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REVIEW

Multifunctional role of oral bacteria in the progression of non-alcoholic fatty liver disease

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Abstract

Non-alcoholic fatty liver disease (NAFLD) encompasses a spectrum of liver disorders of varying severity, ultimately leading to fibrosis. This spectrum primarily consists of NAFL and non-alcoholic steatohepatitis. The pathogenesis of NAFLD is closely associated with disturbances in the gut micr-obiota and impairment of the intestinal barrier. Non-gut commensal flora, particularly bacteria, play a pivotal role in the progression of NAFLD. Notably, *Porphyromonas gingivalis*, a principal bacterium involved in periodontitis, is known to facilitate lipid accumulation, augment immune responses, and induce insulin resistance, thereby exacerbating fibrosis in cases of periodontitis-associated NAFLD. The influence of oral microbiota on NAFLD *via* the "oral-gut-liver" axis is gaining recognition, offering a novel perspective for NAFLD management through microbial imbalance correction. This review endeavors to encapsulate the intricate roles of oral bacteria in NAFLD and explore underlying mechanisms, emphasizing microbial control strategies as a viable therapeutic avenue for NAFLD.

Key Words: Non-alcoholic fatty liver disease; Oral bacteria; Gut bacteria; Periodontitis; Non-alcoholic steatohepatitis

Core Tip: Non-alcoholic fatty liver disease (NAFLD) is a significant concern within the realm of chronic liver diseases, notably affecting economic health. The disruption of intestinal flora balance by oral bacteria accelerates the progression of NAFLD. Moreover, through the inflamed oral mucosa, these bacteria and their virulence factors may enter the bloodstream, leading to systemic inflammation. Therefore, an innovative therapeutic approach for NAFLD involves strategic adjustments to the microbial balance within the oral cavity and gastrointestinal tract. This review succinctly delineates the roles and mechanisms of oral bacteria in NAFLD, providing a foundational framework for future therapeutic strategies.

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INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) covers a spectrum of liver disorders, varying in severity from fatty liver to advanced fibrosis, including NAFL and non-alcoholic steatohepatitis (NASH). In the United States, the prevalence of NAFLD was reported at 83.1 million cases in 2015, approximately 25% of the population, and is projected to rise to 100.9 million by 2030[1]. In China, current prevalence rates hover around 30%[2]. Within a timeframe of 2-3 years, 15%-20% of NAFL cases and 10%-20% of NASH cases may advance to cirrhosis[3]. NAFLD is a critical factor in the progression to end-stage liver disease and hepatocellular carcinoma[4], with those affected exhibiting a 65% heightened risk of cardiovascular diseases compared to the general populace[5]. The global recognition of NAFLD as a leading cause of chronic liver disease underscores its escalating prevalence and the significant economic challenge it poses.

The human oral cavity ranks as one of the most microbially diverse regions within the body, harboring around 776 unique bacterial species. According to the Human Oral micro-biome Database (https: www.ehomd.org/), 58% of these species are identified, 16% remain unnamed yet cultivated, and 26% are known solely as uncultivated phylotypes. Disruptions in the balance of the oral microbiota can precipitate a variety of oral health issues, such as periodontitis and dental caries, while also exerting wider systemic impacts. Increasingly, evidence suggests that oral bacteria influence the gut microbial ecology and liver metabolism through both the bloodstream and direct ingestion.

The oral-gut axis demonstrates a substantial correlation with NAFLD, including the translocation of bacteria from the oral cavity to the gastrointestinal tract and the interplay between oral and gut microbiomes[6]. Bacterial migration occurs *via* three primary pathways: The enteral route, the hematogenous route, and immune cell migration[7]. Notable periodontal pathogens, such as *Porphyromonas gingivalis* (*P. gingivalis*), *Fusobacterium nucleatum*, and *Aggregatibacter actinomycetemcomitans* (*A. actinomycetemcomitans*), significantly affect the gut microbiota[8-10]. Conversely, by altering the gut ecosystem, oral dysbiosis may intensify chronic liver diseases, such as NAFLD. Furthermore, oral dysbiosis could mirror the intestinal dysbiosis induced by hepatic diseases[11].

This review delves into the interactions between oral bacteria and NAFLD, scrutinizing potential mechanisms and exploring prospective therapeutic strategies for NAFLD.

EPIDEMIOLOGY, ETIOLOGY, AND CLINICAL DIAGNOSIS OF NAFLD

NAFLD epidemiology

Among chronic liver diseases globally, NAFLD boasts the highest prevalence, with rates varying from 13.5% in Africa to 31.8% in the Middle East[12]. This variability can be attributed to numerous factors including dietary caloric intake, levels of physical activity, distribution of body fat, socioeconomic status, and genetic factors. Notably, the African-American population exhibits the lowest incidence of NAFLD, while the Hispanic demographic shows a higher prevalence of NASH[13]. A significant correlation exists between NAFLD and metabolic syndrome, with high prevalence rates in individuals manifesting type 2 diabetes, central obesity, dyslipidemia, and metabolic syndrome-affecting 47.3%-63.7% of patients with type 2 diabetes and up to 80% of obese individuals[14,15]. Importantly, NAFLD can also develop in individuals with healthy body mass indices (BMIs), often classified as non-obese or lean NAFLD[16], which typically presents with central obesity or other metabolic risk factors[17].

