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Unravelling the gut-liver axis: The role of gut microbiota-mitochondria interactions in the pathogenesis and management of metabolic-associated fatty liver disease (MAFLD)

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ABSTRACT

Metabolic-associated fatty liver disease (MAFLD) has emerged as a prevalent chronic liver disease. Our review of the existing literature reveals that the interplay between gut microbiota, mitochondria, and the liver is a key mechanism in the development of MAFLD. This paper distills the pathogenic role of gut microbiota in MAFLD through its influence on mitochondria and outlines the therapeutic mitochondrial mechanisms of MAFLD that leverage gut microbiota. It also touches on the traditional Chinese medicine perspective on the liver-intestine connection and the concept of "*qi*" in relation to mitochondria, as well as its modern medical counterpart. We conclude that the gut microbiota and their metabolites can directly or indirectly affect the intestinal mitochondria, leading to structural and functional changes. These changes include shifts in mitochondrial membrane potential, changes in permeability, and dysregulation of signaling pathways. As a result, the permeability of intestinal epithelial cells may be increased, and the integrity of the intestinal barrier may be compromised. The gut microbiota and their metabolites can then influence hepatic mitochondria through the hepatic-intestinal axis, triggering liver pathology. When liver damage occurs, their metabolites can enter the intestine and affect intestinal mitochondria and microbiota, which in turn can lead to a disrupted intestinal barrier and microbiota and a dysregulated homeostatic balance. Our extensive literature review suggests that the gut microbiota may mediate the treatment of MAFLD through mitochondrial pathways. The therapeutic approach of modulating the gut microbiota to regulate mitochondrial function and restore liver health is promising. Traditional Chinese medicine diets are particularly well suited for this strategy. Further research is warranted to fully elucidate the underlying mechanisms. By protecting the body's own mitochondrial function through the gut microbiota, we can effectively combat liver injury, providing a novel therapeutic avenue for the treatment of liver disease.

1. Introduction

Non-alcoholic fatty liver disease (NAFLD) has emerged as one of the most common chronic liver diseases worldwide. This liver disease is associated with metabolic dysregulation and occurs in the absence of significant alcohol consumption or other etiological factors, such as medications and viral infections.[1] In 2022, an international expert panel proposed a new terminology of NAFLD into metabolic-associated fatty liver disease (MAFLD), emphasizing that the new nomenclature more accurately reflects the current understanding of the metabolic dysfunction underlying fatty liver disease.[2] This renaming sparked widespread debate and was largely accepted by the scientific community. Consequently, the term "MAFLD" will be used in the following discussions to refer to both "NAFLD" and "MAFLD". The global prevalence of MAFLD is

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estimated to be 30%–40% in adults.[3] The disease burden of MAFLD is substantial, with a general population prevalence of approximately 25.2%, rising to over 50% in high-risk cohorts, including those with diabetes and obesity.[4] Research suggests that 15%–20% of individuals with MAFLD may progress to non-alcoholic steatohepatitis (NASH), which may further progress to cirrhosis and hepatocellular carcinoma, posing a significant health risk in terms of liver-related morbidity and mortality worldwide.[5] The prevalence of MAFLD extends beyond the obese population to include non-obese individuals.[3] A report in 2024 concluded that the new nomenclature and criteria for metabolic dysfunction-associated steatotic liver disease (MASLD) and "steatotic liver disease" (SLD) are more applicable to lean patients with NAFLD than the previous criteria for MAFLD.[6]

The pathogenesis of MAFLD is multifactorial and includes dietary habits, aging, insulin resistance, diabetes mellitus, environmental factors, and changes in the gut microbiota.[7] MAFLD is characterized by the accumulation of hepatocellular lipids, primarily triglycerides. The "two-hit hypothesis" was introduced to describe the progression of the disease: the first "hit" is the accumulation of triglycerides in the liver,[8] while the second "hit" includes mitochondrial dysfunction, endoplasmic reticulum stress, bacterial endotoxins of intestinal origin, and inflammation.[9] This hypothesis explains the transition from MAFLD to NASH, although the precise mechanisms remain incompletely understood. The more recent "multiple parallel hits hypothesis" proposes that changes in the liver, intestine, and adipose tissue are involved.[10,11] This hypothesis suggests that dietary and environmental factors, along with obesity, lead to elevated serum levels of free fatty acids (FFAs) and cholesterol (CH), the development of insulin resistance, adipocyte hyperplasia and dysfunction, and changes in the gut microbiota. These conditions increase hepatic free fatty acid flux, precipitating two key outcomes: triglyceride (TG) synthesis and accumulation, and a "toxic" concentration of fatty acids, free cholesterol, and other lipid metabolites. This milieu triggers mitochondrial dysfunction and oxidative stress, as well as the generation of reactive oxygen species (ROS) and endoplasmic reticulum (ER) stress, culminating in hepatic inflammation.[12] The evolution from the "two-hits hypothesis" to the "multiple parallel hits hypothesis" underscores the intricate interplay between the gut microbiota, mitochondria, and liver as central to the pathogenesis of MAFLD.

Mitochondria are ubiquitous organelles found in nearly all eukaryotic organisms, including plants, animals, fungi, and protists. These highly dynamic structures play critical roles in ATP production, maintenance of intracellular calcium homeostasis, ROS-mediated cellular signaling, and regulation of programmed cell death (apoptosis).[13] Mitochondria contain their own genomic DNA (mtDNA), which is located in the mitochondrial matrix.[14] mtDNA is subject to continuous mutation, clonal amplification, and loss of point mutations or deletions, and these changes contribute to various tissue-specific and systemic diseases.[15] Mitochondria are essential for lipid metabolism, energy production, the urea cycle, and amino acid and iron metabolism, thereby regulating these signaling pathways and modulating the innate immune response to control inflammation and related diseases.[16] They are a major source of intracellular ROS and are also susceptible to ROS-induced damage. Oxidative stress can lead to mitochondrial dysfunction and damage, triggering the mitochondrial permeability transition and the release of pro-apoptotic proteins such as chromogranin C that induce cell death.[17] Mitochondrial autophagy is a critical process for removing damaged mitochondria and maintaining mitochondrial homeostasis. Impaired mitochondrial autophagy can result in the accumulation of dysfunctional mitochondria, leading to uncontrolled increases in ROS, mutations in mitochondrial DNA, energy deficits, and ultimately cell death. Numerous studies have shown that the accumulation of damaged mitochondria is associated with mitochondrial dysfunction and increased apoptosis.[18,19] As the metabolic hub of the cell, mitochondria produce approximately 80% of the ATP required by the organism and release a variety of signaling molecules essential for cellular homeostasis. Moderate levels of ROS can be beneficial to individual organisms and may protect against diseases such as colitis.[20] However, excessive ROS can cause severe damage to cellular structures. Mitochondria also play a critical role in maintaining the barrier function of intestinal epithelial cells. Disruption of this barrier can lead to increased intestinal permeability, facilitating the translocation of harmful substances and pathogens into the bloodstream.

The gut microbiota is a complex ecosystem composed of bacteria, archaea, protozoa, fungi, and viruses whose composition is influenced by environmental and host factors. This microbiota is predominantly composed of four phyla: Firmicutes (Gram-positive bacteria), Bacteroidetes (Gram-negative anaerobes), Bifidobacteria, and Actinobacteria, with the first two phyla making up approximately 90% of the total bacterial population.[21] The intestinal flora is distributed throughout the gastrointestinal tract, from the stomach to the rectum, and is established by exposure to maternal vaginal and fecal flora at birth. The total microbial population in the gut is estimated to exceed 10^{14} cells, weighing approximately 1.5 kg.[22,23] Upon arrival of food in the gut, most host products are fermented by anaerobic microbial communities, yielding a diverse array of metabolites. In healthy adults, the primary fermentation products are gases and organic acids, particularly the three short-chain fatty acids (SCFAs): acetate, propionate, and butyrate, typically in a 3:1:1 ratio, with their combined concentration in the colon ranging from 50 to 150 mM. A smaller fraction of these metabolites are generated by anaerobic respiration, producing nitrate, sulfate, and various organic compounds that serve as electron acceptors.[24] Mycobacterial metabolites, including SCFAs and hydrogen sulfide (H_2S), act as signaling molecules for colonic epithelial and immune cells, affecting their metabolism, epigenetics, and gene expression.[14]

Despite the growing body of research, there is a lack of comprehensive literature reviews addressing the intrinsic relationship between gut microbiota and liver-gut mitochondrial function in the context of MAFLD. Therefore, this paper aims to summarize the pathological processes of MAFLD induced by gut flora through its effects on mitochondria, as well as the mitochondrial mechanisms involved in MAFLD treatment based on gut microbiota, by reviewing a substantial amount of existing literature. In addition, the relationship between liver and intestine in traditional Chinese medicine (TCM) is briefly discussed.

2. Ethnomedicine understanding of liver and intestinal diseases

In TCM, MAFLD is classified as "subcostal pain" and "masses in the liver". The primary etiological factors are identified as dietary irregularities, imbalance between work and rest, emotional disturbances, weakness due to chronic diseases, and constitutional insufficiency. The pathogenesis is characterized by a deficiency of "ben" (root) and an excess of "biao" (branch), with spleen deficiency and impaired transportation and transformation being the root, and phlegm opacity and blood stasis being the branch. The pathological factors are dampness, phlegm, opacity, heat, and blood stasis. The liver is primarily affected, with secondary involvement of the spleen and kidneys.[25] Treatment strategies mainly focus on strengthening the spleen, soothing the liver, tonifying the kidney, transforming phlegm, eliminating dampness, and promoting blood circulation.[26]

In TCM theory, the liver is responsible for the free flow of "*qi*", while the spleen governs transportation and transformation. Their interrelationship is an elaborate encapsulation of their physiological functions. Ye Tianshi, a renowned TCM practitioner, said "Wood can dig the earth, and the spleen is stagnant to move." The Golden Mirror of Medicine (Yi Zong Jin Jian) explains that "The liver is made of wood *qi*, which is completely dependent on the earth to nourish it and water to irrigate it." When the liver *qi* is sufficient, it supports the transportation of the spleen and stomach and the distribution of nutrients throughout the body. Conversely, healthy movement of spleen *qi* supports the storage of liver blood and its normal elimination. Their mutual support is described as "mutual assistance in dispersal and transportation, and coordinated unity in storage and elimination".[27] The liver is the resolute organ, and the liver likes free will and hates to be suppressed. A normal flow of liver *qi*

facilitates the discharge of essence *qi* into the stomach and intestines, helping the spleen and stomach to break down food and drink, or allowing the spleen *qi* to rise and disperse the essence of water and grain. Both processes contribute to the management of the middle burner and the nourishment of the entire body.

