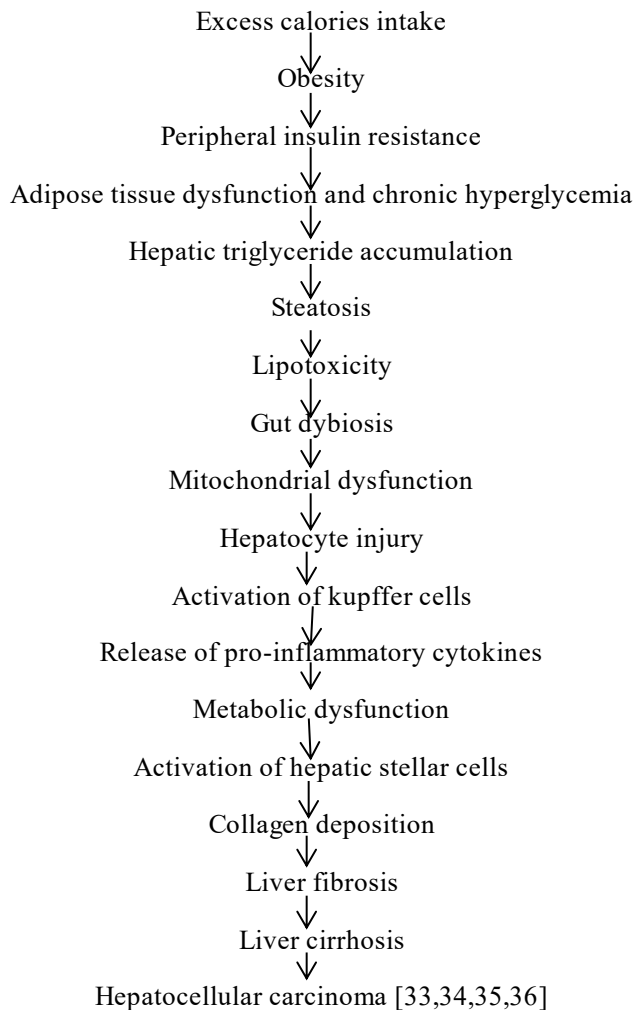
4.2 NAFLD (Non-alcoholic fatty liver disease) – a metabolic disease

One of the most prevalent causes of liver illnesses in the globe is nonalcoholic fatty liver disease (NAFLD), which was recently renamed metabolic-associated fatty liver disease (MAFLD) [27]. The clinical burden of non-alcoholic fatty liver disease (NAFLD) has been demonstrated over the past ten years to be not limited to liver-related morbidity and mortality. Additionally, there is increasing evidence that NAFLD is a multisystem disease that affects multiple extra-hepatic organs and regulatory pathways [28]. Hepatic macrovesicular steatosis is the main feature of NAFLD, a clinical condition. The histology and clinical manifestations of NAFLD range from NASH to a nonalcoholic fatty liver [29]. Nonalcoholic fatty liver disease (NAFLD) has become more common, along with a global rise in metabolic syndrome and diabetes. The course of nonalcoholic fatty liver disease (NAFLD), a spectrum of liver disorders ranging from nonalcoholic fatty liver (NAFL) to nonalcoholic steatohepatitis (NASH), varies but can result in cirrhosis and liver cancer [30]. Hepatic fat buildup, changes in energy metabolism, and inflammatory signals from many cell types, including immune cells, are the reasons behind these processes, which are not fully understood. It has been suggested that lipoxins, mitochondrial function, cytokines, and adipocytokines are important factors in both T2DM and NAFLD. Insulin resistance is frequent in NAFLD patients. However, many T2DM patients experience NASH, an inflammatory consequence of NAFLD [31].

a) Pathogenesis of NAFLD

Because it is a location of lipid intake, synthesis, oxidation, and transport to peripheral tissues, the liver plays a special role in lipid metabolism. Hepatocytes, or parenchymal cells, make up around 78% of the liver's total cell population. Hepatic NK cells, hepatic stellate cells (HSCs), Kupffer cells (KCs), and liver sinusoidal endothelial cells (LSECs) are examples of non-parenchymal cells. KCs are crucial in liver inflammation, whereas hepatocytes have been linked to the liver's basic functions, such as lipid metabolism [32].

Increased lipotoxicity from high levels of free fatty acids, free cholesterol, and other lipid metabolites occurs concurrently with the accumulation of fat in the liver as triglycerides. This leads to mitochondrial dysfunction with oxidative stress and the generation of reactive oxygen species (ROS) and endoplasmic reticulum (ER) stress-associated mechanisms.



4.3 Obesity – a metabolic disease

The current global obesity pandemic is the leading cause for the soaring rates of metabolic diseases, especially diabetes, cardiovascular disease, hypertension, and non-alcoholic hepatosteatosis [37,38]. The burden of obesity on health extends across multiple organ systems and diseases.