NAFLD etiology

Day *et al*[18] initially proposed the "two-hit" theory for the pathogenesis of NAFLD, suggesting a two-step process involving lipid accumulation in hepatocytes in 1998. However, this theory has since been considered oversimplified, with current understanding acknowledging the complexity of NAFLD pathogenesis through multifaceted interactions across various stages. The disease is primarily driven by ectopic fat accumulation due to macrophage infiltration of visceral adipose tissue. Lipid metabolic imbalances lead to the generation of lipotoxic lipids, which trigger cellular stress (oxidative and endoplasmic reticulum stress), inflammasome activation, cellular death, tissue regeneration, and fibrosis [19,20]. Furthermore, NAFLD is associated with metabolic dysregulation and inflammation, influenced by interactions

between the liver and both the intestinal and oral microbiota. Epidemiological evidence suggests periodontitis as an independent risk factor for NAFLD progression[21], supported by findings of hepatic lipid deposition in mice with *P. gingivalis*-induced periodontitis and altered gut microbial compositions in NAFLD patients[22], highlighting a potential pathogenic mechanism of the disease and NAFLD patients have altered gut microbial compositions[23,24].

NAFLD clinical diagnosis

The diagnosis of NAFLD involves identifying steatosis in the absence of secondary causes such as alcoholic hepatitis, followed by stratifying the risk for NASH and fibrosis[25]. Abdominal ultrasonography, which shows a bright hepatic echo texture and blurred hepatic vasculature[26], is the most commonly used method to detect steatosis. However, its sensitivity for detecting mild steatosis is limited, necessitating additional magnetic resonance imaging evaluations[27]. Risk stratification based on the presence of significant fibrosis is crucial for all NAFLD patients, given its critical role in prognosis. Non-invasive methods include the enhanced liver fibrosis score[28], serum aspartate aminotransferase (AST) to alanine aminotransferase (ALT) ratio[27], and ultrasonic imaging[29]. While these methods are notable, limitations exist in early diagnosis, making liver biopsy the gold standard for fibrosis assessment in NAFLD patients.

MICROBIAL DISORDERS IN INTESTINAL EPITHELIUM

In addition to the skin, the intestinal epithelium constitutes the body's second largest physical barrier[30]. It functions selectively, facilitating nutrient absorption, obstructing pathogenic invasions, limiting water and electrolyte depletion, and promoting waste elimination[31]. The epithelium, comprising intestinal epithelial cells, features tall villi interspersed with specialized cells such as paneth cells, goblet cells, enteroendocrine cells, and M cells. Paneth cells protect stem cells by releasing antimicrobial peptides (AMPs), including α-defensins, lysozyme C, and phospholipases[32]. Goblet cells are integral to mucin secretion, critical for forming a mucous layer that lubricates and shields epithelial cells, and aids in antigen presentation alongside M cells[33]. Enteroendocrine cells discharge various hormones, and tuft cells specialize in chemosensation[34]. The intestinal epithelium is increasingly recognized as a pivotal element of mucosal immunity, housing about 70% of the body's lymphocyte population and establishing itself as the largest immune organ[35]. A key feature of intestinal mucosal immunity is the presence of mucosa-associated lymphoid tissue, encapsulated by follicle-associated epithelium, which underpins the intestinal response to external antigens, especially those from ingested bacteria[36]. Ultimately, the barrier function of the intestinal epithelium is multifaceted, encompassing epithelial cells, the mucous layer, the lamina propria, blood circulation, and the microbiota, working collectively to maintain intestinal equilibrium and prevent the entry of harmful substances and microbes.

Dysregulation of symbiotic microbiota and consequent mucosal immune imbalances serve as a common pathophysiological feature in oral inflammatory diseases, especially periodontitis and NAFLD (Figure 1). Extensive research highlights the close link between the development of human NAFLD and gut microbiota imbalances[37,38]. Germ-free (GF) animal models are routinely used to explore the effects of an absent gut microbiota on host physiological functions [39]. Under various dietary conditions, GF animals show resistance to obesity, a phenomenon connected to activity in specific genes and enzymes[40,41]. Microbiota transplantation studies have confirmed the relationship between gut microbiota, obesity, and energy intake[42,43]. Regarding liver conditions, gut microbiota alters specific hepatic gene expressions and metabolism, potentially affecting NAFLD progression[44-46]. In summary, GF conditions influence metabolism, obesity, and NAFLD-related phenotypes. Microbiota transplantation experiments reinforce the causal link between microbiota composition and NAFLD vulnerability[47]. Whole-genome sequencing has identified differences in gut microbiota composition between patients with mild/moderate NAFLD and those with severe fibrosis[24]. Numerous clinical trials indicate that microbial dysbiosis correlates with the severity of NAFLD outcomes, with patients showing increased Bacteroides and reduced *Phylum Firmicutes* facing worse results[48-51]. The progression from NAFLD to NASH may also involve gut microbiota[52]. Regarding bacterial species, specific strains (*e.g.*, *Dorea*, *Lactobacillus*, *Roseburia*, and *Robinsoniella*) are linked to an increased risk or presence of NAFLD[53-55]. Studies also report increased bacterial ethanol production in the intestines of NASH patients[56]. The various mechanisms by which gut bacterial imbalances drive NAFLD progression will be discussed later, but it is clear that microbial dysbiosis plays a significant role in NAFLD development through diverse pathways.