It is obvious that "*qi*" has a pivotal position in TCM fundamentals. The theory of "*qi* monism" is the foundation of Eastern philosophy. According to this theory, *qi* is a microscopic substance that occupies the entire universe and exists in continuous motion. This substance exists in two forms: a higher-order temporary structure (the rich world in this relatively stable state); and a chaotic state (a cyclical combined and decentralized trans-structural energy field). Because *qi* is constantly changing and unifying, it cannot be visualized by ordinary means.[28] Miraculous Pivot (Ling Shu) uses the concept of "*qi*" to explain the composition of human substances and physiological functions and activities. It categorizes *qi* into two groups: first, simple substances such as essence *qi*, zong-pectoral *qi*, ying-nutritive *qi*, wei-defensive *qi*; and second, *qi* that emphasizes the function of the organism, such as heart *qi*, lung *qi*, spleen *qi*, liver *qi*, and kidney *qi*.[29] Through Symbolism-Digit Therapy, Shanyu Li and Stevenson Xutian have found that the interaction of invisible energies (*qi*), which reflect the true connection between the human body and the universe, can promote a better understanding of the nature of TCM.[30] Modern acupuncture research has shown that the conduction of *qi* has been separated from the central nervous system, introducing a separate cellular communication channel, with calcium waves acting as the second messenger. Mechanical waves, transverse acoustic waves, and calcium waves turned out to come from the same source, and these different forms of waves seemed ideally suited to describe what the ancient Chinese called "*qi*", the mysterious, intangible, untranslatable, and unknowable component of life.[31] Some modern scholars claim that "*qi*" is closely related to mitochondria. *Qi* originates from the innate essence in the kidneys, combines with the essence of water and grain received by the spleen and stomach, and the clear *qi* is inhaled by the lungs. It circulates throughout the body, allowing for normal growth and development. Mitochondria, the only organelles with DNA in animal cells, have independent DNA replication, transcription, and translation systems. Maternal inheritance of mtDNA is a known phenomenon. Mitochondria combine metabolites from ingested food with oxygen from respiration in an oxidative phosphorylation reaction, providing over 90% of the body's energy. A comparison of the two reveals that mitochondria may originate from the innate essence and combine with the essence of water and grain and the clear *qi* of inhalation to drive the growth and development of the human body. Thus, mitochondria may be an important component of *qi*.[32,33]

In TCM, the interaction between the liver and spleen in physiopathology may be mediated by mitochondria. The concept that "the spleen governs the wei-defensive *qi*" comes from Miraculous Pivot. Miraculous Pivot further elaborates: wei-defensive *qi* is that which warms the muscles, fills the skin, enriches the interstices, and is responsible for opening and closing. This indicates that wei-defensive *qi* plays a role in resisting external pathogens and in managing the opening and closing of sweat pores on the body's surface. Given its distribution within the tissues of the intestines, wei defensive *qi* also intrinsically warms the zang-fu organs. In modern medicine, the gut microbiota is recognized for orchestrating the functional immune system by regulating host defense and tolerance through bacterial metabolites and components. Conversely, the gut immune response precisely controls microbial ecology, diversity, and trafficking to prevent aberrant immune responses. Epithelial cells construct chemical and physical barriers that isolate the gut microbiota from immune cells and facilitate mutual symbiosis with the host.[34] The intestinal barrier function separates the external environment from the internal environment, preventing the translocation of microorganisms and their derivatives that can cause liver and systemic inflammation.[35] The spleen, along with the gastrointestinal tissues, is involved in the body's immune defense.[36] This is consistent with the TCM principle that "the spleen governs the wei defensive *qi*". Plain Questions (Su Wen) states: spleen *qi* disperses the essence that rises to the lungs, regulates the water channels, and descends to the bladder. This passage explains the concept of "spleen *qi* dispersing essence", where the spleen disperses nutritious and subtle substances throughout the body for use, and expels cloudy *qi* from the body.[37] In modern medicine, intestinal flora digests nutrients or breaks down substances that are difficult for the body to absorb into short-chain fatty acids and transports them throughout the body via the hepatic and intestinal circulation.[38,39] In addition, probiotics in the gut, such as bifidobacteria and lactobacillus, promote intestinal motility and waste elimination.[40] This demonstrates a high degree of consistency between the functions of the "spleen" in TCM and the "spleen and intestinal tract" in modern medicine.

Currently, there is no unified standard for clinical evidence of fatty liver disease in TCM. According to the "Expert Consensus on Traditional Chinese Medicine Diagnosis and Treatment of Non-Alcoholic Fatty Liver Disease" in 2023, it is mainly divided into patterns such as liver stagnation with spleen deficiency, internalization of dampness and turbidity, damp heat accumulation, and intertwined phlegm and blood stasis.[41] Most of these symptoms are related to damp phlegm, which is attributed to spleen deficiency and the transformation of water-dampness into phlegm, overlapping with the modern medical view that the first "hit" of MAFLD is "lipid accumulation".[42] Synopsis of Prescriptions of the Golden Chamber (Jin Gui Yao Lue) advises "the superior prevents a disease before it arises". When one sees liver diseases, knowing that the liver will spread to the spleen, one should first strengthen the spleen. "Treating the liver and strengthening the spleen" has become a general principle for treating liver and intestinal diseases in TCM clinics. When Li Junxiang et al. applied the "Jianpi Shugan prescription" to treat MAFLD, they found that the improvement of symptoms in the treatment group was significantly better than that in the control group.[43] Sun Jianguang treated MAFLD with a self-prepared formula, Jianpi Huazhuo Yin. Through clinical observation and pharmacological research, it was proved that this formula could effectively improve liver function, blood lipids, fasting blood glucose, and insulin resistance index, and enhance antioxidant function, thus achieving the effect of liver protection and lipid lowering.[44] Professor Wang Lingtai believes that taking care of the spleen and stomach is the most important rule in treating liver disease throughout the entire process. The main purpose of treatment is to take care of the spleen, either by transforming dampness and transporting the spleen *qi*, soothing the liver and strengthening the spleen, regulating the liver and spleen, or tonifying the spleen and kidneys.[45] Modern medical research on the spleen in TCM has found that it is mostly related to the digestive organs. The intestines are related to the digestive system. Therefore, the basis of "treating the liver and strengthening the spleen" is to regulate intestinal microecology.[46]

The "spleen" in TCM may be involved in the entire process of MAFLD development through intestinal microecology, which also provides a rationale for targeting intestinal microecology in MAFLD treatment. In the TCM system, "*qi*" is one of the most important aspects of spleen function. Normal mitochondrial function is also an extremely important aspect of liver and intestinal microecology. However, the deeper mechanisms of these relationships remain unclear and require further investigation.

3. Gut microbiota-induced MAFLD based on mitochondrial function

3.1. The mechanism of interaction between gut microbiota and mitochondria

The gut microbiota is a prolific producer of metabolites that have significant effects on mitochondrial function, including H_2S, butyrate, and pyrroloquinoline quinone (PQQ).[47] The gut microbiota serves as a central source of H_2S, which traverses the intestinal epithelium, thereby energizing the epithelium and other cells within the lamina propria.[48] H_2S is synthesized in the colon through a catalytic process facilitated by

enzymes released by the colonic microbiota, and is subsequently oxidatively metabolized within the mitochondria of colonocytes. During this oxidative metabolism, electrons derived from H_2S are incorporated into the mitochondrial respiratory chain through the action of sulfide: quinone oxidoreductase (SQR). However, at elevated concentrations, H_2S can inhibit the catalytic activity of cytochrome *c* oxidase, culminating in respiratory inhibition in colonocytes. Conversely, micromolar concentrations of H_2S enhance colonocyte respiration and stimulate mitochondrial activity, enabling these cells to detoxify and utilize energy from sulfide present in the intestinal lumen.[49] H_2S also protects mitochondrial integrity and functionality, particularly under hypoxic conditions,[50] but it can also have detrimental effects on intestinal epithelial cells. As a critical mediator in numerous biological processes, including angiogenesis, cytoprotection, metabolism, and inflammation, the pro- or anti-inflammatory effects of H_2S depend on its concentration and the specific cellular environment.[51]

Butyrate, acting as an energy substrate rather than an HDAC inhibitor, can maintain energy homeostasis and inhibit cellular autophagy. Upon translocation into colonocytes, butyrate is metabolized within the mitochondria by β-oxidation to acetyl coenzyme A. This molecule then enters the tricarboxylic acid (TCA) cycle, resulting in the reduction of NAD^+ to NADH. NADH is then incorporated into the electron transport chain, culminating in the production of ATP with CO_2 as a byproduct. Donohoe et al. observed a positive correlation between the presence of parvulum and the severity of inflammation, and a negative correlation with mitochondrial protein expression and the abundance of butyrate-producing bacteria.[52] In pediatric patients with Crohn's disease (CD), the absence of butyrate-producing microorganisms results in decreased butyrate production, which can impair mitochondrial function, potentially leading to ROS production, increased epithelial permeability, and translocation of intestinal microbes across the epithelial barrier. This suggests a central role for mitochondrial dysfunction in the pathogenesis of colitis.[51] Berger et al. demonstrated that HSP60 deficiency-induced mitochondrial dysfunction can disrupt intestinal stem cell homeostasis via a CHOP-independent signaling mechanism.[53] Reduced mitochondrial activity has been shown not only to directly activate inflammatory pathways, but also to trigger pathways initiated by bacterial products. Intestinal inflammation is mediated in part by decreased mitochondrial activity leading to activation of AMPKα2, which promotes NF-κB-dependent IL-8 expression.[54] Mutations in mitochondrial genes have been found to significantly affect the composition of the gut microbial community in mice, with mutations in the mt-Atp8 gene (single mutation, m.7778 G > T) alone resulting in notable differences in gut microbial composition.[55] Many bacteria or viruses disrupt intestinal epithelial cell function by perturbing the mitochondrial network, increasing mitochondrial fission, and enhancing fragmentation. Mitochondrial dynamics, an integral part of the dynamic equilibrium, is closely linked to mitochondrial function.[47]

In conclusion, the gut microbiota can modulate mitochondrial structure and function either directly or indirectly through their metabolites. This modulation can be both beneficial and detrimental and plays a critical role in the etiology of several diseases.

3.2. The mechanism of gut mitochondria-mediated MAFLD

3.2.1. The mechanism of intestinal mitochondrial dysfunction due to gut microbiota disorders

The gut microbiota plays a central role in modulating intestinal homeostasis and metabolic processes of epithelial cells through interactions with mitochondria. Several strains of *Escherichia coli* (*E. coli*) have been identified that infect host cells and thereby manipulate cellular mitochondrial dynamics. Specifically, the adherent invasive *E. coli* strain LF82 has been shown to induce mitochondrial dysfunction in intestinal epithelial cells, characterized by significant Drp1-mediated fragmentation of the mitochondrial network and marked depletion of the OPA1-L protein. It is hypothesized that mitochondrial damage induced by *E. coli* LF82 may be a strategic response to maintain intracellular homeostasis and mitigate the loss of intestinal epithelial barrier function associated with infection.[56] The type III secreted protein MAP (Orf 19), an effector molecule of enteropathogenic *E. coli*, has been shown to target host mitochondria and disrupt the mitochondrial membrane potential. This disruption leads to an influx of calcium ions (Ca^{2+}) into the host cytoplasm, activation of the ADAM10-MAP kinase pathway, and ultimately apoptosis of epithelial cells.[57,58] Similarly, the type III secreted effector protein EspF also targets mitochondria, resulting in loss of mitochondrial membrane potential and cell death. The 16th leucine residue in the EspF protein is critical for its functional mitochondrial targeting signal (MTS).[59] Interestingly, the non-pathogenic *E. coli* strain C25, originally isolated from the human gut as a commensal, can induce mitochondrial swelling and irregularities in the T84 epithelial cell line derived from the human colon. This effect is accompanied by an increase in the permeability of the epithelial monolayer.[60] Lewis and colleagues have shown that co-treatment of the non-pathogenic *E. coli* strain HB10 with DNP results in decreased ATP synthesis and increased permeability of intestinal epithelial cells. This effect is exacerbated by the release of tumor necrosis factor-α (TNF-α) from macrophages.[61]