While its impact on tissues involved in nutrient regulation is manifest in the development of insulin resistance and type 2 diabetes, there are also unexpected connections between obesity and the risk of cancer and pulmonary diseases [39,40]. Numerous other chronic conditions, such as CKD, CVD, NAFLD, and T2D, as well as malignancies such as hepatocellular carcinoma (HCC), are directly and indirectly linked to obesity. For instance, NAFLD is positively correlated with BMI (≥ 35) and can be as high as 70–90% in obese patients. The mortality and morbidity of many chronic diseases are impacted by inflammation, insulin resistance, and metabolic dysfunction brought on by obesity. We go over a few common comorbidities linked to obesity and the variables that contribute to them in this section [41,42]. Adipocyte and adipose tissue dysfunction represent primary defects in obesity and may link obesity to metabolic and cardiovascular diseases. Adipose tissue (AT) dysfunction manifests by a proinflammatory adipokine secretion pattern that mediate auto/paracrine and endocrine communication and by inflammatory cell infiltration, particularly in intra-abdominal fat [43,44]. It has been demonstrated that T cells, intestinal B cells, and terminally developed antibody-secreting cells (ASCs) control metabolic diseases linked to obesity. Reduced intestinal IgA+ ASCs and B cells are linked to diet-induced obesity, which lowers colonic secretory IgA and promotes the development of insulin resistance [45,46].

Epidemiology

In the United States, 9.3% of adults were expected to have diabetes in 2002. By 2031, this is predicted to increase to 14.5%. Age, obesity, inactivity, poor diet, and smoking all raise the risk of type 2 diabetes. Additional risk factors include a history of gestational diabetes, hypertension (HTN), low levels of high-density lipoprotein (HDL), race/ethnicity (African Americans, Latinos, Native Americans, Asian-Americans, and Pacific Islanders), and a family history of diabetes [47,48,49].

V. THERAPEUTIC STRATEGIES FOR METABOLIC DISEASES

Chronic subclinical inflammation in metabolic tissues, including the liver, adipose tissue, muscles, and pancreatic islets, is a hallmark of metabolic disorders. Over the past ten years, it has become more and more clear that a dysbiotic gut microbiota contributes to this inflammatory state by activating several signaling transduction pathways and immunological responses.

Numerous therapeutic strategies against metabolic illnesses have arisen in light of the increasingly complex relationship between nutrition, gut bacteria, and the host immune system [50,51].

a) Targeting BA Receptors as a Therapeutic Option for NAFLD

In a number of preclinical models of NAFLD/NASH, FXR agonism has proven beneficial by causing metabolic changes that lessen inflammation and steatosis [52]. Numerous studies have been conducted on the use of antibiotics in NAFLD with the goal of lowering the intestinal burden of bacteria and the translocation of microbial components. Because it reduces endotoxaemia and proinflammatory cytokine production, Rifaximin, a non-absorbable antibiotic that targets Gram-negative bacteria, has been demonstrated to have positive effects in

patients with NAFLD/NASH. Furthermore, Rifaximin appears to play a "eubiotic role" by promoting the overgrowth of good bacteria like *Lactobacillus*, *Faecalibacterium*, and *Bifidobacterium*, which has an anti-inflammatory impact [53].

b) Glucagon-like Peptide-1 Receptor-based Therapeutics for Metabolic Liver Disease

To regulate metabolism, gut peptides like glucagon-like peptide-1 (GLP-1) have pleiotropic effects. GLP-1, which was first identified as a nutrient-stimulated incretin hormone that increases meal-stimulated insulin secretion, also improves metabolic health in people and animals by lowering glucagon (GCG) production, gastric emptying, gut lipoprotein secretion, food intake, and body weight [54,55]

a) Therapeutic strategies targeting gut-liver-pancreas axis in diabetes

Table-I

Strategy	MOA	Examples
Probiotics	Modulate microbiota composition	<i>Lactobacillus</i>
Prebiotics	Increase SCFA levels	Insulin
Synbiotics	Improve glycemia and lipid profile	Fiber and probiotics
Postbiotics	Reduce systemic inflammation	Acetate and butyrate infusions
Dietary interventions	Reduce hepatic and gut inflammation	Diet
GLP-1 receptor agonist	Enhance insulin secretion	Semaglutide
SGLT2 inhibitors	Improve glycemic control	Dapagliflozin
FXR agonist	Regulate bile acid	Obeticholic acid
TLR4 antagonists	Prevent inflammation	Eritoran
Cytokine inhibitors	Reduce hepatic and gut inflammation	Canakinumab[56,57,58].

Probiotics: The combination of probiotics containing *Bifidobacteriumlactis* LMG P-28149 and *Lactobacillus rhamnosus* LMG S-28148 may modulate the composition of the gut microbiota associated with obesity and restore the abundances of *Akkermansiamuciniphila* and *Rikenellaceae* while decreasing the abundance of *Lactobacillaceae*. Probiotics have been suggested as an effective strategy for preventing metabolic diseases. [59]. The Greek word that means "for life" is where the name "probiotic" comes from. "A live microbial feed supplement which beneficially affects the host animal by improving its intestinal balance" is how Fuller defined probiotics in 1989. Prebiotics, on the other hand, are described as "a non-digestible food ingredient that beneficially affects the host by selectively stimulating the growth and/or activity of one or a limited number of bacteria in the colon" by Gibson et al. in 1995 [60].

Lactic acid bacteria, or probiotics, are frequently added to meals and utilized in medicinal preparations. Numerous research have shown how probiotics affect metabolic disorders. A study has demonstrated the impact of fermented dairy products on serum cholesterol, particularly when certain strains of lactic acid bacteria are present. For instance, it has been discovered that a small amount of the dry culture of *Lactobacillus fermentum* KC4b may eliminate 14.8 mg of cholesterol from the culture medium. Additionally, lactobacilli are crucial in the intestinal deconjugation of bile salts to bile acids, which prevents the production of micelles. Probiotics enhance in vivo lipid metabolism and decrease lipid peroxidation. [61,62]. A probiotic is defined as "a live microbial feed supplement which improves the intestinal balance of the host animal" [63].