MICROBIAL DISORDERS IN ORAL EPITHELIUM

As a critical mucosal barrier, the oral mucosa prevents pathogenic invasions and maintains homeostasis. It is composed of stratified squamous epithelium, divided into masticatory, lining, and specialized mucosae[57]. The masticatory mucosa, found in areas such as the gums and hard palate, is adapted to endure frequent mechanical stress. In contrast, the specialized mucosa, located primarily on the tongue's dorsal surface, contains nerve endings sensitive to taste and general sensations. The rest of the oral cavity, including the inner surfaces of the lips, cheek mucosa, soft palate, and mouth floor, is lined by mucosa that may be partially keratinized or non-keratinized, depending on the area and its exposure to physical stimuli. Unlike the intestinal epithelium, the oral epithelium generally lacks chemosensory cells, hormone, or mucin-producing cells, and harbors a more diverse microbial community. Oral epithelial cells display unique keratin expression patterns, enhancing immune tolerance in the oral mucosa[58]. Nevertheless, this tolerance is not absolute, as the junctional epithelium and tonsillar crypt epithelium are particularly susceptible sites. The junctional

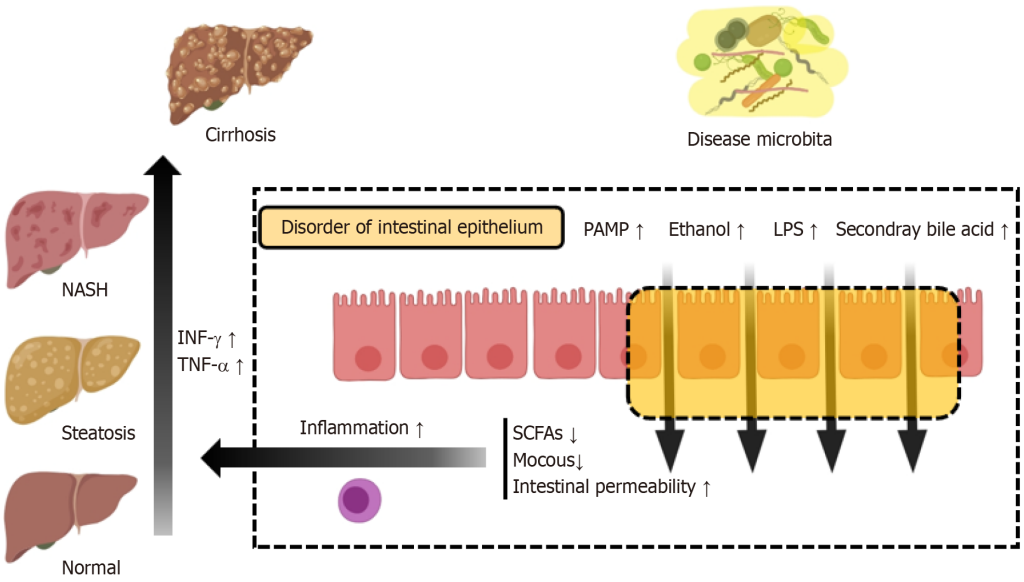

Figure 1 Disruption of intestinal mucosal barriers by pathogenic microorganisms. Pathogenic microorganisms elevate levels of pathogen-associated molecular patterns, lipopolysaccharide, ethanol, and secondary bile acids in the intestinal mucosa, leading to a decrease in protective intestinal mucus and short-chain fatty acids. This exacerbates local inflammation and enhances intestinal permeability. As a result, pathogenic microorganisms and their virulence factors are transported to the liver *via* the portal venous system, facilitating the progression of non-alcoholic fatty liver disease. PAMP: Pathogen-associated molecular; LPS: Lipopolysaccharide; NASH: Non-alcoholic steatohepatitis; TNF-α: Tumour necrosis factor alpha; INF: Interferon; SCFAs: Short-chain fatty acids.

epithelium, connecting teeth and subgingival tissues, is only 3-4 cell layers thick and lies near dental plaque biofilms. The tonsillar crypt epithelium, part of Waldeyer's ring, contains M cells that present antigens to stimulate adaptive immune responses, thus providing structural pathways for pathogens to invade from the mouth[57,59,60].

The oral microbiota is diverse and dynamic[61], with complex microbial communities in the mouth influencing the induction, training, and function of mucosal immunity by forming micron-scale microbial habitats and niches[62]. Microbial imbalances are pathogenic factors for common oral diseases like periodontitis[63] and oral candidiasis[64], where the IL-17/Th17-dependent pathway plays a central role in controlling oral mucosal infections and inflammation. Microbial dysbiosis results in the aggregation of IL-6, IL-23-dependent Th17 cells in the gingival sulcus, leading to neutrophil recruitment and subsequent alveolar bone loss[59]. A delicate ecological balance, maintained by the interplay between the microbiota and the immune system, is crucial. Disruption of this balance results in mucosal immune imbalances and pathological changes. Certain periodontal pathogens, including *A. actinomycetemcomitans*, *P. gingivalis*, *T. forsythia*, and *T. denticola*, can induce inflammatory responses and disrupt intercellular junctions[65,66]. Bacteria possessing virulence factors proliferate in inflamed states and can enter the bloodstream through compromised oral mucosa, thereby exerting deleterious effects on NAFLD (Figure 2).