Salmonella, a pathogenic bacterium, is known to cause severe intestinal infections in humans and animals, primarily through contamination of water and food sources. This bacterium has been shown to impair host mitochondrial energy metabolism by metabolizing sulfur-containing amino acids in the large intestine, resulting in the production of H_2S. This mechanism was elucidated by Leschelle.[50] In addition, Liu's research team provided comprehensive transcriptional profiling of mouse colonic mucosa during *Salmonella* infection and showed that the bacterium suppresses the mitochondrial oxidative phosphorylation pathway in colonocytes. Their sophisticated pathway analysis identified the mitochondrial functional response as a critical event during the early stages of infection, characterized by inhibition of inflammation and induction of oxidative stress within mitochondria.[62] In addition, *Salmonella* targets mitochondria during macrophage infection via its Type Three Secretion System-1 (TTSS-1) effector protein SipB, inducing mitochondrial swelling and the accumulation of autophagic vesicles, which triggers autophagy and macrophage death, ultimately compromising the intestinal immune barrier.[63] One study identified ATP6V0D2, a highly expressed isoform of a V-ATPase subunit in macrophages, as a facilitator of autophagosome-lysosome fusion by promoting the interaction between STX17 and VAMP8. Conversely, ATP6V0D2 deficiency results in increased mitochondrial ROS production and accumulation of damaged mitochondria.[64]

Shigella flexneri, the causative agent of bacillary dysentery (shigellosis), induces epithelial cell death associated with mitochondrial dysfunction upon infection. It has been observed that *Shigella flexneri* causes significant mitochondrial fragmentation and lactate dehydrogenase release in HeLa cells, effects that are attenuated by the DRP-1 inhibitor MDi1 or by DRP-1 knockdown using siRNA. This mitochondrial fragmentation is critical for facilitating bacterial spread between cells.[65] In addition, Shigella infection in the gut triggers loss of mitochondrial inner membrane potential, mitochondrial damage, and necrotic cell death in non-myeloid cells, such as epithelial cells or fibroblasts, through pathways dependent on Bnip3 and cyclophilin D (CypD), both of which are involved in host oxidative stress responses.[66] The Lembo-Fazio team has shed new light on the pathogenesis of shigellosis by demonstrating that Shigella induces rapid intestinal epithelial cell apoptosis through mitochondrial depolarization, activation of capsule-9, and a key role for the eukaryotic stress response factor growth arrest and DNA damage 45 α (Gadd45 α) in colonic epithelial cells.[67]

Helicobacter pylori (HP) is a major risk factor for gastric cancer. Research indicates that VacA, the primary toxin of HP, enters mitochondria in association with the p55 protein and the p33 protein subunit, which are localized to the inner mitochondrial membrane and the mitochondrial intermembrane space, respectively, with the p55 subunit located in the mitochondrial intermembrane space.[68] VacA-induced

disruption of mitochondrial morphology via Drp1-mediated division triggers apoptosis in HP-infected gastric epithelial cells.[69] In addition, HP can induce apoptosis in AGS cells by targeting death receptors on the plasma membrane, leading to caspase-8-mediated disruption of nuclear lamellipodia proteins and subsequent caspase-6-mediated cleavage of Bid to form tBid. This cascade leads to the release of cytochrome *c* and AIF from the mitochondria, activating downstream apoptotic events.[70] In addition, STAT3, a critical factor in inflammation-associated cancers, is involved in HP infection of human and mouse gastric epithelial cells. This infection induces the phosphorylation of STAT3Ser727, which then interacts with GRIM-19 to facilitate the mitochondrial translocation of P-STAT3Ser727, culminating in the loss of mitochondrial integrity and the initiation of autophagy, processes that may contribute to inflammation and gastric cancer.[71]

The bacterium *Listeria monocytogenes* subverts the mitochondrial network and modulates mitochondrial function by secreting the pore-forming toxin listeriolysin O (LLO) during infection. This secretion perturbs mitochondrial dynamics, culminating in diminished mitochondrial membrane potential, attenuated respiratory activity, and reduced intracellular ATP levels, thereby facilitating enhanced intracellular infection.[72] Delving into the kinetic mechanisms, Carvalho[73] conducted comprehensive research revealing that *Listeria monocytogenes* infection elevates the levels of Mic10, a pivotal component of the mitochondrial contact site and cristae organizing system (MICOS), in an LLO-dependent fashion. This elevation induces mitochondrial fragmentation and cellular infections, leading to the loss of mitochondrial integrity in gastric epithelial cells, the initiation of autophagy, and the potential triggering of inflammation and gastric cancer. Intriguingly, Stavru et al.[74] discovered that the pore-forming toxin LLO can regulate mitochondrial fission independently of the canonical mitochondrial fission machinery, with Drp1 being dispensable for LLO-induced mitochondrial network fragmentation. Furthermore, the endoplasmic reticulum was found to be capable of marking mitochondrial fragmentation sites, with evidence of coactivation in mitochondrial fragmentation.

Chlamydia trachomatis, a Gram-negative bacterium, has been implicated in modulating mitochondrial dynamics upon host cell infection. Prior studies have established that mitochondrial ATP is an essential metabolite for the normal development of *Chlamydia trachomatis*, which maintains mitochondrial integrity by reversibly inducing stress within the mitochondrial matrix through miR-30c-5p-dependent inhibition of Drp1-mediated mitochondrial division.[75] Zou et al. identified that *Chlamydia* further restricts DRP1 activation by ubiquitination of the P53 protein via the PI3K-AKT-HMD2 signaling pathway.[75,76] Fischer et al. added that *Chlamydia trachomatis* inactivates Mcl-1 by binding its deubiquitinating enzyme (Cdu)1 to Mcl-1 in membrane-bound vesicles of inclusion bodies, thereby reducing mitochondrial division.[77,78]

Upon invasion of human colonic epithelial cell lines by the enteric pathogen *Vibrio cholerae*, its membrane protein OmpU can translocate to the mitochondria of target cells, leading to a decrease in mitochondrial membrane potential, a shift in mitochondrial membrane permeability, and the release of cytochrome *c* and apoptosis-inducing factor (AIF).[79] Toxins produced by *Vibrio cholerae* induce microvilli reduction, intracellular organelle disruption, mitochondrial response (cohesion and swelling after cristae disruption), myelogram appearance, capillary wall defects, and cytosolic activation.[80] Suzuki[81] also found that the *Vibrio cholerae* T3SS effector VopE interferes with the mitochondrial Miro GTPase as a specific GTPase-activating protein, disrupting mitochondrial dynamics and preventing Mfn1-induced mitochondrial fusion.

Mitochondria-associated protein (Map) causes barrier dysfunction in intestinal epithelial cells by disrupting mitochondrial structure and respiratory chain function in infected epithelial cells following *Citrobacter rodentium* infection.[82] *Citrobacter rodentium* infection induces a decrease in the activity and levels of mitochondrial respiratory complexes I and IV, mitochondrial phosphorylation capacity, transmembrane potential, and ATP production.[83] In addition, *Citrobacter rodentium* infection inhibits substrate supply to the TCA cycle in small intestinal epithelial cells, reduces butyrate uptake by 30%, inhibits mitochondrial cardiolipin biosynthesis, reduces ATP production, and affects gut microbiota composition as a result of conflict between *Citrobacter rodentium* and the host over control of cholesterol biosynthesis and efflux.[84]

It is evident that the aforementioned dysbiosis can facilitate the entry of the pathogen or its toxic substances into cellular mitochondria via various pathways, thereby altering mitochondrial structure and inducing changes or loss of mitochondrial membrane potential (Table 1). This can

Table 1
Intestinal microbiota and mitochondrial dysfunction in the intestine.

Colony/Strain	Target	Function	References
E. coli -LF82	Intestinal epithelial cell	OPA1-L ↓ Mitochondrial rupture ↑ Intestinal barrier function ↓	56
Shigella flexneri	Intestinal epithelial cell	Mitochondrial depolarization ↑ Capsule-9 ↑ Gadd45 α ↑	67
Citrobacter rodentium	Intestinal epithelial cell	Intestinal barrier function ↓ The activity of mitochondrial respiratory complexes I and IV ↓ Mitochondrial phosphorylation capacity and ATP ↓ Transmembrane potential ↓	82–84
Vibrio cholerae	Rabbit intestinal cell	Mitochondrial swelling ↑	80
E. coli	HeLa cell	Mitochondrial membrane potential ↓ ADAM10-MAP ↑	57,58
Shigella flexneri	HeLa cell	Mitochondrial fragmentation ↑ Lactate dehydrogenase ↑	65
Chlamydia trachomatis	HeLa cell	Drp1-mediated mitochondrial fission ↓ DRP1 ↓	75,76
E. coli -C25	T84 cell	Mitochondrial swelling and irregularity ↑ Intestinal epithelial permeability ↑	60
Helicobacter pylori	Gastric epithelial cell	Mitochondrial morphological disruption ↑ STAT3Ser727 phosphorylation ↑ Mitochondrial translocation of P-STAT3Ser727 ↑	69,71
Listeria monocytogenes	Gastric epithelial cell	Mitochondrial membrane potential ↓ Mitochondrial respiratory activity ↓ ATP activity ↓ Mitochondrial rupture ↑ Cellular infection ↑ Autophagy ↑	72,73
Vibrio cholerae	Human colon epithelial cell	Mitochondrial membrane potential ↓ Mitochondrial membrane Permeability transition ↑ Cytochrome *c* and AIF release ↑	79
Salmonella	Colonocyte	Oxidative phosphorylation pathway ↓ Inflammation ↓ Oxidative stress ↑	62
Salmonella	Macrophage	Mitochondrial swelling ↑ Autophagic vesicles ↑ Intestinal immune barrier ↓	63
Shigella flexneri	Non-myeloid cell	Mitochondrial membrane potential ↓ Mitochondrial damage ↑	66
Helicobacter pylori	AGS cell	Cytochrome *c* and AIF ↑	70
Vibrio cholerae	CHO cell	Mfn1-induced mitochondrial fusion ↑	81

lead to the disordered release of signaling factors such as cytochrome *c*, triggering mitochondrial dysfunction, cell death, and subsequent inflammatory responses in the body.