The primary conclusions of the current review were that some of the chosen probiotics can significantly enhance some inflammatory biomarkers linked to the illness as well as some of the clinical aspects of the MetS. Some research have looked into the use of probiotics as potential biotherapies for the treatment of metabolic diseases like diabetes and obesity. Probiotic, CLA, and polyphenol-based dietary methods may have important implications for developing a successful diet plan and/or nutraceutical/pharmaceutical preparations to help obese people reach and maintain a normal body weight [64,65,66].

Prebiotics: A non-digestible food ingredient that benefits the host by selectively stimulating the growth and/or activity of one or a limited number of bacteria in the colon, and thus improves host health" was the original definition of a prebiotic. [67] Prebiotic consumption may affect the metabolic process by controlling the synthesis of gut microbial metabolites such as bile acids and SCFAs. The amounts of acetic and butyric acids in mice with glucometabolic disease were found to be positively correlated with the administration of isomaltodextrin. [68]. Prebiotics are a group of nutritional substances that are grouped together based on their ability to stimulate the growth and/or activity of particular beneficial bacteria (probiotics) in genetically modified organisms, rather than necessarily on their structural affinity. Prebiotics have a variety of health benefits, such as immune modulation through increased intestinal-specific immunoglobulins and immune-regulatory interleukins, reduction of pro-inflammatory interleukins, and production of short-chain fatty acids (SCFAs) like butyrate, acetate, and propionate. Anaerobic fermentation of food fibers in the intestine by the GM produces SCFAs, which are carboxylic acids with aliphatic tails of one to six carbons. SCFAs are a key marker of bacterial fermentation in the colon and are known to enhance gut health by preserving the integrity of the intestinal barrier, producing mucus, preventing inflammation, and lowering the risk of obesity and colorectal cancer. [69,70]. Prebiotics can promote the growth of good bacteria, particularly those that produce short-chain fatty acids (SCFA). Improved satiety and weight reduction, decreased systemic inflammation by strengthening the gut barrier, and enhanced glucose and lipid metabolism are all linked to increased SCFA in the stomach. [71,72].

Synbiotics: Synbiotics are well-known components of functional foods and nutraceuticals, and because they can affect immunity and intestinal microbial ecology, they may have positive health impacts [73,74,75].

When synbiotic supplements containing 10% FOS, Lactobacillus, and Bifidobacterium were given to animals fed a low-fiber, high-fat diet, intestinal and systemic inflammation were successfully reduced [76,77,78]. A synbiotic is a mixture of live microorganisms and substrates that the host microorganisms specifically use to improve the host's health [79,80].

Postbiotics: Through immunomodulation or hormone mimicking, postbiotics can either directly fuel host metabolic pathways or affect endocrine regulation of metabolism. When it comes to metabolic inflammation and metabolic disease, postbiotics' role in the host-microbe relationship should be taken into account [81,82]. The next generation of probiotics are extracts that have potent modulatory effects on the gut flora and are devoid of both living and nonviable bacteria. Vitamin B12, vitamin K, folate, lipopolysaccharides, enzymes, and short-chain fatty acids (SCFAs) are a few examples of vital nutrients that are frequently found in the human diet. Through a number of different routes, postbiotics have been shown to exhibit antiobesity and antidiabetic benefits [83,84]. Preparation of inanimate microorganisms and/or their components that confers a health benefit on the host" is the definition of postbiotics. Compared to probiotics, postbiotics offer special benefits like stability, safety, and broad applicability [85,86,87]. Postbiotics, also known as metabiotics, are structural elements of microorganisms or their metabolites or signaling molecules that can enhance the host's physiological processes. Organic acids, short chain fatty acids (SCFA), tryptophan, cell-free supernatants, exopolysaccharides, enzymes, cell wall fragments, and bacteriocins are the primary postbiotics [88,89,90].

Dietary interventions: A wide range of dietary patterns are included in plant-based diets, which are distinguished by a decrease or restriction in the consumption of foods produced from animals and an increase in the consumption of foods derived from plants, such as fruits, vegetables, nuts, legumes, and grains. Lacto-vegetarian diets limit animal food intake except for dairy products; lacto-ovo-vegetarian diets exclude meat, seafood, and poultry but include eggs and dairy products; and pesco-vegetarians or pescatarians are similar to lacto-ovo-vegetarians but include fish. Strict vegetarian diets, also called vegan diets, are characterized by the exclusion of all animal-derived products, including dairy products, eggs, and honey [91,92]. The most recent data on effective dietary changes that can lower the parameters linked to MetS, such as energy restriction and weight loss, manipulation of dietary macronutrients—either by limiting fat, carbohydrates, or enriching in healthy fatty acids—incorporating functional

foods and bioactive nutrients, and following dietary and lifestyle patterns like the Mediterranean diet and exercise regimens [93,94,95].

