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Review

Prebiotic and Probiotic Foods in MASLD: Microbiome-Mediated Therapeutic Strategies

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ABSTRACT: Through the use of prebiotics and probiotics, fermented foods offer significant health benefits by enhancing host nutrition and microbiota composition while providing distinctive flavor profiles. Fermentation substantially alters the bioactive compounds in these foods compared to their natural state. Additionally, fermented foods contain probiotics that can modulate consumers' gut microbiomes, which in turn regulate host biochemistry to help combat various metabolic diseases. Metabolic dysfunction-associated steatotic liver disease (MASLD) represents a growing global health burden. Gut microbiome dysbiosis, combined with unbalanced nutritional intake, is considered a primary driver of disease pathogenesis. Fermented foods can modify the bioavailability of micronutrients—including carbohydrates, polyphenols, and vitamins—thereby influencing host metabolism. Moreover, the probiotics present in fermented foods, along with their modulatory effects on the gut microbiota, contribute to both the management and prevention of MASLD. Modern fermentation approaches, leveraging synthetic biology, systems biology, and metabolic engineering, can further maximize these health benefits. This review summarizes the components, bioactive compounds, and mechanistic pathways by which fermented foods influence the pathogenesis of MASLD, and highlights the potential applications of modern fermentation technologies to enhance their health-promoting properties.

Keywords: Prebiotics; Probiotics; Metabolic disease; MASLD; Nutrients; Modern fermentation technology; Systems biology

1. Introduction

Fermented foods have historically played a central role in culinary traditions worldwide. Initially developed as a method for long-term food preservation, these foods have undergone continuous refinement, acquiring distinctive flavors and textures through microbial fermentation processes [1]. Such characteristics have contributed to their widespread popularity and recognition across diverse cultural contexts. Based on their primary raw materials, fermented foods can be broadly classified into fermented dairy products, vegetables, grains, legumes, and beverages.

Studies on the spontaneous fermentation of foods using naturally occurring microbial consortiums from the food source, including probiotics and bioactive compounds they contain, combined with a deeper understanding of their role in regulating the gut microbiome, have led to advancements in certain fermented foods as functional foods with tangible health benefits [2]. Advances in synthetic biology have pushed the field of functional foods via engineering and modification of fermentation strains, such as lactic acid bacteria (LAB), *Bacillus*, and other probiotics, alongside improvements in fermentation processes, further enhancing the functional properties of these foods, thereby reinforcing their role in promoting health and supporting dietary interventions [3].

Naturally occurring microbes found on the surface of raw products often help in the spontaneous fermentation of these functional foods, imbuing these foods with health-benefiting properties. The main players that provide these health-benefiting properties are probiotics and prebiotics. Microbes are considered probiotics owing to the health-

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benefiting properties they confer to consumers by regulating intestinal flora, enhancing intestinal barrier function, and modulating immune responses [4]. Additionally, probiotics must survive the harsh environment of the gastrointestinal tract and do not naturally assimilate into the host microbiota [4]. Prebiotics, in contrast, are dietary compounds that resist digestion by the human host, typically in the form of indigestible fibers, which serve as substrates for probiotics in the gut, promoting their growth and activity and leading to the production of beneficial bioactive compounds [4]. The synergistic effect of probiotics and prebiotics, referred to as symbiotic, fosters a favorable intestinal environment increasingly recognized as crucial for metabolic health [4]. The emergence of engineered probiotics aims to deliver targeted health benefits beyond those provided by natural strains, offering new therapeutic functions and opening avenues for dietary and medical interventions.

Studies have linked the gut microbiome to the pathogenesis of various metabolic disorders, including metabolic dysfunction-associated steatotic liver disease (MASLD) and its progression to metabolic dysfunction-associated steatohepatitis (MASH) [5]. Numerous studies have linked MASLD incidences to changes in dietary patterns within communities, especially in East Asian communities adapting Western dietary habits [6]. Dietary intervention remains the cornerstone for managing MASLD progression, even with FDA-approved medications available [7,8]. Strategies such as modulating the intestinal environment and metabolism via probiotics, limiting carbohydrate intake, and increasing consumption of bioactive substances, including short-chain fatty acids (SCFAs) and polyphenols, are considered effective in mitigating MASLD risk [9]. Engineered probiotics and next-generation fermented foods may further strengthen the efficacy of dietary interventions.

This review provides a comprehensive overview of the impact of fermented foods on MASLD, emphasizing the health benefits conferred by probiotics and bioactive compounds. It discusses the nutritional composition, bioactive constituents, and the mechanisms through which probiotics influence liver metabolic processes and the intestinal microenvironment. Drawing upon this body of evidence, the review highlights current dietary strategies as practical approaches to improving liver health and metabolic outcomes, while offering a forward-looking perspective on the role of engineered probiotics and next-generation fermented foods in MASLD dietary management.

2. The Role of Fermented Foods in Preventing MASLD Pathogenesis

Currently, dietary habits, gut microbiome imbalance, and leaky gut are considered the predominant causes of MASLD, where MASLD patients manage the disease via lifestyle changes and dietary interventions [5,9]. Dietary habits that contribute to MASLD progression include overconsumption of calories, saturated fats, sodium, added sugars, and alcohol [5].

Historically, the dietary cultures are shaped by the available crops that grow readily in the region. The nutritional content of different foods varies, giving rise to different results in fermented foods and their attributed health-benefiting properties. Furthermore, the fermentation process itself can significantly alter the nutritional composition of fermented foods compared to the raw materials. For example, sauerkraut has a lower protein content than fermented soy products [10,11]. These fermentative bacteria use nutrients in the food to produce metabolites that improve the nutritional value or flavor profile of the food [2]. For instance, LAB fermentation of milk consumes basic sugars to produce lactic acid, calcium with better bioavailability, conjugated linoleic acids, and fat-soluble vitamins that are useful to the host body [12].

The fermentation of foods may play a pivotal role in reducing the risk of developing MASLD by altering the nutritional values of foods and providing consumers with better access to health-benefiting metabolites (Figure 1).