3.2.2. Intestinal mitochondrial dysfunction leading to disruption of intestinal barrier function and triggering of liver disease

The extensive body of research has consistently shown that perturbations in the gut microbiome can have profound effects on mitochondrial health, leading to damage and dysfunction. Conversely, mitochondria are central to the modulation of gut microbiota and permeability. ROS are integral to normal cellular signaling and play a critical role in maintaining intestinal health and facilitating the recruitment of resident stem cells to support intestinal epithelial cell integrity. However, an overabundance of ROS can disrupt the delicate balance of the gut microbiome and homeostasis.[85] Elevated ROS levels may result from mitochondrial fragmentation and aberrant oxidative phosphorylation.[56] Mitochondrial-derived ROS may modulate intestinal epithelial barrier function. For example, by increasing mitochondrial ROS production, dinitrophenol may induce mitochondrial dysfunction leading to a compromised intestinal epithelial barrier. This, in turn, increases the permeability of intestinal epithelial cells, facilitating the transepithelial passage of *E. coli*.[86] Phosphorylation of ERK1/2 in response to ROS released from the intestinal epithelium as a result of mitochondrial dysfunction can significantly exacerbate intestinal barrier dysfunction, particularly in NOD2-deficient cells. This effect is compounded by the decreased responsiveness of macrophages, dendritic cells, and Paneth cells to bacterial stimuli in individuals with impaired NOD2 function.[87]

Mitochondria play a key role in controlling the intestinal barrier defense mechanisms within the intestinal epithelial cells, thereby regulating intestinal function. Fully functional mitochondria are essential for maintaining energy homeostasis and barrier integrity. The maintenance of intestinal barrier function is highly dependent on mitochondrial ATP production; inhibition of this production can lead to a decrease in the integrity of Caco-2 monolayers.[88] Dysfunctional mitochondria can lead to a reduction in Paneth cells and disruption of the intestinal epithelial barrier, contributing to metabolic imbalances in chronic degenerative gastrointestinal diseases.[85] In addition, increased permeability of the intestinal barrier allows translocation of bacterial products, such as bacterial DNA, lipopolysaccharide (LPS), or even intact bacteria, into the mesenteric portal venous bloodstream. This translocation can interact with the liver via the hepatic-intestinal circulation, potentially leading to systemic inflammation and other pathophysiological consequences.[89] It has been shown that gut microbiota after short bowel syndrome leads to severe dysregulation of bile acid metabolism, which in turn leads to steatosis, persistent diarrhea, and liver damage.[90]

Mitochondria are key to the intestinal barrier defense mechanism and regulation of intestinal function. Well-functioning mitochondria maintain energy homeostasis and barrier integrity. Dysfunction can lead to intestinal epithelial barrier disruption and metabolic imbalance in chronic degenerative gastrointestinal diseases. And the increased permeability of the intestinal barriers can lead to the transfer of bacterial and other products that can trigger systemic inflammation and other consequences. The gut microbiota and mitochondria interact, and their disruption can lead to mitochondrial damage and dysfunction. Mitochondria can also regulate the gut microbiota and permeability.

3.2.3. The link between MAFLD and the mitochondria

The hepatocyte is typically rich in mitochondria, which serve as the central hub of cellular metabolism and are the primary sites of fatty acid oxidation and oxidative phosphorylation.[91] In the context of MAFLD, there is a notable impairment in mitochondrial functionality, with evidence suggesting that mitochondrial dysfunction is a precursor to the onset of MAFLD.[92] However, it is not universal that patients with hepatic steatosis exhibit impaired oxidative function; indeed, some studies have reported an increase in hepatic mitochondrial β-oxidation and tricarboxylic acid (TCA) cycle activity in liver tissue affected by MAFLD.[93] In addition, other studies have demonstrated either unchanged or increased hepatic oxidative mitochondrial activity in adult ob/ob mice and insulin-resistant diabetic Goto-Kakizaki rats.[94] As MAFLD progresses, mitochondria may exhibit structural abnormalities, including swelling, loss of cristae and crystalline inclusions, and other ultrastructural damage.[95] In advanced stages of MAFLD, a decrease in fatty acid oxidation capacity may be manifested, potentially indicating hepatic decompensation.[96] While mitochondrial fatty acid oxidation (mtFAO) is stimulated (or at least preserved) in fatty liver and nonalcoholic steatohepatitis (NASH), it likely acts as an early compensatory mechanism to counteract free fatty acid-mediated hepatocyte toxicity.[97] Oxidative phosphorylation is impaired in non-alcoholic patients, with numerous studies showing reduced activity of mitochondrial respiratory complexes in high-fat diet (HFD) mice, and Koliaki[93] observed lower mRNA expression of complexes I, III, IV, and V compared to controls. Similarly, a reduction in the activity of all mitochondrial respiratory chain complexes has been observed in liver tissue from NASH patients. When the supply of electrons to the respiratory chain is inhibited, proton leak is uncompensated, leading to a decrease in mitochondrial membrane potential and inhibition of ATP synthesis.[98] Mitochondrial uncoupling progressively increases from obesity to steatosis to NASH, with Serviddio et al. highlighting that UCP2-dependent mitochondrial uncoupling is a significant contributor to NASH and cirrhosis, characterized by upregulation of UCP2 and uncoupling of oxidative phosphorylation (OXPHOS), increased proton leak, and decreased ATP synthesis.[93,99] Increased electron leakage in patients with fatty liver disease can react directly with oxygen, leading to increased production of ROS, which in turn can oxidize unsaturated lipids and lead to lipid peroxidation.[93,100] It should be noted that in addition to the electron transport chain (ETC), ROS have other sources within mitochondria, such as NADPH oxidase, monoamine oxidase, and α-glycerophosphate dehydrogenase.[101]

There is a robust correlation between the severity of MAFLD in patients and the extent of oxidative stress. Significantly decreased levels of canonical antioxidants such as superoxide dismutase activity, glutathione peroxidase (GPX), and glutathione, along with increased oxidative markers such as advanced glycosylation end products (AGE), malondialdehyde (MDA), and oxidative damage to DNA/RNA, have been observed in MAFLD patients.[102,103] Peroxidation products can readily interact with proximal mitochondrial DNA and induce deletions, point mutations, and damage to mitochondrial DNA (mtDNA).[104] High-throughput sequencing technology has revealed a significantly higher mutation rate in liver mtDNA from MAFLD patients with a complex mitochondrial genome.[105] It has been found that artificially-methylated mtDNA promotes mitochondrial dysfunction and interferes with cellular lipid metabolism in the hepatic environment.[106]

The balance of mitochondrial dynamics significantly influences the progression of MAFLD. The majority of research indicates that increased mitochondrial fission exacerbates the development of fatty liver disease. *In vitro* studies have shown that treatment of hepatocytes with palmitic acid results in mitochondrial fragmentation, potentially leading to excessive mitochondrial ROS production, subsequent mitochondrial biogenesis, and release of cytotoxic mitochondrial proteins (e.g., Smac), culminating in hepatocyte death.[107] Inhibition of mitochondrial fission has also been shown to alleviate hepatic steatosis in a mouse model of MAFLD.[108] Conversely, decreased levels of the mitochondrial fusion protein MFN2 have been detected in liver biopsies from patients with NASH and in a NASH mouse model, via a mechanism that disrupts the transfer of phosphatidylserine bound to Mfn2 from ER mitochondria.[109] PGC-1α, a key regulator of mitochondrial biogenesis, interacts with nuclear respiratory factors 1 and 2 (NRF-1 and -2) to control the transcription of mitochondrial respiratory chain proteins. In addition, PGC-1α regulates transcription of mtDNA (TFAM) and fatty acid oxidation. It has been shown that PGC1α bioactivity associated with mitochondrial biosynthesis is impaired in the livers of steatotic mice, with reduced interaction between NRF-1 and NRF-2 response elements and PGC1α.[110]

Autophagy plays a critical role in preventing the progression of MAFLD by eliminating damaged mitochondria, thereby reducing oxidative stress and serving as a cellular self-preservation mechanism. Impaired autophagic flux has been observed in hepatocytes from MAFLD patients and mouse models.[111] In obese mice with hepatic steatosis, autophagic flux is slowed by a reduction in lysosomal activity due to inhibition of tissue protease expression.[112] Parkin, an E3 ubiquitin ligase involved in mitochondrial autophagy, has been implicated in the predisposition to hepatic steatosis and insulin resistance in individuals fed a high-fat diet.[113] Wu et al. identified a novel regulatory mechanism for blocking the autophagy pathway in MAFLD, specifically the Mlkl-dependent but Rip3-independent pathway.[114] Dysfunctional autophagy can lead to the accumulation of nonfunctional mitochondria, triggering hepatocellular inflammation and necrosis and exacerbating the severity of MAFLD. Therefore, targeted removal of damaged mitochondria through enhanced mitochondrial autophagy is a promising therapeutic strategy to improve MAFLD.

In conclusion, mitochondrial function is altered in a complex manner in patients with MAFLD (Fig. 1). Impaired mitochondrial function may precede the development of MAFLD, but oxidative function is not impaired in some patients with fatty liver disease, and even hepatic mitochondrial β-oxidation and TCA cycle activity are increased, and in some studies oxidative activity is unaltered or enhanced. Imbalances in mitochondrial dynamics affect the disease, and increased fragmentation exacerbates disease progression. As the disease progresses, mitochondrial structure becomes abnormal and fatty acid oxidation is reduced in advanced stages. Patients with MAFLD have impaired oxidative phosphorylation, reduced activity of the mitochondrial respiratory chain complex, and increased electron leakage, leading to increased ROS production. The severity of MAFLD correlates with oxidative stress, decreased antioxidant activity, increased oxidative markers, and mtDNA damage. This leads to an enhanced inflammatory response and increased accumulation of lipid droplets.

3.2.4. *Effects of gut microbiota or their metabolites on liver mitochondria in relation to MAFLD*

The prevalence of genetic impairments in mitochondrial function is particularly evident in the liver and gastrointestinal tract. Hepatic mitochondrial respiratory chain disorders are often correlated with gut health[115] (Fig. 2). Translocation of endogenously produced ethanol by intestinal bacteria from the intestinal epithelium to the liver via the systemic circulation contributes to the development of MAFLD. This occurs through the induction of hepatic mitochondrial ROS production and mitochondrial DNA damage, leading to a compromise of mitochondrial integrity and functionality.[116] Researchers have identified a high-alcohol-producing Klebsiella pneumoniae strain (HiAlc Kpn) in over 60% of MAFLD patients. HiAlc Kpn-induced MAFLD appears to mimic the molecular mechanisms of alcohol-mediated liver injury, as evidenced by expression profiling microarrays and other analytical techniques. Specifically, HiAlc Kpn-targeted hepatocytes exhibit mitochondrial abnormalities, including disruption of mitochondrial integrity, increased levels of mitochondrial fission proteins DRP-1 and FIS-1, ROS accumulation, decreased membrane potential, lipid peroxidation, and decreased ATP levels, as well as mitochondrial DNA damage.[117] Furthermore, Chen[118] reported that chronic high salt and alcohol consumption leads to microbial imbalances in the gut, characterized by increased *Bifidobacterium* spp. and *Lactobacillus* spp. and increased intestinal permeability. These alterations may drive microbial metabolic changes that result in ultrastructural damage to liver mitochondria, including membrane disruption and disappearance of cristae, culminating in rapid ROS production and subsequent inflammation and liver damage.