VI. CONCLUSION

In summary, the development of liver steatosis is significantly influenced by the gut microbiota, especially in diseases like non-alcoholic fatty liver disease (NAFLD). Metabolic interactions, microbial composition, and dietary variables all have an impact on this relationship. The kind of dietary fat consumed has a major impact on the composition of the gut flora. Saturated fatty acid (SFA)-rich diets can cause dysbiosis, which is characterized by an increase in pathogenic species and a decrease in helpful bacteria. This change increases intestinal permeability, which makes it possible for bacterial components like lipopolysaccharides (LPSs) to enter the bloodstream and travel to the liver, where they can cause steatosis and inflammation [96,97]. In conclusion, probiotics—defined as live bacteria that offer health advantages when ingested in sufficient quantities—have drawn interest due to their possible function in the treatment of type 2 diabetes mellitus (T2DM). The growing understanding of the gut microbiota's impact on metabolic health and the pathophysiology of diabetes is a major factor in this interest. Probiotics' positive benefits on glycemic control may be explained by a number of processes, including gut microbiota regulation, in which probiotics aid in the restoration of dysbiosis, an imbalance in gut microbiota associated with obesity and insulin resistance [98,99]. By focusing on a number of important signaling pathways, including upregulating Akt, AMPK, CPR1 α , ERK, GPR43, NLCR3, NOD2, GLUT2/4, IRF4, p38 MAPK, PPAR α , SIRT1, TLR2, and TRAF6-mediated pathways and downregulating ACE, NF- κ B, NOD1, TLR4, and TNF- α -related pathways [100,101,102]. Meanwhile, the use of systems biology in conjunction with bioinformatics may be a potent tactic to reveal mechanistic insights into how prebiotics affect gut microbes and to comprehend how these substances (and their metabolites) modify host and microbial metabolic processes at the molecular level [103]. Probiotics and prebiotics have been shown in numerous studies to influence T2DM and CVD through altering gut flora, controlling insulin signaling, and reducing cholesterol. Clarifying the relationships between ingested probiotics and gut microbiota is still difficult, though [104].

REFERENCES

- [1] Zeuzem S. Gut-liver axis. *International journal of colorectal disease*. 2000 May;15(2):59-82.
- [2] Tilg H, Adolph TE, Trauner M. Gut-liver axis: Pathophysiological concepts and clinical implications. *Cell metabolism*. 2022 Nov 1;34(11):1700-18.
- [3] Fändriks L. Roles of the gut in the metabolic syndrome: an overview. *Journal of internal medicine*. 2017 Apr;281(4):319-36.
- [4] Agus A, Clément K, Sokol H. Gut microbiota-derived metabolites as central regulators in metabolic disorders. *Gut*. 2021 Jun;70(6):1174-82.
- [5] Peña-Durán E, García-Galindo JJ, López-Murillo LD, Huerta-Huerta A, Balleza-Alejandri LR, Beltrán-Ramírez A, Anaya-Ambriz EJ, Suárez-Rico DO. Microbiota and inflammatory markers: a review of their interplay, clinical implications, and metabolic disorders. *International journal of molecular sciences*. 2025 Feb 19;26(4):1773.
- [6] Tilg H, Adolph TE, Trauner M. Gut-liver axis: Pathophysiological concepts and clinical implications. *Cell metabolism*. 2022 Nov 1;34(11):1700-18.
- [7] Maroni L, Fianchi F, Miele L, Baroni GS. The pathophysiology of gut–liver connection. In *The Complex Interplay Between Gut-Brain, Gut-Liver, and Liver-Brain Axes* 2021 Jan 1 (pp. 97-122). Academic Press.
- [8] Marroncini G, Naldi L, Martinelli S, Amedei A. Gut–liver–pancreas axis crosstalk in health and disease: from the role of microbial metabolites to innovative microbiota manipulating strategies. *Biomedicine*. 2024 Jun 24;12(7):1398.
- [9] Alemany M. The metabolic syndrome, a human disease. *International journal of molecular sciences*. 2024 Feb 13;25(4):2251.
- [10] Nicolai J, Wewer Albrechtsen, Jens Pedersen, Katrine D Galsgaard, Marie Winther-Sørensen, Malte P Suppli, Lina Janah, Jesper Gromada, Hendrik Vilstrup, Filip K Knop, Jens J Holst, The Liver- α -Cell Axis and Type 2 Diabetes. *Endocrine Reviews*, Volume 40, Issue 5, October 2019, Pages 1353–1366.
- [11] Xourafa G, Korbmacher M, Roden M. Inter-organ crosstalk during development and progression of type 2 diabetes mellitus. *Nature Reviews Endocrinology*. 2024 Jan;20(1):27-49.
- [12] Ahmad E, Lim S, Lamptey R, Webb DR, Davies MJ. Type 2 diabetes. *The Lancet*. 2022 Nov 19;400(10365):1803-20.
- [13] Manilla, V., Santopaolo, F., Gasbarrini, A., & Ponziani, F. R. (2023). Type 2 Diabetes Mellitus and Liver Disease: Across the Gut–Liver Axis from Fibrosis to Cancer. *Nutrients*, 15(11), 2521.
- [14] Chatterjee S, Khunti K, Davies MJ. Type 2 diabetes. *The lancet*. 2017 Jun 3;389(10085):2239-51.
- [15] Dai H, Zhang Z. Emerging Insights into the Liver–Pancreas Axis: A Central Hub in the Pathogenesis of Diabetes and Metabolic Diseases. *Biomolecules*. 2026 Apr 21;16(4):613.
- [16] Galicia-Garcia U, Benito-Vicente A, Jebari S, Larrea-Sebal A, Siddiqi H, Uribe KB, Ostolaza H, Martín C. Pathophysiology of type 2 diabetes mellitus. *International journal of molecular sciences*. 2020 Aug 30;21(17):6275.
- [17] Abdul-Ghani MA, Tripathy D, DeFronzo RA. Contributions of β -cell dysfunction and insulin resistance to the pathogenesis of impaired glucose tolerance and impaired fasting glucose. *Diabetes care*. 2006 May 1;29(5):1130-9.

