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Gut Microbiota and Liver Health: The Role of Resistant Starch in Ameliorating Metabolic Dysfunction-Associated Fatty Liver Disease

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Abstract: With lifestyle changes, the prevalence of metabolic dysfunction-associated fatty liver disease (MAFLD), which accompanied by obesity, has been steadily increasing rising and has become the most common chronic liver disease. MAFLD is a multisystem condition that heightens the risk of liver disease and is concomitantly linked to an increased risk of other metabolic disorders, including cardiovascular and renal diseases. Research indicates that resistant starch (RS), a natural compound, influences MAFLD by dietary intervention, regulation of blood glucose and lipids, and reduction of inflammation. These studies augment our comprehension of the processes through which RS ameliorates MAFLD related disorders. This article examines recent research on the role of gut microbiota in enhancing the condition and progression of MAFLD, along with the therapeutic effects of RS. This study also analyzes the prospective advantages and obstacles of employing RS to treat MAFLD patients. Overall, the available evidence suggests that RS significantly improves MAFLD via the gut microbiota. However, these effects vary depending on the type of RS, the patient population, and gender. We recommend that future studies refine RS classification and usage conditions to optimize its application in MAFLD treatment.

Keywords: Metabolic dysfunction-associated fatty liver disease; Resistant starch; Gut microbiota; Metabolomics; Non-alcoholic fatty liver disease

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1. Introduction

Metabolic Dysfunction-Associated Fatty Liver Disease (MAFLD), previously referred to as non-alcoholic fatty liver disease (NAFLD). In early 2020, a panel of 30 experts from 22 countries reached a consensus on a new definition for MAFLD. This statement delineated precise diagnostic criteria for MAFLD, shifting NAFLD from an

exclusionary to an inclusionary diagnosis [1]. The definition of MAFLD underscores the crucial role of metabolic variables in the development of fatty liver disease. A diagnosis of MAFLD can be established if a patient with fatty liver disease has type 2 diabetes, is overweight or obese, or exhibits at least two additional metabolic variables. MAFLD is a global public health issue, with a current worldwide prevalence as high as 30% and continuing to rise [2]. The disease spectrum of MAFLD ranges from simple steatosis to metabolic dysfunction-associated steatohepatitis (MASH) and liver fibrosis, with potential progression to cirrhosis and hepatocellular carcinoma [3]. It increases the risk of liver disease and is also linked to a heightened risk of other metabolic disorders, including cardiovascular disease and kidney disease [4,5]. Furthermore, given the substantial economic burden associated with this disease, there is an urgent need to enhance public awareness of MAFLD and to implement strategies at both local and global levels to mitigate its detrimental effects [6]. The latest clinical practice guidelines for MAFLD, jointly published by the European Association for the Study of the Liver, the European Association for the Study of Diabetes, and the European Association for the Study of Obesity, recommend non-pharmacological measures for the general population to prevent the occurrence and complications of MAFLD, with an emphasis on strengthening preventive strategies for high-risk groups [7]. In 2024, the U.S. Food and Drug Administration approved the first drug for MASH, Resmetirom [8]. This medication is not yet available in the Chinese market, and dietary adjustments and exercise remain the cornerstones of clinical management for MAFLD. Among these, resistant starch (RS) has been reported to improve hepatic steatosis in MAFLD patients in clinical applications and is gaining increasing attention. RS, as a type of dietary fiber, passes through the small intestine undigested and enters the colon. Its structure or processing renders it “resistant” within the human digestive system. For a long time, the benefits of RS for MAFLD have been recognized [9–11]. This review examines the biological properties of RS, its association with gut microbiota, and its impact on MAFLD via the modulation of gut microbiota, emphasizing gut microbiota as a crucial mechanism by which RS enhances MAFLD conditions. It examines the mechanisms of action of RS and the outcomes from randomized controlled trials, providing a theoretical foundation and direction for clinical therapies in patients with MAFLD.