PERIODONTITIS IS A RISK FACTOR FOR NAFLD

Epidemiological studies have indicated a connection between periodontitis and NAFLD, with genome-wide association studies suggesting a positive causal relationship between the two conditions[67]. Periodontitis and elevated serum ALT levels were found to be significantly correlated in the study by Furuta *et al*[68]. In research conducted by Kim *et al*[69], the fatty liver index and periodontal disease were associated, with a greater correlation observed in females. Furthermore, NAFLD and the number of missing teeth are significantly correlated in males, according to the study by Qiao *et al*[70].

Periodontitis is a bacterial oral disease in which *P. gingivalis*, a non-fermentative Gram-negative anaerobic rod, emerges as a crucial periodontal pathogen. A latent connection between *P. gingivalis* and NAFLD has been discovered. Patients with NAFLD exhibit higher levels of *P. gingivalis* and its DNA in the oral cavity or liver compared to controls[71,72]. Furthermore, those infected with *P. gingivalis* and suffering from NASH show more severe fibrosis[71]. Additionally, evidence from numerous *in vivo* experiments suggests that *P. gingivalis* infection can promote lipid accumulation, intensify immune responses, and induce insulin resistance, highlighting its significant role in NAFLD/NASH progression [73]. Translocated oral microbes, such as *P. gingivalis*, disrupt the balance of gut microbiota, which can exacerbate NAFLD through various mechanisms[74-76]. These include altering intestinal permeability, modulating energy absorption evidenced by increased dietary fat intake promoting hepatic fat deposition[41,77-79], regulating bile acid metabolism as seen in changes in bile acid composition due to gut microbiota dysbiosis[80-82], and increasing endogenous ethanol production[56,83].

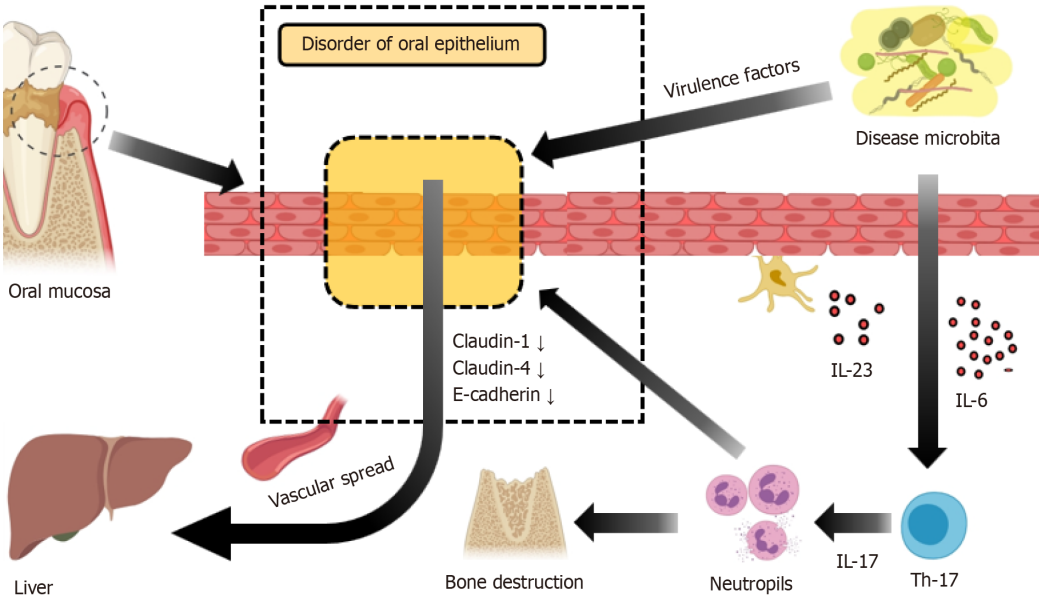

Figure 2 Disruption of oral mucosal barriers by pathogenic microorganisms. Pathogenic microorganisms enhance Th17 cell secretion of interleukin (IL)-17 through stimulating factors, including IL-6 and IL-23, which leads to neutrophil aggregation and activation. Concurrently, oral epithelial cells reduce the expression of Claudin-1, Claudin-4, and E-cadherin, thereby increasing barrier permeability. This alteration elevates the risk of pathogenic microorganisms entering the bloodstream and reaching the liver. IL: Interleukin.

ASSOCIATION BETWEEN ORAL BACTERIAL AND NAFLD

Oral microbiota is implicated in various oral diseases such as periodontitis and dental caries. Recent research has highlighted an increasingly clear link between these microbiota-related oral conditions and NAFLD. The multifaceted interaction among oral microbiota, the intestinal barrier, the immune system, and the liver is susceptible to disruption by environmental and genetic factors, potentially leading to systemic diseases. A significant physiological relationship exists among the oral cavity, intestine, and liver, forming the "oral-gut-liver" axis. In this context, the balance of gut microbiota plays a critical role in NAFLD progression[84]. Additionally, dysbiosis of oral microbiota has been associated with imbalances in gut microbiota[85-87]. The connection between the oral cavity and the liver could be mediated through bacterial translocation, inflammatory responses, bacterial virulence factor toxicity, and disruptions in lipid metabolism (Figures 3 and 4).