- [18] Choi W, Woo GH, Kwon TH, Jeon JH. Obesity-driven metabolic disorders: the interplay of inflammation and mitochondrial dysfunction. *International journal of molecular sciences*. 2025 Oct 6;26(19):9715.
- [19] Xiang L, Wang G, Zhuang Y, Luo L, Yan J, Zhang H, Li X, Xie C, He Q, Peng Y, Chen H. Safety and efficacy of GLP-1/FGF21 dual agonist HEC88473 in MASLD and T2DM: A randomized, double-blind, placebo-controlled study. *Journal of Hepatology*. 2025 Jun 1;82(6):967-78.
- [20] Mohiuddin MS, Neha NT, Mahir JU, Shakib FA, Alam MA, Wahiduzzaman M, Barua R, Shimu SJ, Rahman M, Hossain MR, Shariare MH. Metabolic dysfunction associated fatty liver disease and type 2 diabetes: pathophysiological links, epidemiological trends, and clinical implications. *Frontiers in Endocrinology*. 2025 Oct 27;16:1669478.
- [21] Kang M, Song J, Kang ES, Jang S, Kwak T, Kim Y, Sha M, Lee H, Jeong S. Pathophysiology, development, and mortality of major non-communicable diseases in metabolic dysfunction-associated steatotic liver disease: A comprehensive review. *International Journal of Biological Sciences*. 2025 Sep 3;21(13):5691.
- [22] Mohiuddin MS, Neha NT, Mahir JU, Shakib FA, Alam MA, Wahiduzzaman M, Barua R, Shimu SJ, Rahman M, Hossain MR, Shariare MH. Metabolic dysfunction associated fatty liver disease and type 2 diabetes: pathophysiological links, epidemiological trends, and clinical implications. *Frontiers in Endocrinology*. 2025 Oct 27;16:1669478.
- [23] Marti-Aguado D, Rodríguez-Ortega A, Mestre-Alagarda C, Bauza M, Valero-Pérez E, Alfaro-Cervello C, Benloch S, Pérez-Rojas J, Ferrández A, Alemany-Monraual P, Escudero-García D. Digital pathology: accurate technique for quantitative assessment of histological features in metabolic-associated fatty liver disease. *Alimentary Pharmacology & Therapeutics*. 2021 Jan;53(1):160-71.
- [24] Janah L, Kjeldsen S, Galsgaard KD, Winther-Sørensen M, Stojanovska E, Pedersen J, Knop FK, Holst JJ, WewerAlbrechtsen NJ. Glucagon receptor signaling and glucagon resistance. *International journal of molecular sciences*. 2019 Jul 5;20(13):3314.
- [25] Galsgaard KD. The vicious circle of hepatic glucagon resistance in non-alcoholic fatty liver disease. *Journal of clinical medicine*. 2020 Dec 15;9(12):4049.
- [26] Dai H, Zhang Z. Emerging Insights into the Liver–Pancreas Axis: A Central Hub in the Pathogenesis of Diabetes and Metabolic Diseases. *Biomolecules*. 2026 Apr 21;16(4):613.
- [27] Nassir F. NAFLD: mechanisms, treatments, and biomarkers. *Biomolecules*. 2022 Jun 13;12(6):824.
- [28] Byrne CD, Targher G. NAFLD: a multisystem disease. *Journal of hepatology*. 2015 Apr 1;62(1):S47-64.
- [29] Loomba R, Sanyal AJ. The global NAFLD epidemic. *Nature reviews Gastroenterology & hepatology*. 2013 Nov;10(11):686-90.
- [30] Friedman SL, Neuschwander-Tetri BA, Rinella M, Sanyal AJ. Mechanisms of NAFLD development and therapeutic strategies. *Nature medicine*. 2018 Jul;24(7):908-22.
- [31] Tilg H, Moschen AR, Roden M. NAFLD and diabetes mellitus. *Nature reviews Gastroenterology & hepatology*. 2017 Jan;14(1):32-42.
- [32] Nassir F. NAFLD: mechanisms, treatments, and biomarkers. *Biomolecules*. 2022 Jun 13;12(6):824.
- [33] Guo X, Yin X, Liu Z, Wang J. Non-alcoholic fatty liver disease (NAFLD) pathogenesis and natural products for prevention and treatment. *International journal of molecular sciences*. 2022 Dec 7;23(24):15489.
- [34] Buzzetti E, Pinzani M, Tsochatzis EA. The multiple-hit pathogenesis of non-alcoholic fatty liver disease (NAFLD). *Metabolism*. 2016 Aug 1;65(8):1038-48.
- [35] Cobbina E, Akhlaghi F. Non-alcoholic fatty liver disease (NAFLD)—pathogenesis, classification, and effect on drug metabolizing enzymes and transporters. *Drug metabolism reviews*. 2017 Apr 3;49(2):197-211.
- [36] Vonderlin J, Chavakis T, Sieweke M, Tacke F. The multifaceted roles of macrophages in NAFLD pathogenesis. *Cellular and Molecular Gastroenterology and Hepatology*. 2023 Jan 1;15(6):1311-24.
- [37] Saltiel AR, Olefsky JM. Inflammatory mechanisms linking obesity and metabolic disease. *The Journal of clinical investigation*. 2017 Jan 3;127(1):1-4.
- [38] Cao H. Adipocytokines in obesity and metabolic disease. *Journal of endocrinology*. 2014 Feb 1;220(2):T47-59.
- [39] Lumeng CN, Saltiel AR. Inflammatory links between obesity and metabolic disease. *The Journal of clinical investigation*. 2011 Jun 1;121(6):2111-7.
- [40] McLaughlin T, Ackerman SE, Shen L, Engleman E. Role of innate and adaptive immunity in obesity-associated metabolic disease. *The Journal of clinical investigation*. 2017 Jan 3;127(1):5-13.
- [41] Yang M, Liu S, Zhang C. The related metabolic diseases and treatments of obesity. *In Healthcare* 2022 Aug 25 (Vol. 10, No. 9, p. 1616).
- [42] Jais A, Brüning JC. Hypothalamic inflammation in obesity and metabolic disease. *The Journal of clinical investigation*. 2017 Jan 3;127(1):24-32.
- [43] Conterno L, Fava F, Viola R, Tuohy KM. Obesity and the gut microbiota: does up-regulating colonic fermentation protect against obesity and metabolic disease? *Genes & nutrition*. 2011 Aug;6(3):241-60.
- [44] Blüher MM. Adipose tissue dysfunction contributes to obesity related metabolic diseases. *Best practice & research Clinical endocrinology & metabolism*. 2013 Apr 1;27(2):163-77.
- [45] Khan S, Luck H, Winer S, Winer DA. Emerging concepts in intestinal immune control of obesity-related metabolic disease. *Nature communications*. 2021 May 10;12(1):2598.
- [46] Conterno L, Fava F, Viola R, Tuohy KM. Obesity and the gut microbiota: does up-regulating colonic fermentation protect against obesity and metabolic disease? *Genes & nutrition*. 2011 Aug;6(3):241-60.
- [47] Villarroya F, Cereijo R, Gavalda-Navarro A, Villarroya J, Giral M. Inflammation of brown/beige adipose tissues in obesity and metabolic disease. *Journal of internal medicine*. 2018 Nov;284(5):492-504.
- [48] Koopman RJ, Swofford SJ, Beard MN, Meadows SE. Obesity and metabolic disease. *Primary Care: Clinics in Office Practice*. 2009 Jun 1;36(2):257-70.
- [49] Cottrell EC, Ozanne SE. Early life programming of obesity and metabolic disease. *Physiology & behavior*. 2008 Apr 22;94(1):17-28.
- [50] Marroncini G, Naldi L, Martinelli S, Amedei A. Gut–liver–pancreas axis crosstalk in health and disease: from the role of microbial metabolites to innovative microbiota manipulating strategies. *Biomedicines*. 2024 Jun 24;12(7):1398.