2. Biological characteristics of RS

Starch is a glucose polymer composed of amylose and amylopectin [12]. Starch provides over 25% of caloric intake in many traditional diets. The human body metabolizes it into glucose for absorption via a variety of enzymes, including amylase and glucosidase [13]. In everyday life, RS dietary fiber is crucial, predominantly located in plant-derived foods including unripe bananas, potatoes, cereals, legumes, and nuts [14]. RS demonstrates exceptional resistance to α-amylase digestion, experiencing no enzyme-mediated hydrolysis and remaining intact in the small intestine. It ultimately arrives at the large intestine unaltered, where it is fermented by the gut microbiota [15]. The initial identification of these compounds transpired in 1982, when Englyst et al. noted that, following the enzymatic breakdown of non-starch polysaccharides in vitro, residual starch persisted in the culture medium [16]. There are five commonly recognized categories of RS: RS1 through RS5. These encompass RS types 1 to 5: RS1 (physically inaccessible starch); RS2 (RS granules); RS3 (retrograded starch); RS4 (chemically modified starch); and RS5 (starch-lipid complex). RS1 is challenging to extract and purify, whereas commercial RS5 products have not yet been launched [17]. Thus, contemporary research on the active constituents and effects of RS predominantly concentrates on the remaining three categories.

3. The relationship between gut microbiota and MAFLD

The gut microbiota comprises a diverse collection of microorganisms residing in the human intestinal tract. This intricate community, consisting of bacteria, viruses, fungi, and other microorganisms, is essential for nutrient absorption, regulation of immune function, and the prevention of harmful pathogen invasion [18–20]. Due to its immense scale and vital role in maintaining health, the gut microbiome is regarded as a "new organ" within the human body [21]. The gut microbiota consists mainly of six fundamental bacterial phyla: *Firmicutes*, *Bacteroidetes*, *Actinobacteria*, *Proteobacteria*, *Verrucomicrobia*, and *Fusobacteria*. Gut dysbiosis is significantly linked to multiple metabolic disorders, such as obesity, metabolic syndrome, diabetes, and liver disease. When gut microbiota dysbiosis occurs, it leads to reduced short-chain fatty acids (SCFAs), impaired intestinal barrier function, and increased intestinal permeability. This allows bacterial components to enter the bloodstream, travel to the liver via the portal vein system, and subsequently trigger or exacerbate inflammatory responses and metabolic disorders in the liver [22]. Research indicates that patients with MAFLD exhibit significant gut dysbiosis, characterized by an increased abundance of pro-inflammatory Proteobacteria and a disrupted balance between the Firmicutes and Bacteroidetes phyla, alongside a reduction in specific beneficial bacteria [23–25]. This dysregulation leads to reduced expression of tight junction proteins, directly impairing intestinal barrier function. This allows harmful microorganisms and their metabolic byproducts to breach the intestinal barrier, stimulating the immune system and inducing inflammatory responses, ultimately accelerating the progression of MAFLD and liver fibrosis [26,27].

4. Regulatory effects of RS on gut microbiota

4.1. Gut microbial degradation of RS

Ruminococcus bromii and *Bifidobacterium adolescentis* are acknowledged as the principal degraders of RS. *Ruminococcus bromii*, a prominent member of the human gut microbiota, features a distinctive amylase structure that enables the formation of multi-enzyme complexes adhering to the cell surface, rendering it a crucial species for RS breakdown [28]. The sugars and acetic acid released by ruminal rumen bacteria during RS degradation serve as substrates for other gut microorganisms lacking RS-degrading capabilities, thereby enabling RS to exert beneficial effects [29,30]. *Bifidobacterium adolescentis* and *Brucella rumenis* exhibit similar functions, capable of degrading RS to produce lactic acid and sugars [31].

4.2. Gut microbiota metabolizes RS into beneficial metabolites

SCFAs are produced by certain gut bacteria through the fermentation of carbohydrates. By diminishing lipid synthesis and enhancing the production of hormones such as PYY and GLP-1 in the intestine, they contribute to the regulation of systemic energy metabolism and foster overall metabolic health [32–34]. Gut microbiota degrades RS to produce SCFAs, primarily acetate, propionate, and butyrate, which are the main end products of RS fermentation in the intestine [35]. The promotion of butyrate production by the RS demonstrates considerable individual variation, which may be associated with initial gut microbiota composition, host genetic background, or dietary patterns [36]. RS dietary supplements positively affect the gut flora by creating a prebiotic effect, hence alleviating symptoms related to metabolic diseases [37–39].