Bacterial LPS, a metabolite of Gram-negative bacteria, is abundant in the portal vein and systemic circulation.[119] Intestinal exposure to LPS leads to decreased permeability and impaired mitochondrial function, accompanied by an inflammatory response and increased mitochondrial autophagy.[120] A dysfunctional intestinal barrier facilitates the entry of LPS into the enterohepatic circulation. LPS activates toll-like receptor-4

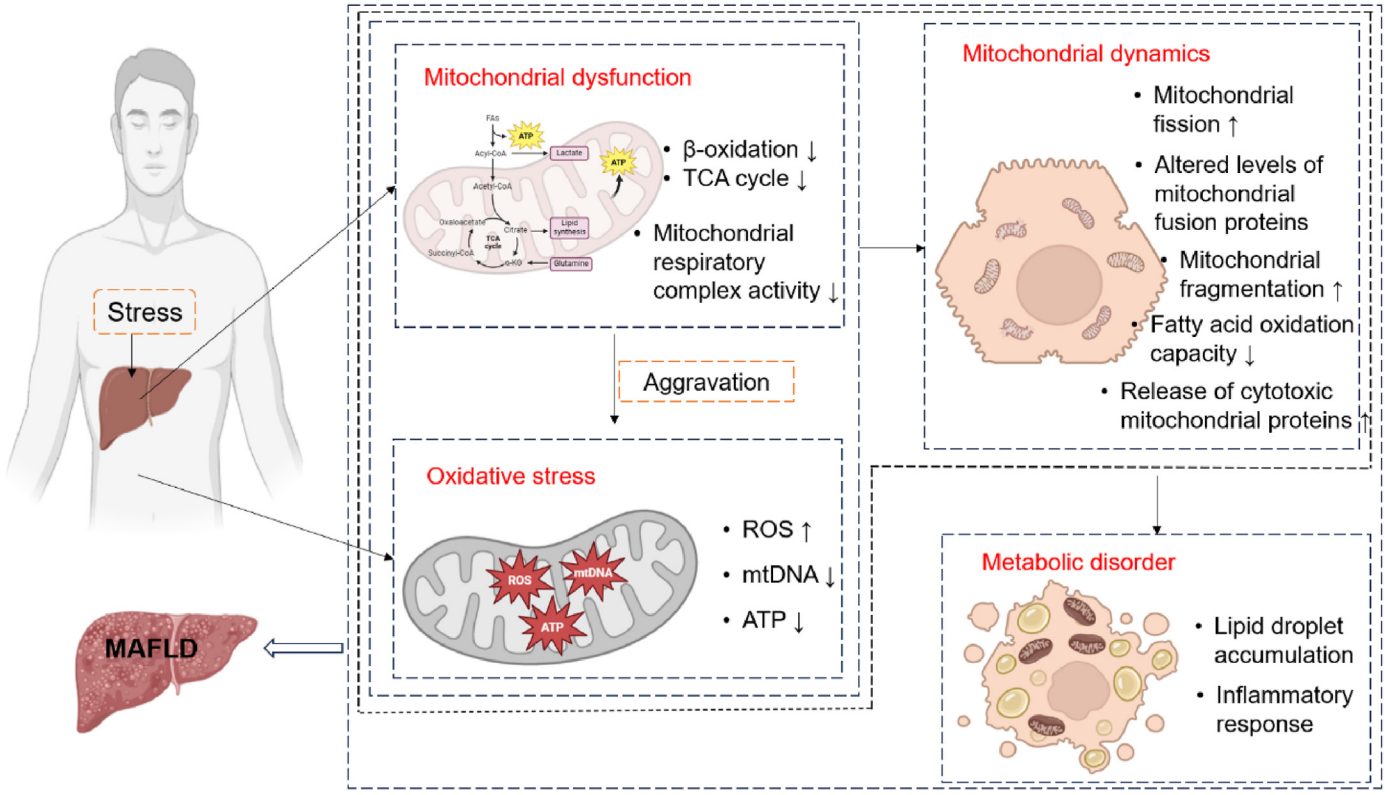

Fig. 1. MAFLD and mitochondria.

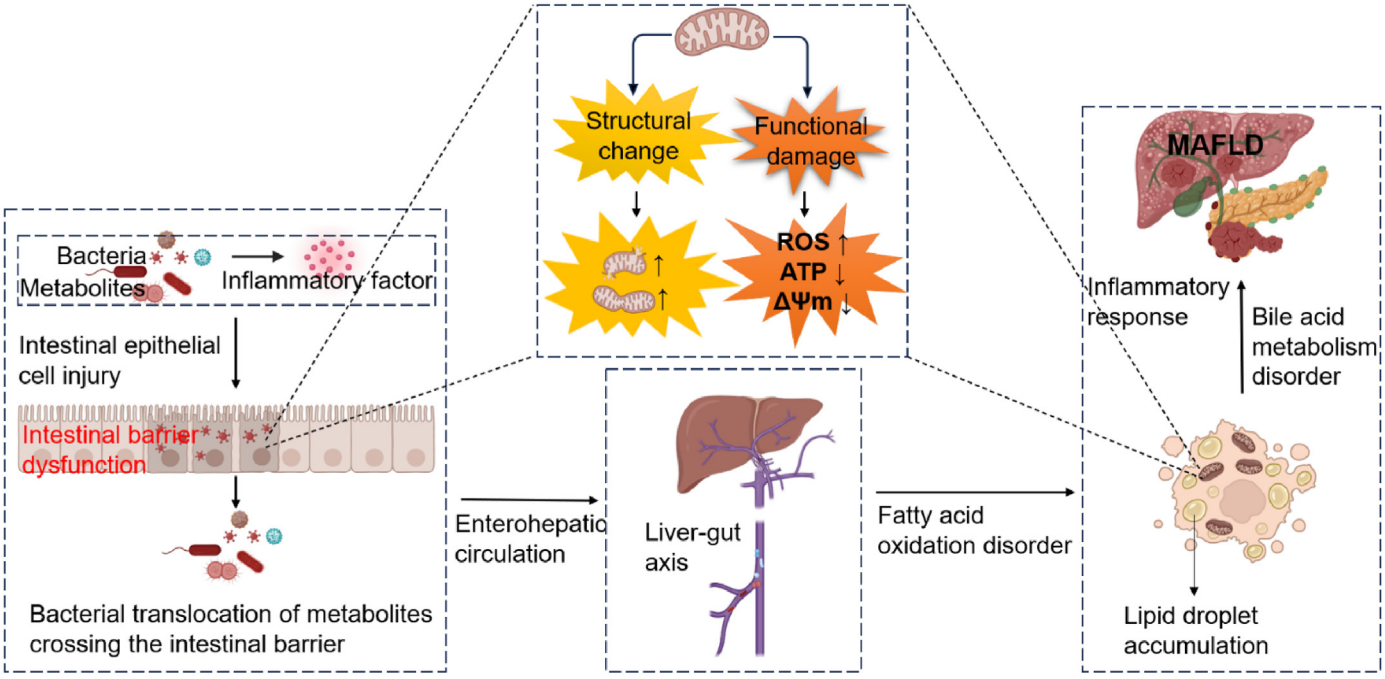

Fig. 2. Effects of intestinal microbiota or metabolites on liver mitochondria leading to MAFLD.

(TLR-4) on Kupffer and hepatic stellate cells, promoting inflammation and MAFLD progression.[121] Studies have shown that LPS treatment in mice upregulates SREBP-1c expression in the liver, leading to hepatic lipid accumulation.[122] Fukunishi[123] showed that LPS exacerbates hepatic steatosis by increasing TNF-α and SREBP-1c expression. Harte[124] reported elevated LPS levels in MAFLD patients, which correlated with disease severity. Fei[125] found that different LPS-producing Gram-negative bacteria induced different degrees of MAFLD in germ-free mice fed a high-fat diet. Verdam[126] observed increased plasma levels of anti-LPS antibodies in NASH patients, consistent with disease progression.

Bile acids, synthesized from cholesterol in the liver and excreted in the bile, serve as signaling molecules that regulate their synthesis and other metabolic processes, including glucose, lipid, and energy homeostasis.[127] They prevent the overgrowth of pathogenic bacteria in the gut.[128] Mitochondria, central to cellular energy metabolism and bile acid synthesis, have been shown to exhibit increased expression of mitochondrial fusion proteins in MAFLD livers. Selective OPA1 defects in hepatocytes protect against high-fat diet-induced metabolic dysfunction by reducing bile acid secretion and dietary lipid uptake.[129] Laura et al.[130] found that STARD1 stimulates bile acid synthesis via the mitochondrial bypass pathway and affects pluripotency and inflammation-related genes. Bile acids modulate the hepatointestinal circulation through receptors such as the farnesoid X receptor (FXR) and TGR5.[131,132] FXR activation attenuates triglyceride levels, bacterial overgrowth, and intestinal permeability, while TGR5-bound bile acids prevent LPS-induced inflammation and metabolic dysfunction by inhibiting NLRP3 inflammasome activation.[133] Intestinal dysbiosis can decrease bile acid secretion, thereby reducing FXR and TGR5 activation and exacerbating hepatic steatosis.[1] Kakiyama[134] linked dysregulation of bacterial ecology in cirrhosis to reduced bile acid intestinal entry. Wang found a decreasing trend in bacterial genera responsible for bile acid metabolism in chronic hepatitis B patients with fibrosis.[135]

Short-chain fatty acids (SCFAs), primarily acetic, propionic, and butyric acids, are derived from intestinal bacterial fermentation of indigestible fiber-rich foods.[136] As signaling molecules, SCFAs influence immune response, energy metabolism, and lipid metabolism.[119] Butyrate, a fermentation by-product, is critical for mitochondrial energy metabolism, providing over 70% of the energy for colonic epithelial cells.[137,138] Decreased SCFAs are associated with MAFLD, with reduced butyrate production impairing mitochondrial function and increasing intestinal permeability.[51] Santhanam[137] found that butyrate oxidizing enzymes were impaired in ulcerative colitis patients. Conversely, Turnbaugh[139] and Singh[140] observed increased acetate and butyrate in obese mice, which was associated with severe intestinal dysbiosis and liver damage. Excessive accumulation of SCFAs can deplete ATP and increase intestinal permeability.[141] The role of SCFAs in the progression of MAFLD is complex and requires further investigation.

Choline, an essential nutrient, is associated with metabolic fatty liver when deficient. Choline hydrolysis leads to the formation of dimethylamine and trimethylamine, resulting in choline deficiency and inhibition of hepatocyte VLDL excretion, leading to triglyceride accumulation.[89] TMAO, a choline metabolite, increases insulin resistance and glucose intolerance, exacerbating MAFLD.[142] Chen[143] correlated circulating TMAO levels with the severity of MAFLD. High-fat diets induce mitochondrial hydrogen peroxide production, impair colonic epithelial mitochondria, and enhance TMA formation from choline in *E. coli*, leading to liver damage.[144]

Tryptophan, an essential dietary nutrient, modulates MAFLD through its metabolites. Ritze[145] showed that tryptophan supplementation ameliorates NAFLD in mice. Indole, a tryptophan metabolite, prevents MAFLD by upregulating PFKFB3 in macrophages and inhibiting pro-inflammatory responses.[146] The hepatoprotective effects of indole are direct and not mediated through adipose tissue or the intestinal barrier.[147] Indole also uncouples OxPhos, inhibits the electron transport chain, and reduces ATP levels.[148] IPA, an indole derivative, protects against MAFLD by inducing tight junction protein expression, improving intestinal barrier function, and inhibiting NF-κB signaling.[149] IAA, another tryptophan metabolite, ameliorates liver lesions by reducing insulin resistance, lipid accumulation, oxidative stress, and inflammatory responses.[150] IAA also inhibits the expression of Fasn and SREBP-1c, thereby reducing the release of pro-inflammatory cytokines.[151] Circulating indole levels are lower in obese individuals, and IAA is reduced in the liver and cecum of mice fed a high fat diet.[146,151] Tryptophan dysfunction due to gut dysbiosis is an important component of MAFLD, and modulation of the tryptophan pathway is a promising MAFLD treatment strategy.