Oral microbial translocation

The translocation of oral bacteria to the gut is a pathogenic step in the development of NAFLD, occurring chiefly through hematogenous routes and direct swallowing. Micro-ulcerations within periodontal pockets facilitate systemic bacterial, endotoxin, and inflammatory mediator dissemination, enabling their access to the liver *via* the hepatic artery. In contrast, healthy gingival epithelium in periodontal tissue acts as a protective barrier against harmful biofilm components[88]. However, inflammation in diseased tissues increases capillary permeability[89], enhances gingival epithelium permeability, and triggers micro-ulceration formation, thus allowing toxic substances and microbes to invade the circulatory system through periodontal tissues. Dental procedures or poor oral hygiene can lead to transient bacteremia, with a noted increase in lipopolysaccharide (LPS) content in circulating bacteria among individuals with periodontal disease compared to healthy ones[90-92]. Studies by Furusho *et al*[71] showed that approximately 53% of NAFLD patients had liver biopsy samples containing *P. gingivalis*, with those suffering from periodontitis displaying higher liver fibrosis scores. Takeuchi *et al*[93] found that hyperglycemia facilitates the movement of *P. gingivalis* from the oral cavity to the liver, suggesting that oral bacteria might influence NAFLD through the bloodstream.

Another potential pathway for communication between oral bacteria and NAFLD involves the ingestion of oral bacteria *via* saliva, which may subsequently impact the gut microbiota and, consequently, NAFLD. An individual swallows up to 1.5 liters of saliva daily, containing approximately 1.5×10^{12} oral bacteria[94]. Animal research suggests that consuming oral bacteria associated with periodontal disease, such as *P. gingivalis* and *Actinomyces*, can lead to gut microbiota changes. These changes disrupt metabolic pathways related to glucose and lipid metabolism, resulting in insulin resistance and hepatic lipid accumulation[95]. It is important to note that the causal relationship between oral bacterial colonization and the development of intestinal dysbiosis is still debated. Although the acidic gastric environment is fatal for most bacteria, oral microbes are often found in the intestines of healthy individuals; a reduced gut microbiota diversity is observed in patients with periodontal disease[96,97]. Alternatively, some studies suggest that oral bacterial colonization in the gut may depend on the disruption of the intestinal milieu, potentially associated with excessive antibiotic and proton pump inhibitor use, poor dietary choices, and high levels of psychological stress[98,99].

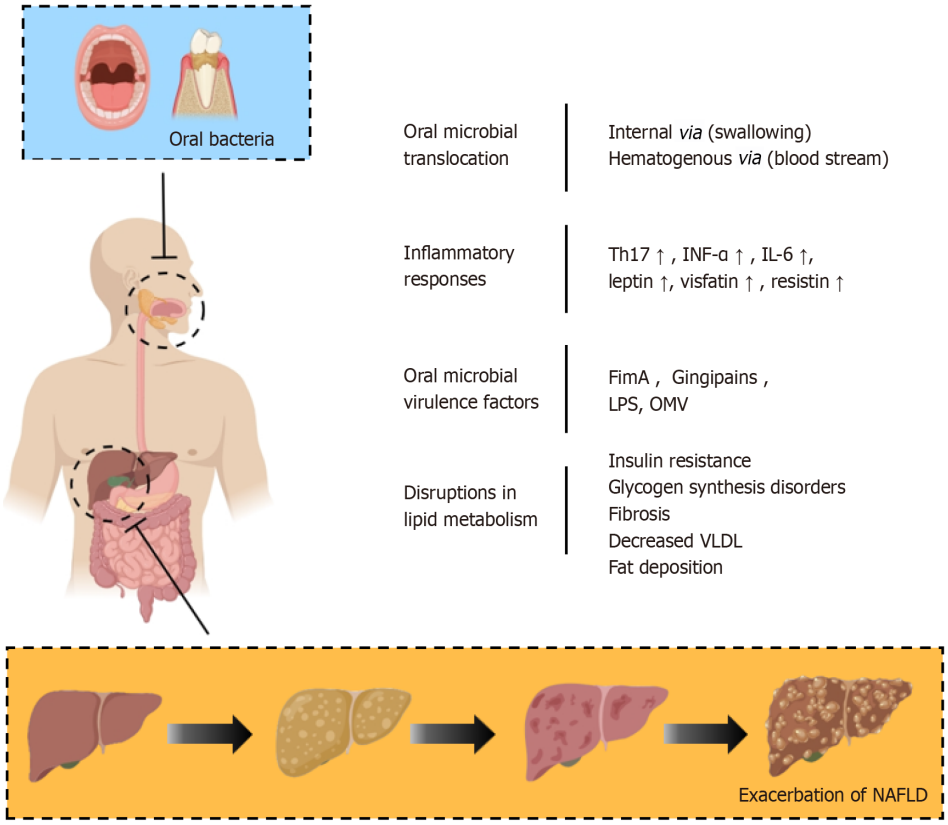

Figure 3 The connection between oral microbiota and non-alcoholic fatty liver disease. Oral microbiota plays a significant role in advancing liver fat deposition, inflammatory responses, and fibrosis, thus expediting the progression from non-alcoholic steatohepatitis to non-alcoholic fatty liver disease. This effect is mediated through four principal mechanisms: Translocation of oral microbes, inflammatory responses, virulence factors of oral microbes, and disruptions in lipid metabolism. OMV: Outer membrane vesicles; LPS: Lipopolysaccharide; INF-α: Interferon alpha; IL: Interleukin; VLDL: Very-low-density lipoprotein; NAFLD: Non-alcoholic fatty liver disease.