4.3. Clinical research on RS regulation of gut microbiota

The regulating impact of RS on gut microbiota has attracted growing interest. Numerous randomized controlled

trials have shown that RS, irrespective of its origin or dosage, influences its prebiotic physiological effects by affecting the makeup of gut bacteria (**Table 1**). A randomized, double-blind, placebo-controlled clinical experiment assessed the impact of daily doses of 3.5 g and 7 g of Solnul resistant potato starch on beneficial gut microbiota and stool consistency over a duration of 4 weeks. Analysis indicated that, relative to the placebo group, the administration of Solnul resistant potato starch at a daily dosage of 3.5 g over a period of 4 weeks had prebiotic effects, promoting an increase in health-promoting beneficial bacteria while diminishing bowel motions linked to diarrhea and constipation [40]. A randomized placebo-controlled crossover trial involving 37 overweight or obese participants demonstrated that supplementation with RS enhanced outcomes related to obesity. The research demonstrated that gut microbiota plays a crucial role in this effect, with the enrichment of *B.adolescentis* through RS being a significant factor associated with the observed weight loss [41]. Additionally, studies have directly compared the effects of different types of RS (RS2, RS3, and RS5) on the gut microbiota of aged mice. Results indicate that RS5 demonstrates superior efficacy in regulating microbiota and promoting health compared to RS2 or RS3, suggesting it may represent a superior functional ingredient for health maintenance [42]. Overall, RS holds significant value as a functional food ingredient for promoting gut health and preventing metabolic diseases.

Table 1. Regulatory effect of RS on intestinal flora

Resistant starch type	Exist in	Increased abundance	Reduced abundance	Effects on metabolism	Ref
RS1	Found in grains and legumes	*Clostridium* and *Butyricicoccus*	*Bacteroides*, *Lactobacillus*, and *Ruminococcus*	Significant reduction in appetite and decreased postprandial blood glucose levels	[43]
RS2	Found in raw potatoes, green bananas, and raw peas	*Bifidobacterium* and *Ruminococcus*, as well as *Faecalibacterium prausnitzii*, *Roseburia faecis*, and *Akkermansia muciniphila*.	*Bacteroides*, *Odoribacter*, *Dorea*, *Lachnospira*, *Rumi nococcus*, and *Eubacterium*	Reduction of postprandial glucose and leptin, improvement of fasting blood glucose and insulin levels and insulin sensitivity, and reduction of serum total cholesterol and low-density cholesterol	[41,44,45]
RS3	Found in cold rice, bread, and fried foods	*Bifidobacterium*, *Prevotella*, *Ruminococcus*, *Blautia*, *Clostridium*, *Veillonella*, and *Coprococcus*.	*Firmicutes*/*Bacteroidetes ratio*, *Clostridium*, *Enterococcus*, *Streptococcus*, *Leuconostoc*, and *Bacillus*	Reduction of body weight, food intake, total cholesterol, triglyceride, low-density lipoprotein cholesterol levels, and liver fat in mice	[46,47]
RS4	Foods using modified starch (e.g., bread, cakes)	*Clostridia*, *Rothbaryomycetes*, and *Brautobacteria*	*Firmicutes*, and the *Firmicutes/ Bacteroidetes ratio*	Reduces blood sugar and insulin resistance, reduces hunger	[48,49]
RS5	Starch-lipid complexes	*Dialister, Collinsella* , *Megamonas*, *Blauti a*, butyrate-producing bacteria such as *Co prococcus*, *Rosebur ia*, *Bifidobacterium*, and *Butyricicoccus*.	*Bacteroidetes* and *Lactobacillus*	Controls fat deposition in the liver, reduces body weight, and lowers blood sugar and lipid levels	[50]