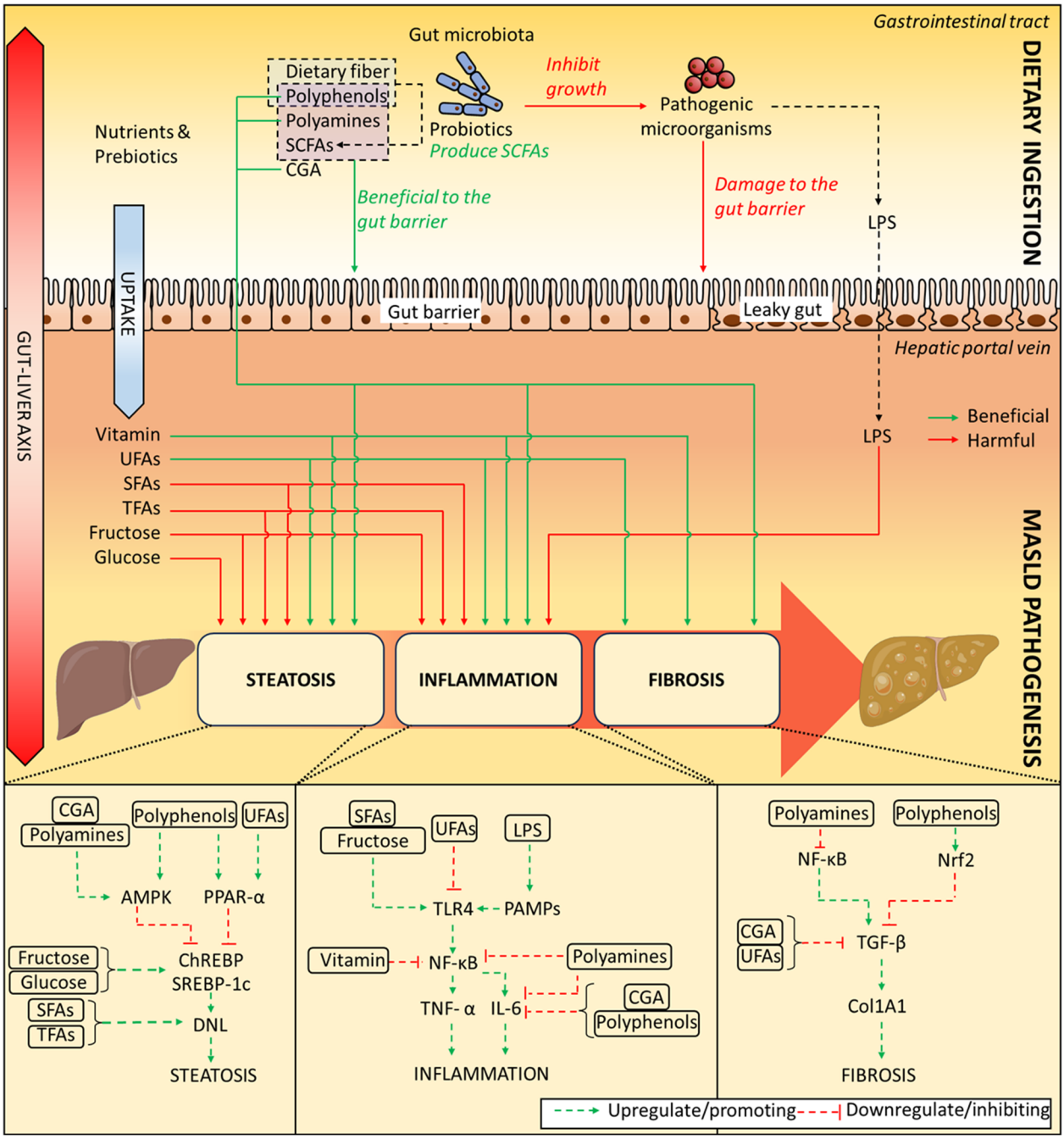

Figure 1. Regulatory role of fermented foods in the management of MASLD. Dietary intervention with fermented foods exerts regulatory effects on metabolic-associated steatotic liver disease (MASLD). Rich in prebiotics and probiotics, fermented foods modulate the complex metabolic networks underlying hepatic steatosis, inflammation, and fibrosis, thereby contributing to both the prevention and management of MASLD. AMPK, AMP-activated protein kinase; CGA, chlorogenic acid; ChREBP, carbohydrate response element-binding protein; Col1A1, collagen type I alpha 1 chain; DNL, *de novo* lipogenesis; IL-6, Interleukin-6; LPS, lipopolysaccharide; MASLD, Metabolic dysfunction-associated steatotic liver disease; NF-κB, nuclear factor-kappaB; Nrf2, nuclear factor erythroid 2-related factor 2; PAMPs, pathogen-associated molecular patterns; PPAR-α, peroxisome proliferator-activated receptor α; SFAs, saturated fatty acids; SCFAs, short-chain fatty acids; SREBP-1c, Sterol regulatory element-binding protein-1c; TFA, trans fatty acids; TGF-β, Transforming growth factor-β; TLR4, toll-like receptor 4; UFAs, unsaturated fatty acids.

2.1. Causes of MASLD: Disorders of Fat Metabolism and Inflammatory Pathways

MASLD is a metabolic disease caused by multiple cumulative disorders of liver lipid metabolism, liver inflammatory pathways, and complex crosstalk between multiple related pathways [13]. The liver is an important organ for lipid metabolism, where approximately 25% of the systemic fatty acids are sequestered in the liver [14]. *De novo* lipogenesis (DNL), which also takes place in adipose and hepatic tissues, is an important biological process that produces endogenous triglycerides (TG) from dietary substrates, where unregulated processes can lead to excessive fatty acid metabolic pressure [15]. Upon breaching the upper threshold of fat metabolic pressure, lipotoxicity occurs,

resulting in a series of downstream reactions such as endoplasmic reticulum stress, mitochondrial dysfunction, and oxidative stress, leading to cell apoptosis, inflammatory response, and exacerbated liver cell damage. Reactive oxygen species (ROS) and lipotoxicity can also activate the c-Jun N-terminal kinase (JNK) pathway, increase the level of inflammatory factors, and induce insulin resistance, further aggravating fat accumulation.

Perturbations in the gut-liver axis and impaired intestinal barrier function (*i.e.*, leaky gut) can allow bacteria and their metabolites, such as lipopolysaccharide (LPS), to enter the hepatic portal vein, activating pathogen-associated molecular patterns (PAMPs) and releasing inflammatory mediators through the toll-like receptor 4 (TLR4) myeloid differentiation factor 88 (MYD88) nuclear factor-kappaB (NF-κB) pathway [14,16]. PAMPs and damage-associated molecular patterns (DAMPs) can also activate the NOD-like receptor family pyrin domain containing 3 (NLRP3) inflammasome pathway, which in turn enhances IL-1β and IL-18 levels through caspase-1, amplifying the immune response [17]. Overall, the inflammation in MASLD is the result of a multifactorial and multi-pathway interaction, including lipotoxicity-induced oxidative stress, gut-derived inflammatory stimulation, stress kinase activation, and the involvement of the NLRP3 inflammasome [18].

Notably, interventions with probiotics and prebiotics have been shown to ameliorate these deleterious processes. Probiotics can competitively inhibit colonization of pathogenic bacteria, upregulate the expression of tight junction proteins (including claudin, occludin, and zonula occludens-1), and enhance mucin secretion, thereby strengthening intestinal barrier integrity [19,20]. Prebiotics selectively stimulate the proliferation and metabolic activity of beneficial gut microbiota, leading to increased production of SCFAs such as acetate, propionate, and butyrate [21]. These SCFAs serve as an energy source for intestinal epithelial cells, modulate local immune responses, and, upon translocation to the liver via the portal circulation, regulate hepatic lipid metabolism and suppress inflammatory signaling [22]. Collectively, probiotics and prebiotics reduce the translocation of microbial products such as LPS, attenuate the activation of TLR4–MYD88–NF-κB and NLRP3 inflammasome pathways, and modulate gut–liver immune crosstalk, thereby exerting protective effects against the progression of MASLD [23].

2.2. Food Nutrients and the Regulatory Effects on MASLD

The nutritional content of fermented foods may regulate MASLD through two main approaches. First, their unique nutritional and bioactive components regulate liver fat metabolism and inflammatory responses. Second, consuming fermented foods can significantly improve consumers' gut microbiome, which also plays a significant role in regulating MASLD [24]. This section will comprehensively elaborate on the nutritional and bioactive components of fermented foods along with relevant clinical or preclinical studies on MASLD patients (Table 1).

2.2.1. Fatty Acids

Fatty acids involved in lipid metabolism can be categorized into saturated fatty acids (SFAs), unsaturated fatty acids (UFAs), and trans fatty acids (TFAs). During the fermentation of dairy products, lipases secreted by LAB can hydrolyze lipids, releasing free fatty acids and thereby increasing the levels of both SFAs and UFAs. Certain LAB are also capable of synthesizing unsaturated fatty acids, such as conjugated linoleic acid, during fermentation [25,26]. Moreover, SFAs can be metabolized by probiotic bacteria into SCFAs, including acetate and butyrate. From a pathophysiological perspective, SFAs are known to promote the development of metabolic dysfunction-associated steatotic liver disease (MASLD) by serving as substrates for DNL and significantly contributing to hepatic triglyceride accumulation [27]. Working synergistically with SFAs, TFAs have a stimulatory effect on MASLD. In contrast, UFAs have been shown to alleviate MASLD [27].

Dietary SFAs are primarily palmitic acid and stearic acid. Palmitic acid is a substrate for DNL, which ultimately leads to TG accumulation and can contribute to the pathogenesis of MASLD [15]. Excessive intake of SFAs can lead to endoplasmic reticulum stress, mitochondrial dysfunction, and oxidative stress, leading to hepatocyte apoptosis [28]. SFAs can also exacerbate insulin resistance. Notably, excessive intake of SFAs impairs the absorption of fat-soluble vitamins A, D, E, and K, which are also thought to be involved in the regulation of MASLD [29]. In addition, SFAs can activate inflammatory pathways related to TLR4 signaling, beyond their effects on lipid metabolism [30,31]. TFAs exacerbate hepatic steatosis by increasing DNL, impairing beta-oxidation, and promoting inflammation; a diet high in TFAs induces features of steatohepatitis [32].