Inflammatory responses

In the oral and intestinal regions, the symbiotic relationship between the immune system, epithelial cells, and microbiota is essential for maintaining tissue function and systemic homeostasis. The immune response to periodontitis and intestinal inflammatory diseases facilitates the growth of pathogenic bacteria. Yao *et al*[100] identified that *Porphyromonas gingivalis* disturbs the Th17/Treg cell balance in the liver and spleen, leading to hepatocyte ferroptosis and increased hepatic inflammation, with the nuclear factor κB (NF-κB) signaling pathway playing a critical role[101]. Kitamoto *et al*[102] found that periodontal disease promotes growth of oral pathogens like Klebsiella and Enterobacter, which can exacerbate intestinal inflammation when they colonize the gut. In mouse models of colitis, heightened intestinal nitrate levels led to a dominance of nitrate-respiring Enterobacteriaceae over anaerobic commensals, exacerbating the disease [103]. Oral microbes are key players in nitrate reduction due to their nitrate reductase activity[104,105]. The TH17 inflammatory pathway also contributes to the progression of intestinal inflammation linked to periodontitis[63,106-108]. Studies have shown that oral TH17 cells can migrate to the gut and stimulate inflammatory reactions there, highlighting the oral-intestinal interconnection in mucosal inflammation[102]. Zhao *et al*[109] demonstrated that topical administration of AMP Mastoparan X alleviates intestinal inflammation induced by *Escherichia coli* and helps restore balance to the gut microbiota.

Oral microbiota can induce systemic inflammatory cytokines and oxidative stress, affecting inflammation. In periodontitis, levels of pro-inflammatory cytokines such as tumour necrosis factor alpha (TNF-α) and interleukin (IL)-6[110], as well as serum pro-inflammatory adipokines (*e.g.*, leptin, visfatin, and resistin), are increased[111,112], whereas the anti-inflammatory adipokine adiponectin decreases, potentially exacerbating inflammatory responses and lipid accumulation. Tomofuji *et al*[113] observed that periodontitis was linked to oxidative DNA damage in the liver. Matthews *et al*[114] reported that peripheral neutrophils from individuals with chronic periodontitis exhibited an increased *in vitro* production and release of reactive oxygen species. Önder *et al*[115] discovered that clinical interventions in periodontal treatment reduced serum reactive oxygen species and lipid peroxide levels in periodontitis patients, indicating that systemic oxidative stress associated with periodontitis may lead to hepatic oxidative damage.

Oral microbial virulence factors

P. gingivalis, a Gram-negative anaerobic bacterium found in the oral cavity, can colonize oral epithelial cells[116]. It possesses numerous virulence factors such as fimbriae, LPS (including LPS-induced endotoxemia), gingipains, and outer membrane vesicles (OMV). These factors are pivotal in the bacterium's survival, dissemination, and pathogenicity[117,

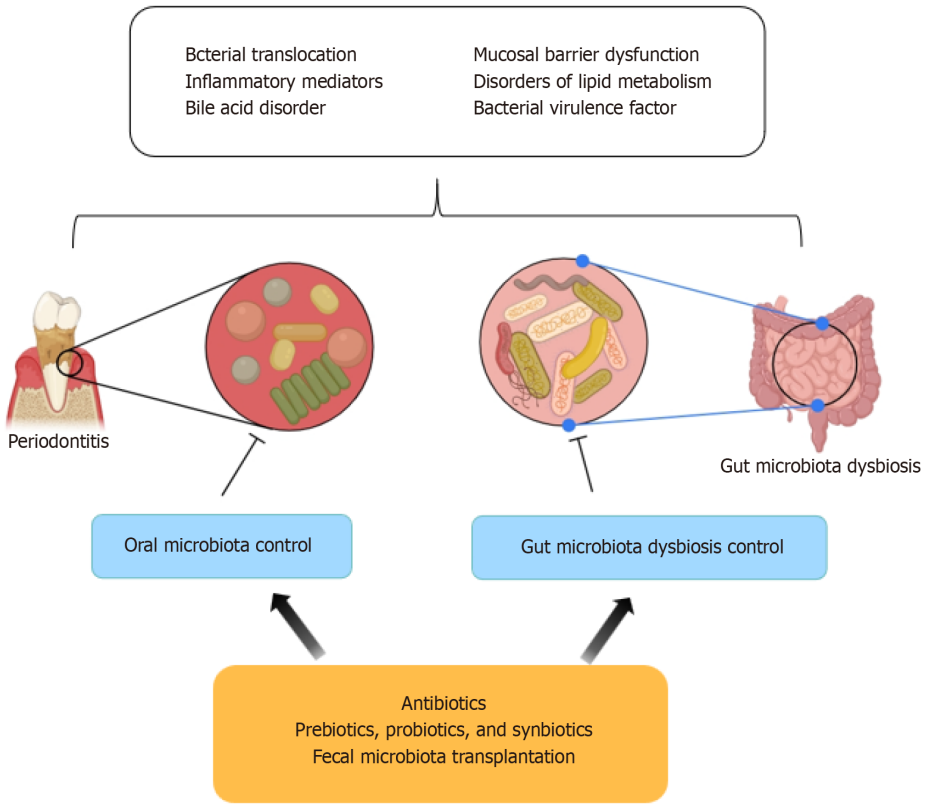

Figure 4 Microbial control strategies for treating non-alcoholic fatty liver disease. The management of non-alcoholic fatty liver disease (NAFLD) through microbial control includes the use of antibiotics, prebiotics, probiotics, synbiotics, and fecal microbiota suppression to regulate oral and gut microbiomes, maintain microbial balance, and protect mucosal barriers, ultimately reducing the bacterial influence on NAFLD.