- [51] Li X, Watanabe K, Kimura I. Gut microbiotadysbiosis drives and implies novel therapeutic strategies for diabetes mellitus and related metabolic diseases. *Frontiers in immunology*. 2017 Dec 20;8:1882.
- [52] Svegliati-Baroni G, Patrício B, Lioci G, Macedo MP, Gastaldelli A. Gut-pancreas-liver axis as a target for treatment of NAFLD/NASH. *International journal of molecular sciences*. 2020 Aug 13;21(16):5820.
- [53] Fianchi F, Liguori A, Gasbarrini A, Grieco A, Miele L. Nonalcoholic fatty liver disease (NAFLD) as model of gut–liver axis interaction: From pathophysiology to potential target of treatment for personalized therapy. *International Journal of Molecular Sciences*. 2021 Jun 17;22(12):6485.
- [54] Yabut JM, Drucker DJ. Glucagon-like peptide-1 receptor-based therapeutics for metabolic liver disease. *Endocrine Reviews*. 2023 Feb 1;44(1):14-32.
- [55] Clemente-Suárez VJ, Martín-Rodríguez A, Redondo-Florez L, López-Mora C, Yáñez-Sepúlveda R, Tomero-Aguilera JF. New insights and potential therapeutic interventions in metabolic diseases. *International journal of molecular sciences*. 2023 Jun 26;24(13):10672.
- [56] Abdalla MM. Gut-liver axis in diabetes: Mechanisms and therapeutic opportunities. *World Journal of Gastroenterology*. 2025 Aug 7;31(29):109090.
- [57] Portincasa P, Khalil M, Mahdi L, Perniola V, Idone V, Graziani A, Baffy G, Di Ciaula A. Metabolic dysfunction–associated steatotic liver disease: from pathogenesis to current therapeutic options. *International Journal of Molecular Sciences*. 2024 May 22;25(11):5640.
- [58] Siddiqui S, Kahkasha K. Gut–pancreas–metabolism axis: emerging anti-diabetic roles of gut-derived bioactive molecules. *Diabetes Research and Clinical Practice*. 2026 Jun 19:113383.
- [59] Li HY, Zhou DD, Gan RY, Huang SY, Zhao CN, Shang AO, Xu XY, Li HB. Effects and mechanisms of probiotics, prebiotics, synbiotics, and postbiotics on metabolic diseases targeting gut microbiota: a narrative review. *Nutrients*. 2021 Sep 15;13(9):3211.
- [60] Yoo JY, Kim SS. Probiotics and prebiotics: present status and future perspectives on metabolic disorders. *Nutrients*. 2016 Mar 18;8(3):173.
- [61] Aggarwal J, Swami G, Kumar M. Probiotics and their effects on metabolic diseases: an update. *Journal of clinical and diagnostic research: JCDR*. 2013 Jan 1;7(1):173.
- [62] Kumar M, Nagpal R, Kumar R, Hemalatha R, Verma V, Kumar A, Chakraborty C, Singh B, Marotta F, Jain S, Yadav H. Cholesterol-lowering probiotics as potential biotherapeutics for metabolic diseases. *Journal of Diabetes Research*. 2012;2012(1):902917.
- [63] Yoo JY, Kim SS. Probiotics and prebiotics: present status and future perspectives on metabolic disorders. *Nutrients*. 2016 Mar 18;8(3):173.
- [64] Le Barz M, Anhê FF, Varin TV, Desjardins Y, Levy E, Roy D, Urdaci MC, Marette A. Probiotics as complementary treatment for metabolic disorders. *Diabetes & metabolism journal*. 2015 Aug 17;39(4):291.
- [65] Tenorio-Jiménez C, Martínez-Ramírez MJ, Gil Á, Gómez-Llorente C. Effects of probiotics on metabolic syndrome: A systematic review of randomized clinical trials. *Nutrients*. 2020 Jan 1;12(1):124.
- [66] Mallappa RH, Rokana N, Duary RK, Panwar H, Batish VK, Grover S. Management of metabolic syndrome through probiotic and prebiotic interventions. *Indian journal of endocrinology and metabolism*. 2012 Jan;16(1):20.