UFAs can be divided into monounsaturated fatty acids (MUFAs) and polyunsaturated fatty acids (PUFAs), which can alleviate MASLD by regulating lipid metabolism and inflammatory responses [33]. Oleic acid is a MUFA that is abundant in olive oil, which can reduce the severity of MASLD and is a key component of the Mediterranean diet [34].

MUFAs affect signaling pathways by replacing SFAs in cell membranes, thereby improving insulin sensitivity and lipid profiles. PUFAs include omega-6 and omega-3 fatty acids. Omega-3 fatty acids include eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), which can inhibit sterol regulatory element-binding protein-1c (SREBP-1c) by activating peroxisome proliferator-activated receptor α (PPARα) and suppress DNL [35]. In mouse models, omega-3 PUFAs can alleviate high fat diet (HFD)-induced steatosis by stimulating the proliferation and differentiation of preadipocytes [36]. PUFAs can also reduce inflammatory responses in MASLD. Linoleic acid, an omega-6 fatty acid, can inhibit inflammatory responses by inhibiting the JNK pathway and NF-κB. EPA and DHA mediate anti-inflammatory effects by activating GPR120 [37]. DHA also alleviates liver inflammation by inhibiting hepatic expression of CD14 and TLRs and consequently suppressing NF-κB [38,39]. In addition, DHA reduces the gene and protein expression of collagen type I alpha 1 chain (Col1A1) in hepatic stellate cells (HSCs) by attenuating transforming growth factor-β (TGF-β) signaling, thereby alleviating liver fibrosis [40]. Therefore, DHA has a better therapeutic effect than EPA. However, in clinical practice, the therapeutic effects of EPA and DHA are inconsistent [41–45].

2.2.2. Carbohydrates

Dietary carbohydrates can be categorized into sugars (monosaccharides, disaccharides, and oligosaccharides) and dietary fiber. During food fermentation, the composition and concentration of carbohydrates undergo substantial alterations, largely determined by the metabolic characteristics of the fermenting microorganisms. In most LAB–mediated fermentations, sugars are metabolized through glycolytic and heterofermentative pathways to yield lactic acid, ethanol, acetic acid, and, in some cases, carbon dioxide. The total dietary fiber content may decline during fermentation, primarily due to microbial enzymatic degradation. In legumes, for instance, soluble dietary fiber typically decreases, whereas the insoluble fraction remains relatively stable [46]. These fermentable fibers can be further utilized by probiotic microorganisms during fermentation process or within the gastrointestinal tract, leading to the production of SCFAs that exert beneficial effects on host metabolism and gut health. The monosaccharides fructose and glucose play a key role in the progression of MASLD [15]. Excessive intake of these sugars can lead to hepatic steatosis, insulin resistance, and systemic inflammation.

While both glucose and fructose can increase DNL levels, their mechanisms are different. Glucose stimulates hepatic DNL primarily by enhancing carbohydrate response element-binding protein (ChREBP) and SREBP-1c [47,48]. High blood glucose levels are associated with insulin resistance, which in turn maintains the sensitivity of the SREBP-1c pathway, leading to elevated SREBP-1c levels. DNL may produce diacylglycerol and ceramides, which promote insulin resistance, thereby creating a positive feedback loop and further exacerbating disease progression [49,50]. Fructose primarily activates ChREBP, but can also induce SREBP-1c activation in an insulin-dependent or -independent manner, or enhance DNL through the liver X receptor (LXR) and PGC-1β pathways involved in TG metabolism [51–53]. In addition, excess fructose is metabolized to acetate by gut microbes in the small intestine, which is then converted to acetyl-CoA by ACSS2 and enters the TG production pathway of DNL as a new, independent substrate [54]. Therefore, the lipogenic effect of fructose is considered to be stronger than that of glucose.

Various studies have been conducted to validate that excessive sugar intake exacerbates inflammatory responses. Murine models fed fructose showed TLR4 signaling activation, leading to inflammatory responses via increased expression of the inflammatory cytokines IL-6 and TNF-α [55,56]. Additionally, excessive fructose intake induces oxidative stress caused by both increased lipid metabolic pressure and the production of uric acid from fructose metabolism [57].

Dietary fiber, typically a non-digestible polysaccharide, is often added to foods as a prebiotic [58]. Gut microbes metabolize ingested dietary fiber to produce SCFAs that exert beneficial health effects [59]. Dietary fiber intake can improve hepatic fat metabolism, delay blood sugar absorption, reduce insulin spikes, inhibit lipogenesis, and promote lipolysis, which are beneficial for reducing fat accumulation in the liver [60]. Studies have shown that intake of total fiber, cereal fiber, fruit fiber, and plant fiber is negatively correlated with the risk of non-alcoholic fatty liver disease (NAFLD) [61]. Dietary fiber can also improve intestinal barrier integrity and reduce the translocation of inflammatory factors [60].

2.2.3. Vitamins

Vitamins are essential micronutrients for human health, as humans cannot synthesize them or their precursors endogenously, and must acquire them through dietary intake. The alterations in vitamin content during fermentation are complex and depend on microbial activity and substrate composition. In general, fermentation enhances the levels of B

vitamins and vitamin K, which are synthesized as metabolic byproducts of fermenting microorganisms. For instance, increased concentrations of B vitamins have been observed in yogurt, fermented soy products, and kimchi, while vitamin K levels rise notably in natto [62]. In contrast, vitamin C, a water-soluble and chemically unstable compound, tends to degrade easily, although it may remain relatively stable during the early stages of vegetable fermentation [63]. Overall, fermentation processes generally improve the bioavailability and nutritional value of vitamins [62].

In the context of liver health, accumulating evidence indicates a strong association between vitamin deficiencies and liver disease. There is a synergistic relationship between vitamins and liver function, reflected by the intricate interplay between vitamins and the liver–adipose axis [64]. It was found that liver impairment leads to poor vitamin uptake, while vitamin deficiencies were found to worsen hepatic pathology. Corresponding, intestinal absorption of vitamins A, D, K, and C is impaired in patients with disrupted bile secretion [65]. While there is evidence supporting the vitamins and liver–adipose axis, it remains poorly understood and is currently an emerging area of clinical investigation [66].

Vitamins regulate hepatic metabolism and influence the progression of liver disease primarily through their effects on lipid metabolism. These vitamins include:

- **Vitamins A and K** play a complex, reciprocal role in MASLD regulation. Vitamin A prevents lipid accumulation in white adipose tissue (WAT) and brown adipose tissue (BAT) [67]. Its metabolite, retinoic acid, exerts therapeutic effects in NAFLD by enhancing fatty acid oxidation and activating RAR-mediated thermogenic pathways, although these effects are not always liver-specific [68]. Conversely, NAFLD progression increases circulating levels of the vitamin A transporter RBP4, leading to chronically elevated vitamin A and impaired mitochondrial lipid oxidation [69]. Vitamin K, as a fat-soluble nutrient, is prone to sequestration in excessive adipose tissue, resulting in deficiency [64]. Nonetheless, vitamin K may alleviate hepatic steatosis by modulating the AMP-activated protein kinase (AMPK)/SREBP1/PPARα signaling cascade through GAS6 activation [70].
- **B vitamins** Evidence linking B-vitamins to NAFLD remains limited and occasionally inconsistent [66]. Niacin (vitamin B3), as a precursor of NAD and NADPH, modulates lipid metabolism, enhances hepatic redox balance, and reduces TG accumulation, although prolonged supplementation may impair insulin sensitivity [71]. Folate (vitamin B9) deficiency promotes hyperhomocysteinemia and hepatic lipid deposition, whereas supplementation may activate AMPK, thereby mitigating steatosis [72]. Vitamin B12 deficiency interferes with mitochondrial β-oxidation via disrupted methylmalonyl-CoA metabolism, correlating with increased fibrosis severity [73]. Similarly, vitamin B6 deficiency elevates homocysteine levels, inducing endoplasmic reticulum stress and SREBP-1c–driven lipogenesis [66]. Collectively, these findings highlight the potential metabolic and hepatoprotective roles of B-vitamins in NAFLD pathogenesis, though clinical evidence remains inconclusive.
- **Vitamin C** reduces circulating and hepatic TG, enhances lipolysis, and decreases microsomal TG transfer protein (MTP) levels [74]. In addition, it promotes AMPK phosphorylation, inhibits nuclear translocation of LXR, and suppresses DNL [75].
- **Vitamin D** plays a critical role in lipid homeostasis, and its deficiency promotes macrophage infiltration into WAT, thereby driving fibrosis and aggravating MASLD [76]. Supplementation with vitamin D has been shown to attenuate WAT-associated inflammation and hepatic steatosis [77,78].
- **Vitamin E** exerts robust protective functions in MASLD. Specifically, α-tocopherol inhibits DNL through its antioxidant capacity and lipid solubility [79]. Various isoforms of vitamin E also demonstrate synergistic activity and may represent therapeutic targets for reducing lipid deposition and inflammation in both adipose tissue and liver, in part by suppressing NF-κB signaling and activating PPARα [80].