* RS: Resistant Starch

5. The improvement of MAFLD by RS through the gut microbiota

A healthy diet can reduce the likelihood of obesity and fatty liver disease [51]. Currently, the ketogenic diet, Med-

iterranean diet, and intermittent fasting are all being utilized to improve MAFLD [52–54]. RS is increasingly recognized as an important dietary component, not only for its direct impact on gut health but also for its broader metabolic effects, particularly in relation to metabolic syndrome [55]. Given the critical role of dietary therapy in MAFLD, the corresponding role of RS in MAFLD has also garnered increasing attention (**Table 2**). A review of the literature reveals that alterations in gut microbiota may play a pivotal role in RS-mediated improvement of MAFLD. By increasing beneficial bacteria and reducing harmful bacteria, RS exerts positive effects on MAFLD. Therefore, gut microbiota can be considered a key target for RS in improving MAFLD.

Table 2. Effects of RS on MAFLD-related parameters: evidence from a randomized controlled trial

Types of resistant starch	Subject of intervention	Control subjects	Intervention time	Impact on MAFLD-related indicators	Ref
RS 2	200 participants with NAFLD	Taking control of starch with equal energy supply (CS)	4 months	Absolute reduction in intrahepatic triglyceride content and decreased abundance of *Bacteroides merdae*.	[56]
RS	37 overweight or obese participants	Study participants were randomized into two groups: RS-eluting-CS or CS-eluting-RS	8 weeks	Weight reduction, increased abundance of *Ruminococcus* and *Bifidobacterium*, and decreased abundance of *Bacteroides vulgatus*, *Odoribacter splanchnicus*, *Parabacteroides merdae*, and *Bacteroides vulgatus*.	[41]
RS3	115 patients with hyperlipidemia	Preparation of an identical placebo containing plantain taro natural starch, Ce-NS	12 weeks	Significant reductions in total cholesterol, low-density lipoprotein cholesterol, and non-high-density lipoprotein cholesterol levels.	[57]
RS3	High-fat diet Kunming mice	The negative control group was fed a normal standardized laboratory animal diet, while the blank control group was fed a high-fat diet supplemented with an additional 100 g/kg lard and 10 g/kg cholesterol	4 weeks	Significant reduction in serum total cholesterol, triglycerides, low-density lipoprotein cholesterol and liver fat levels.	[58]
RS5	Mice fed a high-fat diet	Control group 1: received rice starch treated with moist heat; Control 2: received untreated rice starch	8 weeks	Serum oxidative stress levels were significantly improved, and the levels of alanine aminotransferase, aspartate aminotransferase, and alkaline phosphatase were reduced	[59]
Natural corn starch (65% RS content)	Rats on a high-fat diet	Received a high-fat diet without added resistant starch	36 weeks	Reduction in total cholesterol, triglyceride, and low-density lipoprotein cholesterol levels, as well as an increase in high-density lipoprotein cholesterol levels	[60]

* RS = Resistant Starch; CS = Control Starch

5.1. The effect of RS on obesity via the gut microbiota

The increasing prevalence and severity of MAFLD are associated with the rising trend of obesity [61]. Because the early stages of MAFLD typically present no obvious symptoms, the prevalence of obesity-driven MAFLD and its subsequent incidence can be considered one of the major health crises of the coming decade [62,63]. Several strains have been demonstrated to exert positive effects in reducing obesity, body weight, and energy intake. *Bifidobacterium* and *Lactobacillus* are the most common probiotic species exhibiting these characteristics [64]. Research indi-