Zearalenone affects the liver through gut microbiota and metabolite interactions. It decreases gut microbial diversity and increases metabolites in the hepatic glycerophosphate pathway, leading to hepatic mitochondrial apoptosis and autophagy, exacerbating MAFLD.[152] Trimethyllysine metabolism by gut microbes produces trimethylamine valeric acid, which inhibits carnitine synthesis and promotes steatosis.[153] Wu[154] found that long-term glucocorticoid use decreases microbiota abundance and diversity, increases colonic inflammatory cell infiltration, decreases mucus secretion, and impairs hepatic mitochondrial function, leading to fat accumulation. Mitochondrial dysfunction is central to the pathogenesis of MAFLD, increasing ROS production, oxidative stress, inflammation, and liver fibrosis. Proinflammatory cytokines decrease hepatic insulin sensitivity and promote insulin resistance and steatosis.[91] Late hypertensive syndrome of pregnancy in a high-temperature environment disrupts the gut microbiota ecology, increases the abundance of Mycobacterium species, compromises intestinal integrity, and leads to hepatic mitochondrial dysfunction and metabolic disorders.[155]

From the above studies, it can be concluded that gut microbiota and their metabolites cause intestinal barrier dysfunction after damaging intestinal mitochondria, which allows these metabolites and the harmful substances they produce to easily cross the intestinal barrier and enter the liver through the hepatic-intestinal cycle, causing hepatic mitochondrial dysfunction and the release of pro-inflammatory factors and other factors that promote hepatocellular steatosis and accumulation of fat in the liver, causing MAFLD.

4. Improve mitochondrial function to modulate gut microbiota for MAFLD

Dysregulation of gut microbiota homeostasis has been implicated as a key factor in the pathogenesis and progression of MAFLD. Therapeutic strategies targeting the gut microbiota offer promising avenues for MAFLD patients.[119] Studies have shown that administration of the probiotic bacterium *Akkermansia muciniphila* significantly enhances mitochondrial oxidative metabolism and bile acid turnover in the gut-liver axis, mitigates oxidative stress-induced intestinal apoptosis, and reshapes the composition of the gut microbiota, thereby effectively alleviating MAFLD manifestations such as hepatic steatosis, inflammation, and liver injury.[156] Extensive evidence suggests that mitochondrial dysfunction compromises the intestinal barrier, facilitating the translocation of bacteria and their metabolites to the liver via the hepato-intestinal circulation, leading to hepatic mitochondrial dysfunction and an inflammatory cascade culminating in liver injury. Thus, maintaining the integrity of the intestinal barrier is critical for maintaining the homeostasis of the intestinal environment, and mitochondrial function in intestinal epithelial cells represents a potential therapeutic target for the prevention and intervention of liver disease.

4.1. Antibiotics act on the liver and gut by modulating mitochondrial function and intestinal microbiota

Antibiotics modulate mitochondrial function and intestinal microbiota in the liver and intestine, thereby exerting clinical efficacy in the treatment of intestinal diseases. However, their potential side effects should not be overlooked. Antibiotics have been associated with adverse effects on the intestinal epithelium, with implications for mitochondrial function.[157] used bioinformatics to show that antibiotics can lead to dysregulated expression of genes encoding mitochondrial ribosomal proteins and mitochondrial respiratory chain components in epithelial cells. This leads to a reduction in mitochondrial number and downregulation of immune gene expression, culminating in apoptosis of intestinal epithelial cells. Furthermore, they observed that depletion of the gut microbiota by antibiotics induces immunosuppression.

High-fat diets combined with antibiotic use synergistically increase the risk of pre-inflammatory bowel disease by impairing epithelial mitochondrial function, promoting the expansion of Enterobacteriaceae, and inducing microbial dysbiosis that amplifies mucosal inflammation.[158] Prolonged consumption of a high-salt diet and the use of penicillin have been shown to induce dysbiosis of the intestinal microflora and their metabolites, such as tryptophan and indole derivatives. This leads to increased intestinal permeability and hepatic lipid accumulation, which in turn causes mitochondrial damage characterized by hepatic mitochondrial swelling, mitochondrial membrane rupture, overproduction of mitochondrial reactive oxygen species (mtROS), and accelerated mitochondrial fragmentation, contributing to the development of MAFLD.[159]

Tetracycline, known to cause gut microbial dysbiosis and antibiotic resistance,[160] also induces hepatic lipid accumulation and decreased cell viability when exposed to excess palmitic acid.[161] elucidated the biochemical mechanism behind this steatosis, showing that tetracycline induces oxidative stress-sensitive proteins in hepatic mitochondria and inhibits key enzymes involved in fatty acid β-oxidation.

Isoniazid, an antibiotic used to prevent tuberculosis, has been reported to induce oxidative stress and apoptosis in hepatocytes through interactions with the mitochondrial electron transport chain, lipid peroxidation, decreased mitochondrial membrane potential, and cytochrome *c* release.[162] In addition, isoniazid has been associated with reduced intestinal microbial diversity, barrier damage, and colonic immune-related inflammation.[163]

With the widespread use of antibiotics leading to bacterial resistance and other side effects, alternative treatments have been explored. Alginate oligosaccharide (AOS), derived from brown algae, has attracted scientific interest due to its low molecular weight, high water solubility, and safe, non-toxic profile. Research suggests that AOS supplementation can improve intestinal morphology and barrier function in weaned piglets and reduce enterocyte apoptosis by inhibiting mitochondria-dependent cell death.[164] Fecal microbiota transplantation (FMT) is emerging as an alternative to antibiotics to restore the gut microbiota.[165] found that FMT in AOS-supplemented mice regulated the gut microbiota by increasing beneficial bacteria and decreasing harmful bacteria. FMT also improved small intestinal function by restoring cellular adhesion molecules, increasing the expression of genes related to digestion and absorption, and increasing connexin protein levels, thereby ameliorating small intestinal mucositis. Autologous fecal microbiota transplantation (autoFMT), in which a person's feces is stored in a healthy state for future use in restoring the gut microbiota after perturbations, is a novel therapeutic approach to combat antibiotic resistance.[166] showed that after exposure to amoxicillin-clavulanic acid (Amox-Clav), autoFMT treatment restored microbial species composition, metabolic capacity, and resistance genes to their pre-treatment state, highlighting the safety and tolerability of autoFMT.

Although many alternative therapies to antibiotics have been proposed, they are not enough. TCM monomers and nutritional therapies undoubtedly have great potential that needs to be further explored.

4.2. Chinese medicine and food that target the liver and the intestine by modulating the function of the mitochondria and the intestinal microbiota

Many studies have found that traditional medicines may be effective in treating MAFLD by affecting the gut microbiota through the mitochondria (Table 2). Zhao et al. conducted in vivo and in vitro studies demonstrating that the triterpenic acid enriched fraction (CPT) from *Cyclocarya paliurus* (CP) ameliorates high-fat diet-induced MAFLD. CPT was found to enhance antioxidant defenses by activating and translocating Nrf2 to the nucleus, thereby preventing high-fat diet-induced inhibition of hepatic mitochondrial respiratory chain complexes I and IV and accumulation of peroxides associated with mitochondrial dysfunction.[167] Furthermore, CP-derived polysaccharides have been shown to reduce hepatic inflammation in mice by modulating gut microbiota composition and downregulating TLR4 and MAPK pathways.[168] Research indicates that *Gynostemma pentaphyllum* (GP) preserves intestinal integrity and reverses dysbiosis in high-fat diet-induced MAFLD

Table 2
Natural products on the liver and intestine through modulation of mitochondrial function and intestinal microbiota.

Name	Target	Function	References
Cyclocarya paliurus	Liver mitochondria	Nrf2 ↑ Mitochondrial respiratory chain complex I, IV ↑ Peroxides ↓	167
Gynostemma pentaphyllum	Liver mitochondria	PPAR-α ↑ Lipid accumulation ↓ Oxidative stress ↓ Mitochondrial swelling ↓ CL high-saturation conversion ↑	170,171
Spirulina	Liver mitochondria	PGC-1α/Tfam/mtDNA ↑ SREBP-1c ↓ Inflammation response ↓	172
Emodin	Liver mitochondria	Regulates intestinal flora ↑ LKB1-AMPK ↑ Hippo-YAP1 ↑ Mitochondrial membrane potential ↑ Oxidative stress ↓ AMPK, ACC, CPT1 ↑ SREBP1c and FASN ↓	173,174
Picroside II	Liver mitochondria	Oxidative stress ↓ Mitochondrial structural damage ↓ Mitochondrial ATPase ↑	175
Kuijieyuan Decoction	Liver mitochondria	Inflammation response ↓ ROS ↓ Oxidative stress ↓	176
Curcumin	Liver mitochondria	Intestinal barrier damage ↓ ROS ↓ Oxidative stress ↓	177,178
Quercetin	Liver mitochondria	TLR-4-NF-κB pathway ↑ Free fatty acid ↓ CYP2E1-dependent ↓ Endoplasmic reticulum stress ↓	179
Chlorogenic acid	Liver mitochondria	Toll-like receptor 4 ↓ Inflammation response ↓	180
Cyclocarya paliurus	Gut microbiota	Composition and abundance of the gut microbiota ↑ TLR4 ↓ MAPK pathways ↓	168
Gynostemma pentaphyllum	Gut microbiota	Dysbiosis of intestinal ecology ↓	169
Chicory	Gut microbiota	AMPK-mediated Nrf/Keap1 ↑ NF-κB ↓ Oxidative stress ↓ Inflammation response ↓	181
Spirulina	Gut microbiota	Abundance of anamorphic bacteria ↓ Firmicutes/Bacteroidetes ↓ TLR4/MyD 88/NF-κB ↓ Inflammation response ↓ Intestinal permeability ↓	182
Emodin	Gut microbiota	Beneficial gut microbiota ↑ Harmful bacteria ↓ Barrier damage ↓	183
Chlorogenic acid	Gut microbiota	Composition and abundance of the gut microbiota ↑ Inflammation response ↓ Tight junction proteins ↑	184
Glucoraphanin	Gut microbiota	Nrf2 ↑ NF-κB ↓ Composition and abundance of the gut microbiota ↑	185
Resveratrol	Gut mitochondria	Oxidative stress ↓ Intestinal barrier damage ↓ ROS ↓ Mitochondrial membrane potential ↑ Mitochondrial ultrastructural damage ↓ PINK1 and Parkin ↑ SIRT1 ↑	186,187
Curcumin	Gut mitochondria	Parkin-dependent AMPK-TFEB ↑ Intestinal barrier damage ↓	177,178
Picroside II	Gut microbiota and mitochondria	TLR-dependent PI3K/AKT/NF-κB ↓ Oxidative stress ↓ Inflammation response ↓ Intestinal barrier damage ↓	188
Kuijieyuan Decoction	Gut microbiota and mitochondria	TLR4-dependent PI3K/AKT/NF-κB ↓ Intestinal barrier damage ↓ Intestinal ecological dysregulation ↓ Inflammation response ↓ Serum SCFAs concentration ↑ Oxidative stress ↓	189,190

rats.[169] Gypenosides from GP were shown to ameliorate hepatic steatosis by upregulating PPAR-α expression, reducing hepatic lipid accumulation, and alleviating oxidative stress and mitochondrial structural disturbances.[170] Müller et al. found that GP extract increased the stability of the mitochondrial phospholipid cardiolipin (CL) by promoting the conversion of CL fatty acid residues to more saturated forms, thereby protecting primary hepatocytes from free fatty acid-induced damage.[171]