2.2.4. Polyphenols

Polyphenols constitute a structurally diverse class of plant-derived bioactive compounds with antioxidant, anti-inflammatory, and metabolic regulatory properties [81].

Polyphenols constitute a structurally diverse class of plant-derived bioactive compounds endowed with potent antioxidant, anti-inflammatory, and metabolic regulatory activities [81]. In food matrices, phenolic compounds are frequently present in conjugated or macromolecular-bound forms, such as complexes with glycosides, cellulose, starch, or proteins, which substantially limit their bioaccessibility and bioavailability. During fermentation, microorganisms not only engage in the metabolic transformation of substrates but also secrete a wide array of enzymes with specific catalytic functions, including tannase, esterase, phenolic acid decarboxylases, and glycosidase [82]. These enzymes effectively hydrolyze or depolymerize bound polyphenols, thereby releasing free phenolic acids, flavonoids, and other

low-molecular-weight phenolics. Specifically, tannase catalyzes the depolymerization of complex high-molecular-weight tannins into simpler phenolic acids or catechin derivatives; esterase cleaves ester linkages between hydroxycinnamic acid derivatives and macromolecules such as proteins, lignin, or cellulose; phenolic acid decarboxylases mediates the redox transformation of hydroxycinnamic acids, modifying their structural and antioxidant properties and generating volatile phenolic compounds; while glycosidase hydrolyzes glycosidic bonds between polyphenols and sugars, thereby enhancing the bioactivity and bioavailability of flavonoids [82]. Collectively, these enzymatic transformations increase the solubility and intestinal absorption of phenolic compounds, thereby augmenting the antioxidant, anti-inflammatory, and antimicrobial potential of fermented foods and ultimately improving their nutritional and health-promoting properties.

In the field of MASLD research, curcumin, hesperidin, naringenin, genistein, catechin, and silymarin have demonstrated direct therapeutic potential against MASLD [83,84]. Specifically, curcumin reduces liver enzyme levels, TG, total cholesterol, and insulin resistance, while attenuating hepatic steatosis, inflammation, and fibrosis through modulation of AMPK, nuclear factor erythroid 2-related factor 2 (Nrf2), TGF-β, and IL-6 signaling pathways [85]. Silymarin lowers liver enzyme levels and diminishes hepatic lipid accumulation via the FXR pathway [86]. Catechins, abundantly present in tea, effectively mitigate TG levels and insulin resistance, where green tea extract-derived catechins confer hepatoprotective effects through activation of mitochondrial respiratory chain complexes, SIRT1, and AMPK [87–89]. Hesperidin enhances hepatic metabolic function via SIRT1/PGC1α activation, resulting in reductions in alanine aminotransferase (ALT) and aspartate transaminase (AST) levels and attenuation of inflammatory markers [90,91]. Resveratrol alleviates lipid accumulation and inflammatory responses by upregulating SIRT1 and AMPK, although its efficacy varies across studies [92–94].

Additionally, polyphenols indirectly modulate MASLD pathogenesis by altering the gut microbiota. Silymarin changes microbial composition and reduces liver stiffness through FXR-mediated mechanisms [95,96]. Fermented black buckwheat exhibits decreased rutin content, increased total phenolics (quercetin and kaempferol), and elevates populations of *Lactobacillus*, *Faecalibaculum*, and *Allobaculum* in murine models [97]. Fu brick tea polyphenol extracts ameliorate intestinal oxidative stress and inflammation, reinforce intestinal barrier integrity, and promote gut microbial diversity, thereby enhancing *Akkermansia muciniphila*, *Alloprevotella*, *Bacteroides*, and *Faecalibaculum* [98]. While most of these studies did not directly assess overall hepatic health, these studies established that the interplay between MASLD and the gut-liver axis suggests that these microbial alterations contribute to hepatic benefits.

Despite their extensive bioactivities, polyphenols are characterized by limited oral bioavailability and a short biological half-life. Polyphenols with lower molecular weight or aglycone forms generally exhibit higher physiological activity. Probiotic fermentation enhances the bioactivity of polyphenols by converting high-molecular-weight compounds into smaller, more bioactive forms. Consequently, the polyphenol composition of fermented foods differs substantially from that of raw materials [82]. For instance, rutin and isoquercetin in fermented black buckwheat, jujubes, and sourdough bread are hydrolyzed to quercetin, whereas glycosyl glycosides (daidzin and genistin) in soybeans are reduced, with concomitant increases in aglycones (daidzein, glycitein, and genistein) [97,99,100]. These alterations in polyphenol composition confer functional advantages, as evidenced by the enhanced antioxidant activity and DNA-protective properties of fermented soy products [101].

2.2.5. Polyamines

Aliphatic polycations, commonly referred to as polyamines, play a critical role in the pathogenesis of MASLD by modulating cellular lipid accumulation, mitochondrial function, and fibrosis progression [102]. Polyamines can be synthesized endogenously through intrinsic metabolic pathways or acquired exogenously via the diet, with principal sources including whole grains, soy products, mushrooms, and fermented foods. During fermentation, polyamines undergo a series of dynamic transformations, encompassing microbial decarboxylation of amino acids—such as ornithine conversion to putrescine, lysine to cadaverine, and arginine to spermidine—followed by oxidative deamination and interconversion reactions [103]. These processes are tightly regulated by factors including the composition of the microbial community, fermentation duration, pH, and redox conditions, which collectively shape the polyamine profile of the final product [103]. Furthermore, commensal and probiotic gut microorganisms, including *Fusobacterium* and *Bacteroides*, are capable of synthesizing polyamines, with spermidine and putrescine concentrations in the intestinal lumen of healthy individuals typically ranging from 0.5 to 1 mM [104]. This evidence suggests that polyamines derived from both dietary intake and the gut microbiota contribute synergistically to the maintenance of host metabolic homeostasis.

Among them, spermidine has been the most extensively studied for its relation to MASLD. Preclinical studies indicate that spermidine ameliorates hepatic steatosis and inflammation in MASLD models by inducing autophagy and activating AMPK [105]. Dietary supplementation with spermidine reduces hepatic lipid accumulation, mitigates liver injury, and attenuates fibrosis by suppressing proinflammatory cytokines, including TNF-α and IL-1β [105]. Additionally, spermidine regulates lipid metabolism through activation of SIRT1 and inhibition of the mammalian target of rapamycin (mTOR), which contributes to improved hepatic insulin sensitivity and decreased oxidative stress [106]. Spermine has also been shown to confer hepatoprotective effects in preclinical models. Supplementation can attenuate acute liver injury by suppressing proinflammatory responses in liver-resident macrophages via an ATG5-dependent autophagy pathway [107]. In addition, spermine enhances liver barrier function, regulates amino acid transporter activity, and inhibits apoptosis, further supporting its protective role in hepatic homeostasis [108].