cates that under RS intervention, the abundance of *Lactobacillus* and *Bifidobacterium* increases [65,66]. These lactic acid-producing bacterial communities support the growth and metabolic activity of butyrate-producing bacteria by increasing lactic acid availability, thereby promoting SCFA production to improve obesity and MAFLD [67]. Studies conducted among obese populations indicate that the intake level and intervention duration of high-amylose cornstarch (HA-MRS 2) in the diet are key factors influencing its efficacy. Higher intake levels combined with longer intervention periods yield greater reductions in abdominal fat, more significant weight loss, and improved outcomes in other obesity-related metabolic indicators. An animal study similarly confirmed the dose-response effect of RS: Obese mice were fed potato RS at varying concentrations (5%, 15%, and 25%) for 12 weeks. Results demonstrated that RS alleviated high-fat diet-induced metabolic syndrome in a dose-dependent manner; Its mechanisms include reducing the *Firmicutes*/*Bacteroidetes* (F/B) ratio, regulating the relative abundance of gut microbiota such as *Bifidobacterium*, *Ruminococcus*, *Bacteroides*, and *Faecalibacterium*, and promoting the production of beneficial microbial metabolites like propionic acid and acetic acid [68].

5.2. The effect of RS on liver lipid metabolism via the gut microbiota

The liver is the central regulator of serum cholesterol and triglycerides [69]. When lipid intake exceeds the liver's metabolic capacity, it disrupts triglyceride and cholesterol metabolism, leading to fatty degeneration and lipotoxicity. This promotes the development of metabolic disorders such as MAFLD and hypercholesterolemia [70,71]. Research indicates that RS significantly influences lipid metabolism factors via the gut microbiota, thereby preventing and controlling hyperlipidemia, affecting hepatic lipid metabolism, and improving MAFLD. A recent clinical study first applied RS in MAFLD patients. Over 4 months, RS intake positively impacted hepatic triglyceride levels in MAFLD patients through gut microbiome regulation. Following HAM-RS2 intake by 200 MAFLD patients, an absolute reduction in hepatic triglyceride levels and decreased fecal Bacteroides abundance were observed. This improvement was independent of weight loss [56]. Animal studies also provide compelling mechanistic evidence. In an investigation examining the effects of lotus seed RS on hyperlipidemic mice induced by a high-fat diet and its potential mechanisms, RS intervention significantly reduced weight gain and fat index in high-fat diet mice. It also markedly lowered serum levels of total cholesterol, triglycerides, and LDL-cholesterol while increasing HDL-cholesterol levels. Mechanistic investigations revealed that RS significantly modulated genes associated with fatty acid degradation, fatty acid elongation, and triglyceride metabolism [72]. In another study using a high-fat diet rat model, 36 weeks of intake of a RS-rich corn starch (containing 65% RS) improved serum lipid profiles by reducing total cholesterol, triglycerides, and LDL-cholesterol, and by increasing HDL-cholesterol. Concomitantly, this treatment modulated the gut microbiota, increasing Firmicutes and maintaining Bacteroidetes abundance [60].

5.3. RS modulates hepatic inflammatory responses via the gut microbiota

Reactive oxygen species (ROS) and oxidative stress induced by inflammatory responses are key mechanisms causing hepatocyte damage [73]. Excessive hepatic lipids induce alterations in cellular redox status and accumulation of oxidative damage to biomolecules [74]. Subsequently, excessive ROS production suppresses the capacity of other antioxidant defense systems in MAFLD, leading to further oxidative damage [75]. Compared to healthy individuals, MAFLD is characterized by a reduction in beneficial anti-inflammatory microbes (*Ruminococcus* and *Faecalibacterium*) and an increase in the abundance of harmful pro-inflammatory microbes (*Fusobacterium* and *Escherichia*) [67,76–78]. These alterations indicate that gut microbiota dysbiosis may trigger inflammatory responses in the liver, thereby influencing the progression of MAFLD. Animal studies confirm that RS2 intervention reduces

the abundance of multiple obesity- and inflammation-associated pathogens in mice, such as *Desulfovibrio* and *Ruminiclostridium* 9, demonstrating its potential to antagonize inflammation by regulating the microbiota [79].