- [67] Yoo JY, Kim SS. Probiotics and prebiotics: present status and future perspectives on metabolic disorders. *Nutrients*. 2016 Mar 18;8(3):173.
- [68] Li HY, Zhou DD, Gan RY, Huang SY, Zhao CN, Shang AO, Xu XY, Li HB. Effects and mechanisms of probiotics, prebiotics, synbiotics, and postbiotics on metabolic diseases targeting gut microbiota: a narrative review. *Nutrients*. 2021 Sep 15;13(9):3211.
- [69] Megur A, Daliri EB, Baltruikienė D, Burokas A. 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*. 2022 May 29;23(11):6097.
- [70] Nakamura YK, Omaye ST. Metabolic diseases and pro-and prebiotics: mechanistic insights. *Nutrition & metabolism*. 2012 Jun 19;9(1):60.
- [71] O'Connor S, Chouinard-Castonguay S, Gagnon C, Rudkowska I. Prebiotics in the management of components of the metabolic syndrome. *Maturitas*. 2017 Oct 1;104:11-8.
- [72] Barends ME. Gut microbiota, prebiotics, probiotics, and synbiotics in management of obesity and prediabetes: review of randomized controlled trials. *Endocrine Practice*. 2016 Oct 1;22(10):1224-34.
- [73] Eslamparast T, Zamani F, Hekmatdoost A, Sharaafkhah M, Eghtesad S, Malekzadeh R, Poustchi H. Effects of synbiotic supplementation on insulin resistance in subjects with the metabolic syndrome: a randomised, double-blind, placebo-controlled pilot study. *British journal of nutrition*. 2014 Aug;112(3):438-45.
- [74] Sáez-Lara MJ, Robles-Sanchez C, Ruiz-Ojeda FJ, Plaza-Díaz J, Gil A. Effects of probiotics and synbiotics on obesity, insulin resistance syndrome, type 2 diabetes and non-alcoholic fatty liver disease: a review of human clinical trials. *International journal of molecular sciences*. 2016 Jun 13;17(6):928.
- [75] Li HY, Zhou DD, Gan RY, Huang SY, Zhao CN, Shang AO, Xu XY, Li HB. Effects and mechanisms of probiotics, prebiotics, synbiotics, and postbiotics on metabolic diseases targeting gut microbiota: a narrative review. *Nutrients*. 2021 Sep 15;13(9):3211.
- [76] Bock PM, Telo GH, Ramalho R, Sbaraini M, Leivas G, Martins AF, Schaen BD. The effect of probiotics, prebiotics or synbiotics on metabolic outcomes in individuals with diabetes: a systematic review and meta-analysis. *Diabetologia*. 2021 Jan;64(1):26-41.
- [77] Barends ME. Gut microbiota, prebiotics, probiotics, and synbiotics in management of obesity and prediabetes: review of randomized controlled trials. *Endocrine Practice*. 2016 Oct 1;22(10):1224-34.
- [78] Kassaian N, Feizi A, Aminorroaya A, Amini M. Probiotic and synbiotic supplementation could improve metabolic syndrome in prediabetic adults: A randomized controlled trial. *Diabetes & Metabolic Syndrome: Clinical Research & Reviews*. 2019 Sep 1;13(5):2991-6.
- [79] Liu X, Tong Y, Qin J, Zhao Y. Efficacy and safety of probiotic and synbiotic supplementation in metabolic syndrome: a systematic review and meta-analysis. *Nutrition, Metabolism and Cardiovascular Diseases*. 2025 Sep 1;35(9):104100.
- [80] Mishra N, Ashique S, Farid A, Garg A, editors. Synbiotics in metabolic disorders: Mechanisms, therapeutic potential, and future perspectives. CRC Press; 2024 Nov 25.
- [81] Fang H, Rodrigues e-Lacerda R, Barra NG, KukjeZada D, Robin N, Mehra A, Schertzer JD. Postbiotic impact on host metabolism and immunity provides therapeutic potential in metabolic disease. *Endocrine Reviews*. 2025 Feb;46(1):60-79.