Direct clinical evidence regarding the effect of putrescine on MASLD progression is currently lacking. In animal models, putrescine supplementation has been shown to exert anti-inflammatory and antioxidant effects by inhibiting NF-κB and IL-6 signaling pathways, thereby alleviating hepatic injury [109]. Conversely, other studies have reported that elevated endogenous putrescine levels and increased ornithine decarboxylase activity are positively correlated with MASLD severity, with higher putrescine concentrations leading to enhanced CK-18 release [109].

2.2.6. Caffeine and Chlorogenic Acid

Caffeine and chlorogenic acid (CGA), commonly present in coffee and tea, have been proposed to exert hepatoprotective effects in MASLD. Epidemiological evidence suggests an inverse association between caffeine and CGA intake and MASLD progression; however, findings are inconsistent, with some studies reporting contrasting results [110–112]. Some of these findings discovered that these compounds modulate hepatic lipid metabolism by suppressing DNL and enhancing fatty acid β-oxidation [113–116]. Despite accumulating evidence supporting a protective role of caffeine and CGA, the precise molecular mechanisms remain poorly understood.

Current research on the mechanisms of caffeine and CGA has revealed that caffeine reduces hepatic TG accumulation by inhibiting SREBP-1c and ChREBP while upregulating PPARα and CPT1 [113]. It also activates AMPK signaling, resulting in decreased hepatic lipid content and improved insulin sensitivity. CGA attenuates hepatic steatosis by suppressing lipogenesis and enhancing fatty acid β-oxidation, and activates AMPK signaling, inhibits SREBP-1c and LXRα, thus reducing hepatic TG levels [117]. Both caffeine and CGA mitigate inflammation and fibrotic pathways through modulation of IL-6/STAT3 signaling [118]. Furthermore, CGA has been shown to slow fibrosis via the TGF-β1/Smad7 pathway [119].

The reported variability in the effects of caffeine and CGA on MASLD may stem from differences in experimental models, dosage, treatment duration, age, and sex of subjects [120]. Accordingly, further studies are warranted to elucidate the parameters and limitations of using caffeine and CGA to regulate MASLD and MASH pathogenesis and progression.

2.2.7. Probiotics and Microorganisms

The role of microorganisms in food fermentation relies heavily on their interaction with other microbes and the nutritional composition of the foods. While most microbes would not survive gastrointestinal passage, the metabolic products from the fermentation process and probiotic microbes within the fermentation communities exert their influence on MASLD pathogenesis. Studies of intestinal microbiota indicate that some bacterial populations may have complex or even detrimental effects on MASLD progression.

Evidence indicates that gut microbiota composition changes progressively across MASLD and MASH stages [121]. At the phylum level, *Bacteroidetes* are consistently reduced, whereas *Firmicutes* and *Proteobacteria* are expanded [121]. At the family level, *Enterobacteriaceae* are enriched, while *Rikenellaceae* and *Ruminococcaceae* are depleted [121]. At the genus level, *Escherichia*, *Dorea*, and *Peptoniphilus* are increased, whereas *Anaerosporobacter*, *Coprococcus*, *Eubacterium*, *Faecalibacterium*, and *Prevotella* are reduced [121]. These shifts indicate a dysbiotic microbial community favoring pro-inflammatory and endotoxin-producing taxa [121,122].

Table 1. Impact of dietary nutrients and bioactive compounds on MASLD metabolism.

Category	Effect on MASLD Metabolism	References
Fatty Acids		
SFAs	DNL↑, insulin resistance↑, inflammation↑	[28–31]
TFAs	DNL↑, beta-oxidation↓, inflammation↑; hepatic steatosis↑	[32]
MUFAs	Insulin sensitivity↑, reduce the severity of MASLD	[33,34]
PUFAs	EPA: DNL↓, inflammation↓ DHA: DNL↓, inflammation↓, fibrosis↓	[35–45]
Carbohydrates		
Fructose	DNL↑, insulin resistance↑, inflammation↑	[47,48,51–53]
Glucose	DNL↑, insulin resistance↑	[47–50]
Dietary fiber	Lipogenesis↓, lipolysis↑, improve gut barrier	[58–60]
Vitamins		
Vitamin A	Fatty acid oxidation↑, prevents lipid accumulation in adipose	[67–69]
Vitamin K	Hepatic steatosis↓	[70]
Vitamin B	Modulates lipid metabolism, TG↓, hepatic steatosis↓ Vitamin B12 deficiency: fibrosis↑; Vitamin B6 deficiency: Lipogenesis↑	[66,71–73]
Vitamin C	TG↓, lipolysis↑, DNL↓.	[74,75]
Vitamin D	Deficiency: macrophage infiltration in WAT↑, fibrosis↑; Supplementation: inflammation↓, hepatic steatosis↓	[76–78]
Vitamin E	DNL↓, lipid deposition↓, inflammation↓,	[79,80]
Polyphenols		
Curcumin	Hepatic steatosis↓, inflammation↓, fibrosis↓	[85]
Silymarin	Lipid accumulation↓	[86]
Catechins	TG↓, insulin resistance↓	[87–89]
Hesperidin	Inflammation↓	[90,91]
Resveratrol	Lipid accumulation↓, inflammation↓	[92–94]
Polyamines		
Spermidine	Lipid accumulation↓, Hepatic steatosis↓, inflammation↓, fibrosis↓	[105,106]
Spermine	Inflammation↓	[107,108]
Putrescine	Inflammation↓	[109]
Others		
Caffeine	TG↓, insulin sensitivity↑, inflammation↓, fibrosis↓.	[113,118]
CGA	Lipogenesis↓, fatty acid β-oxidation↑, inflammation↓, fibrosis↓	[117–119]
Probiotics	Hepatic steatosis↓, inflammation↓, improve gut barrier	[121–136]

SFAs: saturated fatty acids, TFAs: trans fatty acids, MUFAs: monounsaturated fatty acids, PUFAs: polyunsaturated fatty acids, CGA: chlorogenic acid, MASLD: metabolic dysfunction-associated steatotic liver disease, DNL: *De novo* lipogenesis, TG: triglyceride, EPA: eicosapentaenoic acid, DHA: docosahexaenoic acid, WAT: white adipose tissue. (↑: upregulated metabolic processes or accumulation of metabolites; ↓: downregulated metabolic processes or depletion of metabolites).

A key functional consequence of these changes is the altered production of SCFAs, which are critical for maintaining intestinal epithelial integrity, stimulating mucus secretion, and preventing bacterial translocation [123]. Specifically, *Bacteroides* are primary producers of acetate, while *Firmicutes* predominantly generate butyrate [124]. Reduced butyrate availability is associated with impaired barrier function and enhanced inflammatory signaling along the gut-liver axis [125].

Given these insights, probiotic interventions have been explored to restore microbial balance and mitigate liver injury. In mouse models of hepatic steatosis, four-week probiotic administration significantly reduced liver fat accumulation [126]. Multiple strains, including *Lactobacillus casei*, *L. rhamnosus*, *L. bulgaricus*, *Bifidobacterium longum*, and *Streptococcus thermophilus*, have demonstrated anti-inflammatory effects in the liver [127]. Long-term supplementation with *B. longum* combined with fructo-oligosaccharides (FOS) and lifestyle interventions significantly reduced TNF-α, C-reactive protein (CRP), AST, homeostasis model assessment of insulin resistance (HOMA-IR), and serum endotoxin levels, while improving hepatic steatosis and the MASH activity index [128]. In other models, *Faecalibacterium prausnitzii* supplementation restored intestinal barrier integrity, and four-week supplementation with *Lactobacillus acidophilus* NCFM® improved insulin sensitivity via reductions in LPS levels, modulation of TLR

signaling, and cytokine regulation [129,130]. Experiments with MIYAIRI 588, a butyrate-producing probiotic, in NAFLD rat models also demonstrated reductions in hepatic TG accumulation, insulin resistance, serum endotoxin levels, and markers of liver inflammation [131].