5.4. RS maintains stable blood glucose levels through the gut microbiota

Due to its slow absorption rate, RS regulates glucose and insulin levels by lowering fasting and postprandial blood glucose and enhancing insulin sensitivity, thereby promoting glucose homeostasis in the body. In the liver, smaller β-glycogen granules can aggregate into larger composite α-granules. In diabetic mouse models, these hepatic glycogen granules exhibit fragility at the molecular level. A high-RS diet can prevent the fragility of hepatic glycogen α-granules, thereby contributing to blood glucose control. Beyond directly regulating blood glucose, RS can also indirectly influence metabolism through fermentation by gut microbiota. *Clostridium butyricum*, a bacterium that degrades RS, can grow on various types and sources of RS, producing large amounts of butyrate during the degradation process. Butyrate improves insulin sensitivity by enhancing energy expenditure and fat oxidation in the colon. Additionally, research indicates that RS, when fermented by gut microbiota, produces SCFAs that stimulate the release of anorexigenic hormones such as peptide YY (PYY) and glucagon-like peptide-1, thereby increasing satiety and reducing calorie intake. Existing studies have demonstrated the positive effects of adjusting dietary RS intake on glycemic control, insulin sensitivity, and gut health. Human studies also provide direct evidence: In a study involving 37 overweight or obese participants, the effects of RS as a dietary supplement on obesity-related outcomes were examined. Results indicated that RS improves hepatic steatosis and increases insulin sensitivity by modulating the gut microbiota to enhance secondary bile acid production [41].

6. Limitations of RS in MAFLD applications

Despite the significant potential of RS in improving MAFLD, its clinical application remains limited. A cohort study of Korean adults revealed gender-specific associations between RS intake and metabolic syndrome: high RS intake significantly reduced the risk of metabolic syndrome in men, whereas no similar association was observed in women [5]. Furthermore, the mechanism of action of RS is highly dependent on the reconstitution of the gut microbiota. The substantial individual variation in patients' baseline gut microbiome composition is the primary reason for the inconsistent therapeutic efficacy. Patients with more severe gut dysbiosis may require longer intervention periods to observe significant improvement. This suggests that the efficacy of RS intervention may vary depending on gender and individual microbiome characteristics, and future studies should further explore its mechanisms. Current research primarily focuses on patients with mild to moderate MAFLD [56]. Its intervention effects are evident during the simple fatty liver stage. For patients who have progressed to non-alcoholic steatohepatitis (NASH) or liver fibrosis, there is currently insufficient evidence to determine whether resistant starch can reverse liver damage. Overall, while RS represents an innovative intervention strategy for MAFLD, further development of personalized gut microbiota modulation approaches and expanded efficacy assessments in advanced-stage patients are needed to enhance its clinical applicability.

7. Conclusions

The gut microbiota is essential for our health. In the therapy of MAFLD, preserving gut microbiota equilibrium is crucial for hepatic health. Studies demonstrate that dysbiosis is significantly linked to the initiation and advance-

ment of MAFLD. A decline in beneficial bacteria and an increase in pathogenic bacteria may incite inflammatory responses, compromise liver function, and ultimately facilitate the onset of MAFLD. Consequently, modifying and improving gut microbiota composition by RS presents considerable potential for the prevention and treatment of MAFLD. The European Food Safety Authority and the U.S. Food and Drug Administration have both sanctioned health claims for RS in diabetes control, endorsing its application in diabetic treatment. This validates the beneficial impact of RS on metabolic diseases. Nevertheless, investigations of RS in MAFLD, a metabolic disorder similar to diabetes, are limited, a situation that necessitates thorough examination. Nonetheless, current research provides initial insights. Numerous studies suggest that the consumption of RS products beneficially affects fatty liver diseases via gut flora. Significantly, RS encounters difficulties in the treatment of MAFLD. Diverse RS varieties have distinct impacts on gut flora, and individual and gender variations may considerably affect RS responsiveness. Future study requires additional cohort studies focused on specific patient populations, meticulously structured clinical trials, and a comprehensive investigation of RS's molecular processes and therapeutic effectiveness. These investigations will provide a more accurate assessment of appropriate RS intake amounts and varieties, elucidate its function as a viable therapeutic strategy, and yield tailored, evidence-based therapy regimens for MAFLD patients, while guaranteeing the safety and efficacy of RS-based therapies.

Disclosure statement

The authors declare no conflict of interest.

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