Chicory, a medicinal and edible plant, contains chicoric acid (CA), which has hypoglycemic, digestive, and hepatoprotective effects. Investigations into the regulatory effects of CA on gut flora and MAFLD have shown that it inhibits oxidative stress and inflammatory responses associated with NAFLD by activating the AMPK-mediated Nrf/Keap1 pathway and downregulating the NF-κB pathway, thereby enhancing gut microbial diversity and liver health.[181] *Spirulina*, an ancient prokaryotic organism processed as a functional food or herbal remedy, is widely used in the management of type 2 diabetes mellitus (T2DM) due to its lipid-lowering, anti-inflammatory, and antioxidant properties. It has been shown to reduce hepatic SREBP-1c expression by activating the mitochondrial PGC-1α/Tfam/mtDNA pathway and to exert anti-inflammatory effects that improve lipid metabolism in T2DM.[172] *Spirulina* also significantly reduces the prevalence of Proteobacteria and the ratio of Firmicutes/Bacteroidetes in rats with high-fat diet-induced intestinal dysbiosis, inhibits inflammatory responses and the elevation of pro-inflammatory cytokines by blocking the TLR4/MyD88/NF-κB pathway, and reduces intestinal permeability to alleviate inflammation.[182]

Emodin, an herbal compound with diverse pharmacological properties including antibacterial, anti-inflammatory and anticancer activities, has been extensively studied. It protects mice from *E. coli* O1-induced intestinal barrier damage by enriching beneficial gut microbiota and suppressing harmful bacteria.[183] Alisif reports that rhubarb-derived emodin inhibits inflammation, lipid accumulation, and oxidative stress in rats with hepatic steatosis.[191] Lee et al. elucidated the antioxidant mechanism of emodin, suggesting that it restores mitochondrial membrane potential and alleviates hepatic oxidative stress by modulating the LKB1-AMPK and Hippo-YAP1 pathways.[173] Tzeng et al. added that emodin reduces adipogenesis and promotes mitochondrial fatty acid β-oxidation by upregulating AMPK, ACC, and CPT1 activities and downregulating SREBP1c and FASN protein expression.[174] However, Cui et al. found that excessive emodin can disrupt mitochondrial membrane potential and induce ROS production in grass carp hepatocytes, leading to oxidative imbalance, hepatocyte toxicity, and apoptosis.[192] Zhang's

proteomic analysis revealed that long-term emodin exposure can directly affect hepatocyte acadvl/complex IV, inhibit fatty acid β-oxidation, TCA cycle, oxidative phosphorylation, and cause mitochondrial dysfunction, resulting in hepatic oxidative stress.[193]

Resveratrol, a plant-derived antitoxin, was shown by Hong et al. to alleviate deoxynivalenol-induced intestinal oxidative stress and barrier damage in piglets when added to their diets, and to improve mitochondrial function by reducing ROS levels and increasing mitochondrial membrane potential.[194] Hao et al. and Yin et al. reported similar effects of resveratrol on diquat-induced oxidative stress in piglets.[195,196] Cao et al. found that resveratrol attenuated diquat-induced ultrastructural mitochondrial damage, improved mitochondrial membrane potential, mitochondrial DNA content, and mitochondrial complex I-IV activity, reduced ROS-induced oxidative stress, and induced PINK1- and Parkin-mediated mitophagy.[186] Chen et al. explored the specific mechanism of resveratrol in targeting epithelial mitochondria to alleviate oxidative stress-induced intestinal injury and demonstrated that resveratrol and its derivative pterostilbene alleviate mitochondrial oxidative stress through the SIRT1 signaling pathway, promote mitochondrial biogenesis and the activity of mitochondrial complexes I-IV, and protect mitochondrial membrane potential to reduce intestinal epithelial cell apoptosis.[187]

Pilose antler peptide, a major active component of deer antler in TCM, has been used to treat inflammation and ischemia/hypoxia-induced brain injury.[197,198] Ni et al. demonstrated for the first time that in addition to brain damage, ischemia/hypoxia-induced injury also causes peripheral tissue dysfunction, including liver inflammation and lipid accumulation, changes in gut microbiota composition and diversity, and mitochondrial dysfunction, which can be reversed by pilose antler peptide.[199] Piao et al. investigated the protective effects of Picroside II in a model of acute pancreatitis-induced intestinal barrier injury and found that it ameliorated intestinal barrier injury by inhibiting TLR-dependent PI3K/AKT/NF-κB signaling, reducing oxidative stress and inflammation, and improving the intestinal microbiota ratio, while preventing the expansion and disorganization of intestinal mitochondrial size and structure.[188] Another study found that Picroside II significantly attenuated hepatocellular injury induced by CCl4, D-GalN, and APAP, scavenged free radicals, protected normal mitochondrial membrane structure, and increased mitochondrial ATPase activity, thereby regulating hepatic energy metabolism.[175]

Kuijieyuan decoction (KD), a TCM formula, is clinically used for the treatment of ulcerative colitis. Liu et al. investigated the protective mechanism of KD against ulcerative colitis, with HPLC analysis identifying paeoniflorin and baicalin as the main active components.[189] Interestingly, KD improves gut microbiota by blocking TLR4-dependent PI3K/AKT/NF-κB oxidative and inflammatory pathways, increasing beneficial bacteria and decreasing harmful bacteria.[188] Baicalin was found to correct intestinal ecological dysregulation and increase permeability by reducing the Th17/Treg cell ratio, attenuating intestinal inflammation, and increasing serum SCFA concentration. In addition, baicalin was found to possess ROS-scavenging properties and antioxidant capacity.[190] Baicalin has also been reported to treat MAFLD through antioxidant effects, neutralizing ROS, reducing oxidative stress damage to hepatocytes, and protecting mitochondrial structure and function, thereby attenuating FFA-induced MAFLD apoptosis.[176]

Curcumin, derived from the rhizome of turmeric, has a broad spectrum of anti-inflammatory, antioxidant, and antimicrobial properties.[200] Cao et al. elucidated the molecular mechanism by which curcumin protects small intestinal epithelial cells from oxidative stress by promoting Parkin-dependent mitophagy through the AMPK-TFEB pathway, which attenuates oxidative stress-induced intestinal barrier damage and mitochondrial injury.[177] Zhang et al. demonstrated that curcumin scavenges ROS overproduction, ameliorates mitochondrial dysfunction and apoptosis by enhancing the antioxidant defense system and inhibiting oxidative stress-mediated gene expression, and exerts a protective effect against D-GalN/LPS-induced acute liver injury in mice. The study suggested that the therapeutic effect of curcumin on liver injury may involve antioxidant effects through regulation of the Sirt1 pathway or Sirt1-regulated autophagy; however, further research is needed to elucidate the molecular mechanisms of curcumin therapy.[178]

Polyphenol-rich foods offer numerous benefits to humans and animals, with antioxidant activity potentially serving as a key mechanism in the prevention of MAFLD. Carrasco-Pozo et al. demonstrated that apple peel polyphenol extract protected the gastrointestinal tract from oxidative, inflammatory, morphological, and barrier alterations induced by indomethacin.[201] Yeganeh et al. highlighted the preventive and therapeutic effects of dried apple peel powder on dextran sodium sulfate-induced colitis, noting that it partially reversed mitochondrial abnormalities related to size, density, redox homeostasis, fatty acid β-oxidation, ATP synthesis, apoptosis, and regulatory mitochondrial transcription factors.[202] Elkahoui et al. found a strong correlation between the expression of the liver enzyme Cyp51 and dietary polyphenol content in mouse feces, suggesting that polyphenols may regulate cholesterol metabolism. Their analysis of fecal polyphenols and bacterial taxa revealed a relationship between fecal microbiota composition and dietary polyphenol metabolism.[203] In addition, Li's team reported that apple polyphenol extract ameliorated high-fat diet-induced MAFLD through mechanisms involving inhibition of bile acid synthesis and modulation of microbiota diversity.[204]

Quercetin, a potent antioxidant abundant in fruits and vegetables, is a dietary polyphenol found in a variety of plants, particularly peppers, onions, cauliflower, and grapes. It is metabolized by intestinal microorganisms to 3,4-dihydroxyphenylacetic acid (3,4-HPAA), which has been shown to prevent heme chloride-induced mitochondrial dysfunction in the colonic epithelium.[205] Quercetin has demonstrated significant ameliorative effects on MAFLD by restoring intestinal dysbiosis through activation of the TLR-4-NF-κB pathway, blocking FFA- and CYP2E1-dependent lipotoxicity, and counteracting inflammatory vesicle-initiated responses and induction of endoplasmic reticulum stress pathways.[179]

Plant-based foods such as coffee, honeysuckle, tulsi, and cabbage are particularly rich sources of chlorogenic acid. This compound acts as a mitochondria-targeted antioxidant, protecting the intestinal tract from oxidative stress by strengthening the antioxidant defence system and alleviating H_2O_2-induced mitochondrial damage and dysfunction, particularly the reduction in respiratory complex activity. Regular consumption of foods rich in chlorogenic acid may thus contribute to the prevention of intestinal disorders.[206] In addition, chlorogenic acid neutralises mtROS-induced damage in hepatocytes through its antioxidant properties and alleviates liver inflammation by suppressing the overexpression of toll-like receptor 4.[180] A previous study showed that chlorogenic acid can inhibit metabolic endotoxemia and protect the intestinal barrier in mice on a high-fat diet by modulating the composition and abundance of the gut microbiota. The compound's protective effects against obesity and metabolic syndrome are attributed to its ability to modulate changes in the structure, diversity and relative abundance of the gut microbiota at different taxonomic levels. It also suppresses systemic low-grade inflammation by upregulating the expression of tight junction proteins in the intestinal epithelium and preventing the translocation of LPS from the intestinal lumen into the bloodstream.[184]

In addition, various diets and dietary extracts influence liver health and metabolic diseases by modulating the gut microbiota. Blackberry leaves and fruits, rich in flavonoids and anthocyanins, have been shown to protect MAFLD rats from hepatic lipid deposition, inflammation, and oxidative stress-induced damage while maintaining intestinal integrity and promoting intestinal *_Lactobacillus_* and *_Akkermansia_* proliferation.[207] Broccoli seed extract (BSE), rich in glucoraphanin (GRP), is converted by intestinal microorganisms to sulforaphane (SFN), which has potent anti-inflammatory and antioxidant properties. The high GRP content in BSE, which is converted to SFN by gut microbes, ameliorated LPS-induced acute liver injury by activating Nrf2 and inhibiting the NF-κB pathway. BSE supplementation also altered the composition of the

gut microbiota.[185] L-arabinose, a plant polysaccharide derived from vegetable gums, corn stover, or sugar beets, induces hydrogen release by regulating the balance between hydrogen-producing and hydrogen-consuming intestinal microorganisms, modulates hepatic lipid metabolism genes and mitochondrial function associated with respiratory complexes, and ultimately alleviates high-fat diet-induced metabolic syndrome.[208] Dietary supplementation with human milk (HM) or donkey milk (DM) reduces inflammatory markers, which is associated with improved lipid and glucose metabolism. Modulation of the Nrf2-FGF21 pathway, bacterial nutrient metabolism in the gut, and release of bioactive compounds (SCFAs) promote competitive interactions with host cell targets to control energy metabolism and inflammatory states. The Nrf2 pathway is induced by DM and HM, resulting in decreased FGF21 expression. DM and HM also affect the composition of the gut microbiota and increase SCFA levels, which in turn regulate Nrf2.[209]

In TCM, there is the concept of "homology of medicine and food", which means that many foods are medicines and there is no absolute boundary between them. This concept reflects the close relationship between nutrition and health, food and medicine, and has far-reaching implications and positive significance for the modern health industry and people's healthy lifestyles. Summarizing the above studies, we found that TCM monomers extracted from Chinese medicines have unique advantages in protecting liver and intestinal mitochondria and intestinal barrier function, which mainly protect liver and intestinal cells by reducing oxidative stress and inflammatory response. Chinese medicines are effective in the treatment of MAFLD with few side effects, while many TCM monomers play an important role in the treatment of MAFLD. This provides a very good idea for us to study the targeted drugs for the treatment of MAFLD.