Nonetheless, the clinical efficacy of probiotics remains controversial. While some trials suggest that combinations of *Lactobacillus*, *Bifidobacterium*, and *Streptococcus* are most effective, other studies have failed to replicate these findings [127,132]. Variations in probiotic formulations, dosage, treatment duration, and patient populations contribute to inconsistent outcomes.

Overall, probiotic supplementation represents a promising adjunctive therapy for MASLD/MASH, yet well-designed randomized controlled trials are required to determine optimal strains, combinations, and treatment regimens. Engineered probiotics have the potential to enhance the viability and therapeutic potential of beneficial strains. Next-generation fermented foods can more effectively control microbial composition, thereby improving their impact on MASLD management.

2.2.8. Engineered Probiotics

Probiotics, including *Lactobacillus* and *Bifidobacterium*, have been shown to improve liver function parameters, attenuate hepatic steatosis, and modulate glucose, insulin, and lipid profiles in MASLD [133]. Engineered strains have emerged as novel therapeutic strategies beyond conventional probiotics.

Preclinical studies demonstrate that IL-22, an IL-10 cytokine family member, delivered via engineered *Lactobacillus reuteri*, induces localized expression of the antimicrobial protein regenerating islet-derived 3-gamma (Reg3γ), effectively reducing bacterial translocation and mitigating ethanol-induced liver injury, steatosis, and inflammation [134].

Similarly, glucagon-like peptide-1 (GLP-1) delivered through engineered *Escherichia coli* Nissle 1917 or *Lactobacillus gasseri* enhances insulin secretion, decreases body weight, improves lipid profiles, and ameliorates liver biochemistry and histopathology [135,136]. These findings underscore the therapeutic potential of both conventional and engineered probiotics in MASLD.

2.3. The Impact of Fermented Foods on MASLD

Fermented foods confer multiple benefits for liver health. Firstly, microbial fermentation substantially increases the levels of bioactive metabolites within these foods. Secondly, certain nutrients such as fructose and glucose, which may be detrimental in MASLD, can serve as metabolic substrates for microbial growth and are converted into beneficial bioactive compounds, including PUFAs. Additionally, the fermentation process often breaks down large molecules into smaller, more bioavailable forms, such as polyphenols [82]. Enhanced bioavailability of polyphenols following microbial fermentation contributes to their health-promoting effects. Moreover, consumption of fermented foods frequently modulates the intestinal microbiome, and probiotics, such as LAB, are commonly incorporated into these products.

2.3.1. Fermented Dairy Products

Fermented dairy products—including yogurt, kefir, and cheese—are widely consumed, available in diverse forms, and have been extensively investigated as potential interventions for the management of MASLD [137–139]. Notably, kefir, a fermented dairy beverage containing diverse probiotics and yeasts, has been shown to reduce hepatic lipid accumulation, lower serum ALT levels, and attenuate inflammatory responses in preclinical MASLD models [140]. Another study further suggested that regular consumption of fermented dairy products improves insulin resistance and lipid profiles, thereby exerting protective effects [139]. The underlying mechanisms include bioactive peptides and SCFAs generated during LAB fermentation [141].

2.3.2. Fermented Legume Products

Fermented soy products are regarded as having numerous health benefits [142]. Fermentation enhances the bioavailability of key bioactive compounds, such as SCFAs, polyphenols, and antioxidant peptides, thereby improving their physiological effects [143,144]. Common fermented soy products, including natto, miso, and tempeh, have demonstrated benefits in the prevention and management of MASLD [145–147]. Evidence from animal studies indicates that miso and natto can attenuate hepatic steatosis and inflammation, primarily through modulation of the gut

microbiota [147]. Although large-scale randomized controlled trials remain limited, current findings suggest that fermented soy products represent a promising dietary strategy for MASLD management [142].

2.3.3. Fermented Plant-Based Beverages

Fermented beverages constitute another important category of fermented foods. While many fermented beverages traditionally contain alcohol, such as beer and red wine, a wide range of non-alcoholic alternatives—including fermented juices and teas—are also widely consumed. Although research in this area remains limited, existing studies indicate that fermented juices may exert protective effects against liver disease [148,149].

The effects of alcoholic fermented beverages, such as wine and beer, on MASLD remain inconclusive. Because excessive alcohol intake is a well-established cause of alcoholic liver disease, most studies investigating this topic are confined to moderate consumption levels (≤30 g/day for men and ≤20 g/day for women) [150]. Beer contains a variety of bioactive compounds, including polyphenols such as xanthohumol, isoxanthohumol, and phenolic acids, as well as bitter and α-acid derivatives derived from hops (humulones, lupulones, and isohumulones) [151]. Wine, in contrast, is particularly rich in polyphenolic constituents, comprising stilbenes (e.g., resveratrol), phenolic acids, and flavonoids (including flavan-3-ols, anthocyanins, and quercetin) [151]. These compounds have been reported to exert antioxidant, anti-inflammatory, and lipid metabolism–modulating effects. Nevertheless, it remains uncertain whether such bioactive components can counteract the hepatotoxic effects of alcohol itself [151]. Overall, the influence of alcohol consumption on MASLD is still controversial: the available evidence is limited, and findings across studies are inconsistent with respect to the significance and direction of this association [152].

Among non-alcoholic beverages, kombucha, a fermented tea that has gained global popularity, is notable for its abundance of polyphenols, organic acids, and water-soluble vitamins, as well as its documented antioxidant and anti-inflammatory properties [153]. Evidence from murine models demonstrates that kombucha supplementation reduces hepatic steatosis, lowers TG levels, and decreases markers of liver injury [154]. Moreover, kombucha has been shown to modulate the gut microbiota, thereby potentially alleviating inflammatory stress along the gut-liver axis [155]. Collectively, these findings suggest that kombucha represents a promising adjunct to dietary interventions for the management of MASLD.

3. Applications and Technologies of Engineered Fermentative Bacteria

With the advancement of the modern food industry, fermentation technology has evolved significantly. Progress spans from the selection and breeding of fermentative strains to their modification through genetic techniques and metabolic engineering; from naturally occurring multi-strain fermentations to single-strain fermentations for controlled quality; and to co-culture fermentations designed to enhance flavor and nutritional value [156]. The development of food fermentation is closely intertwined with advances in modern biotechnology, with contemporary fermentation emphasizing not only flavor and texture but also functionality and process controllability [157]. Figure 2 highlights the principal technological innovations that drive contemporary advances in fermentation.

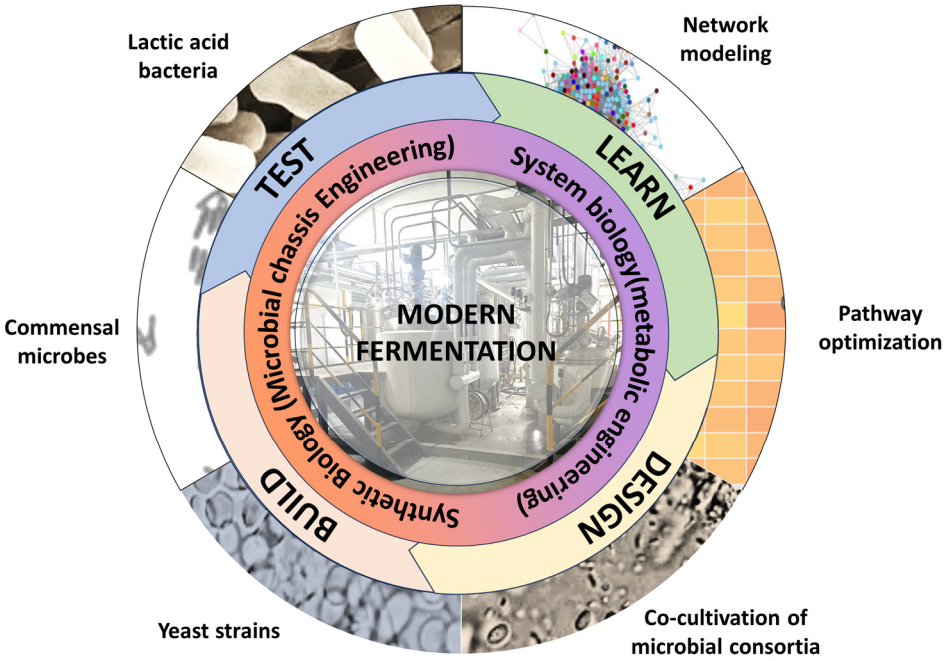

Figure 2. Conceptual framework of modern fermentation.