118].

FimA, a specific fimbria found in *P. gingivalis*, is associated with the onset of NAFLD[119]. FimA can interact with various host receptors, activating adhesion and immune-inflammatory pathways, thereby promoting bacterial colonization and triggering host cell inflammation[120-122]. FimA binds to Toll-like receptor 2 (TLR2), triggering the activation of the NF-κB system and leading to the production of inflammatory cytokines[123]. Furthermore, through its interaction with complement receptor 3, FimA activates the innate immune system, thereby stimulating macrophages/monocytes. This enhances the persistence and survival of *P. gingivalis*[124].

Gingipains are primary virulence factors linked to the pathogenicity of *P. gingivalis*[125]. They play a crucial role in biofilm formation and elicit immune-inflammatory responses by activating various immune cellss[124,126]. Gingipains may evade the host's adaptive immune system by modulating T-cell immunity[127]. Furthermore, gingipains could be implicated in glucose metabolic damage and insulin resistance, meriting additional research.

Biofilms and OMVs represent two crucial structures produced by microbes, which play essential roles in bacterial survival, dissemination, and pathogenicity[128,129]. The OMV of *P. gingivalis* have the capability to transport virulence factors, including gingipains and LPS. These vesicles can release these virulence factors into the environment, contributing to *P. gingivalis*'s involvement in diseases associated with bacteria[130,131]. OMVs may also play a role in the development of NAFLD by adversely affecting glucose metabolism and insulin sensitivity[132]. In summary, the virulence components of *P. gingivalis* contribute to bacterial defense, activating various risk factors for NAFLD and influencing its pathogenicity.

LPS, a component of the outer membrane of Gram-negative bacteria, is vital for microbial pathogenicity[133,134]. Its active component, lipid A, is known for its pyrogenic, pro-inflammatory, and toxic effects on humans and animals. To mitigate these effects, the human innate immune system harbors cells that express LPS receptors, such as TLR4 and CD14, which elicit a strong inflammatory response to LPS[135]. In NAFLD, increased gut-derived endotoxemia, marked by elevated blood LPS levels due to higher gut permeability, is a crucial factor driving disease advance[136-138]. This leads to systemic inflammatory reactions, including raised levels of C-reactive protein, IL-6, and TNF-α[139]. LPS significantly contributes to the activation of host inflammatory responses through Toll-like receptor (TLR) activation[140]. Studies have shown that *P. gingivalis* LPS's impact on NAFLD may involve higher expression of TLR2, mRNA levels of inflammasomes, and increased production of pro-inflammatory cytokines[71]. Specifically, in the context of a fatty liver, there is an enhanced sensitivity to LPS, likely due to Kupffer cell proliferation and augmented expression of Toll-like receptors [141,142].

Disruptions in lipid metabolism

NAFLD is recognized as the hepatic manifestation of metabolic syndrome, characterized by obesity, insulin resistance, hypertension, and dyslipidemia, common to both conditions[143]. Insulin resistance, leading to hepatic fat accumulation,

initiates NAFLD, triggering inflammatory responses that may result in liver fibrosis[144]. The oral microbiota contributes to NAFLD progression by promoting insulin resistance, leading to metabolic syndrome. In animal models with ligature-induced periodontitis, increased inflammatory factors, total cholesterol, and triglycerides altered liver glucose and fat metabolism, evidenced by increased liver cell lipid droplets and enlarged mitochondria[145-147]. Obesity and diabetes, components of metabolic syndrome, are significant risk factors for periodontal disease, suggesting NAFLD may indirectly influence periodontal disease pathophysiology through the shared pathway of metabolic syndrome.

The intracellular mechanisms activated by *P. gingivalis* primarily result in the inhibition of hepatic glycogen synthesis, which leads to fat deposition and the promotion of fibrosis. In the context of hepatic glycogen synthesis, Ishikawa *et al* [148] documented the internalization of *P. gingivalis* into HepG2 human liver cells. This process is linked to the inhibition of glycogen synthesis, affecting the phosphorylation of insulin receptor-1, serine/threonine kinase, and glycogen synthase kinase 3β (GSK3β). Another investigation on *P. gingivalis* showed that its gingipains might be transported to mouse liver *via* OMVs, impairing the Akt/GSK3β signaling pathway[149]. This disruption leads to hindered hepatic glycogen synthesis, thereby affecting insulin response. Zaitsu *et al*[150], employing an *in vitro* model of NAFLD, discovered that *P. gingivalis* could inhibit lipid droplets in liver cells by modifying lysosome formation and autophagy. Concerning fibrosis, Nagasaki *et al*[11] identified that gingipains from *P. gingivalis* could prompt the production of TGF-β2, subsequently upregulating Smad and extracellular signal-regulated kinase phosphorylation, which activates hepatic stellate cells. These pathways may be exacerbated in fatty liver due to the increased receptor expression related to hepatic fat accumulation.