- [82] Li HY, Zhou DD, Gan RY, Huang SY, Zhao CN, Shang AO, Xu XY, Li HB. Effects and mechanisms of probiotics, prebiotics, synbiotics, and postbiotics on metabolic diseases targeting gut microbiota: a narrative review. *Nutrients*. 2021 Sep 15;13(9):3211.
- [83] Mishra N, Garg A, Ashique S, Bhatt S. Potential of postbiotics for the treatment of metabolic disorders. *Drug Discovery Today*. 2024 Apr 1;29(4):103921.
- [84] Li S, Sohoul M, Li Z. The effect of postbiotics supplementation on obesity and metabolic health: a systematic review and meta-analysis of randomized control trials. *Nutrition & Metabolism*. 2025 Nov 13;22(1):140.
- [85] Zhong Y, Wang T, Luo R, Liu J, Jin R, Peng X. Recent advances and potentiality of postbiotics in the food industry: Composition, inactivation methods, current applications in metabolic syndrome, and future trends. *Critical Reviews in Food Science and Nutrition*. 2024 Jul 2;64(17):5768-92.
- [86] Doke R, Chande K, Dingare S, Vinchurkar K, Singh S. Demystifying the role of postbiotics in inflammation mediated metabolic disorders: an updated review: R. Doke et al. *Food Science and Biotechnology*. 2026 Feb;35(3):463-84.
- [87] Hájová E. Postbiotics as metabolites and their biotherapeutic potential. *International journal of molecular sciences*. 2024 May 16;25(10):5441.
- [88] Nazarinejad Z, Molani-Gol R, RoozbehNasirae L, Ebrahimzadeh-Attari V. Postbiotics as a novel intervention for obesity management and improving metabolic parameters: a systematic review and meta-analysis of animal studies. *Journal of translational medicine*. 2025 Aug 14;23(1):913.
- [89] Palade CM, Vulpoi GA, Vulpoi RA, Drug VL, Barboi OB, Ciocoiu M. The biotics family: current knowledge and future perspectives in metabolic diseases. *Life*. 2022 Aug 19;12(8):1263.
- [90] Rodríguez-Pastén A, Pérez-Hernández N, Añorve-Morga J, Jiménez-Alvarado R, Carriño-Cortés R, Sosa-Lozada T, Fernández-Martínez E. The activity of prebiotics and probiotics in hepatogastrointestinal disorders and diseases associated with metabolic syndrome. *International Journal of Molecular Sciences*. 2022 Jun 29;23(13):7229.
- [91] Clemente-Suárez VJ, Martín-Rodríguez A, Redondo-Florez L, López-Mora C, Yáñez-Sepúlveda R, Tomero-Aguilera JF. New insights and potential therapeutic interventions in metabolic diseases. *International journal of molecular sciences*. 2023 Jun 26;24(13):10672.
- [92] Castro-Barquero S, Ruiz-León AM, Sierra-Pérez M, Estruch R, Casas R. Dietary strategies for metabolic syndrome: a comprehensive review. *Nutrients*. 2020 Sep 29;12(10):2983.
- [93] Xu H, Li X, Adams H, Kubena K, Guo S. Etiology of metabolic syndrome and dietary intervention. *International journal of molecular sciences*. 2018 Dec 31;20(1):128.
- [94] Bagchi D, Nair S, editors. *Nutritional and therapeutic interventions for diabetes and metabolic syndrome*. Academic Press; 2018 May 25.
- [95] Andersen CJ, Fernandez ML. Dietary strategies to reduce metabolic syndrome. *Reviews in Endocrine and Metabolic Disorders*. 2013 Sep;14(3):241-54.
- [96] Cerullo M, Armeli F, Mengoni B, Menin M, Crudeli ML, Businaro R. Curcumin modulation of the gut-brain axis for neuroinflammation and metabolic disorders prevention and treatment. *Nutrients*. 2025 Apr 24;17(9):1430.
- [97] Clemmensen C, Finan B, Müller TD, DiMarchi RD, Tschöp MH, Hofmann SM. Emerging hormonal-based combination pharmacotherapies for the treatment of metabolic diseases. *Nature Reviews Endocrinology*. 2019 Feb;15(2):90-104.
- [98] Rondanelli M, Borromeo S, Cavioni A, Gasparri C, Gattone I, Genovese E, Lazzarotti A, Minonne L, Moroni A, Patelli Z, Razza C. Therapeutic strategies to modulate gut microbial health: approaches for chronic metabolic disorder management. *Metabolites*. 2025 Feb 13;15(2):127.
- [99] Fiorucci S, Distrutti E. Bile acid-activated receptors, intestinal microbiota, and the treatment of metabolic disorders. *Trends in molecular medicine*. 2015 Nov 1;21(11):702-14.
- [100] Mishra N, Garg A, Ashique S, Bhatt S. Potential of postbiotics for the treatment of metabolic disorders. *Drug Discovery Today*. 2024 Apr 1;29(4):103921.
- [101] Procopciuc LM, Hangan AC, Lucaci RL. The Gut-Brain Axis in Metabolic Syndrome: Emerging Mechanisms and Perspectives in Personalized Medicine. *International Journal of Molecular Sciences*. 2026 Jul 24;27(15):6622.
- [102] Li HY, Zhou DD, Gan RY, Huang SY, Zhao CN, Shang AO, Xu XY, Li HB. Effects and mechanisms of probiotics, prebiotics, synbiotics, and postbiotics on metabolic diseases targeting gut microbiota: a narrative review. *Nutrients*. 2021 Sep 15;13(9):3211.
- [103] Megur A, Daliri EB, Baltruikienė D, Burokas A. 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*. 2022 May 29;23(11):6097.
- [104] Yoo JY, Kim SS. Probiotics and prebiotics: present status and future perspectives on metabolic disorders. *Nutrients*. 2016 Mar 18;8(3):173.