3.1. Comparison of Traditional and Modern Fermentation

Traditional fermentation relies on natural bacterial flora or empirically selected strains, often resulting in substantial batch-to-batch variability and low process stability [158]. In contrast, modern fermentation typically employs standardized or engineered strains, allowing controlled fermentation through single-strain or co-culture approaches. The application of metabolically engineered strains of LAB, *Bacillus*, and yeast can increase yields of target metabolites, reduce undesirable byproducts, and inhibit the growth of harmful microorganisms [159,160].

Traditional methods of improving the fermentation process involve isolating strains that have undergone directed evolution over many iterations of fermentation [161]. This process can be observed in historically documented instances of starter cultures that have been maintained by selective brewers and fermentation experts, where certain starter cultures used in fermentation confer improved flavor profiles, color, aroma, and health-benefiting properties. This selection process represents the domestication of strains that have been conditioned to use a particular nutrient source over many generations of fermentation, allowing the microbial community to enhance their selected characteristics. These selected characteristics are often the result of genetic enhancements within the microbe, selected by evolutionary pressure to gain an advantage over other microbial counterparts. An overall comparative overview of the distinguishing features of traditional versus modern fermentation is presented in Table 2.

Table 2. Comparison between traditional and modern fermentation.

Feature	Traditional Fermentation	Modern Fermentation
Strain type	Natural microbial communities or empirically selected strains	Standardized or engineered strains (e.g., LAB, *Bacillus*, yeast)
Process control	Difficult to control, dependent on natural selection/experience	Highly controllable, employing single strains or co-culture methods
Process stability	Low, often leading to large batch-to-batch variability	High, with predictable and standardized outcomes
Product optimization	Directed evolution through multiple fermentation cycles (time-consuming)	Genetic technologies and metabolic engineering (rapid and efficient)
Main advantages	Development of unique flavors, colors, and textures	Increased yield of target metabolites, reduced undesirable byproducts, and inhibition of harmful microorganisms
Technical basis	Accumulated empirical knowledge, strain domestication	Modern biotechnologies (e.g., CRISPR, metabolic engineering, synthetic biology)

3.2. Applications of Engineered Bacteria in Fermentation

Engineered strains are increasingly used to produce a variety of bioactive compounds to address unmet nutritional needs. PUFAs, for example, are natural products that are difficult to synthesize chemically [162]. Researchers have developed microbial production platforms, using prokaryotic and eukaryotic organisms with polyketide synthase (PKS) pathways, to synthesize DHA and EPA. Marine bacteria such as *Colwellia psychrerythraea*, *Moritella marina*, and *Shewanella pneumatophori* serve as microbial hosts for PKS-mediated PUFA biosynthesis [163–166]. The selection of these microbial chassis for engineering stems from the native ability of the microbe to generate sufficient CoA precursors needed to power the PKS catalysis. Biosynthesized DHA and EPA are now utilized as functional food additives [167].

LAB and *Bacillus amyloliquefaciens* are mature biological platforms suitable for engineering as fermentation strains [168]. CRISPR-based genetic toolkits enable rapid gene knockout and integration of functional genes in *B. amyloliquefaciens*, thereby enhancing its utility in food applications [169]. For instance, metabolic engineering has increased γ-poly glutamic acid (γ-PGA) production in fermented corn [170]. *B. amyloliquefaciens* also exhibits probiotic properties; feeding *B. amyloliquefaciens* strain SC06 to mice on a high-fat diet reduced fat accumulation, improved insulin sensitivity, and attenuated liver inflammation, along with decreased levels of inflammatory markers such as IL-6 and TNF-α [171]. Engineered LAB fermentation in dairy products has been used to enhance conjugated linoleic acid production, contributing to the mitigation of MASLD progression [172].

Similarly, CRISPR-based genetic engineering has been used extensively to remove competing pathways within microbial cells to enhance the production of targeted therapeutics and value-added chemicals within fermented foods [173]. Other approaches leverage the use of engineered microbes to ferment ingested unfermented foods within the gastrointestinal tract of the host, allowing the preservation of sensitive metabolites that would not otherwise survive the gastrointestinal passage [174].

3.3. Systems Biology and Synthetic Biology in Fermentation

Modern fermentation has progressed from traditional methods using natural strains to highly efficient systems that integrate molecular biology, metabolic engineering, and synthetic biology. Synthetic biology enables precise design and reconstruction of microbial genomes, metabolic pathways, and regulatory networks, rendering fermentation processes more controllable, high-yielding, and functional. LAB and *B. amyloliquefaciens* serve as primary "biological chassis" in food fermentation, with gene editing technologies such as CRISPR-Cas facilitating insertion, deletion, or regulation of target genes to enhance production of PUFAs, polyphenols, SCFAs, and antioxidant peptides [175,176]. For example, by using CRISPR/Cas to reconstruct the expression architecture of the PUFA synthesis gene cluster in *Yarrowia lipolytica*, the researchers significantly increased the production of DHA, proving that precise engineering of the PUFA metabolic pathway can indeed increase the output of functional lipids [177].

Metabolic pathway optimization is central to modern fermentation. By using in silico prediction and modeling to regulate key enzymatic activities, substrate flux, and byproduct formation, engineered strains can achieve a dynamic balance between product yield and cell growth [178]. Modular design and controllable co-culture strategies allow different strains to specialize in distinct functional modules, achieving metabolic division of labor and enhancing production efficiency [179]. For example, in the co-culture system of *Aspergillus oryzae* and *Lactobacillus plantarum*, the former is mainly responsible for the hydrolysis of starch to release fermentable substrates, while the latter uses these substrates to ferment and produce organic acids and increase the content of protein and amino acids [180]. The protein content and amino acid improvement effect of the co-culture output are significantly better than those of single-strain fermentation.

Synthetic microbial consortia (SMCs) have recently emerged as a rapidly expanding research frontier in microbial biotechnology. By leveraging metabolic modeling, co-culture engineering, and multi-omics–guided strain selection, these systems enable the rational design and optimization of microbial communities, thereby achieving more precise control over interspecies interactions and metabolic fluxes in fermentation processes [181]. Such approaches enhance the efficiency, stability, and functionality of fermentation systems, ultimately improving the flavor complexity, nutritional quality, and bioactive compound profiles of fermented foods [182]. For example, OuYang et al. developed an SMC comprising *Lactobacillus plantarum* NF2 and *Acetobacter pasteurianus* NF171 to optimize citrus vinegar fermentation [183]. This defined consortium markedly increased the production of ethyl acetate, a key contributor to desirable aroma, while simultaneously promoting the accumulation of several phenolic acids (such as chlorogenic and ferulic acids) and flavonoids (including rutinarin and nobiletin) [183]. These findings highlight the potential of SMC-based strategies to tailor microbial metabolism for enhanced sensory and functional attributes in fermented food products.

In the field of probiotics, the application of defined microbial consortia represents an emerging paradigm shift that departs from the conventional single-strain approach, which often produces inconsistent or limited physiological outcomes [184]. Lactobacillus and Bifidobacterium species, for instance, are well recognized for their capacity to generate SCFAs that contribute to gut and metabolic health [185]. Building upon this concept, Ye et al. developed a synthetic microbial consortium composed of seven well-characterized gut commensals—*Alistipes putredinis*, *Barnesiella intestinihominis*, *Coprococcus catus*, *Dorea longicatena*, *Agathobacter rectalis* (formerly *Eubacterium rectale*), *Faecalibacterium prausnitzii*, and *Roseburia hominis*—and fermented it with a prebiotic mix [186]. In elderly participants, the intervention markedly enhanced the relative abundance of beneficial taxa and stimulated SCFAs production, indicating improved microbial metabolic activity [186]. Collectively, these findings underscore the therapeutic and nutritional potential of synthetic microbial consortia as a next-generation probiotic strategy capable of targeted modulation of the gut ecosystem and host metabolism.