ORAL AND GUT MICROBIOME-TARGETED THERAPY: A NEW POTENTIAL TREATMENT OF NAFLD

Dietary habits are widely recognized as a crucial factor influencing NAFLD, with the management of caloric intake and the incorporation of appropriate physical activity serving as a key non-pharmacological therapeutic strategy for NAFLD [151]. Recent research has underscored the beneficial effects of addressing periodontal disease in individuals with NAFLD, as demonstrated by the reduction in AST and ALT levels, improvement in serum inflammatory mediators, and decrease in endotoxins[152,153]. The newly established "oral-gut-liver" axis reveals innovative strategies for the prevention and treatment of NAFLD, particularly through the reduction of oral pathogens and correction of gut microbiota imbalance.

Oral microbiota control

Owing to periodontal disease's substantial impact on NAFLD, enhancement of oral hygiene and strategic management of pathogenic oral bacteria represent effective interventions for NAFLD associated with bacterial infection. As noted earlier, *P. gingivalis* plays an essential role in the interplay between oral bacteria and NAFLD, thus targeting it is an emerging approach. Strategies include employing AMPs to obstruct *P. gingivalis* adherence to host cells[154], deploying anti-CR3 receptor agents to diminish bacterial attachment[155], utilizing gingipain inhibitors to alleviate periodontitis and related systemic conditions[156], and regulating OMV production to impede biofilm development[133]. However, current research on these agents in the context of NAFLD related to pathogenic oral bacteria like *P. gingivalis* is preliminary and warrants further investigation.

Improve gut microbiota dysbiosis

Numerous methods exist to manipulate the gut microbiota, which include the use of antibiotics, prebiotics, probiotics, or a combination thereof termed synbiotics. These agents can influence the development of NAFLD through anti-inflammatory effects, enhancement of epithelial barrier function, reduction in ethanol production by gut microbiota, and modulation of bile acid and choline metabolism[157-159].

Appropriate antibiotic therapy

While the widespread use of antibiotics necessitates caution due to their potential to eliminate essential microbial species and foster antibiotic-resistant strains, their impact on NAFLD has been explored in various studies. For instance, alternating the administration of norfloxacin and neomycin has been effective in reducing small intestinal bacterial overgrowth and improving liver function in individuals with cirrhosis[160]. Additionally, long-term oral antibiotic treatment in animal models has been effective in suppressing gut bacteria, lowering portal secondary bile acids, and mitigating hepatic inflammation and fibrosis[161]. Concurrent administration of neomycin, bacitracin, and streptomycin has also been associated with decreases in hepatic triglycerides, lipid accumulation, and serum ceramide production in murine models[162]. Thus, while antibiotics can alter the gut microbiota and potentially slow the progression of liver diseases, their therapeutic use is limited due to the risk of developing antibiotic resistance.

Prebiotics, probiotics, and synbiotics

Prebiotics, non-digestible food components, foster the growth of beneficial gut microbiota[163]. They stimulate gut-mediated metabolic alterations, including the reduction of bacterial hepatotoxins, fortification of the intestinal epithelial barrier, and reduction in inflammation, potentially aiding in the mitigation of NAFLD. Prebiotics enhance bacterial synthesis of short-chain fatty acids, encouraging the proliferation of *Bifidobacteria* and *Lactobacilli*[164]. Probiotics, consisting of live bacteria or yeast, have been thoroughly researched, with many studies demonstrating their effectiveness in improving NAFLD. For instance, *Lactobacillus rhamnosus GG* supplementation has been linked with decreased ALT levels and anti-peptidoglycan-polysaccharide antibodies, offering benefits to NAFLD patients[165]. AMPs from *Lactobacillus*, such as lactococcin, exhibit antibacterial properties against pathogens with a lower propensity for fostering

antibiotic resistance[166,167]. Probiotic supplementation may also increase GLP-1 levels, contributing to ameliorations in fatty liver and BMI[168]. Synbiotics, which combine probiotics and prebiotics, are proposed to yield synergistic effects in NAFLD treatment[169].

Fecal microbiota transplantation

Fecal microbiota transplantation (FMT) entails transferring fecal matter from a healthy donor to a patient, with the goal of restoring gut microbiota balance. FMT has demonstrated efficacy in combating *Clostridium difficile* infections and is viewed as potentially applicable to a range of non-gastrointestinal diseases[170].

CONCLUSION

In summary, a growing compendium of clinical and fundamental research corroborates the association between oral bacteria and NAFLD, particularly among individuals with diabetes and metabolic syndrome. *P. gingivalis* emerges as a principal agent in fostering hepatic lipid accumulation and inflammation. Oral bacteria precipitate NAFLD *via* multiple pathways, including bacterial translocation, induction of inflammatory responses, secretion of toxic factors into the bloodstream, and perturbation of liver lipid metabolism. Furthermore, these microorganisms may alter the equilibrium of the gut microbiota through mechanisms such as hematogenous dissemination and direct ingestion. In this context, a dysbiotic gut micro-biome may produce deleterious substances (*e.g.*, LPSs and ethanol), compromising the intestinal barrier and adversely affecting liver health. However, elucidating the precise mechanisms through which oral bacteria impact NAFLD remains challenging, hindered by the complexity of *in vitro* culturing of oral bacteria and the individual variability in the "oral-gut-liver" axis, influenced by dietary habits. Additionally, the synergistic interactions between oral and gut microbiota and their contribution to insulin resistance in the context of periodontitis, diabetes, metabolic syndrome, and NAFLD warrant further investigation.

FOOTNOTES

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