4.3. Prebiotics and probiotics regulate liver and gut health by regulating mitochondrial function and gut microbiota

Probiotics provide beneficial microbial strains that regulate the distribution of intestinal microbiota, thereby restoring mitochondrial function in intestinal epithelial cells and improving the intestinal lumen environment. They may serve as endogenous modulators and represent a novel approach for the prevention and treatment of metabolically associated fatty liver disease (MAFLD). In the context of intestinal mitochondrial damage, impaired mitochondrial phagocytosis and intestinal inflammation caused by *Salmonella* infection in newly weaned piglets, pre-treatment with the oral probiotic **Lactobacillus johnsonii** L531 was shown to alleviate intestinal inflammation by inhibiting the activation of NLRC4 and NLRP3 inflammasomes as well as the NF-κB signaling pathway. This intervention mitigates mitochondrial damage and accelerates the degradation of damaged mitochondria via autophagy.[210] Trevisi et al. evaluated the effects of **Saccharomyces cerevisiae** CNCM I-4407 (Sc) on the transcriptomic profile of the jejunal mucosa 24 h after infection with **E. coli* F4 in weaned piglets. Their results showed that the addition of this yeast strain to the diet downregulated genes associated with jejunal mucosal damage, significantly enriched genes involved in mitosis and mitochondrial development, and mitigated the deleterious effects of enterotoxigenic **E. coli* (ETEC) on the intestinal health of piglets.[211] During HIV-1 infection, dysregulation of gut microbial ecology, mitochondrial damage, and impairment of the intestinal epithelial barrier, coupled with a substantial decrease in $CD4^+$ T cells and Th17 cells in the gastrointestinal tract, predispose individuals to bacterial translocation into the circulation, triggering systemic inflammation.[212,213] Ren et al. demonstrated that blueberry juice and probiotics (BP) significantly reversed MAFLD-induced hepatic mitochondrial damage, mitochondrial swelling, and hepatic necrosis, possibly by modulating SIRT1 expression, which protects against mitochondrial dysfunction in MAFLD rats.[214] Furthermore, Xin et al. reported that **Lactobacillus johnsonii* BS15 alleviated mitochondrial abnormalities in MAFLD mice, characterized by decreased uncoupling protein-2 levels and increased cytochrome *c* levels. This strain also decreased serum LPS levels, downregulated hepatic TNFα mRNA levels, and reduced serum C-reactive protein levels by improving intestinal barrier function and modulating gut microbiota, suggesting its efficacy in preventing high-fat diet-induced MAFLD.[215]

A study by Lensu et al. found that **Faecalibacterium prausnitzii* prevented MAFLD in mice, and a specific prebiotic dietary supplement, xylo-oligosaccharides (XOS), ameliorated MAFLD by improving hepatic oxidative metabolism and mitochondrial function, which may be related to gut microbiota.[216] Zhang et al. observed that changes in gut microbiota structure, mitochondrial dysfunction, and hepatic steatosis occurred in mice after two months on a high-fat diet. Dietary supplementation with resistant dextrin restored gut microbiota structure, improved microbial metabolism (including tryptophan and bile acid metabolism), reduced gut permeability and inflammatory cytokine levels, maintained a healthy gut microenvironment, improved mitochondrial function, and alleviated hepatic steatosis.[217] Tsuji suggested that prebiotics targeting mitochondrial autophagy through modulation of PI3K/AKT/mTOR or PINK1/Parkin pathways to eliminate damaged mitochondria may be a promising strategy for the treatment of MAFLD. In addition, the efficacy of prebiotics in the treatment of MAFLD has been suggested to involve modulation of the PI3K/AKT/mTOR/AMPK pathway.[218]

Prebiotics and probiotics are effective in the treatment and prevention of MAFLD, but they need to be taken over a long period of time and can be used as an adjunct to prevent MAFLD.

4.4. Others

Other pharmacological agents also modulate mitochondrial function and intestinal flora in the liver and intestine. Mitochondria-targeted ubiquinone (MitoQ) has been shown to attenuate acute intestinal injury by inhibiting mtROS production and the subsequent inflammatory cascade in a dextran sodium sulfate-induced acute colitis model.[219] In addition, MitoQ has been reported to protect against liver injury by targeting liver mitochondria and ameliorating hepatic steatosis and oxidative damage.[220,221] MitoQ does not ameliorate ethanol-induced damage to hepatic mitochondrial respiration or enzyme activity, but instead protects the liver from ethanol damage by inhibiting ROS/RNS production and HIF1α activation.[220] And MitoQ does not alter respiration in isolated liver mitochondria, but does reduce hepatic hydroperoxide levels.[221] Overall, MitoQ is a promising targeted mitochondrial therapeutic for liver and intestinal diseases. Val-Val-Tyr-Pro (VVYP), a compound derived from the digestion of health food pellets, has been conclusively shown to be therapeutic for non-alcoholic steatohepatitis (NASH), which is demonstrated to regulate microbial imbalances by increasing beneficial bacteria and decreasing *Lactobacillus* counts, upregulating the expression of genes related to intestinal tight junction proteins, inhibiting methionine-choline-deficient-induced hepatic lipid accumulation and inflammation, and reversing mitochondrial dysfunction characterized by vacuolization, swelling, and fragmentation, thereby exerting a significant protective effect against NASH.[222] Supplementation of broiler diets with niacinamide and sodium butyrate under high-density conditions has been shown to increase antioxidant capacity by improving mitochondrial function associated with ATPase activity. In addition, the increased abundance of beneficial bacteria such as *Lactobacillus* and *Bifidobacterium* may improve growth performance and potentially mitigate lipid accumulation in broilers.[223]

5. Conclusion

The gut microbiota has emerged as a promising therapeutic avenue for a variety of diseases. Mitochondria, indispensable organelles in eukaryotic cells, serve as the primary generators of cellular energy. Recent research has highlighted the prevalence of mitochondrial dysfunction in the liver and gastrointestinal tract, with hepatic

respiratory chain disorders often correlating with gut health.[125] Intestinal microbiota, including *E. coli*, *Citrobacter rodentium* and other Gram-negative bacteria, produce metabolites that can induce mitochondrial dysfunction in intestinal epithelial cells. This dysfunction manifests as disruptions in the mitochondrial network, alterations in mitochondrial membrane potential, structural changes, and impaired energy metabolism, culminating in cell death. Such mitochondrial impairments can lead to compromised intestinal epithelial barrier function, increasing permeability and facilitating the translocation of microbes and their metabolites into the mesenteric portal circulation. This interaction with the liver via the hepato-intestinal axis may induce hepatic mitochondrial dysfunction. As a result, this hepatic mitochondrial dysfunction triggers an inflammatory response that further disrupts hepatic metabolism and promotes the accumulation of metabolites such as triglycerides, potentially leading to MAFLD.

The gut microbiota is a complex and diverse ecosystem that includes both beneficial and harmful bacteria that produce a spectrum of metabolites with varying effects on health. Metabolites from beneficial bacteria can help maintain gut health, enhance the immune system, and improve nutrient absorption. Conversely, metabolites from harmful bacteria can compromise the gut barrier, induce inflammatory responses, and disrupt physiological homeostasis. Thus, maintaining a balanced gut microbiota is critical for overall health. Strategies to promote the dominance of beneficial bacteria and enhance the production of health-promoting metabolites have become central to the prevention and treatment of disease and the maintenance of human health. Current research indicates that the gut microbiota can be modulated by prebiotics, probiotics, and dietary interventions, with TCMs and their extracts showing particular promise in regulating the gut microbiota and promoting the production of beneficial metabolites. Increasingly, studies are reporting that herbal compounds such as ginsenoside, resveratrol, and curcumin can protect or restore mitochondrial function through their influence on the gut microbiota. These compounds may directly or indirectly modulate the intestinal microbiota, thereby protecting the integrity of intestinal mitochondrial function and maintaining a healthy intestinal barrier. They also exert effects on hepatic mitochondria via the hepatointestinal circulation, improving mitochondrial redox balance and attenuating inflammatory responses.

The gut microbiota is increasingly recognized for its therapeutic potential in several diseases, with a strong link between gut health and mitochondrial function. Studies have shown that certain gut bacteria can induce mitochondrial dysfunction in epithelial cells, leading to increased intestinal permeability and liver inflammation, which may contribute to MAFLD. The balance of the gut microbiota is critical for overall health, with beneficial bacteria promoting gut and immune health, while harmful bacteria can trigger inflammation and physiological dysfunction.

With the obvious side effects of antibiotics, the serious damage to the human body from prolonged use, the emergence of drug resistance, and the severe impact on the composition and abundance of the gut microbiota, there has been an urgent need to find new ways to replace the use of antibiotics. Interventions such as prebiotics, probiotics, and TCMs have been explored to modulate the gut microbiota and support mitochondrial health. Herbal compounds such as gypenoside, resveratrol, and curcumin have been shown to have protective effects on mitochondrial function through their influence on the gut microbiota. These new approaches have few side effects, readily available raw materials, and promising applications for effective treatment of disease. Despite their potential, these natural interventions face many challenges in their implementation: experiments at this stage have small sample sizes and short observation periods due to objective constraints, leading to weak generalization of conclusions; their application in the clinic is also challenging because individual differences make it difficult to adapt them to the precise use of drugs. There is a need for an effective screening system to identify their commonalities in preparation for large-scale development, and for further studies to elucidate the mechanisms of action of the gut microbiota and mitochondria leading to MAFLD.

CRediT authorship contribution statement

Binzhi Zhang: Writing – original draft, Data curation, Conceptualization. **Xia Luo:** Writing – original draft, Data curation, Conceptualization. **Song Lei:** Writing – original draft, Data curation, Conceptualization. **Wenbo Gao:** Writing – original draft, Data curation, Conceptualization. **Zhipeng Chen:** Writing – original draft, Data curation, Conceptualization. **Qing Zhu:** Supervision. **Lizheng Huang:** Writing – review & editing, Supervision, Project administration, Funding acquisition, Conceptualization. **Qinqiang Long:** Writing – review & editing, Supervision, Project administration, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors have no conflicts of interest to declare.

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