The pursuit of improved nutrient utilization systems is a key goal in fermentation science, specifically, aiming to mitigate excessive microbial catabolism of beneficial nutrients. Limiting microbial consumption during fermentation is crucial for maximizing nutrient content and maintaining the sensory properties of the final fermented product [187,188]. Precision fermentation uses precise genetic perturbations to reprogram microbial metabolic pathways, thereby conferring desirable nutrients and flavors to food [189]. This advanced bioprocess utilizes genetically engineered microbial hosts (such as yeast or fungi) as cell factories to synthesize single, specific target molecules (such as proteins, enzymes, or lipids) [189]. Engineered strains incorporate biosensing capabilities, enabling them to respond to nutrient gradients and other environmental cues by inhibiting or inducing cellular functions, thereby ensuring efficient, high-purity production of the desired compound [189]. For instance, Sathivel et al. demonstrated how harnessing quorum sensing in microbial consortia could impart distinctive sensory properties to red wine [190].

The integration of systems biology and machine learning has further improved strain design and fermentation process optimization. By analyzing genomic, transcriptomic, and metabolomic data, researchers can predict metabolic bottlenecks, regulatory networks, and inter-strain interactions, providing guidance for the application of engineered strains in functional fermented foods [158]. For instance, Josephs-Spaulding et al. applied transcriptomics combined with machine learning to reconstruct the regulatory network of *Limosilactobacillus reuteri*, identifying key modules of riboflavin and fatty acid metabolism, which guide metabolic optimization for functional food applications [191]. Peerapat et al. applied machine learning to the design-build-test-learn cycle, demonstrating that machine learning has great potential to accelerate and optimize metabolic engineering processes [192]. Overall, modern synthetic biology-based fermentation not only increases the concentration of health-promoting ingredients in fermented foods but also offers new strategies for supporting liver health and managing metabolic diseases, such as MASLD, while maintaining food safety, stability, and sensory quality.

4. Challenges and Outlook

Despite the availability of pharmacological treatments for MASLD, dietary interventions and healthy lifestyle modifications remain the primary strategies for mitigating disease progression [9]. In recent years, the Mediterranean diet has been recognized as an effective reference for dietary intervention in MASLD. However, due to regional dietary habits and limitations in food accessibility, the Mediterranean diet is not universally applicable, as individuals differ in their biochemical, genetic, and microbiome makeup. In contrast, fermented foods offer distinct advantages for MASLD management. They provide functional nutrients, including polyphenols, SCFAs, PUFAs, and antioxidant peptides, which have demonstrated potential therapeutic effects in preclinical and some clinical studies by improving hepatic lipid metabolism and reducing oxidative stress and inflammation. Moreover, the fermentation process imparts unique flavors such as sour, aromatic, and umami, enhancing sensory appeal, acceptability, and adherence to dietary regimens. Fermented foods with local characteristics are found globally, many of which exhibit potential therapeutic benefits for MASLD. Compared with single functional supplements, functional fermented foods can address chronic metabolic disorders without requiring significant dietary changes, making them widely applicable and feasible for MASLD prevention and treatment.

Fermented foods not only provide functional nutrients but also offer a distinctive sensory experience. Nevertheless, the strong flavors of certain fermented foods can limit their widespread adoption. For instance, natto, a traditional Japanese fermented soy product, possesses a sticky texture and a characteristic ammoniacal odor, often described as “unpleasant” or “like rotten garbage”. Although it is rich in beneficial nutrients, including probiotics, dietary fiber, protein, and vitamin K2, its intense flavor has impeded global acceptance [142]. To overcome this limitation,

researchers are exploring the use of engineered LAB to enhance flavor profiles. Co-cultivation with specific LAB strains can modulate volatile compound production, reduce the release of undesirable odors, and improve overall sensory quality [193]. Additionally, substituting traditional soybeans with alternative fermented substrates such as red lentils, green peas, or chickpeas in natto production has been shown to reduce off-flavors while maintaining or enhancing nutritional content [194]. These flavor modification strategies increase the acceptability of fermented foods and expand dietary options for MASLD patients. By integrating functional nutrients with improved sensory properties, fermented foods are poised to become a vital component of MASLD intervention.

Modern biotechnology, including gene editing, holds promise for increasing the yield of functional products and optimizing metabolic pathways in engineered fermentation strains. Nonetheless, these approaches face significant limitations, particularly for commonly used fermentation bacteria such as LAB and *B. amyloliquefaciens*. Regulatory constraints and safety considerations are the primary limiting factors. Because fermented foods are intended for human consumption, transgenic strains generated through conventional gene editing are generally classified as genetically modified organisms (GMOs). In Europe, the United States, and numerous other countries, GMO food approvals are stringent, and consumer acceptance is low, restricting the commercial application of engineered strains [195]. Even strains demonstrating excellent metabolic performance in laboratory settings may encounter legal and market barriers that hinder practical implementation.

To address these challenges, several complementary strategies can be pursued. From the standpoint of regulation and societal acceptance, the establishment of clearer classification frameworks for gene-edited microorganisms and the development of more comprehensive risk assessment systems would facilitate the safe and responsible integration of new technologies into the food industry. Concurrently, enhancing public awareness and understanding of the potential benefits and associated risks of these technologies is essential for improving societal acceptance, a process that is inherently gradual and often contentious. The adoption of novel biotechnological tools in domains closely related to human health and nutrition is therefore expected to follow a prolonged and carefully regulated trajectory.

At present, however, several technical strategies may enable the attainment of desired functional improvements without contravening existing regulatory frameworks. First, non-GMO approaches such as laboratory-directed evolution and random mutagenesis can be employed to enhance strain performance while avoiding the introduction of exogenous DNA, thereby circumventing transgenic regulatory constraints. Second, the development and application of SMC present considerable potential in this context. Without the need for gene-editing interventions, such consortia can leverage quorum-sensing mechanisms and the inherent metabolic capabilities of distinct strains to enhance the production of target compounds in fermented foods or to introduce novel functional and sensory attributes. For instance, as noted previously, OuYang et al. demonstrated that this strategy could be applied to enrich citrus vinegar with additional flavor and bioactive constituents [183]. Future research exploring the utilization of synthetic microbial communities in fermented food production, either to confer specific health-promoting properties or to design next-generation probiotic formulations, represents a highly promising and forward-looking direction for the field.

Engineering efficiency and strain characteristics further constrain the use of traditional gene editing. LAB, despite their widespread use in food fermentation, often exhibit low transformation efficiency and limited genetic tool availability. Gene knockout or overexpression may impair growth or fermentation performance. While *Bacillus subtilis* demonstrates robust environmental resistance and high product potential, gene editing may affect spore formation or disrupt metabolic balance, compromising industrial fermentation stability. Traditional gene editing primarily targets single genes, making comprehensive metabolic network optimization challenging. Fermentation bacteria possess complex metabolic pathways in which the synthesis of multiple products is interdependent and substrate-competitive. Consequently, single-gene modifications rarely achieve global metabolic optimization and may lead to byproduct formation or impaired cell growth. Additional challenges arise in industrial-scale production: strains optimized under laboratory conditions may experience metabolic drift or trait instability in large-scale fermentation, affecting product consistency and functionality. In multi-strain co-culture systems, engineered strains may fail to compete effectively with native strains, reducing overall fermentation efficiency and target metabolite yield.

To achieve safe, efficient, and acceptable production of functional fermented foods, modern fermentation technologies must integrate metabolic engineering, synthetic biology, modular design, co-culture strategies, and computational simulation optimization. Such approaches aim to balance strain functionality with sensory quality, thereby enhancing the potential of fermented foods in MASLD intervention and the broader health food market.

Statement of the Use of Generative AI and AI-Assisted Technologies in the Writing Process

During the preparation of this manuscript, the author(s) used Grammarly in order to improve grammar, refine wording, and enhance the overall clarity of the text. After using this tool/service, the author(s) reviewed and edited the content as needed and take(s) full responsibility for the content of the published article.

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